PWS

Pharmacy World & Science

A journal dedicated to rational drug use

Supplement J

Supplement to Pharmacy World & Science
Volume 17, Number 5, 22 September 1995

Abstracts of Papers and Posters

Advanced Activities in Pharmaceutical Care

24th European Symposium on Clinical Pharmacy

Prague (Czech Republic), 10-13 October 1995

Organized by the European Society of Clinical Pharmacy, the Czech Pharmaceutical Society and the Czech Medical Association J.E. Purkyně

PHARMOCOKINETICS IN CHILDREN: IMPLICATIONS FOR OPTIMAL THERAPY

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There is ample evidence that the pharmacokinetics of drugs in infants and children may differ markedly from those in adults. The goals of pharmacokinetics is to maximize efficacy, minimize toxicity and drug interactions, enhance compliance, and reduce cost of medications. Studies with drugs including anticonvulsants, antimicrobials, digoxin, methotrexate and theophylline have demonstrated that these goals are achievable. Genetic and racial background, underlying disease, concurrent drugs, and nutritional status can influence pharmacokinetics. Population pharmacokinetics can provide useful data even when limited number of samples are available from a large number of patients. Pharmacokinetic monitoring is influenced by numerous factors including dose and dosage form, method of drug administration, times of sample collection, analytical and forecasting methods, and implementation of dosage recommendations. The future of pharmacokinetics, in large part would depend on correlating its parameters to the markers of efficacy and/or toxicity of medications. The ultimate goal of pharmacokinetics should be to improve the quality of life and health outcomes in infants and children.

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New substrates in artificial nutritions - lipids

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In the last 10 years animal experiments and clinical investigation has expanded knowledge of the nutritional and metabolic effects of fatty acids in health and disease. The role of fatty acids w-3 and w-6 has been demonstrated in the membrane structure and function, gene expression and in many processes such as inflammatory reaction, immunity, thrombogenesis, multiorgan failure (MOF), adult respiratory distress syndrom (ARDS) etc.
Recognition of the biological and pharmacological effect of polyunsaturated fatty acids (PUFA) w-3 and w-6 opens the possibility to develope organ specific (disease specific) products for parenteral nutrition such as medium chain triacylglycerols (MCT/LCT) and w-3 enriched lipid emulsions. Imbalance and deficit in essential PUFA are present most frequently in severely stressed, malnourished and catabolic patients. Thus disease specific formulations in artificial nutrition rich in essential PUFA are indispensible in prevention and treatment of PUFA deficiency. Minimal dose of w-3 PUFA is 100-200 mg/day in stabilised and 400 mg/day and more in malnourished and catabolic patients (0.4 % of the total energy requirement). Minimal daily requirement of oleic acid is 290 - 390 mg in stabilised and at least 1200 mg in catabolic and malnourished patients. Pharmacological doses of w-3 PUFA in artificial nutrition shifts the pathophysiological state to one that is antithrombotic, antiaggregatory with decreases in the blood viscositv. Pulmonary capillary vasoconstriction and permeability is decreased in patients with MOF and ARDS supplemented with high doses of w-3 PUFA. Further animal studies have shown that supplementation of w-3 PUFA prevents or diminishes the developments of arrhythmia (Charnocks, 1992). Leukotriene B4 (LTB) and prostaglandin E2 (PGE2), both products of w-6 PUFA (arachidonic acid) are increased in patients with inflammation (rheumatoid arthritis, ulcerative colitis). Supplementation with w-3 PUFA in clinical studies resulted in improvement shown by histological findings, weight loss and reduction in the dose of prednisone in comparison with placebo group (Stenson et al. 1992).
Several experimental studies have shown that eicosanoids produced by eicosapentaenoic acid (20:5 w-3) and docosahexaenoic acid (22:5 w-3) modulate the induction, proliferation and invasiveness of tumor cells by altering cell membrane composition, immune function, oncogene expression and possibly modulating growht factors function. In clinical studies artificial nutrition enriched by w-3 PUFA reduces body weight loss in cancer patients. These recent investigations indicate the importance of balanced w-3 and w-6 PUFA content in lipid emulsions that are used intravenously and in tube feedings for metabolic regulations and as adjuvants to drugh therapy.

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PHARMACOECONOMICS OF THERAPEUTIC DRUG MONITORING

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In recent years, the growing rate of inflation and the reality that resources for medical care are clearly finite has led to significant changes in reimbursement policies for pharmacy services. These influences have convinced leaders in healthcare to closely evaluate innovative health programs and services in terms of the benefits and costs. It is suggested that new health services be cost-justified in order to exist in the future. This will be crucial to the expansion of pharmaceutical services and the adoption of new health technology.

Application of economic evaluations is not new to the health-care sector. As health-care expenditures have escalated over the past two decades, the number of applications of these techniques has increased. Especially significant are cost-benefit and cost-effectiveness evaluations of medical practice, pharmaceuticals and other health care technologies,. Yet, until recently, there were no incentives to transform this interest into widespread utilities.

Pharmacoeconomic analyses is an important tool to assist in the evaluation of new pharmaceutical services and technologies. Essentially, economic analytical methods are used to weigh the positive and negative consequences of alternative courses of action. The usefulness of pharmacoeconomic analyses is in resource allocation, with the aim of achieving the highest return on investment or accomplishing a given objective in the least costly manner.

Unfortunately, very few clinical pharmacy service programs have been evaluated using economic techniques designed for this purpose. Therefore, the purpose of this presentation is to present various methodologies to assess the economic value of therapeutic drug monitoring services in society and for specific patient populations. Additionally, various issues regarding application of such evaluations will be presented. It is hoped that the evaluation methodologies delineated will be helpful in demonstrating not only the effectiveness but the efficiency of such services, therefore creating greater acceptance by providers, administrators, payers, and the public.

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NEW SUBSTRATES IN ARTIFICIAL NUTRITION - AMINO ACIDS

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In past decennia several hypotheses have been developed, according to which in trauma, critical illness, renal and hepatic failure, the amino acid part of the nutritional regimen should be modified to meet the specific requirements of the particular disease state. These hypotheses have generated much research and knowledge concerning amino acid metabolism, but not much clinical efficacy. Recently the concept "Immuno-nutrition" has been developed which regards glutamine and arginine as semi-essential amino acids especially required in excess of the content in normal protein during the depleted state and during severe illness.
Arginine has been claimed to have beneficial effects on immunefunction, whereas Glutamine may have beneficial effects on gutbarrier function and immunefunction. Arginine can be given both in enteral and parenteral regimens as the free amino acid added to whole protein (for enteral use) and to amino acid mixtures(for parenteral use) in the required amounts, although the effects of the free amino acid added to enteral nutrition on digestion and resorption of the protein has not been studied in detail. Glutamine is badly soluable in free form and unstable so that special measures should be taken to ensure solubility and to prevent toxicity during parenteral use. To circumvent this problem dipeptides (alanyl- and glycyl-glutamine) have been developed which are stable and highly soluable so that they can be safely added to the parenteral amino acid-lipid-glucose mixture. Immediate hydrolysis yielding the individual amino acids takes place shortly after parenteral administration. Enteral enrichment with free glutamine has been performed in experimental settings. Preliminary evidence suggests that the availability of Glutamine administered in this manner is suboptimal but, even worse, that addition of free Glutamine possibly interferes with normal resorption of the other amino acids in the diet. A potential manner to solve this problem is to compose mixtures of only very partially hydrolyzed naturally occuring proteins containing high quantities of Glutamine.

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DEVELOPING PARENTERAL NUTRITION SERVICES IN BOTH THE HOSPITAL AND THE COMMUNITY

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Intestinal failure is defined as the reduction in functioning gut mass below the minimum amount necessary for adequate digestion and absorption of nutrients. In cases of severe intestinal failure, total parenteral nutrition (TPN) is required. Additionally patients with other pathologies such as cancer are often prescribed TPN. In the early days of parenteral nutrition, patients received their nutrition as separate ingredients in bottles and bags, but over the past few years this method has been superseded by the "all in one" or "big" bag. Pharmacists have two important roles to play in the care of patients on TPN. Firstly the clinical role, as a member of the nutrition team and secondly, in the formulation and compounding of the solutions. These roles are often carried out by different pharmacists.The most cost effective approach to the management of clinical nutrition is the implementation of a fully operational nutrition team. This team should be responsible for carrying out defined policies and protocols, as well as, on a day to day operational basis, assessing and treating patients with clinical nutrition needs. The ideal team should comprise, senior clinician (team leader), junior doctor, nutrition nurse, dietitian, clinical pharmacist, microbiologist and clinical pathologist. The pharmacist's role, as a member of this team, includes formulation design, patient education, patient monitoring and acting as a resource to other members of the team and to professionals working in primary health care. A number of factors need to be considered when preparing parenteral nutrition solutions in a ready to use form. Aseptic facilities - clean rooms or isolators. Isolators protect the products from operator contamination, they can be located in a room with a lower specification, they do not require the use of sterile clean room clothing and they are flexible in design. They are, therefore, very economical to use. However, if large numbers of TPN solutions are being prepared, they may be too restrictive.

Licensed manufacturing units - UK "specials" licence from Medicines Control Agency

Audit and inspection. Quality control and quality assurance - contract with quality control laboratory.

Product presentation. Stability and quality.

Manufacturing specification. Indemnity insurance - £2 million liability insurance.

Delivery, storage and packaging - lifting/handling legislation.

Home parenteral nutrition services are developing rapidly in many European Countries. Details from the UK home nutrition register show that one new patient per million population enters the home nutrition programme each year. This represents about 55 new patients per year. The figures across Europe are similar. A dedicated and responsive organisation is needed to provide high quality home care to patients in order to ensure safe, effective and economic programmes. The following elements make up a focused service for the home patient:- Care plan - development of a plan of care tailored to the individual patient's requirements. This is reviewed, periodically, by members of the nutrition team. Patient assessment - requires liaison between hospital doctors, family doctor, clinical nutrition team, home care provider and patient's relatives. Patient training - patients require training in the general principles of IV therapy, aseptic techniques and catheter care. Training will normally begin in the hospital and be reinforced in the home setting. Training manuals are provided.

Aseptic preparation - nutrition solutions are prepared in a ready to use form with a shelf life of 30 - 90 days, depending on formulation. Infusion control devices - infusion pumps and other equipment are supplied and maintained by the home care agency. Ancillary supplies - antiseptic solutions and consumables are supplied as necessary. Delivery - drugs, solutions, equipment and consumables are delivered to the patients' homes and "sharpes" and waste products are removed in a safe manner for destruction. Administration - Patients are taught to self administer. This process is usually monitored by a nurse specialist who visits the patient on a regular basis. Records - patient records are kept by members of the nutrition team, the pharmacist keeping details of formulations, quantities issued, expiry dates and transport dates. Communications - the nutrition team remains in communication with the patient, the patient's relatives, the family doctor and the home care agency. Monitoring - blood samples are taken regularly for biochemical analysis. 24 hour availability - the pharmacist member of the team is available in deal with emergencies at all times.

Pharmacists have an important role to play in providing good quality health care to patients on long term home parenteral nutrition. The opportunity must not be missed.

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PHARMACOKINETIC OPTIMIZATION OF A 5 DAY 5-FLUOROURACIL / CALCIUM FOLINATE REGIMEN IN PATIENTS WITH ADVANCED COLORECTAL CANCER

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5-Fluorouracil (5-FU) is frequently combined with calcium folinate (CFOL) in the treatment of colorectal cancer due to more pronounced inhibition of thymidilate synthase enhancing tumor response and toxicity. Although different schedules of 5-FU and CFOL have been used the optimal dosage regimen has not been defined yet. Detailed knowledge of the pharmacokinetic characteristics of 5-FU and CFOL in combination is essential for rational dosing.

This investigation focussed on two main aspects: 1. Relationships between plasma levels of 5-FU and toxicity, 2. Pharmacokinetic differences between the active (6S)-diastereomer and the inactive (6R)-diastereomer of CFOL.

6 patients with advanced colorectal cancer received a 5 day continuous infusion of 5-FU (650 mg/m^2) and CFOL i.v. as diastereomeric mixture (100 mg/m^2) over 15 min b.i.d. Serial blood samples were drawn on the first day and at steady state (3rd, 4th or 5th day). Plasma was analyzed for 5-FU by reversed phase ion-pair HPLC and for (6S)- and (6R)-CFOL by chiral HPLC.

Mean 5-FU steady state plasma concentration (C_{ss}) was found to be 190±54 ng/ml. Mucositis was the major observed toxicity. The patient with the highest observed C_{ss} (273 ng/ml) developed a hand-foot-syndrome suggesting that adaptive dosage control might help prevent patients from this severe toxicity.

Pharmacokinetic parameters of CFOL (mean ± SD) were estimated separately for (6S)- and (6R)-CFOL using a one-compartment model. Considerable differences were found in pharmacokinetic parameters of both diastereomers.

	Day	AUC (µg·h/ml)	Cl_{tot} (ml/min)	$t_{1/2}$ (h)
(6S)-CFOL	1	4.5±3.0	519±314	0.7±0.6
(6S)-CFOL	3-5	3.7±0.9	485±115	0.6±0.2
(6R)-CFOL	1	56±35	40±22	6.9±4.7
(6R)-CFOL	3-5	59±15	32±10	7.6±4.3

The active (6S)-CFOL showed lower AUC, higher total clearance and shorter half-life compared to the inactive (6R)-diastereomer. During 5 day treatment pharmacokinetics of the diastereomers did not change significantly (*Student's* paired t-test). Investigations are currently extended to CFOL dosage of 20 mg/m^2 in order to compare two different CFOL dose intensities.

In conclusion, adaptive dosage control of 5-FU as well as the different pharmacokinetics of (6S)- and (6R)-CFOL should be considered for pharmacokinetic optimization of the investigated 5-FU/CFOL regimen.

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USE OF PHENOBARBITONE TO EVALUATE COMPLIANCE FOR SHORT COURSES OF TREATMENT

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Compliance has been identified as a major cause of treatment failure[1] for medicines that are taken over months or years. Low dose phenobarbitone has been used as a marker of compliance by inclusion of phenobarbitone (1-2mg) in the tablet under investigation[2]. Phenobarbitone was selected because it has a low clearance and little individual variation in pharmacokinetics. To date it has been used in studies of chronic medication only. There are occasions when compliance is critical for short courses of medicine such as anthelmintic. We investigated the potential for phenobarbitone to provide useful information about compliance with a medicine taken once daily for five days.

The pharmacokinetic estimates of clearance and volume of distribution for phenobarbitone were obtained from 10 heathy volunteers together with estimates of the population variance of these parameters.

This data was used to simulate the proposed dose regimen for a new anthelmintic and to predict the blood concentration of phenobarbitone at 144 and 168 hours from day one and the expected range of concentrations. The simulation was repeated omitting one or more doses for example omitting the dose on day 2, omitting the doses on day 2 and day 4 etc.

Comparison of the predicted values indicated that the plasma levels at 168 hours were sufficiently different to detect a dose missed on any day and to distinguish between 1 dose and 2 doses missed.

Use of phenobarbitone would be a reliable indicator for identifying non compilers with critical short term medication enabling a repeat course to be undertaken under close supervision.

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VANCOMYCIN PHARMACOKINETICS AND DOSAGE GUIDELINES IN NEONATES OF POSTCONCEPTIONAL AGE UNDER 33 WEEKS.

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The objective of the present study was to analyze the pharmacokinetic behaviour of vancomycin in premature neonates with postconceptional age (PCA) under 33 weeks, the factors that may influence it, as well as to design proper vancomycin dosage guidelines. All neonates admitted to the Neonatal Intensive Care Unit with PCA under 33 weeks and with suspected or documented gram-positive infection who had received intravenous vancomycin between October'88 and June'94 were included in this study (n=44). Initial vancomycin dosages ranged from 17 to 20 mg/Kg every 18 h, according to previous studies. Peak and trough plasma vancomycin levels were determined the third day of therapy and renal function was monitored frequently. The analytical method for vancomycin analysis was fluorescence polarization immunoassay. The individual pharmacokinetic parameters were determined by using a one-compartment model and a non-linear regression method. When necessary, the vancomycin dosage was readjusted to obtain plasma levels within the therapeutic range (Peak-2h after 1 h infusion-: 20-25µg/mL and trough: 5-10µg/mL). Nine out of 44 neonates were treated with indomethacin within the week prior to study and 23 out of 44 were submitted to mechanical ventilation.

Results (mean ± SD)

I	MV	Cr_s (µmol/L)	N	PCA (weeks)	WEIGHT (Kg)	T½(h)	Vd (L/kg)
NO	NO	71.5±18.8	18	31.0±0.9	1.192±0.216	8.0±2.8	0.73±0.28
NO	YES	95.4±51.0	17	30.0±1.8	1.215±0.348	10.0±4.9	0.66±0.16
YES	NO	73.0±1.4	3	32.0±0.0	1.343±0.129	6.3±1.7	0.82±0.16
YES	YES	148.2±31.3	6	30.0±2.2	1.165±0.565	17.6±5.6	0.68±0.17

I: Indomethacin Cr_s: Serum creatinine T½: Elimination half-life
MV: Mechanical Ventilation Vd: Volume of distribution

Conclusion: The elimination of vancomycin was greatly influenced by the concomitant treatment with indomethacin and mechanical ventilation and consequently by changes in renal function. According to our results, an initial dose of 15 mg/kg of vancomycin every 12 to 24 h would suit neonates under 33 weeks of PCA who had serum creatinine ≤ 120 µmol/L. Those who had higher serum creatinine values would need a loading dose of 20 mg/kg followed by 15 mg/kg every 36 h. However, close monitoring of renal function of the neonate and vancomycin plasma levels are mandatory, specially when the above factors prevail.

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CLINICAL PHARMACOKINETICS AND TIME-DEPENDENT BINDING OF HIGH-DOSE CARBOPLATIN TO PLASMA PROTEINS AND DNA

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Although carboplatin is used in various high-dose regimens in cancer patients there is limited information on its binding characteristics to endogenous compounds. Binding to plasma proteins (only unbound molecules can penetrate into cells) and DNA (mode of cytotoxic action) is of high importance for therapeutic outcome and toxic effects. The extent of binding, however, may vary considerably among patients. Therefore, pharmacokinetic studies including measurements of protein and DNA binding might help define individual dosage regimens.

The pharmacokinetics and protein binding of carboplatin were investigated in 10 germ cell tumor patients receiving 1500mg/m^2/3d carboplatin (1h iv infusion), etoposide and ifosfamide. Plasma samples were analyzed for total platinum (Pt) and ultrafiltrated plasma for unbound Pt by flameless atomic absorption spectroscopy (AAS). Pharmacokinetic parameters were calculated using a biexponential equation. Protein binding was quantified by the fraction unbound (f_u) in plasma. The extent of the Pt-DNA adduct formation was assessed by an *in-vitro* assay incubating calf thymus DNA with two different concentrations of carboplatin for 24 and 72 h. After DNA isolation, the amount of nucleotides was determined by UV-absorption spectroscopy. Pt was quantified by flameless AAS and the Pt-DNA ratio was calculated.

	Fraction unbound (f_u)		Pt-DNA ratio 16µg/ml Pt	Pt-DNA ratio 84µg/ml Pt
1 h	0.98 ± 0.25	24 h	0.7 : 1000	6 : 1000
24 h	0.14 ± 0.09	72 h	6 : 1000	20 : 1000

F_U declined from 0.98 (at Cmax) to 0.14 (at Cmin) with a large interpatient variability. Whereas $t_{½,\alpha}$ did not differ significantly between total and unbound Pt, total Pt exhibited a significantly longer $t_{½,\beta}$ (99±40h) than unbound Pt (44±18h; p<0.01, Student's t-test). At the beginning of the high-dose schedule we found measurable levels of Pt in 80% of the patients originating from previous conventional Pt containing regimens. The observed long-term retention reflects irreversible binding of Pt in the body. The extent of Pt-DNA adduct formation was higher after 72 h of incubation compared to 24 h for both concentrations suggesting time-dependent cytotoxic activity.

In conclusion, carboplatin exhibits time- and/or concentration-dependent protein and DNA binding. Further investigations will focus on the significance of Pt binding for safety and efficacy of Pt-containing high-dose chemotherapy.

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CLINICAL PHARMACOKINETICS OF HIGH-DOSE ETOPOSIDE: SYSTEMIC EXPOSURE PREDICTS HEPATOTOXICITY

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Etoposide is used in numerous high-dose chemotherapy regimens. While irreversible hematotoxicity can be prevented by stem cell rescue, non-hematological toxicity becomes dose-limiting. Dosage individualization based on pharmacokinetic parameters might minimize toxic risks. However, knowledge of the relationships between pharmacokinetic parameters and toxicity is crucial before pharmacokinetic monitoring can be implemented in clinical routine.

