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Drug-nutrient interactions in the intensive care unit: literature review and current recommendations

Interação fármaco-nutriente em unidade de terapia intensiva: revisão da literatura e recomendações atuais

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ABSTRACT

Objective: To describe the interactions between drugs and nutrients and their frequency in the intensive care unit and to assess the professional team's awareness regarding this subject.

Methods: The keywords "drug interactions" and "nutrition therapy" were searched in the PubMed (specifically MeSH) electronic database. The studies were systematically reviewed for descriptions of the types of interactions between drugs and nutrients, including their frequency and consequences.

Results: Sixty-seven articles were found. Among these, 20 articles were appropriate for the methodology adopted and accomplished the objectives of the study. Of these 20 articles, 14 articles described interactions between drugs and enteral nutrition, three described interactions between drugs and parenteral nutrition, and three described the importance and care required to avoid such interactions.

Conclusions: The literature about drug and nutrient interactions is limited and suggests the inability of health care teams to recognize the potential for these interactions. Possibly, the elaboration of a protocol to evaluate drug-nutrient interactions will increase the safety and efficacy of therapeutics.

Keywords: Pharmaceutical preparations; Nutrients; Nutrition therapy; Intensive care; Critical care; Drug interaction

INTRODUCTION

The interaction between drugs and nutrients is a constant feature in the evolution of hospitalized patients, particularly in areas where the number of prescription drugs is usually higher, such as the intensive care unit (ICU). The interactions are eventually intentional but usually occur without the proper awareness of the health care team and consequently can put the patient at risk. The interactions can occur during drug and food administration, during the digestive process, or subsequently, during the distribution or elimination of the drug.[1,2]

This review systematically addresses these interactions to further improve safety in seriously ill patients. Concomitantly, we assessed the knowledge of professionals working with seriously ill patients regarding these interactions.

METHODS

The MeSH keywords "drug interactions" and "nutrition therapy" were searched in the PubMed electronic database. The search was limited to articles that were published within the previous 10 years (between August 2002 and August 2012), written in English and Portuguese, and reported studies performed in humans.

Conflicts of interest: None.

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Initially, titles and abstracts were evaluated; subsequently, articles describing nutritional or drug interventions without discussing their interactions were excluded. Next, the remaining studies were critically read, and those that met the predefined quality criteria, such as clarity of the information, appropriate methodology, and clinical relevance, were selected.

RESULTS

Sixty-seven articles were found using the selected keywords. After selection by title and abstract, 12 articles that were not available in full text were excluded; 35 articles did not meet the criteria regarding the discussion of interactions between drugs and nutrients. Twenty studies achieved the objectives of the study and were selected for the discussion presented in the present review. Of these, 14 describe the interactions between drugs and enteral nutrition, three discuss the interactions between drugs and parenteral nutrition (PN), and three review the importance of and care necessary to avoid such interactions. Table 1 summarizes these articles.

DISCUSSION

During hospitalization, particularly in the ICU, the combination of multiple drugs is common. This useful strategy aims to enhance the therapeutic effects of combined compounds, compared with their isolated use. The evaluation of all the factors that may modify the expected pharmacological response requires knowledge of the sources of variability so that interactions between drugs and nutrients can be identified.[23] Unfortunately, the literature addressing this topic is not extensive, and the recommendations provided from prospective studies are limited, given the absence of studies with optimal designs (i.e., prospective, controlled, and blind studies).[17,18]

Drug-nutrient interaction is defined as an alteration of the kinetics or dynamics of a drug or nutrient, or the impairment of the nutritional status caused by drug administration. Kinetics refers to the quantitative description of a drug or its availability, which includes absorption, distribution, metabolism, and excretion. Dynamics characterizes the clinical or physiological effect of the drug.[24] Thus, the nutrient availability may be affected by the drug, or the drug effect may be modified by the nutrient, including the risk of adverse effects.[25] The route, dose, and timing of the drug administration in relation to the nutrition, as well as the drugs' physicochemical characteristics and presentation may be determinants of this interaction.[26]

Table 2 summarizes the possible mechanisms of interaction between drugs and nutrients.

Table 1 - Summary of the articles found in MedLine that described drug-nutrient interactions

Reference	Type of study	Comment
Mink et al.[3]	Prospective cohort	Non-blind study; analysis of drug-nutrient interactions was not the primary objective of the study; enteral administration was associated with lower serum levetiracetam
Bacopoulou et al.[4]	Prospective cohort	Non-blind study; there was no significant interaction between netilmicin and parenteral nutrition in neonates
Manessis et al.[5]	Prospective cohort	Non-blind study; serum levothyroxine levels were reduced concomitantly with enteral nutrition by a mechanism unrelated to adsorption to the feeding tube walls
Matsuba et al.[6]	Prospective cohort with historical control	Evaluated the introduction of a protocol to prevent obstruction of the feeding tube when drugs and dietary substances were simultaneous administered
Barichella et al.[7]	Randomized and prospective cohort	Non-blind study; reduction of the protein intake via enteral nutrition prevented a reduction in serum levodopa levels
Fay et al.[8]	Prospective cohort	Non-blind study; there was no significant interaction between levetiracetam and enteral nutrition
Kanji et al.[9]	Prospective cohort	Non-blind study; there was no significant interaction between gatifloxacin and enteral nutrition in the intensive care environment
Bailey & Briggs[10]	Cross-sectional study	Changes in the serum levels of several drugs concomitant with parenteral nutrition were evaluated
Dickerson et al.[11]	Retrospective case series	Enteral nutrition reduced the therapeutic effect of warfarin
Williams[12]	Case report	Voriconazole absorption was reduced by simultaneous enteral nutrition
Bonnici et al.[13]	Case report	Association between levodopa and high protein enteral nutrition favored the occurrence of the neuroleptic malignant syndrome
Cooper et al.[14]	Case report	High protein enteral nutrition decreased levodopa absorption
Krajewski & Butterfoss[15]	Systematic review	There was a significant interaction between warfarin and the enteral nutrition components
Salih et al.[16]	Systematic review	There was no significant interaction between anticonvulsants and parenteral nutrition
Wohlt et al.[17]	Systematic review	Few published reports existed regarding drug-nutrient interactions
Phillips & Nay[18]	Systematic review	There were no high-quality studies in the area, and the recommendations were based on weak levels of evidence
Dickerson[19]	Systematic review	Mechanism of interaction between warfarin and enteral nutrition
Williams[20]	Literature review	Recommendations for enteral nutrition and drug administration to minimize drug interactions.
Magnuson et al.[21]	Literature review	Mechanisms of the interactions and suggestions for their reduction
Harrington & Gonzalez[22]	Literature review	Review of the mechanisms of drug-nutrient interactions