The aim of this investigation was to relate pharmacokinetics and toxicity of etoposide during high-dose chemotherapy in 10 germ cell cancer patients. The treatment consisted of 2400 mg/m^2/4days etoposide as 1h iv infusion, 1500 mg/m^2/3days carboplatin as 1h iv infusion and 10g/m^2/4days ifosfamide as constant rate infusion. Toxicity was evaluated according to WHO criteria. Plasma samples were analyzed for etoposide by reversed-phase HPLC. Pharmacokinetic parameters were estimated using a two-compartment model.

Plasma concentrations declined biexponentially with $t_{1/2,\alpha}$ of 3.9±1.8 h followed by a considerably longer $t_{1/2,\beta}$ of 20.0±7.8 h. AUC as a measure of drug exposure was related to toxicity. We found that patients with hepatotoxicity grade 2 and 3 (n=3; 3918±44 µg•h/ml) exhibited significantly higher etoposide AUC values compared to those with no or mild (grade 1) hepatotoxicity (n=7; 2672±553 µg•h/ml). Treatment-induced increase of serum transaminase (SGOT, SGPT) levels correlated significantly ($p<0.05$) with etoposide AUC, but they did not correlate with peak etoposide concentration. No relationship was observed between etoposide pharmacokinetics and other types of toxicity.

In conclusion, our data suggest a relationship between systemic etoposide exposure and hepatotoxicity during high-dose chemotherapy. Further investigations will evaluate whether monitoring of etoposide plasma levels in addition to daily measurements of SGOT and SGPT is a feasible approach to reduce the risk and severity of hepatotoxicity.

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NEW AND ESTABLISHED CRITERIA TO ASSESS SUSTAINED RELEASE (SR) PERFORMANCE OF DILTIAZEM SR FORMULATIONS

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The three classical pharmacokinetic parameters used to assess bioequivalence: AUC, Cmax and tmax, are suitable to determine the extent and rate of absorption of immediate release drug products. However, they may fail to evaluate the pharmacokinetic performance, particularly the rate of absorption of sustained release (SR) formulations which yield flat plasma curves with multiple peaks. This paper evaluates the inclusion of the following criteria for bioequivalence assessment of diltiazem SR formulations: MRT, Cmax/AUC, peak occupancy time (POT), tapical, Capical, percent fluctuation and flatness of the curve as assessed by the % CV of the Css values obtained during a dosing interval at steady state.
The above proposed criteria, as well as the classical parameters AUC, Cmax and tmax were utilized in a recent pharmacokinetic study of a new SR product of diltiazem, Dilapress 240. Dilapress 240 was analyzed in 18 healthy subjects following single (240 mg) and multiple (240 mg qd for 6 days) dosing at steady state (day 6) in comparison to Cardizem CD. The bioavailability of Dilapress 240 relative to that of Cardizem CD following single and multiple dosing was 92 ± 28% and 90 ± 24%, respectively. The 90% confidence intervals (CI) over a mean AUC ratio of 89% were: 78%-101% (single dose - SD) and 77%-101% (multiple dose - MD). Following the administration of Dilapress 240 and Cardizem CD identical mean values of the peak plasma concentration were obtained: 84 ng/mL (SD) and 132 ng/mL (MD). The 90% CI over a mean Cmax ratio of 100% were: 83%-115% (SD) and 86%-115% (MD). In the SD study, subject 8 had a relative bioavailability value of 24% which deviated by 7.5 standard errors (SE) from the meand AUC ratio. Consequently, the single dose analysis was repeated without subject 8. The mean bioavailability data was 97±37% with a 90% CI of 80%-114% over a mean AUC ration of 92%. ANOVA analysis did not show any formulation or period effect in all tested pharmacokinetic parameters. Based on the above, Dilapress 240 was found to be bioequivalent to Cardizem CD. In contrast to the AUC and Cmax ratio, the 90% CIs associated with the ratio of the proposed criteria with the exception of Capical, did not fall within the acceptable limits. The proposed criteria are theoretically more sound than the single point parameters Cmax and tmax for rate of absorption assessment. However, in this study, a discrepancy was found between them and the classical parameters regularly used for bioequivalence assessment.

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THE END-LINE FILTRATION OF "ALL-IN-ONE" PARENTERAL NUTRITION ADMIXTURES.

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Introduction: The clinical importance of the removal of particulate matter and bacteria has been shown by Puntis *et al*[1] and the clinical impact of the presence of fungal organisms such as *Candida species* has been reviewed by Driscoll[2]. The problems of particulate matter was further highlighted in 1994 by an FDA alert on the presence of precipitated materials in total parenteral nutrition (TPN) admixtures containing lipid emulsions, which led to the FDA recommending the routine use of 1.2µm end-line filters[3]. The filtration of TPN admixtures containing fat emulsion has presented a number of problems when the nominal pore size of the filters was less than 5µm. Amongst these problems was the blocking of the filter due to the emulsion globules being electrostatically attracted to the filter surface. The TNA-1 filter (Pall Biomedical) is an advance on previous filter media in this context.

Aim of Study: To investigate the filterability of TPN admixtures through two commercially available end-line filters of nominal pore rating 1.2µm (Gelman Sciences and Pall Biomedical), to determine the effect of the filters on the lipid emulsion globule size distribution, and to challenge the fungal retentive capacities of the filters with *Candida albicans*. Flow rates of between 100 and 200ml.hr^{-1} were used for some typical peripheral and central All-in-One TPN regimens.

Method/Results: The maintenance of the preset flow rates during the delivery of the total volume of the admixtures was used as a measure of filterability, while the pressure upstream of the filters was monitored and in all cases showed no clinically significant changes. The globule size distributions of the lipid emulsions were determined by laser diffraction (Malvern Mastersizer®) on samples collected upstream and downstream of the filter, all samples were shown to be unchanged. Finally filtrates from innoculated TPN admixture delivered through the filters were tested for the presence of *Candida albicans* over a 24 hour period with the results shown below.

Filter	Minimum *Candida* challenge	Average total number of recovered organisms.
Pall Biomedical	6 x 10^8 CFUs	0 CFUs
Gelman Sciences	6 x 10^8 CFUs	3.29 x 10^4 ± 2.46 x 10^4 CFUs

Conclusion: The results demonstrate that the filters do not impede the flow rate or influence the lipid emulsion globule size distribution, however the Pall filter shows total retention of *Candida*, whilst the Gelman filter does not. This may be due to differences in the pore size distribution of the two filters as was indicated by Bubble Point pressure tests carried out on the filters, where the Gelman filter readings were approximately 15-20% lower than those of the Pall filter indicating a broader pore size distribution.

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MONITORING OF ARTIFICIAL NUTRITION IN PATIENTS WITH PANCREATIC DISEASE

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Patients with pancreatitis are often malnourished and need nutritional support. One of the goals of the current therapy is to promote pancreatic rest by decreasing pancreatic secretion. Total Parenteral Nutrition (TPN) has not been shown to have a direct beneficial effect on the course of pancreatitis, but it can provide adequate nutrition for extended periods of time. Enteral feeding (EN) should be used when abdominal pain, ascites or an increase in serum amylase does not restrict use of the gastrointestinal tract.
In Verona Hospital a consolidated Artificial Nutrition (AN) team associated to Pharmacy Service has existed since 1980.
The clinical pharmacist monitors the artificially nourished patients (pts.) registrating daily their biochemical parameters, visiting them twice a week in departments and preparing parenteral and enteral admixtures.

Objective: An epidemiological study was undertaken with the aim to analyze the duration, the composition, the AN-related complications and the final outcome of artificially nourished patients with pancreatic disease.

Materials & Methods: All patients with pancreatic disease who required AN (TPN or/and EN) during the past year 1994 in the University Hospital of Verona were analyzed.

Results: 78 pts. (17.1% of 457 pts. who required AN) received AN during the course of acute pancreatitis (42), pancreatic cancer (30), fistula (3) and pseudocyst (3). 68 (87.2%) of them received TPN alone and 4 pts. (5.1%) received EN alone. In 6 pts. (7.7%) TPN was associated whith EN.
The mean nonprotein energy intake was 2120 Kcal (range 1000-3000) for parenterally fed pts. and 40% of these calories was provided from lipid. 9 pts. (12.2%) didn't receive lipids.
Enterally fed patients received a mean daily intake of 1000 calories (range 500-1500) by jejunostomy placed at the time of operation.
The mean duration of AN was 26 days (2-116) for TPN and 12 days (7-20) for EN.
Catheter sepsis was the most frequent complication occurring in parenterally fed pts. (13.5%). Only one patient who was given EN developed diarrhea.

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TOTAL PARENTERAL NUTRITION IN A DISTRICT HOSPITAL. A REVIEW OF 9 MONTHS' PRACTISE.

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The indications for Total Parenteral Nutrition (TPN) are becoming fewer. To see if modern practise was applied in our institution, we reviewed the use of all portions of TPN for a 9 months period (2.6.93 - 11.3.94).
The nutritional team comprising 3 nurses, 2 dietitians, 2 doctors and 1 pharmacist went through all records of 54 patients who had been given TPN (34 general surgery, 2 ortopedic surgery, 3 gynecological, 14 internal medicine, 1 psychiatric). The main indications were postoperative nutrition and malnutrition. TPN was used in a mean of 10 days (range 1 - 26). TPN volume 19,2 liters per patient (1,25 - 65).
The nutritional team evaluated in each patient if the indication for TPN was absolute (enteral nutrition contraindicated or could not be delayed); if TPN could have been substituted totally or partially by enteral nutrition; or if TPN could have awaited if enteral nutrition was successful. Criteria for not using TPN: Normal or near normal function of the gastro-intestinal tract, end-stage disease, routine perioperative nutrition, expected short duration of TPN, anorexia.
Results: TPN could possibly have been avoided in 22 patients (40,7 %); in 14 patients (26 %) the period of TPN could have been shorter or the amount smaller. Only in 18 patients (33,3 %) we judged TPN to be absolutely indicated.
Conclusions: With the limitations of a retrospective review, we found that TPN could have been saved in about 50 % of the patients. Frequent ajustments of the indications for use of TPN are nessesary, and to that respect we find the nutritional team valuable also in a smaller district hospital.

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AMPHOTERICIN B PHARMACOKINETICS: COMPARISON OF THE CONVETIONAL FORMULATION WITH A FAT EMULSION IN A GROUP OF PATIENTS WITH NEUTROPENIA.

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Objective: To compare the pharmacokinetics of amphotericin B administered in a conventional 5% dextrose solution with a 20% fat emulsion, in sixteen neutropenic patients hospitalized for haematological malignances and with proven or suspected fungal infections.
Material and Methods: All the patients received 50 mg (approximately 1mg/kg/day) of amphotericin B daily in random order, either as a 50ml lipid emulsion (Group I) or in 500ml of 5% dextrose (group II). Five serum samples were taken during the 24 h after drug administration and levels of amphotericin B were measured by high-pressure liquid chromatography (HPLC).
Results: The maximun amphotericin B serum concentration was significantly lower when the drug was administered in 20% Intralipid® (1.46±0.61 vs 2.83±1.17 mcg/ml, P=0.02). The AUC (0-24h) was also much lower in Group I (17.22±11.15 vs 28.98±15.46 mcg x h/ml). The $T_{1/2}$ alpha was approximately three times longer in Group I (2.92±2.34 vs 0.64±0.24 h, P=0.011). Conversely the $T_{1/2}\beta$ was approximately equal (11.44±5.18 vs 15.23±5.25 h). The MRT was also similar en both groups (19.41±11.16 vs 19.65±7.86 h). The Cl and the Vd_{ss} in Group I were about twice as great as that in Group II (62.97±35.51 vs 33.01±14.33 ml/kg/h) and (1043.92±512.10 vs 562.32±152.05 ml/kg, P=0.034) respectively. Finally, the Vd_c was greater in Group I (618.17±231.80 vs 328.19±151.71 ml/kg, P=0.013) but there were no differences in Vd_p (425.75±352.87 vs 234.14±75.92
Conclusion: Amphotericin B has a different pharmacokinetic profile when is administered in lipid emulsion compared with the standard 5% dextrose form and that the main difference is due to a clear-cut in Vd_{ss}, specially in Vd_c.

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ANALYSIS OF TOTAL PARENTERAL NUTRITION UTILIZATION IN HOSPITAL PATIENT

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The use of total parenteral nutrition (TPN) has rapidly increased in the Czech Republic. To study the utilization of TPN, using methodology recommended by the World Health Organization, classification of components in accordance with the anatomical therapeutic chemical clasification (ATC) and defined daily dose (DDD) system is necessary. The WHO Collaborating Centre for Drug Statistics Methodology has classified „Solution for parenteral nutrition" in ATC group and has assigned ATC code to amino acids, fat emulsions and carbohydrates. DDD's for the components of TPN are difficult to establish, because they have never been used in monotherapy, but all the same they have a definite interrelation.
In study of Frankfort et al. [1] the all-in-one DDD methodology to study utilization of TPN was presented and DDD for the individual components proposed.
The objective of this study is to validate existing DDD methodology in a University Hospital in the Czech Republic.
In a prospective study, from April to May 1995 at the University Hospital, patients using only TPN were included. The following data were collected from every patient: age, sex, the main diagnosis, reason for TPN administration, composition of TPN each day and duration of this administration.
Actually prescribed amounts of amino acids, fat emulsions and carbohydrates were assessed per day, and the average amount per patient was calculated. The mean value was presented as prescribed daily dose (PDD) and compared with the all-in-one DDD methodology by Frakfort et al. [1].
Adapted ratios of PDD and DDD for amino acids, fat emulsion, and carbohydrates were 0,98 ± 0,20; 0,88 ± 0,32 and 0,66 ± 0,11 (mean ± SD). The ratio of the number of TPN DDD's to the number of TPN treatment days was 0,84 ± 0,21. It was shown that the proposed all-in-one DDD methodology can be used to describe the utilization of TPN and its components.

1. Pharm Worl Sci 1994;16(5):225-230.

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PHARMACOKINETIC PROFILE OF CYCLOSPORINE NEORAL IN LIVER TRANSPLANT RECIPIENTS WITH EXTERNAL BILIARY DIVERSION

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INTRODUCTION:
The usefulness of Sandimmun® (Cyclosporin (CsA)), is limited in liver transplant recipients during the early postoperative period, due to poor drug absorption resulting from gastrointestinal disturbances and biliary system disruptions. It has been suggested that the absortion of Sandimmun Neoral® (a new oral microemulsion formulation of CsA) is independent of bile flow.
AIM:
We describe a pharmacokinetic study, examining the effect of bile on CsA absorption following a single dose of Sandimmun Neoral® in liver transplant recipients with external biliary diversion during the early postoperative period.
METHOD:
Six liver transplant recipients (4 female) with open T-tubes, aged between 30 and 57 years (mean 43 years), were studied at day 8 posttransplantation. CsA was given endovenously during a mean of 3 days and then CsA-Neoral orally at a dose which was adjusted to maintain therapeutic levels between 250 and 350 ng/ml (the mean CsA dosage was 13.5±1.6 mg/kg/d). Blood samples were obtained before and 1,2,3,4,6,8,10 and 12 hours after dosage administration. CsA was analyzed by Specific Monoclonal Fluorescence Polarization Immunoassay (TDx, Abbott) on whole blood samples. Pharmacokinetic parameters were estimated using PKs, a sofware package by Abbott (utility sub-routine).
RESULT AND DISCUSSION:
Pharmacokientic data derived from patients with open T-tubes:

Patient	AUC (μg/ml/h)	Cmin (ng/ml)	Cmax (ng/ml)	C_{av} (ng/ml)	Tmax (h)
1	4.64	153	703	386	4.16
2	3.79	193	613	316	2
3	4.29	200	764	357	3
4	4.23	200	548	352	4
5	3.94	238	516	328	4.1
6	6.13	295	854	510	3
	4.5±0.85	213±148	666±130	375±70	3.4±0.86

All patients with open T-tubes and consequent malabsortion of Sandimmun® achieved good therapeutic levels with sandimmun Neoral®. Previously , these patients would have required a continous infusion of CsA. Absorption is good and uniform, and a single early peak concentration in blood was detected. The requirement for intravenous CsA exposes the liver transplant recipients to an increased risk of severe side effects, at a time when these patients are particularly vulnerable to such toxicity.
CONCLUSION:
This study has demostrated the improve absoption characteristic of CsA-Neoral in patient with external biliary diversion. CsA-Neoral is absorbed in the early postoperative period following liver transplantation, obviating the need for intravenous CsA.

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CLINICAL APPLICATION OF POPULATION PHARMACOKINETICS PARAMETERS OF CAFFEINE IN PREMATURE NEONATES

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[2]Supported by JNICT - Programa Ciência. Portugal

INTRODUCTION: Neonatal apnea is a common problem: it occurs in 25% of infants under 2500 gr and 80% of infants under 1000 gr. Caffeine is widely used for the treatment of this condition since 1977.

OBJECTIVE: The aim of the present work was the explanation and interpretation from a clinical point of view of the dynamic pharmacokinetics parameters obtained through a mixed effect modeling process using the NONMEM software package.

MATERIAL & METHODS: The model-building process was based upon retrospective information from 75 hospitalized patients with a total of 145 measured serum caffeine concentrations. The data analysis was made using a nonlinear mixed-effects modeling implemented with the NONMEM, a computer program developed for population pharmacokinetics analysis. The influence of the selected covariates in drug disposition is investigated by using a simulation study with a prototype patient.

RESULTS: The final model obtained for the caffeine kinetic profile characterization in premature newborns is the following one:

$$Cl\ (ml/h) = (\theta_1 * WT + \theta_2 * PNA) * \theta_{PN} * \theta_{LGA}$$

$$V_d\ (ml) = \theta_3 * WT$$

η^{CL} - proportional model ($\omega_{CL} = 14.87\%$)

ε_i - proportional model ($\sigma = 18.44\%$)

where WT is the current body weight (kg), PNA is the postnatal age (weeks), PN denote parenteral nutrition and LGA denote low gestational age (≤ 28 weeks). This model allows four differents clinical possibilities that could be developed in a prototype patient: 1) patient with > 28 weeks of gestational age and without parenteral nutrition; 2) patient with > 28 weeks of gestational age and subject to the parenteral nutrition; 3) patient with ≤ 28 weeks of gestational age and without parenteral nutrition; 4) patient with ≤ 28 weeks of gestational age and subject to the parenteral nutrition (tables and graphics will be presented later due the limited space allowed for abstracts).

CONCLUSIONS: The predictive capacity of our model when compared with the available bibliographic values allow us to conclude that it could be very useful in the design and adjustments of caffeine dosage schedules in premature neonates with apnea of prematurity.

PREDICTION OF AMIODARONE TOXICITY: PLASMA AMIODARONE AND DESETHYLAMIODARONE CONCENTRATION CUTOFF VALUES

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The purpose of this study was to determine the relationship of steady-state plasma levels of amiodarone and desethylamiodarone to adverse effects during long-term amiodarone therapy and the performance characteristics of the cutoff value as test for predicting toxicity were calculated.

PATIENTS AND METHODS

Patient population. The study included 28 patients who were treated with a fixed maintenance dose of amiodarone 200 mg /day, five days per week, for atrial fibrillation. All patients were treated for more than two years (mean 2.7 ± 1.4). The mean age of the patients was 61.85 ± 10.32 years with an average weight of 73.51 ± 11.48 K_g. The gender distribution was 50% male and 50% female.

Drug assay. Concentrations of amiodarone and desethylamiodarone were measured by high-performance liquid cromatographic method.

*Data analysis.*The plasma amiodarone and desethylamiodarone concentration cutoff as test to distinguish toxicity from nontoxicity was studied. This test has allowed to discriminate positive from negative response by the sensitivity, specificity and positive and negative predictive values.

RESULTS

The observed side effects atributed to the amiodarone treatment were corneal microdeposits (n=6), pulmonary toxicity (n=1) and hypothyroidism (n=1). In no cases hepathic toxicity was detected. There were no signs of digestive intolerance or photosensitive reactions.

Due to the pneumonitis the dosage discontinuation of amiodarone treatment became necessary in one patient. The patient with hypothyroidism required daily administration of 100 mg of thyroxine.

The relationship between toxicity and plasma amiodarone and desethylamiodarone concentrations is showed in the table.

Cutoff value	*TPR*	*TNR*	*PPV*	*NPV*
Amiodarone : 2 mcg/ml	0.43	0.95	0.75	0.83
Desethylamiodarone: 1mcg/ml	0.29	0.95	0.66	0.80

TPR= true-positive result (sensitivity); TNR= true-negative result (specificity); PPV= positive predictive value and NPV=negative predictive value

DISCUSSION

For a amiodarone cutoff value of 2 mcg/ml the obtained results showed that just 75% of patients with plasma amiodarone concentration > 2 mcg/ml were correctly classified as having toxicity, but 83% of patients with concentrations ≤ 2 mcg/ml were accurately identified as not having toxicity. The greater probability for negative as compared with positive predictive value suggest that the test are more effective at ruling out toxicity than ruling it on and it is happening when the prevalence of a condition is relatively low

The measurement of plasma desethylamiodarone concentrations did not increase the sensitivity or specificity of the amiodarone level in the identification of patients at risk for adverse amiodarone effects.

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PHARMACOKINETICS OF CEFTAZIDIME IN FEBRILE PATIENTS NEEDING NUTRITIONAL SUPPORT

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Nutritional support is needed in malnutrition which is usually connected with a decrease in plasma concentrations of various proteins. It was therefore interesting to study how a decrease in concentrations of proteins (albumin, prealbumin, and transferrin) and the activity of another protein, pseudocholinestrase can influence pharmacokinetic parameters of ceftazidime. Ceftazidime was administered for the blind treatment of nonspecific infectious diseases to 12 patients, 7 males and 5 females, aged between 34 and 81 years (body temperature > 38°C) who were admitted to the Intensive Care Unit (ICU) of the Department of Metabolic Care and Gerontology, University Hospital in Hradec Králové. Six of these patients were transferred to the ICU from the Department of Surgery because of septic syndrome as a consequence of various surgical interventions. Other 6 febrile patients were admitted to the ICU on the basis of the following concomitant disorders: dyspeptic syndrome, pancreatic cancer, myocardial infarction, cholangoitis, and chronic pancreatitis (2 cases). All patients were in different states of nutrition. Mean value of body mass index equalled 21.7 ± 5.5 $kg.m^2$. Seven patients on the basis of not biochemical results only, but also on the grounds of clinical appearance were considered to be malnourished and were selected for nutritional support. The following pharmacokinetic parameters after intravenous administration of 1 000 or 2 000 mg of ceftazidime were observed: An apparent volume of distribution in steady state (Vd_{ss}) was 16.36 ± 7.35 L, mean values of biological half-life ($t_{1/2}$) were 79 ± 34 min, and mean values of systemic clearance (Cl_s) of ceftazidime were 0.13 ± 0.16 $L.min^{-1}$. Regression analysis revealed that there are significant close negative relations in plasma levels of albumin, the apparent volume of distribution, and biological half-life of ceftazidime. The reduced plasma levels of albumin were obviously responsible for an increase in the apparent volume of distribution of ceftazidime and for a partial elongation of its biological half-life.

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VANCOMYCIN PHARMACOKINETICS AND DOSAGE REQUIREMENTS IN NEUTROPENIC PEDIATRIC PATIENTS

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Antibiotic administration plays an essential part in the management of neutropenic pediatric patients. Vancomycin is a common agent given to these patients. Both efficacy and toxicity of vancomycin are related to plasma concentrations. During routine therapeutic monitoring of vancomycin serum levels, we observed a tendency to have antibiotic serum levels under the therapeutic range.

The aim of the present study was to determine steady-state vancomycin plasma levels reached after the administration of a conventional dose, to determine the pharmacokinetic parameters of vancomycin in neutropenic pediatric patients and to establish dosage guidelines for this population.

All neutropenic pediatric patients admitted in our hospital requiring vancomycin treatment since 1992 were included (N=30). Patients with renal failure were excluded. The patients' age, weight and serum creatinine were 8 ± 4 years, 31.2 ± 14.4 Kg and 45.6 ± 8.9 µmol/L, respectively. The mean vancomycin starting dosage was 51 mg/Kg/day. The dosing intervals were 12h (N=3), 8h (N=20) and 6h (N=7).

Steady-state vancomycin plasma levels were determined (trough concentrations were drawn inmmediately before a dose and peak concentrations 3 hours after the beginning of the infusion). The analytical method was fluorescence polarization immunoassay. Individual pharmacokinetic parameters were estimated by non linear regression analysis assuming a one compartment pharmacokinetic model. The desired peak level was < 30 µg/ml and the targeted trough was 5-10 µg/ml.

Vancomycin levels and pharmacokinetic parameters were:

	Trough µg/ml	*Peak µg/ml*	*Vd L/Kg*	*Cl L/h/Kg*	*$t_{1/2}$ h*
Mean	*4.0*	*14.9*	*0.633*	*0.177*	*2.5*
Range	*0.5-9.2*	*2.6-41.7*	*0.289-1.201*	*0.095-0.315*	*1.4-4.4*

To our knowledge, there have been no other reports on vancomycin pharmacokinetics in pediatric patients with haematologic malignancies. In our study 80% of the patients treated with a mean initial dosage of 51 mg/Kg/day did not obtain levels within the therapeutic range. The high Cl and the short $t_{1/2}$ in neutropenic pediatric patients suggest a risk of underdosage if conventional vancomycin regimens are used to treat such patients.

Based on the results obtained in our study we suggest an initial vancomycin dosage of 15 mg/Kg every 6 hours. However, the broad interpatient variability in vancomycin pharmacokinetics in this population indicates the need for dosage individualization based on patient specific pharmacokinetic data.

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AMIKACIN PHARMACOKINETICS IN ICU PATIENTS WITH NOSOCOMIAL PNEUMONIA

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Infections caused by gram-negative bacilli are probably the most common cause of hospital-acquired pneumonia in intensive care unit (UCI) patients. Amikacin is frequently used in combination with a beta-lactam antibiotic to treat this kind of infection.

The aim of our study was to estimate the pharmacokinetic (PK) parameters of amikacin in adult ICU patients treated with this antibiotic for nosocomial pneumonia. Relationships between PK parameters and other physiologic variables were also analysed.

Forty-four patients (32 males/12 females), mean age 56 years (21-76), mean weight 67 kg (38-87) with creatinine clearance (CL_{Cr}) over 50 mL/min were included. Initial amikacin therapy ranged from 250-750 mg (mean= 7.8 mg/kg) every 8-24 hours (mean= 12h). Amikacin treatments lasted at least one week. Serum concentrations of amikacin were determined early in the therapy and dosing regimens individualized to achieve one-hour peak levels ≥24 μg/mL and trough levels ≤4 μg/mL. Aminoglycoside PK profile was fitted to a one-compartment model and parameters estimated by non-linear regression. Serum levels were measured by FPIA.

Amikacin pharmacokinetic parameters

	ASL/treatment	Vd (L/Kg)	Cl (mL/min)	t1/2 (h)
Mean (SD)	6.5 (3.1)	0.430 (0.137)	87.38 (50.87)	4.9 (4.3)

ASL= average number of control serum levels

Seventy-seven percent of patients (n=34) required higher doses than those initially prescribed. We found that the mean volume of distribution (Vd) in our patients was higher than that reported for the general ICU population and non-critically ill patients, but similar to that reported for surgical ICU patients with septic shock (0.41 L/Kg). Total body clearance (Cl) and elimination half-life (t1/2) varied dramatically among patients. There were statistically significant but weak linear correlations between CL_{Cr} and Cl for all patients, as well as between CL_{Cr} and t1/2, which only accounted for about 24% of the total variability. Probably, other factors such as stress, mechanical ventilation or underlying diseases might have had an additional effect on amikacin Cl and t1/2 in our ICU patients.

In summary, most adult ICU patients with gram-negative pneumonia are likely to need higher doses of amikacin than the standard 7.5 mg/kg. A suitable starting dosage regimen could be 10 mg/kg of amikacin every 12-24 hours in ICU patients with gram-negative pneumonia and Cl_{Cr} over 50 mL/min. However, because of the great inter and intraindividual PK variability present in this kind of patient and the association between aminoglycoside plasma levels and favourable outcome in gram-negative pneumonia, dosage should be adjusted early in the treatment according to the individual PK parameters.

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BIOEQUIVALENCE STUDY OF AMBROXOL TABLETS FROM TWO MANUFACTURERS

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Ambroxol - (4-//(2-amino-3,5-dibromophenyl) - methyl / amino / cyclohexanol) is a pharmacologically active metabolite of bromhexine. It has mucolytic properties, and in therapy is used as an expectorant. The absorption of ambroxol is considered to be fast and complete, and in the man it is metabolized to pharmacologically inactive metabolites. Half-life of elimination of ambroxol, which is unchanged followed in pharmacokinetic stidies, is about 8 to 10 h. The aim of this study was to investigate pharmacokinetic behaviour of ambroxol in the man, after administration of ambroxol tablets from two different manufacturers, in order to estimate their biological equivalence.

The study was crossover, open, randomized, approved and carried out in twelve healthy volunteers of both sexes (4f+8m). The subjects were of age between 28 and 45 yr (39±5; x±SD), and of body mass between 60 and 100 kg (82±16; x±SD) All of them were medically and biochemically screened before the study, and gave signed their informed consents.They were given single oral doses of ambroxol of 30 mg on two occasions (AMBROSAN^R tablets of 30 mg - "SLAVIAMED" was the investigated, and MUCOFAR^R tablets of 30 mg - "FARMAKOS" the standard preparation), after an overnight fast, and with washout period of five days. The food (standardized breakfast) was given 3 h after the drug administration, and blood (plasma) samples were collected during 24 h period (just before, and at 1, 1.5, 2, 3, 4, 6, 9, 12 and 24 h after administration of one tablet of ambroxol). Ambroxol in plasma was determined by slightly modified and checked high performance liquid chromatographic (HPLC) method, developed by Botterblom et al (1). Pharmacokinetic parameters necessary to describe bioavailability (C_{max}, t_{max} and AUC) were obtained by model-independent pharmacokinetic analysis, and in order to estimate bioequivalence, were compared statistically, using both Westlake's and Nonparametric probability test.

The results obtained from this controlled pharmacokinetic study have shown expected behaviour, and concentrations of ambroxol in plasma corresponding to the dose given, with very similar concentration-time profiles for the two preparations. Consequently, pharmacokinetic parameters obtained are of very similar values for both test and reference preparation, respectively (C_{max}: 65±15 vs 57±15 μg/L ; t_{max} : 1.7±0.3 vs 1.8±0.2 h and $AUC^{0-\infty}$: 658±176 vs 560±162 μgh/L). Statistical comparison of these values has shown bioequivalence for all the parameters (all were within allowed ± 20% limits i.e. 80-120 %). On the basis of these results it has been concluded that the two compared ambroxol preparations are bioequivalent, and therefore interchangeable where indicated.

1. Botterblom MHA, Janssen TJ and Guelen PJM , Rapid and Sensitive Determination of Ambroxol in Human Plasma and Urine by High-Performance Liquid Chromatography. J Chromatogr - Biomed Appl 1987; 421: 211-15.

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FENOFIBRATE PHARMACOKINETICS IN PATIENTS AND ITS DISTRIBUTION IN LIPOPROTEIN FRACTIONS

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Group of 14 patients (age 35 - 50) with dyslipidemia of the IIb or IV phenotype was treated with fenofibrate. Pharmacokinetics of the main metabolite i.e. fenofibric acid (**FA**) as well as its distribution in the lipoprotein fractions have been followed.

After single dose of fenofibrate (200 mg *p.o.*) the concentrations of the **FA** in the blood plasma were determined by HPLC with UV detection. The samples were taken at different time intervals after administration. **FA** was determined in the VLDL, LDL, IDL a HDL fractions of the blood plasma.

Avereged pharmacokinetic parameters exhibit relatively good and rapid bioavailability of the drug :

AUC(0-72h) = 113.398 μg.h/ml
AUC(0-∞) = 130.561 μg.h/ml
t(1/2) = 25.22 h
C(max) = 5.947 μg/ml
t(max) = 3.29 h

The FA levels in the HDL fraction has been shown to be up to 3.5 times higher than in the other lipoprotein fractions. This fact may be explained by high affinity of the FA to proteins (as the relative amount of proteins in this particular fraction is higher than in the VLDL, IDL and LDL ones).

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MONITORING GENTAMICIN IN ELDERLY PATIENTS WITH RESPIRATORY TRACT INFECTIONS

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Gentamicin (G) is the most prescribed aminoglycoside in hospitalized patients with documented or presumed gram-negative respiratory tract infections (RTI). Aminoglycosides concentrations in lung tissue are approximately half of those achieved in serum and peak serum G concentrations below 7 μg/ml appear to be inadequated for treating pneumonia. Major concern with the use of G is the development of nephrotoxicity and ototoxicity in association with excessive serum concentrations. Elderly patients are particularly at risk of toxicity because renal function generally decreases with increasing age. To evaluate the clinical utility of our therapeutic drug monitoring (TDM) service for G in this patient population a retrospective analysis amongst hospitalized patients on 2 internal medicine services at Hospital de Santa Maria between march 94 and march 95 was carried out.

Fourty-three elderly patients treated with G for documented or presumed RTI were included. Median age 78.2 (65 - 91) years; 21 female, 22 male. Thirty-six (81.4%) patients presented, at least, one associated pathology and 23 (51.2%) two or more. A normal serum creatinine (Scr < 110 μmol/L) was measured in 27 (62.8%) patients; the mean value of creatinine clearance (Clcr) in this group was 61.7 (33.2-90.6) ml/min/1.73 sq m (Jelliffe equation); 16 (37.2%) patients had a Scr ≥ 110 μmol/L with a Clcr mean value of 28.4 (13.1 - 40.1) ml/min/1.73 sq m. Edema was refered in 7 patients and 2 of these also presented renal failure. The initial most prescribed dosing regimen was 80 mg (mean 1.28 mg/kg), IV q 12 h (22 patients of which 9 had a Scr ≥ 110 μmol/L). Individual pharmacokinetic parameters were estimated using a ss trough level (EMIT, Cobas Mira, Syva) by a Bayesian software (PKS, Abbottbase PK System, version 1.0, Abbott Lab). The mean values (± SD) of the volume of distribution (Vd, L/kg), elimination rate constant (Ke, h^{-1}) and half-life (T½, h) were 0.27 (± 0.065), 0.198 (± 0.095) and 5.18 (± 6.22), respectively. The mean values of Vd, Ke and T½ in the subgroups considered on the basis of existing pathologies known to influence G pharmacokinetic parameters are shown in the table:

Patient Subgroups		Pharmacokinetic parameters Vd (L/kg)	Ke (h^{-1})	T½ (h)
Scr < 110 μmol/L (n = 27)	mean	0.27	0.234	3.4
	range	0.19 - 0.48	0.107 - 0.570	1.2 - 6.5
Scr ≥ 110 μmol/L (n = 16)	mean	0.27	0.137	8.2
	range	0.20 - 0.51	0.017 - 0.261	2.7 - 40.8
Edema (n = 7)	mean	0.31	0.175	4.4
	range	0.24 - 0.48	0.107 - 0.277	2.5 - 6.5

Toxic trough levels (> 2 μg/ml) were measured in 4 patients. All but one of the 22 patients who were prescribed 80 mg, IV q 12 h had trough levels within the therapeutic range. However, only 4 of these patients had peak levels greater than 7 μg/ml (measured and/or predicted). None of the 7 patients with an initial dose of 120 mg, IV q 12/24 h had measured and/or predicted peak levels < 7 μg/ml. The mean peak values achieved following doses of 80 mg and 120 mg were 5.7 (3.4 - 7.6) and 7.6 (7.1 - 9,7) μg/ml, respectively. On the basis of estimated individual pharmacokinetic parameters and of an unsuccessfull therapeutic outcome to previous dose schedule 17 (39.5%) patients adjusted G dosing regimen.

These results clearly indicate that elderly patients are an heterogeneous population group. In most of the elderly patients with RTI a dosing regimen of G 80 mg, IV q 12 h, though avoiding toxicity, does not allow to achieve adequated peak levels. These patients should be dosed individually and closely monitored using TDM.

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Distribution of Gentamicin to the ocular aqueous humor after intramuscular injection

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Systemic administration of antimicrobials delivery drug to the eye through the blood perfusing the ocular tissues. The concentration of drug obtained within the eye depends on the free drug blood concentration - time profile, the ability of the drug to cross the blood-ocular barrier and the rate of drug removal from the eye.
The object of this study was to determine the pharmacokinetic parameters of gentamicin in the ocular aqueous humor (OAH).
45 patients participated in the study. Patients received intramuscular gentamicin 2 mg/kg. Blood samples and OAH were collected at the same time from 0,25 to 6 h. The gentamicin concetntration in serum and OAH were measured using FPIA method.
Gentamicin was rapidly absorbed from serum to OAH in most patients following intramuscular injection. Distribution of gentamicin to OAH is poor (AUC of fitted gentamicin profile obtained in OAH / AUC of gentamicin fitted profile in serum was 0,43). Ratio of concentration of gentamicin OAH/serum ranged from 0,08 to 0,5 (mean 0,27 +/- 0,12) and was time independent.

Mucoviscidosis and out-patient clinical pharmacy : antibiotic therapy at home

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A close collaboration has been set up between pharmacists, an out-patient clinical pharmacy unit, the pneumology and pediatry divisions of the University Cantonal Hospital of Geneva (HCUG) and the nurses of the SASCOM for patients suffering from mucoviscidosis.

Objective

To define the requirements for treatment at home in this type of situation.
To show the possibility of integrating clinical pharmacy into the framework of treament at home.

Method

1. Elaboration of the protocol for the treatment of patients suffering of mucoviscidosis.
2. Assessment of the benefits provided by treatment at home.
3. Verification of the effects of the treatment by means of the pulmonary functions recorded at the hospital before and after the antibiotic treatments (FEV_1).

Results

The protocols for treatment at home were used by all the medical staff concerned and have shown to be an essential working tool for the follow-up of the patient.
SOS Pharmacists have taken part in a total of 296 days of treatment at home which correspond to the number of days in hospital saved by these patients, i.e. a 75% decrease in hospitalization.
None of the patients needed to be hospitalized during his/her treatment at home.
9 treatments (=5 patients) show a >15% improvement in FEV_1.
The other changes can not be interpreted.
The other assessment criteria before and after antibiotic treatment are: clinical condition, the volume and appearence of the expectorations.

Discussion

During their numerous stays in hospital the young adults who are in good general health have had the opportunity to become familiar with perfusion treatment and the health care equipment. Consequently they are able to take an active part in their treatment and do whitout nurses (the fixed catheter being attended to at the weekly consultation).
The number of children likely to receive their treatment at home is limited by the fact that it requires the participation of city nurses, on the one hand, and the confidence of their parents despite the absence of the hospital environment, on the other.
As far as the clinical improvement of the patient is concerned, the parenteral antibiotic treatments are only one aspect of the treatment, since physiotherapy, dietary intake and the other medicines (corticosteroids, oral anti-infectious agents etc) play equally important roles.

Conclusion

The protocol for the treatment at home of patients suffering from mucoviscidosis provides an essential aid for maintening the interface between the city and the hospital. The i.v. antibiotic treatment at home performed by a clinical pharmacy service contributes two elements guarantees of quality of manufacture and of therapeutic follow-up. They make it possible to provide a hospital-type treatment at home, even though an initial hospitalization remains necessary.
The quality of life of these young patient population studied, assessed before and after the antibiotic treatment by the hospital services, has not shown differences between those follow-up treatments conducted entirely in the hospital and those conducted partially at home.

PENETRATION OF AMINOGLYCOSIDE ANTIBIOTICS IN THE LOWER AIRWAYS DURING ONCE-DAILY DOSING

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It is generally accepted that the clinical efficacy of an antimicrobial therapy is directly correlated to the levels of the drug at the site of infection. The aim of our study was to evaluate the penetration of aminoglycoside antibiotics into lung tissue by using the bronchoalveolar lavage (BAL) technique after once-daily administration of high doses of aminoglycosides.
The study was performed in a group of 10 ventilated patients of a surgical intensive care unit. All patients had bacterial respiratory tract infections and they were treated with aminoglycoside antibiotics (amikacin, gentamicin or netilmicin). The concentrations of these antibiotics in serum and alveolar lining fluid (ALF) were measured by FPIA (TDx, Abbott). Urea was used as an internal marker of dilution to quantify the apparent volume of ALF. The concentrations of investigated antibiotics in ALF ranged from 5.25 to 11.01 mg/l for netilmicin and gentamicin and from 7.68 to 28.35 mg/l for amikacin. A large amount of interpatient variability was found in the penetration ratios (i.e. the ratios of the concentrations in ALF versus those in serum), which ranged from 28% to 96% and they did not seem to depend on the type of aminoglycoside used. These results indicated that aminoglycosides readily penetrated in the lower airways. In patients with longer half-lives the penetration ratios tended to be higher. Despite the higher aminoglycoside plasma concentrations, no side effects of aminoglycoside antibiotics were observed in the patients involved in this study.
In conclusion, the present study suggests that administration of high aminoglycoside doses leads to high concentrations of aminoglycosides at the site of the bacterial infection, and moreover, prolongation of dosage interval decreases the risk of toxicity.

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Use of a Therapeutic Drug Monitoring for pharmacokinetic service monitoring of aminoglycoside therapy. The cost-benefit of this service - survey of literature

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A survey of literature with aim to disclose the situation of actual cost-benefit of the therapeutic drug monitoring (TDM) and pharmacokinetic service was started. We specially refer to the group of antibiotics - aminoglycosides, where TDM could straightway optimise the patient outcome and where the side effects (specifically nephrotoxicity) is possible to document.
We searched the Medline, Ipa and Health&Plan databases in period 1990-May1995 under the keyword: Therapeutic drug monitoring/economics. The articles describing TDM of aminoglycosides were retrieved. All the articles retrieved (No.=10), except the articles-review (No.=3), were used for the evaluation. From 7 articles which were suitable for evaluation, only 5 directly evaluated the real impact of Clinical Pharmacokinetic Service (CPS) and were used for further analysis. Indicators followed in all 7 studies were: length of stay in the hospital, therapeutic response, adverse reactions and the influence of TDM on these indicators with special attention to physician- and pharmacists-based (CPS) interpretation of laboratory analysis and cost of the hospitalisation.
We conclude that there are only several works published, which try to elucidate the problem of the impact of CPS on the hospitalisation of patients. There are no doubts that TDM influence positively the patient-associated and economic outcomes of hospitalisation. The CPS monitoring was proven at least so effective as the ward physicians recommendations in all analysed studies and in 3 of them the CPS show significantly higher effect on several outcomes (especially therapeutic response). Because of variability of outcomes (especially pharmacoeconomic) it was not possible to compare real cost-benefit of particular studies.

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PHARMACOKINETIC MONITORIZATION OF GENTAMICIN-ANALYSIS BY BAYESIAN METHOD

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S.Francisco Xavier Hospital is a General, Central Hospital, in Lisbon, with nearly 300 beds. During 1994, all patients submitted to therapy with gentamicin were monitored, as a result a protocol establieshd between the Pharmacy and the other facilities in the hospital.Our study includes 240 patients.
This project included patients interned in Internal Medicine Facility and Medical Intensive Care Unit and Surgery Facility and Surgical Intensive Care Unit. The main goal of this project was to achieve adequate serum levels of gentamicin, which were determined by the hospital's Clinical Pathology Laboratory, within 24 - 48 hours, and maintain them during the treatment,to:
- Assure efficacy
- Avoid adverse effects, particularly nephrotoxicity.
The Pharmacokinetic parameters were determined by Bayesian method(1), this method shows a good efficacy in terms of results (2) (3).
The autors make a comparative analysis of the patient's pharmacokinetic caracteristics.
It was also assessed the percentage of terapeutic, toxic and under-therapeutic serum levels obtained.

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TITLE : EVALUATION OF TOTAL PARENTERAL NUTRITION USE IN A TEACHING HOSPITAL (1991-1994)

AUTHORS : C. BEAUFILS*, M. LE DUFF*, P. ZAMPARUTTI*

INTRODUCTION

Prescription of Total Parenteral Nutrition (TPN) is the result of a complex decision. Even if TPN is indicated in many either acute or chronic syndromes, its widespread use may result in increase cost and side effects. To avoid inapropriate use, it's necessary to audit prescriptions. This should improve control and interest in TPN.

MATERIELS AND METHODS

- Analysis of 1994 TPN prescriptions
- Trends from 1991 to 1994 (765 patients overall; 15 906 nutrition bags)
- Studied criteria
  - . Number, age, gender of patients
  - . Hospitalisation departments, main pathologies
  - . Average and median TPN duration
  - . Calories per prescription
  - . Average costs
  - . Mortality, number of patients resuming enteral or oral nutrition

RESULTS

- 229 patients in 1994 (66 % of male); average age : 46.8 years
- 4 patients receive TPN at home
- Main diseases : gastro-intestinal (37 %), pancreas (17 %), infectious including AIDS (17 %) and respiratory (7 %)
- Average TPN duration : 18.7 days (range 1-188 days) ; median : 13 days
- Causes of TPN discontinuation :
  - . Mortality : 17 % (up to 36 % in some wards). 78 % of deaths, were from Pneumology, Infectious Diseases wards and Medical Intensive Care Unit. Death occurs, on average, after 15 days.
  - . 46 % of patients resume enteral or oral nutrition .
- Prescriptions are of low calories (under 2000 kcal. for 63 % of patients)
- Average cost of preparations : 8 820 F.F.(1815 $)/patient - 408 F.F.(84 $)/day

CONCLUSION

. Stagnation of the number of TPN prescriptions for hospitalised patients
. Trends for the last 4 years show :
  - . a diversification of pathologies
  - . an increase in prescription of low calories nutrition bags
. Average and median duration of TPN are quite stable since 1991
. Difficulty to predict duration.

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PHARMACOKINETICS OF A NEW ORAL ORAL FORMULATION OF CYCLOSPORIN-A IN BONE MARROW TRANSPLANT – A PRELIMINAR STUDY

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Cyclosporin-A (CsA) is one of immunossupressive drugs used to prevent Graft Versus Host Disease in allogenic Bone Marrow Transplant (BMT). CsA therapeutic monitoring is mandatory because this drug has a low therapeutic range. Indeed in our BMT Unit, pre-transplant tests used to be performed in order to obtain a pharmacokinetic profile of CsA and so recommendations for oral posology after transplant could be established. However, a poor correlation between pre-transplant Areas Under the Curve ($AUC_{0-\infty}$) from pre-transplant oral doses and post-transplant trough values were obtained. Since new microemulsion formulation of CsA seems to provide an improved dose linearity, we began a new study design with the same objective using this new presentation. Only four patients have been studied so far. AUC's are being estimated under "steady-state" conditions during a 12 h period, at the fourth day after intravenous and oral regimens. Whole blood CsA levels are obtained by monoclonal FPIA (Polarized Immunofluorescence - TDX-Abbott). Pharmacockinetics parameters are calculated using subroutine PKS-Utility (Abbott). The preliminar pharmacokinetics results are shown in the following table:

Administration	Dose (mg/kg/d)	AUC_{ss} (ng × h/ml)	Cl (L/kg/h)	V_d (L/kg)	$T_{½}$ (h)	$\frac{Cl_w}{F}$ (L/kg/h)	F
Intravenous	3,0	5 247 (1 587)	0,32 (0,12)	3,5 0,7	8,15 (2,50)	–	0,76 (0,32)
oral	3,7 (1,4)	4 545,6 (2 544,8)	–	–	–	0,54 (0,28)	

In conclusion, we can say that the oral daily dose used in this population is lower than the usual average recommendations. Comparing with a small group of historic patients to whom conventional oral CsA was administered it appears that a better correlation between D / AUC (r^2 = 0,80) and AUC / C^{ss}_{min} (r^2 = 0,74) with CsA microemulsion is obtained. However due to the small number of cases, a definitive statement on the benefits of the new formulation will have to wait until wider experience is gained.

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STABILITY OF CALCIUM AND PHOSPHATE IONS IN ELECTROLYTES PRE-MIXED SOLUTIONS USED IN TOTAL PARENTERAL NUTRITION

P. Assicot*, M. Le Duff*, P. Zamparutti*

Precipitation of calcium phosphate in Total Parenteral Nutrition (TPN) may cause significant problem.

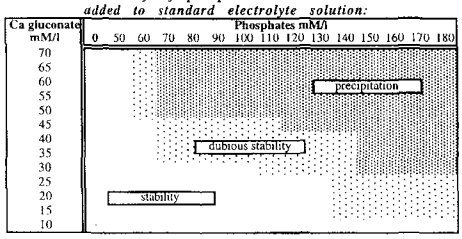
Whereas numerous studies[1,2] have attempted to establish guidelines for maximum concentrations of various phosphate-calcium combinations, differences in study design limit their applicability.

In our hospital pharmacy, we use a standard electrolyte solution containing : 4g Sodium chloride, 4g Potassium chloride, 1g Calcium gluconate and 1g Magnesium chloride (step 1). For each patient, necessary amounts of these salts, together with phosphate needs are added to this former vial (step 2). This final solution is then mixed to the TPN formulation (step 3).

The purpose of this study was to determine calcium and phosphate stability limits in the concentrations ranges of combined solutions mentionned in step 2.

To do this, an increased phosphate load (range 0-33 mM) was added to pre-mixed solutions containing various calcium concentrations (range 13 mM/l - 70 mM/l). Solutions were then stored at room temperature for 7 days. Calcium dosage was done immediately after addition of phosphate then at 2 hours, 1, 2, 7 days storage. Precipitation was defined as any calcium concentrations falling below 90% of initial mesured values.

Stability of phosphate and calcium added to standard electrolyte solution:



This table points out a critical area where a potential risk of calcium-phosphate precipitation exists. When it happens, it always occurs quickly after mixing.

These data show that calcium and phosphate combinations should not exceed critical levels.

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TOTAL PARENTERAL NUTRITION IN MARSEILLES CHR: A USE REVIEW

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Total Parenteral Nutrition (TPN) exhibited considerable increase since the sixties. Therefore, we studied the use of these products during the last four years (1991-1994) in the whole Marseille CHR (4000 active beds, an average 1 000 000 hospital days per year), and thus, use the different TPN solutions in the best conditions.

Drugs developped within the framework of this TPN are now separated into preparations made of separate or associated nutriments: aminoacids, carbohydrates, lipids.

Five commercially available TPN solutions were considered: isolated aminoacids solutions, isolated and highly concentrated carbohydrates solutions, solutions of aminoacids and carbohydrates, solutions of aminoacids and fat emulsions, fat emulsions, ternary mixtures.

We calculed, for each medical field, Defined Daily Dose (DDD) (this unit of measurement is recommanded by the World Health Organisation): in the whole Marseilles CHR, an average 1,10 DDD per 100 beddays.

DDD per 100 beddays	AMINOACIDS	CARBOHYDRATES	LIPIDS
1991	0,68	1,72	0,80
1992	0,73	1,67	0,92
1993	0,78	1,49	1,05
1994	0,79	1,50	1,07

For each year and each medical field, especially surgery, gastro-enterology, neurology, burn center, intensive care and pediatrics, we calculated the amount of added aminoacids, carbohydrates and lipids to compare the different uses according to the medical field: on average, there were 49% carbohydrates, 22% aminoacids and 29% lipids . However, the study of DDD for each medical field shows a difference of prescription: in neurology and gastro-enterology, the preference is generally given to lipids, while for burn center these are aminoacids that are privileged.

In fact, this study presents the interest for each medical field, to situate its consumption of the different solutions of TPN and of their components (aminoacids, carbohydrates and lipids) by report to the others.

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A CONCEPTION OF PATIENT-CARE IN ENTERAL NUTRITION

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As an important part of the therapy the nutrition of a patient has to be supplemented artificially if he is not able to eat. In the hospital two ways of artificial nutrition are common, parenteral and enteral. Recently enteral nutrition has become more important since it has several advantages. The functional and morphological integrity of the digestive system is maintained. There are fewer complications compared with centralvenous nutrition. Contrary to parenteral nutrition enteral diet resembles natural food. The lower cost involved is an additional advantage.
Gastral nutrition can be applied via two lines: nasogastral and with a PEG (Percutan endoscopic controlled gastrostomy). For short periods of enteral nutrition (up to 14 days) nasogastric tubes are prefered due to their non-invasive character. Long lasting enteral nutrition should be applicated with a PEG. It is inconspiciuous. The patients are better integrated in normal life. Less pressure sores are induced and there is no foreign-body-feeling. The patient feels comfortable. Nasogastric tubes disturb much more.
Often PEG-patients retain their autonomy. They can feed themselves or their relatives take care of them without the need of any nursing assistence. Therefore PEG-patients or their relatives have to be well informed about and trained in the handling of the tubes, the care of the puncture site, the handling of the enteral nutrition and the management of problems that may occur. Before they are discharged from the hospital they are adviced by the PEG-patient-service, consisting of a physician and a pharmacist and get educational material. Handling-instructions will be presented.

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PARENTERAL NUTRITION UNIT - INDIVIDUALIZED ADMIXTURES COMPOUNDING IN A GENERAL HOSPITAL

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Since the 70's Parenteral Nutrition (PN) has been carried out in our hospital as an organized therapy, supported by a multidisciplinary team. However, the compounding of PN individualized admixtures has started only in Dec. 92. A retrospective analysis of the Parenteral Nutrition Unit (PNU) activity during the last two years is presented.
From Dec. 92 to Dec. 94 the total of patients and individualized admixtures analysed were 548 and 7.220, respectively.
In our hospital the individual PN is evaluated and prescribed by physicians of the Clinical Nutrition Team. Our current working conditions are the following: **a)** PNU operating - clean room (air conditioned controlled by HEPA filters - class 1000) with positive pressure and horizontal laminar air flow cabinet (E.C.H. - Baker Company, Inc. class 100). **b)** Filling process: negative pressure and volumetric measuring system (Medi Mix 2001, Braun). **c)** Macronutrients: amino acids solutions (adults - 12,5%, paediatrics - 6,5% with taurine), glucose solutions (5 - 50%), lipid emulsions MCT/LCT 10% and 20%. **d)** Schems of PN were set within caloric values of normonutrition. Of the 548 patients studied we selected two main groups corresponding to 80.4% of total patients (1) **Intensive Care Units** - *Haematology*: mucositis caused by antineoplastic agents in bone marrow transplantation; *Gastroenterology*: acute pancreatitis, upper GI bleeding, inflammatory bowel disease; *Respiratory*: ileus caused by atropine therapy in organophosphorus pesticides poisoning; *Neonatology*: very low birth weight preterm infants. (2) **Surgery** - enterocutaneous fistules and GI surgery.

Groups	Patients (n)	Admixtures (n)	PN Duration (days) Mean	Range
(1) **Intensive Care Units**				
• Haematology	84	1281	15.3	2 - 104
• Gastroenterology	45	478	10.6	1 - 40
• Respiratory	49	388	8.0	1 - 20
• Neonatology	55	1227	22.3	2 - 209
(2) **Surgery**	208	2422	11.6	1 - 43
Total	441 **(80.4%)**			

Haematology and respiratory patients did not receive lipids.
The work at PNU has been performed in close collaboration with the clinical team.
No microbiological contamination was ever found in our individual admixtures compounding.
This represents a very good standard of operation which is encouraging to further improve our performance.

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HOME TOTAL PARENTERAL NUTRITION FOR TREATMENT OF SHORT-BOWEL SYNDROME PATIENT: A CASE REPORT

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Home total parenteral nutrition (HPN) is still rare in Finland. This poster reviews a clinical case of a 30 year old woman treated at home with TPN therapy for 14 years. At the age of 16 her spleen had been removed because of the rupture of splenic cyst caused by cytomegalovirus infection. A few days later a mesenteric venous thrombosis was verified and her small intestine was resected. During the next months she tried to live by oral nutrition which led to marasmus and serious psychiatric disorder. Thereafter parenteral nutrition support was initiated. Her weight increased from 29 kg to 38 kg during four months. She learnt to change TPN bags herself, which made HPN possible.

TPN bags are prepared in an aseptic room at the hospital pharmacy by assistant pharmacists. The latest formula for this patient consisted of 1100 ml of solution containing:

Vamin 18	(proteins	43.5)
Intralipid	(fat	20.0)
Glucosteril 30 %	(glucose	150.0)
vitamins		
electrolytes		
trace elements		

TPN bags are delivered to the patient's home three times a week. Transport takes three hours and is arranged by the hospital. Nutrition is infused via central venous catheter at night, leaving the daytime free for other activities.

For 14 years this patient has had many problems typical of long-term total parenteral nutrition, for example infections. She is, however, pleased with her life. She has just finished the school of household management and is happily married. Because nutrition treatment will obviously be continued for the rest of her life, to ensure quality of life, it is necessary to offer hospital pharmacy services of good quality.

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TITLE: PREPARATION OF PARENTERAL NUTRITION MIXTURES , ALL IN ONE, USING A SYSTEM OF PLASTIC ISOLATORS.
AUTHORS: L. Morató, L.Lorente, J. Muñoz
INTRODUCTION: For the elaboration of nourishment mixtures parenteral total (NPT) must be employed a methodical of work that assure the sterility of the preparation area. Customarily they are used work zones equipped with sterile cabins of horizontal laminar flow air. In our case we opt for the isolators utilization, since not dispose of a suitable location to work with cabins.
AIM: Description of the methodical of work with isolators and presentation of the microbiological contamination results found from the acquisition of the isolators in March of 1989 to April 1995.
METHODS: An isolator is a closed physical space by means of a plastic transparent PVC cover, that is swollen with sterile and filtered air (HEPA), to manner of a bubble. (photographs)
To manipulate in its interior have gauntlets with gloves.
In our service we work with two isolators, with capacity to work two persons in each one. In one of them is accomplished the preparation of the mixtures and in the other is effected the load and sterilization of material to use every day. The isolators are sterilized through peracetic acid steams, that are produced by warming of the same. The sterile isolators are comunicated by means of an ingenious round doors system, known as D.P.T. (double transfer door).
Before its implementation in the year 1989, we made a validation of the sterilization data of the isolators facilitated by the manufacturer, to adapt them to our particular case. We verify, for our customary material load in the isolator, the volume of peracetic acid to evaporate and the contact time of the peracetic acid with the surface of the objects to sterilize, so that the load resulted sterile. The calculated securities were 190 ml of acid peracetic and a sterilization time of 2 hours 30 minutes to a speed of air flow among 40-45 L/min. We accomplish microbiologicals controls of all and each one of the bags of PN that we prepare. For this we take two samples of 10 ml of each ready mixture. Furthermore, we control the airtinght of the isolator through the ammonia test . We have accomplished a summary of all the microbiological data from March of 1989 to date.
RESULTS: Of 12.310 control culture accomplished have detected some type of growth in 39 samples (Fig. 1), but alone in a case (Ps. putida) could be confirmed with the result of the second cultivation and there was not no relationship to the clinical state of the sick.
DISCUSSION: These data show us a small series of positive microbiological results, that subsequently are not confirmed in the second cultivation of control.
CONCLUSION: The use of insulators is a good system of mixtures preparation of intravenous use in sterility conditions, not easy to obtaining, in the contaminated environments of the hospitals. To be a closed system protects of possible contaminations. Its disadvantage is the physical capacity, because limits the volume of daily work.
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PRESCRIBING AND PATIENT SAFETY DRUG INTERACTION DATABASE

Nicole Petitcollot - OVP Editions du VIDAL

The drug interaction database developed by OVP Editions du VIDAL has been designed to help healthcare professionals prescribe and dispense drugs in full safety.

The drug interactions included in the database originate from the substance-based drug interactions which have been approved by the Agence de Médicament (the French Drug Agency).

Only those drug interactions which have a significant clinical impact have been included in the system. Routes of administration as well as dosages have also been taken into account.

The drug interactions are classified under 4 categories corresponding to the following warning levels;

- CONTRA-INDICATION: this warning indicates the occurrence of an absolute contra-indication.
- NON ADVISED: here a relative drug interaction is possible which is better avoided unless specific clinical measures have been taken.
- PRECAUTION: a drug association is possible if the briefly described recommendations are adhered to.
- TO BE TAKEN INTO CONSIDERATION: this warning draws attention to a potential drug interaction
  - no recommendation is given to the practitioner who is free to determine the course of action.

Currently 14,900 drug specialities (under their French pharmaceutical code number - CIP) are included in the database which is regularly updated. The database is available on several types of electronic support which facilitates easy access by doctors, pharmacists as they exercise their professional activities.

The innovative feature of the system is that on signalling a drug interaction during the writing of prescription, the system will automatically propose other substitute drugs which correspond to the therapeutic aim of the first drug chosen by the practitioner. The system will also automatically re-check the substitute drug for patient suitability and other potential drug interactions.

ADMINISTRATION OF AMPHOTERICIN B INTO LIPID SOLUTION USED FOR PARENTERAL NUTRITION: STUDY OF THE STABILITY FORMULATION; CLINICAL EVALUATION, PRELIMINARY RESULTS.

Ph MONGES[1,5], A BLANCARD[2], B LACARELLE[3], JP DENIS[4], M-C BONGRAND[5], Ch PENOT-RAGON[1], F GOUIN[4].

The aim of our works was two fald :
- Study in vitro of the stability of galenic mixtures from the incorporation of Amphotericin B(Fungizone®) into parenteral fat emulsion : Ivélip 20%® or Intralipid 20%®.
- Retrospective evaluation of the clinical tolerance of these mixtures.

MATERIALS AND METHODS

Two modes of drug's regeneration are studied(1 mg/ml) :
- Preparation 1 is a direct mixture of the Fungizone in the Ivelip 20%.
- Preparation 2 begins with solubilization of Fungizone® in 5 ml of glucose 5% before the mixture in the Ivelip 20%®. The galenic study is consists of with visual observation, measure of pH and osmolality, granulometric analysis of the preparation.

In the same way, Amphotericin B dosage, at the end of the electric syringe by HPLC, has allowed to raise perfusion's Kinetics.

The clinical tolerance of Fungizone® perfusion, according to Preparation 1 is evaluated on 25 patients treated from May 1992 to January 1994 in the « service de Réanimation polyvalente »

RESULTS AND DISCUSSION

The results of galenic stability determination show no cremage phenomon and no oil trace or phase separation with any mixtures.

In the same way, pH and osmolalite are not significantly different from the values obtained with the reference Ivelip 20%® pure. Further, the study shows a bad homogeneity of the Preparation 1 and therefore, a formation of a yellow deposit and a massive unloading of Amphotericin B during the last hour of administration, which is shown by dosage at the end of the electric syringe. The direct contribution of Fungizone® in the lipidic emulsion destabilizes it : two different granulometric populations are present. The first population has a mean diameter of 0,347 µm which is the droplett dimension of the lipidic emulsion. The second population , which stands between 10 µm and 100 µm, has a mean dimension of 42 µm and represents 25% of all measured particules. The 2nd Preparation shows a better homogeneity and the Fungizone® contribution does not disturb the emulsion granulometric population. The clinic tolerance measured for 25 patients is studied on 302 days of treatment and so, 222 days of perfusion. The renal tolerance is analysed for 16 out of the 25 patients. 14 patients showed a normal creatinine rate before and after the cure. One patient presented a reversible increase of the creatinine, and the antifongic was stopped for a patient who had a cumulated toxicity of the Amphotericin B and the Aminosides. The most important secondary effect is the hypokaliemia : 13 patients out of 19 showed a hypokaliemia not compensed by an exogen potassium addition, a compensed kaliemia appearead with 4 patients and only 2 patients had a normal kaliemia. Just one thermic bout was individualized.

CONCLUSIONS

The direct mixing of the Fungizone® in the Ivelip 20%® is nor stable neither homogenous in the time. Therefore, it must be abandonned. The clinical consequences bound to this regeneration's mode ; in particular, the massive unleading of Amphotericin B at the end of the perfusion could not be measured during this retrospective study.

The carrying out of emulsioned mixing, with an adaptation more specific to a parenteral administration of the Fungizone®, must be dealt with new galenic and pharmaco-kinetic studies.

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COMPUTERIZED CODIFICATION OF CLINICAL INTERVENTIONS, A QUALITY MANAGEMENT TOOL FOR CLINICAL SERVICES PROVIDED BY PHARMACIST RESIDENTS .

I. Tinguely, J. Beney, S. Marty*, J.-Ph. Reymond

The Institut Central des Hôpitaux Valaisans provides a one year post-graduate training in clinical pharmacy. Two residents work as staff pharmacist in departments of internal medicine in the hospital of Sion-Hérens-Conthey. « Patient Medication Record » is used for providing and documenting clinical interventions. To move from this quality assurance to a quality management tool, it has been decided to quantify the clinical interventions. They have been indexed by categories to be integrated in a computer database.

Categories have been developed based on a logical practicable sequence expressed in non ambiguous alphanumeric codes. Indexation of the type of recommendation is worked out in accordance with our drug information request recording system. Coding is established after each patient round on the Patient Medication Record. A computerization on an easy to use data base developed with the software Access® 2.0 for Windows® allowed homogenous encoding between pharmacists and further statistical analysis. This system has been tested over a two month period.

The code entered in the database is made up of six components that constitute the answer to five questions : who ? e.g. proposal of the pharmacist ; what ? e.g. dosage, specifically dosage correction; how ? e.g. immediate answer; result of the intervention ? e.g. discussed but not accepted; cost saving ? e.g. intervention with economical impact.

282 interventions have been recorded over the test period. 85% have been accepted, 15% have been discussed without repercussion or treatment modification. 29% of the interventions were demands of the health-care team, mainly by the physician resident. 60% of the interventions concerned indication, dosage or treatment selection.

Documentation of the ward activities based on an individualized approach has been expanded to a codification allowing retrospective analysis of the clinical services and identification of the health-care team's needs. Access® allows personalized requests and answer can be given in practically any format. The system's limit is therefore not the database but the codification; it is essential to find an optimum between overcomplicated and rudimentary codification. For example cost-saving codes are not sufficient but the objectives in this area must be bettter defined before further development.

The codification is a necessary stage for the quantification of clinical interventions. Computerisation allows storage and data processing to produce a management information system which is not only a tool for the staff pharmacist but also for the supervisor and the chief-pharmacist. In fact, information provided is essential to conduct training and services.

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A quantitative and qualitative Comparison among three Methods for the Preparation of IV drug Administration

Bussels J.[1], Robays H. [2]*

Introduction:
The preparation of drugs by means of a perfusion bag can be done by conventional syringe-needle and transfer needle method. Both are well established and have distinct disadvantages in terms of costs, preparation time, waste, risks of infection and needle pricks. Monovial ®, a new administration device, is a drug container with an integrated transfer system.

Aim:
The aim was to measure and to compare the total cost of each administration method and to examine the opinion of the nurses concerning the use of the two conventional methods with the Monovial ® administration device.The assesment was carried out in four hospital wards of the University Hospital of Gent.

Methodology:
As a first step all relevant costs of each method were established.
Secondly the cost of each activity was calculated.
In a third step these global costs were extrapolated to a sample of 10 drugs commonly used in the hospital.
Finally the opinion of 31 nurses was examined by means of two open and 9 score statements.

Results:
The transfer-needle method was the most expensive way to prepare drugs for IV administration (31,73 BEF for one single preparation if the transfer needle is included and 15,35 if not). Monovial ® is the cheapest method for the preparation of IV drug administration (10,71 BEF). The syringe-needle method costs 23,23 BEF. Hence the Monovial ® method reduces the total cost with 54% and 66% respectively. Based on a sample of ten most used drugs, this represents 1.000.000 BEF and 1.700.000 BEF respectively.
In the general opinion of the nurses, the preparation of IV drugs by means of the Monovial ® is an improvement in terms of speed, ease of use and the reduction of the amount of waste, safety and asepsy.

Conclusion:
New administration devices can diminish preparation time and help to balance time from technical care to direct patient care.

Acknowledgement:
Katlijn Kint [2] is acknowledged for the observations and registrations during the study.

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THE EXPERIENCE OF HOME DIALYSIS AND ITS IMPACT ON THE INFORMAL CARER

M.S. Salek, S. Turpin, E. Derby*, B. Millar#, C. Maggs#

Quality of life (QoL) studies are particularly important in patients with chronic conditions, such as renal failure, for whom improved technology and treatment have extended lives. Dialysis is a life-saving treatment with ramifications for the patient as well as those close to them. The importance of psychosocial support, particularly associated with the family, has been established based on the patients own perception and regarding their overall health. Patients on home dialysis invariably have someone living with them who helps take care of them and this is particularly true for home haemodialysis (HHD) patients. Identified concerns of carers include: lack of family support; role changes; impaired social life; machine-related anxieties. The aims of this study were therefore 1) to evaluate the QoL of home dialysis patients and their carers 2) to increase knowledge and understanding of specific factors associated with the QoL of home dialysis patients and their carers and 3) to specify directions for adapting services towards enhancing QoL of HHD patients and their carers.

Twenty-seven age and postcode matched pairs of HHD and continuous ambulatory peritoneal dialysis (CAPD) patients were randomly recruited from the register of the Renal Unit, Cardiff Royal Infirmary. Eleven patients did not take part in the study. Forty-three patients (20 HHD, 23 CAPD; mean age=45 yrs, age range=24-72 yrs; 33 male, 10 female; mean duration of dialysis (DD)=$4^{8}/_{12}$ yrs, range DD=$^{3}/_{12}$ to 25 yrs) and their carers (10 male, 33 female; mean age = 47 yrs, age range=24-74; spouse=29, others=14) who agreed to take part and signed the informed consent were visited at their homes by the researchers. The patients were asked to complete a general QoL measure, the United Kingdom Sickness Impact Profile (UKSIP) and a renal-specific QoL instrument, the Renal Quality of Life Profile (RQLP). In addition, they rated their overall health on a 5-point scale (very good to very poor). The carers were asked to complete the carer's version of the UKSIP which is the carer's assessment of patients QoL and the Home Dialysis Carers Profile (HDCP) which focuses on the issues relating to the care of home dialysis patients. In addition, 18 randomly selected carers took part in taped, structured interviews to identify any concerns that may not have been considered in the HDCP.

The QoL scores for patients (ie. level of physical and psychosocial functional behaviour) assessed by patients themselves and their carers were considerably high with scores for patients own assessment being slightly higher (more impairment). There were 3 areas of daily activity where the carer's assessment score was higher: ambulation (patient's assessed=20.2, carer's assessed=25.4); emotional behaviour (patient's assessed=16.5, carer's assessed=29.3). However, there were close correlations ($p<0.01$) between patient's and carer's assessment across all categories of the UKSIP and rating of overall health. Comparing QoL of HHD and CAPD, the differences were in the same direction for both patient's and carer's assessed scores. CAPD patients scored much higher in physical activities, but in psychosocial activities, HHD were more impaired with regard to alertness behaviour. HHD patients were also more impaired in recreational activities and eating/drinking functions. These differences were also confirmed by RQLP scores for patients. In particular, recreational and leisure activity is highlighted by RQLP (HHD=70.5, CAPD=58.8). Result from HDCP demonstrated that the carers are involved quite a bit with helping the person with diet and fluid restriction as well as with the actual dialysis. Sixty-five percent of carers never received respite care. Family life is significantly disrupted when caring for a home dialysis patient. Information about what the future holds for the person on dialysis and a sense of hope for the future were ranked as very important areas of concern for carers.

These findings indicate that HHD patients appear to have a better QoL especially with physical functioning. The need for the availability of formal respite care is clearly identified. More preparation and training for home dialysis and family counselling is required.

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PATIENT-ORIENTED PHARMACY - EXPERIENCES ON A SPECIAL WARD

A.Litzinger*, R.Rohde-Böhler*

In Germany patient-oriented pharmacy has not yet been well established compared to other European countries.
A pilot project on a special ward for spinal injuries (25 beds) of the Berufsgenossenschaftliche Unfallklinik Ludwigshafen should exemplarily demonstrate the effect of patient-oriented pharmacy done by the hospital pharmacy staff.
The aim of this project was to improve the effective, safe and economic use of drugs in paraplegic patients.
In the past the nurses on the ward dispensed the drugs. Since 1994 February 1st the distribution of oral drugs on this ward has been carried out by the hospital pharmacy. The pharmacists participated in the ward rounds. The patients' medication charts were checked by the pharmacists e.g. for drug interactions, adverse reactions, possible alternative drugs and monitoring of laboratory data. Councelling incoming patients regarding their drug use the pharmacists gave help and information to the physicians.
The pharmacists' activities resulted in clinical interventions and changes in drug therapy. If necessary, written instruction for individual drug use was given directly to a patient.
During one year under review (1994 February 1st - 1995 January 31st) 123 patients were treated on the ward, the average time to stay was about 77 days. Over this period the pharmacists collected 111 relevant questions and data, which led to pharmaceutical interventions. In 15% of these cases interventions by the pharmaceutical staff avoided interactions which can lead to negative outcome.
In total drug consumption of drugs on the ward has been reduced.
The increasing number of questions by the medical staff and the pharmacists' interventions demonstrate an improving cooperation between the medical and pharmaceutical staff. Advice and information promoted the safety of drug use and optimized drug therapy.
This project in patient-oriented pharmacy on a special ward is a first step in advanced activities in pharmaceutical care and should be extendedto other wards for patients' benefit.

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Results of a dietary trial in patients with hyperlipidaemia

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Diet should constitute the first step in the treatment of patients with hyperlipidaemia. However, the value and the effectiveness of dietary interventions have been questioned since the results of a meta-analysis of 16 dietary trials with a duration of at least 6 months (1) did not show significant differences in blood lipid changes due to dietary interventions. Despite such findings, the European Atherosclerosis Society recommends a 3 month period dietary trial before drug intervention, unless genetically determined forms of hyperlipidaemia are diagnosed. The aim of the present study was, therefore, to evaluate the efficacy of diet in lowering elevated blood lipids.
An open, prospective study of patients newly diagnosed as hyperlipidaemic was carried out at a family physician surgery. All patients recruited to the study went on diet for the first three month period. For those who ended up without reaching desirable blood lipid levels, drug therapy was then initiated.
48 patients (27 males) were sequentially recruited. Hypercholesterolaemia was present in 37 patients, while the remaining 11 presented mixed hyperlipidaemia. After the dietary trial blood lipid modifications were as follows: total cholesterol (TC) was reduced 6.6%, triglycerides (TG) decreased 14.7% and high density lipoproteins (HDL) increased 10.4%. 26 patients (54%) reached diserable blood lipid levels while 22 started drug therapy.
These findings support the recommendations of the European Atherosclerosis Society and provide evidence for the rational of dietary trials before drug interventions being considered.

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PHARMACIST AS CO-THERAPIST IN ANTIEMETIC THERAPY: EXPERIENCE IN MODERATELY EMETOGENIC CHEMOTHERAPY.

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INTRODUCTION: The Pharmacy Department drew up new antiemetic protocols for chemotherapy-induced emesis in October 1994. These protocols, based on a single 8 mg ondansetron dose and adjuvant medication, were presented to and approved by the Oncology Department. An effectiveness and safety evaluation was also included. To implement the new protocols both deparments developed a new working system where the pharmacist increases his clinical involvement ans plays a coordinating role. His/her most important functions are: dispensing medication, informing the patient, evaluating treatment's efficacy and toxicity and making therapeutic suggestions to the oncologist.
AIM: To evaluate effectiveness and safety of the new antiemetic regimens in moderately emetogenic chemotherapy and to asses the economic impact of the new protocols.
METHOD: The study hospital is a 108 bed cancer center with an outpatient clinic. The study was carried out over a five-month period (Dec 94 - April 95). The study includes a 5-day follow-up assesment through an evaluation form filled in by the patient which is collected when the pharmacist interviews him before the following course. Acute emesis, delayed emesis, nausea and side effects are discused separately. To evaluate the economic impact of the new protocols the average medication cost per course was compared with previous data.
RESULTS AND DISCUSSION: 264 chemotherapy courses corresponding to 91 patients have been evaluated.

ACUTE EMESIS (emetic episodes(EE) in the first 24 h)	
Complete response (EE=0)	86.7 %
Mayor response (EE=1 or 2)	6.4 %
Failure (EE>2)	6.9 %

DELAYED EMESIS (emetic episodes from day 2 to 5)	
Complete response (EE=0)	87.1 %
Mayor response (EE=1 or 2)	6.8 %
Failure (EE>2)	6.1 %

NAUSEA (VAS from 0 to 10 cm)	
Worst day < 3 cm	87.5 %
Worst day between 3 and 4 cm	2.3 %
Worst day between 4 and 5 cm	2.7 %
Worst day between 5 and 6 cm	1.5 %
Worst day > 6 cm	6 %

SIDE EFFECTS	
Headache	15.2 %
Flushes	30.3 %
GI disturbances	11 %
Diarrhea	7.6 %
Excesive sedacion	22.3 %
Extrapyramidal reactions	1.1 %
Burning of the perineal area	2.6 %

The average cost of antiemetic medication per course has been 3.371 pesetas. Same data from a previous period was 5.382 pesetas. Implementation of the new protocols has meant a 37 % cost reduction. A saving of nearly 2.000.000 pesetas per year can be estimated by this concept.
CONCLUSIONS:
1. The new antiemetic protocols for moderately emetogenic chemotherapy have demostrated their efficacy and safety.
2. Implementation of the new protocols has meant an important drug cost reduction (37%).
3. Pharmacist has increased his clinical involvement demonstrating his competence in non distributive functions. He has also proved to be an adequate partner of oncologists in the program and a link between them and the patient.

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STUDY OF DRUGS UTILIZATION IN ONCOLOGY TERMINAL PATIENTS BELONGING TO A PALLIATIVE CARE SERVICE

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The pain is one of the more frequent symptoms associated to cancer. The 50% of the patient suffering cancer stands a pain from slight to moderate, and the 30% left stands an unbearable pain.
During last years, advancements have been produced in the treatment of the pain on oncology patient due to the major utilization of morphine and coadjuvants and to the employment of alternative routes of administration.

OBJECTIVES
- Report the drugs used in this group of patient.
- Identify the necessary associations for the correct control of the symptoms and prevention of adverse effects.
- Define the dose utilized of morphine, another analgesics and coadjuvant medications.

PATIENTS AND METHODOLOGY
Prospective study carried out in the second quarterly of the year 1994, that includes to 51 oncology patients in terminal phase belonging to the Palliative Care Unit of our Hospital. The facts of administered medication, dose, duration of the treatment and route of administration have been gotten by means of the unit dose distribution system, starting from the medical daily prescription. For the study the Anatomical Therapeutic Chemical classification was followed.

RESULTS
The average stay was from 9.5 days (range: 1-50).
The average of utilized drugs by patient was from 8,4.
The 56% of the utilized medications are within the group of analgesics, coadjuvants and anxiolytics: analgesics 23,6%, benzodizepins 17%, neuroleptics 6,8% and corticosteroids 7,7%. The remainder includes: laxatives 10,9%, antispasmodics 5,8% and antiinfectives 3,5% between another ones.
The more utilized analgesics were the opioids, concretely morphine. It was administered to a 98% of the patient (a 52% of patients only received morphine and the remainder also carried another analgesic medication).
The daily mean dose of morphine for oral administration was from 252 mg as oral solution (range: 2015-58) and in form of tablet of slowed liberation it was 183 mg (range: 560-20).
For subcutaneous administration the daily mean dose was from 119 mg (range 1000-5).
It's important to emphasize the high proportion of the oral route of administration (56%) and the subcutaneous route (30%) versus the go down utilization of the intravenous route (2%).

CONCLUSIONS
In oncological patients in terminal phase, the treatment of the pain correctly should be the major objective.
The chronic pain of neoplastic origin, in the majority of patients, can be controlled with morphine in adequate oral or subcutaneous dose.
The subcutaneous route is a good alternative when the oral route is not possible or is gotten a partial answer.
It should be carried out a continuous control of the patient, with the objective of fitting the dose of analgesics correctly and prevent the adverse effects adequately.

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Cost-Minimisation Analysis of the MinibagPlus® system in the hospital

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Introduction:

The preparation of drugs by means of a perfusion bag can be done by conventional syringe-needle (SPN) and two-way or transfer needle (TWN) method. Both are well established and have distinct disadvantages in terms of costs, preparation time, waste, risks of infection and needle pricks. MinibagPlus ® (MBP), a new administration device, is a drug container with an integrated transfer cap (docking cap).

Aim:

The aim was to measure and to compare the total cost of each administration method and to examine the opinion of the nurses concerning the use of the two conventional methods with the Minibagplus ® administration device.

Methodology:

Time measurement data were collected during three different subsequent stages of the study.
First, three nurses at two selected wards had to prepare an intravenous solution as per the three admixing techniques with 1 gram glucose (artificial setting).
Second, the same nurses were monitored at the ward using these techniques with real intravenous drugs (clinical setting).
Last, three dummy drugs (glucose 1 G., lactose 100Mesh 1 G., lactose 200Mesh 1G.) were prepared with the three methods (SPN,TWN,MBP) in the pharmacy (artificial setting).
At the end, all persons in the study were asked to fill out an appreciation form in which given features were asked to be ranked and then to be rated.
Time measurements were analysed with Anova, whereas appreciation data were analysed with non parametric techniques.
Cost calculation was done for each item used and contained acquisition costs, purchasing, management, storage costs and waste costs.

Results:
The transfer-needle method was the most expensive way to prepare drugs for IV administration (29.77 BEF) Minibagplus ® is the cheapest method for the preparation of IV drug administration (10,13 BEF). The syringe-needle method costs 21,55 BEF.
In the general opinion of the nurses, the preparation of IV drugs by means of the MinibagPlus ® is an improvement in terms of ease of use, speed and diminishing risk of needle pricks

Conclusion:
New administration devices can diminish preparation time and help to balance time from technical care to direct patient care.

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MICROBIOLOGICAL AND CHEMICAL STABILITY OF A MIXTURE OF HOMATROPIN, PHENYLEPHRINE AND PROCAINE IN AN AQUEOUS SOLUTION

R.K. Ojala*, K.M. Kontra and T.J.P. Naaranlahti

An ocular injection containing homatropin 20 mg, phenylnephrine (metaoxedrin) 25 mg and procain 12,5 mg in 5,0000 g of water (Schepens' solution) has been used as a strong mydriatic in some opthalmological procedures. Usually the injection is made extemporaneously because of lack of the stability data. Aim of this study was to analyse the chemical and microbiological stability of Schepens' solution in different conditions.

Schepens' solutions was made aseptically and packed in glass vials of 5 ml with rubber stoppers. The vials were stored at 8 °C, 23 °C, 37 °C 47 °C, 57 °C and exposured to light. The samples for both chemical and microbiological studies were collected immediately after production of the solutions and after storage periods of one, 2, 4, 8 and 12 weeks after preparation. Assay was by high performance liquid chromatography. Sterility of the solutions was tested using membrane filtration method (Ph. Eur.).

All the injections tested were sterile throughout the storage period. Chemical stability of solutions was good in cool and dark conditions. Degradation of all three drugs were under 10 % when stored 12 weeks at 8 °C, 23 °C and 37 °C. When exposured to light the solution discoloured. By using Arrhenius technique the stability of solution (i.e. stability of procaine) was estimated to be 6 months at 8 °C and 3 months at 23 °C in dark place.

The data from this study indicate that Schepens' solution was found to be chemically stable and sterile at least 3 months stored in cool (8 °C or below) and dark place.

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VARICELLA ANTIBODY CONTENT IN INESPECIFIC IMMUNOGLOBULIN PREPARATIONS

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Introduction. Varicella can develop severe complications in immunocompromised patients. Prophylactic administration of varicella-zoster immunoglobulin (VZIg) is known to decrease the severity of varicella. It has been reported that inespecific immunoglobulins can be used as an alternative. Since VZIg has recently been withdrawn from our pharmaceutical market, it is the aim of this study to determine the varicella antibody content in different inespecific immunoglobulin preparations commercially available in our country.

Methods. 3 lots of 4 commercial preparations have been studied: Polyglobin IV 5%(Bayer)(A); Flebogamma IV 5%(Grifols)(B); Endobulin IV 5%(Inmuno) (C); Globuman IM 16% (Berna) (D). All the preparations were tested at 50 mg protein/ml. Varicella antibody content was analized by ELISA method. A parallel semiquantitative ELISA assay was done to corroborate the results. Each sample was analized by duplicate. Statistical analysis of the results was performed by One Way Analysis of Variance.

Results. Antibody values (UI/ml) are shown in the next table. Varicella antibody content varies among the different preparations ($p<0.0001$). Preparation A is the richest in content when compared with the average products (14.4 vs 10.03). Assayed IM inmunoglobulin (dil 1:3) show the same order values than the IV preparations. Lot-to-lot variability for all the preparations is small. Semiquantitative analysis fit in with these results.

	Lot No	Varicella (UI/ml)
Polyglobin IV	I-3	15.1
	I-11	14.7
	II-2	13.5
	x (SD)	14.4 (0.8)
Flebogamma IV	I-01	11.0
	I-02	9.3
	I-03	8.1
	x (SD)	9.5 (1.5)
Endobulin IV	I-2	7.8
	I-3	7.3
	I-4	7.4
	x (SD)	7.5 (0.3)
Globuman IM	I-02	9.6
	I-03	7.8
	I-04	8.8
	x (SD)	8.7 (0.9)

Conclusion. The recommended dose given intramuscularly of VZIg is 125 units per 10 Kg body-weight. The specific VZIg could be substituted by inespecific immunoglobulins, either IM or IV, if the varicella antibody content are known. Our study reflects than, in IV immunoglobulins, differences in antibody content can be almost two-fold, so the required volume would be a half, with the consistent clinical and economical implications.

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THE CLINICAL IMPACT OF CATHETER RELATED INFECTION

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INTRODUCTION: Catheter-related infection (CRI) is one of the most common complications of total parenteral nutrition therapy (TPN).

AIM: In order to determinate the importance of this complication the morbidity and potential mortality was studied, depending on the type of microorganism isolated.

METHODS: The study design was central venous catheters used for parenteral nutrition over a 5 year period in Bellvitge's Hospital. The catheters were controlled according to a protocol, this includes microbial cultures for all mixtures and cultures of different segments of the catheter (hub, insertion site and tip).
To evaluate the clinical impact of CRI two types of variables were defined: dependent variables (associated clinical symptoms, bacteriemia or fungemia and clinical outcome); and independent variables (type of germ, presence of other infectious focus and hypercatabolic state).
The data was analyzed with the bivariant analysis Chi-square test and with the multivariant analysis multiple logistic regression test. P values of less than 0.05 were considered significant.

RESULTS: The total of catheters included in the study were 1227, the cultures of 250 (20.4%) showed bacterial growth, but there were 235 catheters selected finally. The isolated germs were: coagulase negative staphylococci (CNS) 139 (59%), Gram negative bacilli (GNB) 35 (15%), fungus 10 (4%), Staphylococcus aureus (S.aureus) 23 (10%), and Others 28 (12%).

CONCLUSIONS: All groups of germs were associated with clinical symptoms but significant statistical differences were not found among the groups. When the presence of bacteriemia and clinical outcome were studied (in a multivariant test), significant statistical differences between CNS and GNB were found.

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The evaluation of a written drug information in the elderly.

An evaluation was carried out on 68 patients (30 men and 38 women; 62-91 years old) at a Geriatric Day Hospital. The frecuency of ilness was: Stroke (47.1%), Hypertension (30.9%), Hip fracture (23.5%) Diabetes Mellitus (17.6%) and Parkinson's Disease (17.6%). The patients' caregivers were: Him or herself (26.2%), Husband/Wife (26.2%), son/daugther (36.9%) and others (10.8%). The number of drugs they received: 1-3 drugs (32.3%), 4-6 drugs (50,7%) and more than 7 drugs (16.9%).

Upon discharge they received time-map, oral and written prescribed drug information system. The comprehension was evaluated in the following two months by means of surveys. Patients had primary studies (68.3%) and had clear ideas about their illness (48.5%). The patients took drugs properly in 87.9%. Slight side effects appeared in 5 patients (7.5%). 94.4% of patients and 82.2% of caregivers found the information useful.

The application of a computer system is a great aid in the information given to the patient on discharge time. We have found the informative paper on patient's treatment a good answer of those patients that didn't have whatever physical or psychical disability and by their usual caregiver. We believe that the effort carried out to inform the patient has been worthwhile and satisfied the proffesional effort.

IMIPENEM/CILASTATIN USE REVIEW PROGRAM IN A UNIVERSITY HOSPITAL

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A drug evaluation program is an structured quality-assurance process designed to ensure that drugs are used appropiately, safely and effectively (1). Antibiotics usually are selected as the targeted agents since they represent a significant proportion of the drug budget. In addition, there is potential for adverse consequences such as antibiotic resistence, adverse drug reactions and misuse (2).
The objective of our study was to do a retrospective evaluation of imipenem/cilastatin (I/C) use in order to identify therapeutic problems as well as to propose measures to improve the quality of antimicrobial therapy.
Phase I: I/C use criteria and standards were established by Infectious Disease Committee (IDC). A follow up of all I/C prescriptions was done for three months (n=58). In order to collect all relevant data, a clinical pharmacist reviewed the medical records. Subsequently, a review team proceeded to assess, interpret and identify therapeutic problems of I/C use.
Phase II: In order to improve the quality of I/C use, IDC proposed specific measures: publising the results of I/C use evaluation during phase I in the Hospital therapeutic bulletin and organazing some meetings with medical staff in each clinical services that had used this drug.
Phase III: With the aim of assessing the impact of the corrector measures, a reevaluation of the use of I/C was carried out following the same method that was used in the first phase of the investigation (n=20). During the first phase of the study, the indications that caused the prescription of I/C were mainly nosocomial pneumonies (24%), intra-abdominal infections (22%) and sepsis (10%). The antibiotic was used in an empirical way in 95% of the patients. In this phase the choice of I/C was made suitable to the diagnosis criteria in 71% of the patients. During the third phase of the study the indications that caused the prescription of I/C were mainly nosocomial pneumonies (15%), intra-abdominal infections (20%) and sepsis (30%). The drug was used in an empirical way in the 100% of the patients. In this phase the use of I/C was made suitable to diagnosis criteria in the 81%. The effectiveness of the corrector measures, that were carried out during the second phase of the investigation, was 53% (standard 90%) referred to diagnosis criteria; it means an improvement in the quality of use of the antibiotic although it was not entirely satisfactory since our settled standard was not got. It is necessary to point out a descent in the dispersion of the prescriptive clinical services during the third phase of the study.
These results show that our I/C evaluation program was an useful tool in identifying therapeutic problems and in improving I/C prescribing practices, although the beginning of new corrector measures would be interesting, being intended to reach the standard settled by the IDC.

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NOSOCOMIAL INFECTION COST

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AIM: The aim of this study is to calculate the nosocomial infection (NI) cost in a Spinal Cord Injury (SCI) Unit with inpatients inside a rehabilitation program.

METHODS: All diagnosed infections in the Vall d'Hebrón Hospital SCI Unit from January the first to March the thirty-first of 1995 were analyzed.
Center for Disease Control (CDC) criterias were followed to diagnose the infections, adapting them to particular characteristics of the SCI patient.
To calculate the tangible costs we have quantified the diagnostic tests employed, antibiotics, other drugs used, fungible material and personnel salary costs acording to the time spent in the infection diagnosis and treatment.
To evaluate the intangible costs, a new variable of health-costs has been created, quantifying as two each day of moderate to severe symptomatology and as one each day of mild symptomatology.
The value of the costs is expressed by means of the tangible total costs, median of each group, and its maximum and minimum values.

RESULTS: 64 patients remain hospitalized in our SCI Unit during this period, 38 of them suffered from a nosocomial infection. This represents an infected patient incidence of 59 % in three months.
42 NI were diagnosed, this means an infection incidence of 65 % in three months. Of these group, 12 were asymptomatic bacteriuria (AB), 18 were urinary tract infections (UTI), 5 were upper respiratory tract infections (URTI), 1 was a sepsis (S), 2 were URTI plus UTI, and 4 were considered as others (1 urethral infection, 1 cutaneous infection, 1 escrotal abscess and 1 AB plus grippal syndrome).

INFECTION TYPE	TANGIBLE * COST TOTAL	TANGIBLE COST TOTAL * MEDIAN (MAX-MIN)	HEALTH COST MEDIAN (MAX-MIN)
AB (12)	102,036	6,976 (26,702- 2,522)	1 (6-0)
UTI (18)	315,270	14,645 (41,030- 6,728)	8 (18-4)
URTI (5)	92,910	19,202 (21,916-14,182)	9 (17-7)
S (1)	76,446		11
URTI + UTI (2)	88,458	44,229 (60,198-28,260)	12.5 (16-9)
OTHERS(4)	55,444	14,709 (20,718- 5,308)	2.5 (7-1)

* Expressed in pesetas (Spanish coin)

The total cost of the 42 infections was 730,564 pts. The diagnostic tests cost was 293,580 pts (40%), the personnel costs was 190,344 pts (26%) and the material cost was 246,876 pts (34%).

DISCUSSION: 40% of the NI cost in our SCI unit was due to diagnostic tests and 34% to the antibiotic treatment cost. A correlation is observed between the severity of the processes and the total costs, as much tangible cost as health costs.

Patients' acceptability of health-related quality of life evaluations in routine practice using the portuguese version of the sickness impact profile (PSIP)

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Patients' acceptability of health-related quality of life instruments is a key issue for the success and usefulness of such instruments in both routine clinical practice and research. During the validation process of the portuguese version of the sickness impact profile (PSIP) a parallel survey on patients' acceptability of the questionnaire was carried out.

The survey was conducted on outpatients recruited from a private surgery for the validation process of the PSIP. After having answered the questionnaire, patients were asked according to: time consumed to fill out the questionnaire (acceptable or to long); difficult to understand (difficult or not difficult) and opinion of whether the questionnaire results should be taken into account for future medical interventions (yes or no). Patients were also asked on their availability for further PSIP administrations. Demographic data and time consumed to answer the PSIP were collected for each patient.

Four hundred forty patients (163 males and 277 females, median age 44 years, range 14-89) completed the study, the average time consumed to fill the PSIP being 19 minutes. 342 patients (77.7%) described acceptable the time spent in filling the questionnaire, while 375 (85.2%) did not find it difficult to understand. The vast majority of patients (77%, n=340) would like to see their answers as a component part of future decisions of medical treatments. Moreover, 415 patients (94.3%) were available for future PSIP administrations.

The present findings showed patients' acceptability of the PSIP, and therefore provided evidence for the feasibility of health-related quality of life evaluations in routine clinical practice when such instrument is used.

APLASTIC ANAEMIA AND TICLOPIDINE

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INTRODUCTION. The aim of this presentation is to report a case of aplastic anaemia presumably related to the use of ticlopidine. Clinical pharmacists work in colaboration with the haemathology department and were consulted in august 1994 about cases reported in literature on ticlopidine and aplastic anaemia. As a result of this consultation ticlopidina was stopped. Ticlopidine is a powerful inhibitor of platelet aggregation frequently used in patients intolerant of acetyl salicylic acid. Its common side-effects include cutaneous eruptions, nausea and diarrhea. Less frequent but more troublesome are cholestatic hepatitis, agranulocytosis, thrombocytopenia and ocasionally aplastic anaemia with only 8 reported cases in literature.

CASE REPORT. A 87-year-old man with a history of hypertension, in treatment with a low-sodium diet only, presented a transient ischaemic attack (TIA) in 1990. Prophylactic treatment with acetyl salicylic acid 200 mg/d was begun. However, despite this therapy he suffered from a reversible ischaemic neurological deficit (RIND) in 1994. Treatment with ticlopidine 500 mg/d was started, suspending the use of acetyl salicylic acid. Two months later he was admitted to our hospital because of a bacterial pneumonia and severe pancytopenia. A bone marrow biopsy revealed a severe generalized hypoplasia compatible with aplastic anaemia. Common causes of aplastic anaemia were excluded. Suspecting ticlopidine as the possible etiologic factor, its administration was suspended and treatment was initiated with androgens, G-CSF(granulocyte colony stimulating factor) and tranfusions with platelets and red blood cells. The leukocyte and granulocyte count returned to normal levels within four weeks. However, the haemoglobin level and the platelet count have recovered only partially (haemoglobin: 84 g/l. and platelets: 29 10^9/l).

DISCUSSION. Among the common causes of aplastic anaemia are drugs, toxins, congenital disorders, viral infections and systemic lupus erythematosus. None of these factors was present in our patient except for the use of ticlopidine, what suggests this drug as the probable etiologic factor. According to the reported cases so far, the aplastic anaemia related to the use of ticlopidine usually appears within the first three months of treatment and is reversible on discontinuation of therapy. However the possibilty of a severe bone marrow failure does exist and we think that the benefit-risk ratio of ticlopidine as an anti-aggregant drug has to be compared carefully w.th other drugs such as acetyl salicylic acid before starting its use. We believe that this shows how the pharmacy department can play an important role in prescription event monitoring.

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EVALUATION OF DRUG INTERACTIONS IN PSICHIATRIC PATIENTS

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INTRODUCTION:
Psichiatry Unit of the Traumatology and Rehabilitation University Hospital Vall d'Hebron controles inpatients who present reactive psichiatric disorders further their organic pathology. This patients receive psichiatric drugs associed to treatment of their main disease. Thus, could be more susceptibles for presenting drug interactions(DI). This study was carried out to detect the theoretical DI that affects to psichiatric drugs and to evaluate their grade, the pharmacologycal groups implicated and their clinical significance.
METHODS:
462 patients' clinical prescriptions controlled by the Psichiatry Unit during 1994 were analized. The incidence of theoretical DI was determined by a interaction database computer program. These theoretical DI were scored as: grade 1 (mild), grade 2 (moderate) and grade 3 (severe) according to their importance. Then, the clinical significance of grade 2
and grade 3 theoretical DI, as well as those cases which there were more than one mild interaction, were evaluated from the clinical histories. A decrease of dose or withdrawal of drug relationed with a possible interaction were the parameters valued. Moreover, since Psichiatry Unit, a control of the questions involved to psichiatric drug was performed.
RESULTS:
462 patients were analized and in 135 of them 176 theoretical DI were detected. 123 of these corresponded to grade 1 and 53 to grade 2. No grade 3 DI were found. The grade 2 DI corresponded: 45 to cimetidine-psichiatric drugs association, 2 to levodopa-benzodiazepine(BZ) and 6 to Triciclic antidepressant(TCA)-phenothiazine association. The most frecuent mild DI corresponded to association of BZ with other drugs (113). 9 theoretical DI were found between TCA and other drugs. One DI was detected between paroxetine and phenobarbital. The theoretical DI could lead to increase of plasmatic concentrations and/or potentiation of adverse events in 171 cases, to decrease of the plasmatic concentrations and/or to diminish the therapeutic effect in 4 cases and to development of hypertensive crises in other case. When the clinical significance was evaluated, only in two cases a decrease of drug dose relationed with a possible interaction were found.
DISCUSSION:
Although the amount of theoretical DI detected was high, in general, a clear clinical consequence has not been observed. A possible explanation could be the psichiatric drug dose used. Because the psichiatric disease are reactive disorders but no their main pathology, generally, the dose received by these patients are low.
We conclude that in our study group the number of theoretical DI is great, but these DI detected are not clinically significant. However, it is suitable the knowledge of the possible consequences of the DI by the physicians.

STUDY OF TOTAL AND NEUTRALIZING ANTIBODY TITERS AGAINST HUMAN CYTOMEGALOVIRUS IN COMMERCIAL INTRAVENOUS IMMUNOGLOBULIN PREPARATIONS

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Pasive transfer of intravenous immunoglobulins (IGIV) has been attempted in numerous studies either for treatment or prophylaxis of cytomegalovirus (CMV) infections. A major problem in the interpretation of the results in these studies is the use of a number of different preparations, all of which could be expected to vary in their titer of CMV specific-antibodies. Moreover, it has been suggest that neutralizing antibodies (NA) are responsibles of the positive clinical effects seen with IGIV use. The aim of this study was to quantify both total and neutralizing CMV antibody titers in commercial IGIV preparations -including one specific CMV antibody preparation- and to evaluate, if present, differences in either parameters and the relationship between total and NA in such preparations.
The total and neutralizing CMV antibody titers were determined in five lots of eight commercial preparations: Flebogamma 5%, Globuman 5%, Cytotect 10%, Endobulin 5%, Gloinar 5%, Gammagard 5%, Polyglobin 5% and Flebogamma liquid pasteuriced 5%. The CMV specific antibody titer was mesured by enzymelinked immunosorbent assay (ELISA) and the NA titer was mesured by an ELISA using recombinant polypeptides derived from glycoprotein complexes of the CMV envelope (gp58, gp86 and gp116).
There were statistically significant differences in the total and neutralizing (gp58, gp86 and gp116) CMV antibody concentration between specific and non-specific preparations, as well as among the polyvalent preparations. The Cytotect product displayed a total, gp58 and gp116 antibody concentration fourfold, twofold and threefold respectively that the polyvalent preparations. The Endobulin product exhibed the lowest CMV antibody titer in all cases (total and neutralizing antibodies). There was a statistically significant linear correlation in both total vs anti-gp58 antibody titer and total vs anti-gp116 antibody titer. There was a weak correlation between total vs gp86 antibody concentration.
According to the results of our study the CMV antibody content varies significantly not only between CMV hyperimmune preparations and polyvalent IVIG but also among different preparations of polyvalent IVIG. In recent years CMV immunodominant domains have been identified which lead to the induction of NA. Moreover, it has been described that it exists a synchronous increase in neutralization capacity and titer against recombinant antigens (gp58, gp116) in transplant patients. Therefore, it might be possible to monitor NA activity in patients by using a ELISA technic which quantifies the recombinant gp58, gp86 and gp116 antigens. The results found in our study for CMV NA content vary significantly not only between CMV hyperimmune preparations and polyvalent IVIG but also among different preparations of polyvalent IVIG. We have found a strong correlation between gp58 and gp116 NA and total CMV antibody content but a weak correlation has been found between gp86 and total CMV antibody titer. Considering that the correlation found does not represent a spurious association, the main CMV neutralizing antibodies (gp 58 and gp116) may be indirectly determined in IVIG commercial preparations by evaluating the total CMV antibody content.
In summary, our study offers precise estimates of the total and neutralizing CMV antibodies content in commercial preparations of IVIG and further studies on the efficacy of CMV immunoglobulin use in CMV-associated disease may benefit of a more accurate estimation of the real content in CMV antibodies of these preparations.

HAZARD ANALYSIS OF SURFACTANT REPLACEMENT THERAPY IN PRETERM NEONATES WITH RESPIRATORY DISTRESS SYNDROME

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The concept of Hazard Analysis Critical Control Points (HACCP) was principally developed by the food industry to ensure quality and safety by minimising microbial contamination in the production process[1]. HACCP places an emphasis on the control of raw materials used and processes involved rather than testing the final product. HACCP has been applied in a clinical setting, namely to the handling of expressed breast milk on a Neonatal Unit, and it has been suggested that it may be of value in controlling hospital-acquired infection on a larger scale[2]. Pharmacists are familiar with the rationale of minimising risks associated with the production of pharmaceuticals, particularly for those intended for intravenous use. However, this study investigated the possibility of applying the concept of HACCP to the intra-tracheal administration of pulmonary surfactant, which is used for the treatment of neonatal Respiratory Distress Syndrome (RDS). There are four stages in the process of HACCP; (1) a careful analysis and description of the process under consideration, which may be in the form of a flow diagram; (2) the identification of risk factors which may include risk of infection or risk of morbidity; (3) reconsideration of the process depicted in step (1) in the light of the identified risk factors - those steps that may have a significant effect on the overall hazard are called the Critical Control Points (CCPs) and these are considered in step (4) where, if necessary, effective control options such as policies or alterations in practice are effected. In this exercise, the administration of two surfactant products (Colfosceril palmitate and Alfa-poractant) were examined using HACCP. Flow diagrams were drawn up for the preparation and administration of both products and the processes were discussed in depth with a consultant neonatologist. Critical control points were identified and the flow diagram was suitably annotated. Although steps (3) and (4) were not fully covered, the principle of the exercise and initial stages are described here to emphasise the importance of explicitly describing the risks involved with the administration of any drug. Hazard analysis is a useful method in bringing together health professionals to discuss the risk management of drug therapy.

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CYCLOSPORINE 2% TOPICAL EYEDROPS: MICROBIAL STABILITY

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INTRODUCTION: Topical cyclosporine, a selective T-cell immunosupressant, is used as profilaxis against rejection in high-risk patients under corneal transplantation. Cyclosporine 2% eyedrops are prepared by the Pharmacy Service, to be dispensed to out-patients along their clinical recovery period (average 1 year). The commercially available oral solution is used, diluted with sterile olive oil. The solution does not contain preservatives and the eyedrops dispensers are pipette glass bottle type. Initially, the given expiry date was 15 days after the opening of the eyedrops vial, and after, in basis of physico-chemical stability studies, the validity period was enlarged to 20 days, with the aim of improving the patient's comfort and of reducing the Pharmacy Service workload. The goal of the study was to assess the microbial stability of the eyedrops solution with the enlarged validity period.

MATERIALS AND METHODS: All patients receiving cyclosporine 2% eyedrops were included in the study. They were required to give back the used eyedrops dispenser, when they came back to receive a new one and the samples were checked for microbial contamination. As there was microbial growth in some samples, the validity period of the opened container was reduced from 20 to 10 days, mantaining one month for the unopened one. Since then, bags containing 3 eyedrops vials were dispensed monthly. Instructions to properly use the cyclosporine eyedrops were given concomitantly, stressing the importance to note the opening date in the container, to control the validity period. To confirm the safety of the new validity period of 10 days, during the first half year after, the microbiological controls were mantained monthly in all patients, taking random one of the three used vials. Thereafter, along another half year, the microbiological culture frequence was changed to quarterly, following the same randomization procedure. After that, only the containers from patients who have had some bacterial growths are studied. Now, the new patients follow the same schema and are droped-out when they have three or more negative samples.

RESULTS:In the first study period (expiry time 20 days), there was bacterial growth in 5 of the 19 cultured samples (4 S. coagulase negative, 1 Bacillus sp.). After reducing the expiry period to 10 days, 115 samples were cultured to detect contamination and none showed bacterial growth.

CONCLUSIONS: In view of the results, cyclosporine 2% topical eyedrops can be used safety during 10 days once opened, attending to the microbial stability.

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PATIENT INITIATION TO LONG-TERM BENZODIAZEPINE USE DURING HOSPITALISATION

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In a previous paper[1] the percentage of patients initiated to benzodiazepine (BZD) use during hospitalisation in a Belgian teaching hospital was roughly estimated at 6.8 % but no information was collected on the evolution of this consumption several weeks later. A second study was designed in the same hospital (729-bed teaching hospital) in order to assess more accurately the proportion of BZD initiated patients, to examine patients' behaviour towards BZD 2 weeks and 3 months after the discharge, and finally to determine which risk factors, during hospitalisation or linked to patient's disease or social environment enable to promote the initiation to a long term BZD utilization.
A first questionnaires was sent to 3000 patients discharged consecutively from the hospital, two weeks after the discharge. More than 1500 replies allowed to identify 4 patient groups according to their BZD utilisation status: NU/NU (non user before/non user after hospitalisation)[51.7%], U/U [38.2%], NU/U [6.2%] and U/NU [3.9%]. 41.2% of patients were already users before admission, which means a ratio much higher than in community, indicating that the health status of those patients had induced stress, anxiety or disconfort that the doctor had tried to relief by a BZD treatment.
The following study was mainly focused on the NU/U group. An analysis of their medical record allowed to underline a few characteristics common to this group of patients: majority of male patients, length of stay higher than the average, severe diseases chronic or at terminal stage, frequent neoplasia, patients admitted in cardiology, neurology or oncology units, multiple hospitalisation antecedents, alcoholism history, continuous intake of often 2 BZD during the stay.
A second survey conducted 3 months later showed that 54% of the NU/U group (± 3% of admitted patients) were continuing the BZD treatment. This little sample did not allow to determine the possible role of factors like loneliness or social distress on BZD long term utilisation after hospitalisation. In about 50% of cases of long-term users, the severity of the disease, sometimes at a terminal step, often justified the use of BZD. In other cases, it is worth being reminded the importance of a good relationship between the hospital specialist and the family doctor, the latter having to periodically re-assess the necessity of sustaining the BZD treatment, established during the previous hospitalisation, with regard to the evolution of the patient health status.

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STABILITY OF MITOMYCIN C IN SOLUTION FOR INTRAPERITONEAL ADMINISTRATION

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Intraperitoneal infusions of cytostatic drugs given early postoperatively have been recommanded after excision of intraabdominal neoplasms since peritoneal sarcomatosis is the most common site for disease recurrence[1]. For this particular purpose, a study was designed to investigate the use of Mitomycin C (MTC) administered in solutions commonly used for peritoneal dialysis. One of these solutions, Dianeal 137^{R} (D137) - Baxter B4954 [Dextrose monhydrate 2.27%, NaCl 0.567%, Sodium Lactate 0.392%, Calcium Chloride Ph Eur 0.0257%, Magnesium Chloride BP 0.0152%, Hydrochloric Acid for pH adjustment] is adjusted at pH 5.5 which is out of the pH stability range of MTC (optimal stability between pH 6 to 10).

As a preliminary to a pharmacokinetic study on human subjects, it was necessary to validate the stability of MTC in peritoneal solutions in administration conditions.

The purpose of the present study was to compare the stability of 18 mg MTC in 1500 ml D137 (measured pH: 5.1) or D137 with an admixture of 6 meq natrium bicarbonate to adjust the pH at 6.7. Peritoneal solutions were stored at 37°C, protected from the light, during 24 hours. Samples for quantitative determinations were taken at hour 0, 4, 8, 12 and 24.

Determinations of MTC were made by HPLC method in the following conditions: C18 5µ Nucleosil pre-column (30mm x 4mm ID), C18 5µ Nucleosil Column (100mm x 4mm ID), mobile phase: ultrafiltrated water/acetonitrile (87.5/12.5), flow rate: 1.5 ml/min, UV detection at 360 nm. Porfiromycin was used as internal standard.

At pH 5.1, a first-order degradation kinetic of MTC was observed with a degradation half-live of 6.9 h (degradation rate constant=0.1007 h^{-1}) while no significant loss of MTC was noticed at pH 6.7.

The results indicate that it is necessary to adjust the peritoneal solution pH at 6.7 to preserve MTC integrity during administrations.

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DEVELOPMENT OF A PEN OF APOMORPHINE IN THE TREATMENT OF PARKINSON'S DISEASE

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Apomorphine has revealed useful as direct-acting dopamine agonist to relieve fluctuations in motor response with long-term use of levodopa, at doses between 2.5-7 mg administered subcutaneously 5-6 times per day. The objective of our study was to develop an easy-to-use administration form for subcutaneous injections of apomorphine, more compatible with the loss of capacity associated to "on-off syndrome" and dyskinesia. The study included 3 steps.

1. Development of apomorphine solution for s.c. injection : the solution had to achieve the following requirements : - minimal concentration of 25 mg/ml apomor-phine hydrochloride which means a higher concentration than saturated water solution;
- good stability during storage in refrigerator or at room temperature; - protection against the risk of microbial contamination inherent to the multi-usage purpose; - good tolerance by the patient.

After multiple assays, a solution composed of apomorphine hydrochloride 25 mg, ascorbic acid 50 mg, phenol 5 mg and water pro injectio ad 1 ml, prepared by aseptic filtration, was selected. The solution is stored in small vials allowing an easy filling of the internal cartridge of the pen (D PEN Disetronic Medical System, Burgdorf, Switzerland). A 3 ml solution provides a 5-6 days autonomy to patients receiving 5 to 6 injections per day of 2.5 mg apomorphine hydrochloride.

2. Determination method for apomorphine : quantitative determinations were made by HPLC method in the following conditions : C18 5µ Nucleosil column (100 mm x 4mm ID); mobile phase : methanol 150 ml, acetonitrile 300 ml, phosphate-citrate pH 3.25 buffered solution [citric acid 0.006 M/l - disodium hydrogen phosphate 0.0037 M/l] 550 ml, sodium dodecyl sulfate 0.144 g; flow rate: 1 ml/min; UV detection at 273 nm.

3. Stability of the solution during storage : solutions stored in vials or in pen cartridges, protected from light, in different temperature conditions (6°c, 22°c [room temperature] or 37°c) were periodically tested for apomorphine assay value. Those stability tests are still running but no significant degradation was detected after a few weeks in any storage condition. The validity period of apomorphine solution in vials or in cartridge will be progressively prolonged, depending on further results of stability tests.

One patient is currently using the apomorphine pen. The S.C. injections are well tolerated, the form easy to handle and offers possibility to adapt the doses easily.

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PHARMACIST AS CO-THERAPIST IN ANTIEMETIC THERAPY: EXPERIENCE IN MODERATELY EMETOGENIC CHEMOTHERAPY.

G. Cajaraville (*)(1), M.J. Tamés (1), M.J. Díaz (1), C. Del Pozo (1), A. Plazaola (2).

INTRODUCTION: The Pharmacy Department drew up new antiemetic protocols for chemotherapy-induced emesis in October 1994. These protocols, based on a single 8 mg ondansetron dose and adjuvant medication, were presented to and approved by the Oncology Department. An effectiveness and safety evaluation was also included. To implement the new protocols both departments developed a new working system where the pharmacist increases his clinical involvement ans plays a coordinating role. His/her most important functions are: dispensing medication, informing the patient, evaluating treatment's efficacy and toxicity and making therapeutic suggestions to the oncologist.

AIM: To evaluate effectiveness and safety of the new antiemetic regimens in moderately emetogenic chemotherapy and to asses the economic impact of the new protocols.

METHOD: The study hospital is a 108 bed cancer center with an outpatient clinic. The study was carried out over a five-month period (Dec 94 - April 95). The study includes a 5-day follow-up assesment through an evaluation form filled in by the patient which is collected when the pharmacist interviews him before the following course. Acute emesis, delayed emesis, nausea and side effects are discused separately. To evaluate the economic impact of the new protocols the average medication cost per course was compared with previous data.

RESULTS AND DISCUSSION: 264 chemotherapy courses corresponding to 91 patients have been evaluated.

ACUTE EMESIS (emetic episodes(EE) in the first 24 h)	
Complete response (EE=0)	86.7 %
Mayor response (EE=1 or 2)	6.4 %
Failure (EE>2)	6.9 %

DELAYED EMESIS (emetic episodes from day 2 to 5)	
Complete response (EE=0)	87.1 %
Mayor response (EE=1 or 2)	6.8 %
Failure (EE>2)	6.1 %

NAUSEA (VAS from 0 to 10 cm)	
Worst day < 3 cm	87.5 %
Worst day between 3 and 4 cm	2.3 %
Worst day between 4 and 5 cm	2.7 %
Worst day between 5 and 6 cm	1.5 %
Worst day > 6 cm	6 %

SIDE EFFECTS	
Headache	15.2 %
Flushes	30.3 %
GI disturbances	11 %
Diarrhea	7.6 %
Excesive sedacion	22.3 %
Extrapyramidal reactions	1.1 %
Burning of the perineal area	2.6 %

The average cost of antiemetic medication per course has been 3.371 pesetas. Same data from a previous period was 5.382 pesetas. Implementation of the new protocols has meant a 37 % cost reduction. A saving of nearly 2.000.000 pesetas per year can be estimated by this concept.

CONCLUSIONS:

1. The new antiemetic protocols for moderately emetogenic chemotherapy have demostrated their efficacy and safety.
2. Implementation of the new protocols has meant an important drug cost reduction (37%).
3. Pharmacist has increased his clinical involvement demonstrating his competence in non distributive functions. He has also proved to be an adequate partner of oncologists in the program and a link between them and the patient.

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PREGRADUAL TEACHING OF CLINICAL PHARMACY

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The course of clinical pharmacy is one of voluntary subjects at the end of pregradual training of students of pharmacy. The main targets include improving of theoretical knowledge and practical experience in:

1. pharmacokinetics
2. pharmacodynamics
3. drug-diease relationship
4. pharmacotherapy
5. communications

1. Application of knowledge of kinetic in model situations, to perfect orientation about processes in individual patients, to evaluate compliance of patients, calculation of steady-states parametres, to construct dosing scheme.

2. Utilisation of mechanisms of drug effects for estimation where and how indicate drugs, - description of the therapeutical plan, better understanding of drug-drug, drug-organism, and drug-disease reationships.

3. To help student better orientation in clinical conditions, individualisation of aproach to therapy, discriminate place of pharmacotherapy in total process, by consulting individual cases to evaluate in which nosological units different groups of drugs should be used.

4.To make perfect knowledge about clinical treatment of frequent diseases; arterial hypertension, ischaemic heart disease, cardiac failure, trombo-embolic disease, peripheral ischaemic disease, peptic ulcer disease, chronic obstructive bronchopulmonary disease, diabetes mellitus etc.

5. Practical training of communication with patients, asking about drug anamnesis, evaluation og information, how to communicate with physicians, possibilities and limits of pharmacists in pharmacy and a clinical ward.

The method used in teaching is individual approach to problems and solutions; lectures, practical seminars and clinical practice have been held in faculty of pharmacy and department of medicine in university hospital. The organisation, themes and education are conducted by a clinically oriented pharmacist-pharmacologist and a physican-clinical pharmacologist.

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A BRITISH-SPANISH COOPERATIVE CLINICAL PHARMACY TEACHING COURSE

Mangues MA*, Dhillon S+, Castro I, Bonal J, Newton M+

An Introductory Course in Clinical Pharmacy (ICCP) consisting of a 2-week block course has been run annually by the Pharmacy Department of the Hospital de la Sta. Creu i St. Pau in Barcelona since 1974.

The goal of the ICCP is very close to that of the Certificate level of the Diploma in Pharmacy Practice run by the School of Pharmacy, University of London.

As the British course has a more practice-based educational programme, we extended the Spanish course by adding a practice-based new module. This new programme builds upon the day-to-day experience in clinical pharmacy activities carried out in the Hospital de la Sta. Creu i St. Pau and on the expertise in practice-oriented teaching at the School of Pharmacy, University of London.

Practice activities developed were: prescription monitoring, patient profile, patient counselling, case presentations and handouts, drug information research, ward rounds, and diary log/clinical portfolio. Total (hours) 36. The new module is taken by students who complete the 2-week block course and pass the formal examination.

This teaching programme has the support of the School of Pharmacy, University of Barcelona.

Tutors teaching the practical module were selected according to their teaching capability. All of them were Staff Pharmacists of Teaching Hospitals in Spain, having an Accredited Postgraduate Pharmacy Specialization Programme: Hospital del Mar (Barcelona), Hospital de la Sta. Crei i St. Pau (Barcelona), Hospital de Granollers, Hospital Juan Canalejo (La Coruña), Hospital de Getafe (Madrid) and Hospital Dr. Peset (Valencia). In order to enhance tutors teaching capability, and to provide them with relevant skills to teach Clinical Pharmacy Practice, a Training Course for Trainers was held before starting the practical module. This 2-day course was taught by the Course Director for the Diploma in Pharmacy Practice of the University of London.

Fifty students from various parts of Spain have undertaken the Barcelona Course, last December, and 15 of them entered for the Certificate in Pharmacy Practice after passing the examination.

This first group of students carried out the practice module last January and took an examination in prescription monitoring. Other elements used for assessment were: tutor's evaluation of student performance, clinical portfolio and case presentation.

The 15 students have succesfully achieved the "Certificate in Pharmacy Practice".

An assessment form to evaluate the programme is also distributed to the students.

This teaching experience has been very satisfactory, for both tutors and students.

Seventeen students have applied for the next practice module.

Mutual cooperation between the two centres promotes effective use of resources and develops expertise in teaching activities as well as in clinical pharmacy practice.

The Certificate Programme in Pharmacy Practice is the first one established in Spain and it is also the first formal postgraduate collaborative programme in Clinical Pharmacy between two European countries.

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THE FIRST EXPERIMENT OF CLINICAL PHARMACY TEACHING IN THE FORMER USSR

I.A.Zupanets*, V.P.Chernyh, N.B.Bezdetko*, S.B.Popov*

At present clinical pharmacy has received all over the world. But owing to certain reasons there was no Department of such type in a high school in the former USSR.

The experience of the world-wide development of pharmacy and medicine promoted the formation and development of the connecting link - clinical pharmacy. The studying of the world development of this branch and the realization of the necessity of clinical way of thinking of the chemists, led to the creation of the Department of the above-mentioned type in the Ukrainian Academy of Pharmacy - the very first department of the given profile in the former USSR.

The aim of our report is to draw attention of the participants of the congress and specialists on clinical pharmacy to a new established cooperation and scientific contacts.

The department has two sections - scientific and medical ones. The scientific section is the leading one in the former USSR in the pre-clinical studying of chondroprotector and antiarthrosis drugs. The maiden experiments of the first home perspective chondroprotector drugs "Glucamine" and "Oxaglucamine" were taken here.

The practical classes with students and the treatment work are done on the base of the medical section. Besides the Department is the base of the Pharmacological Committee of the Ukrainian Health Ministry on clinical approving. And at present 20 new pharmacological drugs are being tested in clinic.

But we feel the lack of communication with foreign specialists who have a great experience in clinical pharmacy. We hope that the rise of the first Department of Clinical Pharmacy in the former USSR will draw attention of the scientific world and thereby facilitate development of this branch in the world.

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ANTICOAGULATION ACTIVITY OF SOME VEGETABLE PREPARATIONS

M.N.Velieva,S.N.Babajeva, Y.D.Mamedov

The natural recources of Azerbaijan help researches to find new medical preparations having effect for treatment of various diseasis in circulation and coagulation of the blood and lymph.During the experiments, we study the obtained preparations influense on hemo- and lympho coagulation (coagulation,anti-coagulation,fibrinolysis) most of all. After having the successful experimental researches on the laboratory animals in vitro and in vivo we succeeded in 110 vegetable objects whith have positive effect on the studying parameters of hemo- and lymphocoagulation period,protrombic index,trombotic period,concentration of fibrinogene,fibrinolytic activity.In advance,we had obtained phytopreparations in the form of aqueaes extract for all the plants what were thicened with 96% etanol in 1:4 radio, then were diluted with natrium natrium chloridi in the isotonic solution.

In vitro and in vivo experiments we differentaited 44 plants with anticoagulative, 32 ones with hypercoagulative and 34 ones with fibrinolytic activity.The optimal conditions for anticoagulation activity in vitro experiments were: consentraton of the preparation - 0,1%-1,0ml temperature-37 C, pH=6,5 - 7,4 , consentration of aeral and dry fibrinogene - 0,2%, of thrombine - 0,1 %

In vivo experiments on intact rabbits,we confirmed the anticoagulation activity of vegetable preparations.Their total anticoagulationsactivity,we studied that:Laurus nobilis,Crocus sativus,Amarantus jminda, Saponaria officinalis,Gypso hila c it , Gypsophila paniculata.Melissa officinalis was more than 10-35% ($p<0,01$)

The results of tromboelastography show that after the intravenous introduction of the preparation with 0,1-1,0ml consentration,theyhelp complete activization of fibrinolysis which has plase for 3 hours.

As shown,the above phytopreparations can be offered to the clinical practice as anticoagulatin preparation in the diseases accompaying by hypercoagulation of blood and lymph.

So we guess the studied vegetable and synthetic preparations which have hemo- and lymphocoagulation activity can be used for prophylaxis and treatment of many diseases accompaying by risk of throm formation and forms of blood- and lymphocoagulation.

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THE LYMPHOSTIMULATIONS ACTIVITY AND PHARMACOKINETIC ANALIS OF PREPARATION GLYCYRRHIZA GLABRA

M.N.VELIEVA,Y.Dj.MAMMEDOV,P.M.VELIEV

Richness and variobility of Azerbaijan flora has attached attention of researchers of pharmacy and medicine for a long time. We had held scientific and researsh work in the investigation of the local plants whish have lymphostimulation activity.With that purpose ,we succeeded in discovering pharmacological activity of the following plants which have lymphostimulation effect:Glycyrrhiza glabra,Gypsophila capitata,Saponaria officinalis,Crocus sativus,Laurus nobelis.

Glycyrrhiza glabra is of the most interest.It makes thick theckets more than in 30 regions of Azerbaijan for 48,000 ha, and the annual harvest of Glycyrrhiza glabra is more than 15,000 tons. Using the modern phytochemical and pharmacological analises' methods, we have obtaiined 10 preparations:Acidi glycyrrhizinici,Glycyrramum,Azglycyrramum,Sirupi Glycyrrhizae,Sirupi Glycyrrhizae cum ferro,Pulvis radicis Glycyrrizae,Extractum Glycyrrhizae siccum,Extractum Glycyrrhizae spissum,Flacarbinum,Liquiritonum.

We were studying the above preparations' effect on blood- and lymph formation and lymph outlow.

It has caryed ont pharmacological and clinical pharmacokinetic analis of this preparation.Wgave this preparation in dose 0,05%-1mg of water extract,we determinethemin a blood in urine 3;6;12;24;48;72; hours.Itis proved that preparatie on the metaboliits.

The results of the pharmacological and clinical researches make us have grounds to confurm that the preparations of Glycyrrhiza glabra have fine lymphostimulate activity,help increasing the parameters of humoral and cellular immunity of a boty ,and standardizing the parametters of sympatico-adrenal system wits some reduction of blood-and lymphocoagulation processes.

This preparation has good effect to endocrine-lymphatic organs ilnessis and also to thymomegalia.It helps to do normalt thymus size and also has effect during immuns diseases and inflamatory ones.

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THE STUDY OF SCUTELLARIA ORIENTALIS SPREADED IN AZERBAIJAN.

A.A.NASUDARI, A.A.BANDALIEVA.

Republig of Azerbàijan has a ļot of herbs. Last Soviet Union has 20000 kinds of herbs, but one part of these has Azerbaijan. One most part of these are drug herbs. More important of herbs is kind of Scutellaria.There are more 180 kinds of these in the world. Since 1944 year it had been producing Scutellaria kind in Sibir. Russia, but soon producing had been stopped. Owing to needs of our population we are going to begin producing of Scutellaria herb in our Republic again. Scutellaria Orientalis, family is Laminaceae, grown in Azerbaijan it is being used in public medicine as during treatment ofheart and vessel diseases. It had been fued by us alkoloids, saponins, owing to chemic analysis of ground and underground parts. The level of flavonoids is more that another. The one part of these flavonoids (baicalin, baicalein, scutellarein, vogonin, vogonozid, luteolin and cinerozid) had been obtained in individual form. Besides it, naving taken from underoround part showed for investigation and called its "Scutin' "Flavscutin" and tinctura of Scutellaria Orientalis.These preparations are hypotenzive, cedative and diuretic drugs which had been obtained during our pharmacologic investigations.

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THE CLINICAL STUDYING OF THE "GLUCAMIN"

I.A.Zupanets, L.S.Kicenko*, S.I.Plusch, S.G.Isaev**

Glucamine is the original antiarthrosis drug with metabolic type of action with great antiinflammatory activity, which was created on the base of aminosugar glucosamine. Experiments on mice and rats show the high effect of this drug on the models of traumatic osteoarthrosis of the caput femoralis and pawn carregenin inflammation. DE_{50} of the glucamine of the antiinflammatory effect was 50 mg/kg. After studying the acute and chronic toxicity and other nessesary preclinical investigations, that testifies about the absence of toxic action of the glucamine, the drug was proposed to the clinical studying.

The aim of the investigation was the comparison of the effectiveness of the glucamine and standart antiinflammatory drugs (Voltaren, Indometacin) in the treatment of patients with ostheoarthrosis. Good and very good results were archieved in the treatment of gonarthrosis - in 87%, coxarthrosis - 83%, spondilites - 82% cases. It was show that more effective drug injection was the intrajoint.

The criteria of the effectiveness were the clinical tests: the lowing of pain syndrome, improving the joint functions and the normalization of composition and properties of the sinovial liquid: stickiness, the contents of the hyaluronic acid and degree of it polimerization, the contents of heparin, chondroitinsulfate, glucose, lactat, proteases. The results of the investigations were worked up statisticaly with the Student criterion t.

The results of the research work give evidence of mark clinical effect of glucamine, that was correlate with voltaren and indometacin on the clinical tests and exel them on the normalization of composition and properties of the sinovial liquid because of metabolic type of action. Besides that the antiarrhythmic effect of the glucamin was discovered during the complex clinical checking.

Thus, the clinical studying of the glucamine gives evidence of mark chondroprotective activity of the drug and the perspertives of the further complex studying of glucamine cardioprotective and antiarrhythmic properties.

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DRUGS LEAD ASTRAY - UNINTENTIONAL USE AND ILLEGAL DISTRIBUTION OF DRUGS

S. Nordbo*, M. Smith-Solbakken, R. Myklebun, W. Berge, M. Thormodsen

The development of the project «Drugs lead astray - unintentional use and illegal distribution of drugs» started in December 1994.

Scientists working on this project have their background in socialscience, philology and pharmacy.

In addition there are local actors such as the police, doctors, county doctors, intoxication care and psychiatrical care for young, connected to the project as extern co-operation partners.

The background for this project is indications from several of these co-operation partners and of earlier researchprojects, that illegal use of drugs is a increasing problem in our society, and the fact that a part of these drugs are distributed thru legal channels to illegal markeds.

Later research have shown that the potential in unintentional use of drugs is increasing. It is not only used as a drug, but as means for achieving greater performance.

The purpose of the project is:

- Reduce unintentional use and illegal distribution of drugs in Sandnes county.
- Develop methods of co-operation between different professional groupings on a local level and among central authorities. The methods have to be useful for corresponding work in other regions.

To achieve these goals, it is necessary to uncover deficient routines and unintentional effects of public regulations on the legal distribution, by studying illegal distributionsystems of drugs. This will form the basis of quality securing routines within the legal distribution. Experiences from different health professions shows difficulties establishing convenient control routines without a co-operation of several actors on the field.

The phase mapping out the illegal distributionsystems of drugs will also form the basis in developing new forms of co-operation between different professions. Such co-operation could further form the basis of developing attitudes and contribute to a raised level of knowledge, about the use of addictive drugs amongst professionals, politicians and the public.

The project is in the first round set to take place in Sandnes county.

First phase started spring 95, and it is the intention that the initiation phase are set to start the first six months of 1996 and go on for two years.

Sandnes Healthy City (Sandnes county), Rogalandsforskning/Rogaland Research Institute, local pharmacies and Co-ordinating Committee for Drug Information.

HYPERTONIC-HYPEROSMOTIC SMALL-VOLUME FLUID RESUSCITATION BY MEANS OF TENZITON IN CARDIOSURGERY.

L.Vokrouhlický*, R. Souček, P. Kuneš, O. Nývlt.

For many years, advantages of hyperosmolar-hyperoncotic small-volume resuscitation from traumatic-hemorrhagic hypotension and/or shock are emphasised. Lately, this method was applied to further indications (i.e. major burns, septic shock, cardiosurgery).

In an open multicenter trial the efficacy of plasmaexpander Tenziton (7,5 % NaCl in 60 % Dextran 70 - Infusia, CR) with the efficacy of conventional products (colloid or crystalloid solutions) in patients undergoing cardiac surgery (conary bypass, valve replacement and/or combinative interventions) was compared. Patients requiring a volume expansion by reason of the simple hypovolemia or the preload increase of the failing myocardium were treated. 45 patients obtained Tenziton, 45 ones conventional products. 4 ml/kg of Tenziton was given into the central vein during 3 - 5 min. by means of a pressure pump. The whole study was performed according to the GCP principles.

Essentially more rapid normalization of systemic hemodynamic parameters was achieved in patients treated by means of Tenziton. In comparison with the control group, they had also statistically significant lower consumption of colloid or crystalloid solutions and of blood transfusions in the course of the whole resuscitation period. No adverse reactions (inclusive allergic or anaphylactic events) were observed.

The use of Tenziton in patients undergoing cardiosurgical interventions and requiring hypovolemia or myocardial contractility correction represent a very suitable method.

The study was supported by Pharmaceutical works Infusia, Hořátev, CR.

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PHARMACOKINETIC STUDIES AS A BASE OF BACTERIAL RIBONUCLEASE ADMINISTRATION AS A MEDICINE

L.A.Potselueva

The term "artificial feeding" may imply the body intake of any substances that are natural to a normal organism but deficient due to some body imbalance. The animal tissue and secretions are known to contain nucleases which perform a number of functions and one of them is the body defence from heterologous RNA and DNA. In other words, the initial level of the normal body nuclease activity is a significant natural biochemical barrier and it predetermines the possible development of a disease in case a viral infection gains entrance. When necessary this level of nuclease activity may be elevated by using exogenous enzymes . RNAase (from Bacillus intermedius) was shown to have an antiviral activity towards RNA-containing viruses which is directly related to its effect on a virus at one of its early reproductive stages (1). Most interesting is the effeciency of bacterial ribonuclease (binase) as regards rabies virus which is considered to be an *neuroinfection*. Studies in microbic enzyme pharmacokinetics predetermined the binase treatment program of RNA infections. Administration of bacterial ribonuclease to the animal organism was stated to result in some significant rise of the RNAase activity level in blood serum, as well as in all organs and tissues under study. Blood serum activity is maintained at a high level for 4 hours from the moment of bacterial ribonuclease administration, which may induce a high therapeutic effect of the agent. Bacterial ribonuclease unlike the pancreatic one is less sensitive to tissue inhibitors, it is more slowly absorbed and is more slowly eliminated which may help to prolong the antiviral effect of the preparation. At the same time bacterial ribonuclease is completely eliminated from the body within 24 hours from the moment of its administration. Kidneys are the main organ participating in the process of elimination . The results of pharmacokinetic studies made it possible to demonstrate the advisability of using different ways of ribonuclease administration, including injections, which may help to provide emergency service, e.g in rabietic animal bites.

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THE SUBSTANTIATION OF THE DIMEPHOSPHONE CONCENTRATION IN OINTMENT COMPOSITION FOR DERMATOCOSMETOLOGY

S.N.Egorova, E.A.Kadirova, L.E.Ziganshina*

The Dimephosphone (dimethyl aether 1,1-dimethyl-3-oxobuthylphosphonic acid) was synthesised in Kazan Institute of Organic and Physic Chemistry named after A.E.Arbuzov. The complex of effects at local application of the Dimephosphone - antiinflammatory, antiallergic, antibacterial - was established on the Department of Pharmacology in Kazan Medical University. 15% water Dimephosphone solution as a local agent for curing wounds, burns, trophic ulceres etc. was allowed in Russia. The Dimephosphone ointment composition as a highly - dispersion Cacao oil - in - water emulsion with emulsional wax as a emulsifier agent was developed on the Department of Pharmaceutical Technology in Kazan Medical University.

The selection of the Dimephosphone concentration in ointment composition for use in dermatocosmetology was the main am. A study of the different concentrations of the Dimephosphone ointment (5%, 10%, 15%, 20%, 25%) on the model inflammatory - allergic delayed reaction caused by 2,4-dinitrochlorbenzole was carried out. The experiment was realized on 67 white male - female mouses with 15 - 20 g. of weight. Mouses were sensibilized by 2,4-dinitrochlorbenzole driped on mouse belly every day during 7 days. Ointment compositions on the each side of mouse right ear during the whole period of sensibilization were spreaded. The influence of the Dimephosphone concentration in ointment composition was estimated on difference between left ear weight (healthy) and right ear weight (inflated). The results were compared with control results (group of mouses received ointment basis without Dimephosphone). The results of the experiment were statistically calculated. The reduce of weight increasing quantity of inflated ear on 14%, 44%, 29%, 20%, 38% after application the Dimephosphone ointment composition in different concentrations - 5%, 10%, 15%, 20%, 25% - accordancely in comparison with control was observed. This prooves the antiallergic, antiinflammatory action of the Dimephosphone ointment.

The best efficiency of the 10% Dimephosphone ointment composition was observed and it may be used in dermatocosmetology.

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ENERGY METABOLISM IN A CRITICAL ILLNESS

L. Sobotka, J. Chaloupka

Nutritional support is an essential part of the treatment of a critically ill patient. A good knowledge of energy needs and balanced intake of energy substrates are crucial conditions for rational parenteral nutrition in septic or seriously ill patients.

Energy expenditure was supposed to be extremely increased in these subjects. However, recenc articles and our own results as well reveals that energy needs are much more lower them expected. Daily energy intake of critically ill patient should be rarely higher than 30 kcal/kg/d.

Carbohydrate tolerance is decreased. Insulin resistance should explain an increase in glucose cycling (especially increased gluconeogenesis in liver) and incomplete glucose oxidation in injured tissues. Maximal rate of direct glucose oxidation usually decreases from 4 mg/kg/min to 2 mg/kg/min (3-4g/kg/d). Increase of glucose intake above this dosage can lead to increase of rate of lipogenesis with subsequent liver steatosis. Moreover, elevated production of carbon dioxide can cause ventilatory problems. An induction of additional substrate cycling leads to an increase in energy expenditure.

According to carbohydrate intolerance lipids are integral part of nutritional support. Maximal rate of lipid oxidation achieves 1.2-1.5 mg/kg/min. However the rate of lipid administration should not exceed 1.1 mg/kg/min (1.4g/kg/d) if lipids are administered as long chain polyunsaturated fatty acids. An excess of long chain fatty acids can increase free radical production and depress the immune defence. Therefore a half of energy given as lipids should be infused in a form of medium chain fatty acids (MCT/LCT lipid emulsion).

Amino acids cover another part of energy needs in critically ill subjects. Especially branched chain amino acids (valine, leucine and isoleucine) are oxidized in muscle tissue. Therefore, energy vs nitrogen ratio in parenteral nutrition of critically ill patient should be decreased to 1g to 80 kcal.

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Industrial Compounding of All in One Mixtures for Parenteral Nutrition

The administration of mixtures of solutions for parenteral nutrition is a routine measure.

The compounding is an asceptic process and must be carried out with appropriate compounding equipment.

In additon to microbiological preventive measures, measures to insure the stability of the emulstion as well as the stability of the individual components must also be considered.

The lecture will include dissucssions of common compounding technologies, examples of recipies, as well as prospects for future developments

L-Carnitine
Metabolism, Function and Clinical Aspects in Parenteral Nutrition

L-carnitine is a small water soluble molecule that is essential for the metabolism of long-chain fatty acids. It also plays an important role in facilitating branched chain alpha-keto acid oxidation, shuttling acyl-CoA conjugates from the peroxisomes to the mitochondria, and modulating the mitochondrial ratio of acyl-CoA to free coenzyme A.

Long term parenteral nutrition can lead to an l-carnitine deficit, which limits lipid metabolism. If lipid emulsions are used for parenteral nutrition, l-carnitine can improve ß-oxidation, increase nitrogen retention and, therefore, improve nitrogen balance.

In preamaturely born children the activity of 4-butyrobetain-hydroxylase is diminished. This leads to a lack of l-carnitine and an insufficient utilisation of parenterally administered lipids. Supplemental l-carnitine plays an important role in optimizing energy production from ß-oxidation.

Because of the importance of l-carnitine in these metabolic processes, l-carnitine is also useful for the treatment of many other conditions which are related to insufficient energy production or disturbed ratio of acyl-CoA to free coenzyme A.

CARNITINE URIN ANALYSIS / RELATION TO HYPOXIA AND TREATMENT - INDICATION

GENGER K. MD HOSP: LEOBEN / AUSTRIA

Over the past decade many reports have suggested that carnitine may be administrated to patients with cardiac diseases. These studies include almost 2000 patients but theire results describe varying data about st - segments, bloodpressure or even ap - history. These data as we all know are not konsistent in clinical life without carnitine. More information we get from the data about exercise, workload and worktolerance, but these are rare and not qualified as we would expect.

Physiological we use carnitine in emergency situations to neutralize acids, e.g. activated FFA in hypoxia when betaoxitation is stoped, and bring them out of vulnerabel parts of the cytoplasma. This quantity of carnitine is lost by urinary excretion. If there are repeted episodes of - carnitine pool depleting - the reduced carnitincapacity causes a part of the heartfailure or arrhythmias and others.

In our paper we describe 1.) the main causes of carnitin pool depletion: heartfailure, sleepapnea, copd, hyperglycaemia, drugs 2.) the analyses of urinary acyl - carnitine and free carnitine due to several clinical situations and 3.) the devision of treatabel and untreatabel carnitine depletion by dynamic urin testing.

PROBLEM BASED LEARNING IN PARENTERAL NUTRITION

The provision of parenteral nutrition requires the pharmacist to master all the skills associated with pharmaceutical care. To support the optimum design and implementation of a nutritional regimen at the bed-side the pharmacist must be able to provide pharmaceutical advice within the context of the overall medical care of the patient. This service requires specialist skills within a general patient orientated approach. The teaching of these skills is a common feature of postgraduate clinical pharmacy education in the United Kingdom.

Clinical pharmacy vocational education benefits from a problem based approach where the stimulus to learn comes from a patient case problem and where the 'student' is encouraged to take responsibility for that inquiry and therefore for the direction of their own learning (1). Problem based learning in this way orientates the 'student' to place high priority on outcomes in patients and to learn to take decisions in pharmaceutical care.

Teachers adopting a problem based approach must acquire a different set of teaching skills to those required for conventional lecture based teaching. The skills which will be explored in the workshop include;

- Designing case studies
- Formulating challenging tasks
- Small group teaching techniques
- Facilitating discussion
- Encouraging group work
- Developing group participating
- Liberating students to learn through their active participation
- Questioning and summarising skills

The following aspects of parenteral nutrition will be used to identify the students' learning objectives and the teacher's approach (2,3).

- Verification of clinical indications for parenteral nutrition
- Assessment of patient's needs
- Design of the regimen at the bed-side
- Patient monitoring of fluid, electrolyte and nitrogen balance
- Clinical assessment during parenteral nutrition

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WORKSHOP: PRINCIPLES OF PHARMACOECONOMICS STUDIES

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During the last decade, there have been many important changes within our healthcare systems. A major issue is dealing successfully with the changing economics of healthcare, a problem common throughout the world. More recently there has been increasing concern about balancing the cost of care with the quality of care. It has become apparent that as a major consequence of this economic and environmental change there is an increasing need for pharmacists to better understand and to better assess the literature with regard to the economic, as well as the clinical aspects of drug therapy. This will enable the pharmacist to make more informed and rational decisions regarding the pharmacoeconomics of drug therapy in the prevention and treatment of disease.

Interestingly, during the past decade, "pharmacoeconomics" has become an important consideration in drug development and marketing by the pharmaceutical industry. Pharmacoeconomic studies attempt to identify, measure and compare the costs (resources consumed) and consequences (outcomes) of pharmaceutical products and services. The research methods and tools such as cost-minimization, cost-effectiveness, cost-benefit, cost-of-illness, cost-utility, decision analysis and quality of life assessment are included within this framework. In essence, pharmacoeconomic analysis employs tools for examining the impact of alternative drug therapies and services related to the drug treatment of patients.

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