Table 2 - Types of interactions between drugs and nutrients

Type of interaction	Comments	Examples
Absorption	Interactions may occur between drugs and nutrients that are only orally administered or by enteral-feeding distribution systems. The oral bioavailability of the active drug may increase or decrease because of these interactions	Tetracycline, alendronate, phenytoin, and levodopa display reduced absorption with food; grape juice reduces the absorption of carbamazepine
Post-absorption	Occurs after the drug molecule or the nutritional component reach the systemic circulation and may result in altered distribution within the various tissues, systemic metabolism, or penetration into a specific site	Foods rich in vitamin K (or its supplementation) alter the pharmacodynamics of warfarin
Elimination	Numerous pathways may be involved, such as antagonism, modulation, or decreased renal or enterohepatic transport	High protein diets increase the elimination of propranolol; alkaline diets increase the excretion of barbiturates, diuretics, sulfonamides, acetylsalicylic acid, aminoglycosides, and penicillins and decrease the excretion of amphetamines

Enteral nutrition administration via a feeding tube is the preferred method of nutritional support in patients who have a functional gastrointestinal (GI) tract but are unable to be fed orally;[20] this procedure is widely used in ICUs to maintain an adequate supply of nutrients.[6] Enteral feeding tubes are classified by the site of insertion and the distal location of the tube.[20] Enteral nutrition may be performed by several methods: continuous, cyclical, bolus, and intermittent. There are different ways to access the digestive tract, and the method is classified based on the combination of two variables: the access site and the location of the distal end. Thus, feeding tubes inserted through the oral or nasal cavities may be gastric (60% of cases) or duodenal (40% of cases). The feeding tubes can also be intragastrically introduced by transcutaneous access with endoscopic assistance (known as PEG, percutaneous endoscopic gastrostomy). Finally, access to the digestive tract can be achieved by performing surgical gastrostomy or jejunostomy.[27-29] It is important to know the position of the tube in the GI tract when drugs are administered by this route. The pre- or postpyloric position of the feeding tube does not yield obvious benefits for nutrition therapy or protection from aspiration pneumonia, nevertheless the latter position of the feeding tube is preferred in certain scenarios, such as in critical patients and in patients with severe pancreatitis.[30] However, depending on the region of the GI tract in which a particular drug is administered, knowledge about the location of the tube is important so that possible changes in the absorption and pharmacokinetics of the administered substance may be anticipated.[1,16,21]

The interaction between nutrients and drugs is a problem of great relevance in clinical practice due to potential changes in the expected effects of the drug.[24] Drugs may interfere with the body's fluid and electrolyte balance and thus influence digestive processes.[21] Table 3[20] summarizes these possibilities.

The enteral administration of drugs can cause functional changes in the digestive tract. The most common pharmacodynamic action occurs with drugs that act on GI tract motility, such as prokinetic agents. Several drugs can cause side effects in the GI tract (e.g., nausea, vomiting, diarrhea, abdominal pain, or a combination of these signs and symptoms) that may affect the quality of nutritional therapy. The main factors described as related with this incompatibility are osmolarity and the vehicles for administering the drugs.[31]

Regarding potential drug and nutrient interactions, the continuous administration of food might be the most challenging method, requiring frequent interruptions of the feeding tube when the drug is administered (Table 3).[20] The difficulties are heightened because oral medications have not been tested or approved by the manufacturers or the Food and Drug Administration (FDA) for use in the enteral feeding system. Thus, patients receiving concomitantly drugs and enteral nutrition via a tube presents additional risk.[31] In addition, solid-form drugs are crushed and often cause obstructions that may necessitate changing the feeding tube, thereby increasing costs and patient discomfort.[32]

The interactions between drugs and nutrients are complex and difficult to recognize. As already emphasized, the possible interactions may cause impair the action of the drug and/or food, which may cause an inappropriate pharmacological effect of the drug or a compromised nutritional status, in addition to the obstruction of feeding tubes. All of these factors may result in the greater cost and length of hospital stay.[20,21,33] Health care teams should be aware and constantly evaluate possible interactions between drugs and nutrients, thereby increasing the likelihood of anticipating unwanted interactions and modifying the form or route of drug administration. For example, enteric-coated capsules and long-action formulations should not be crushed; thus, elixirs and suspensions are preferred for enteral administration.[20] Table 4[18,20] summarizes and suggests precautions that should be implemented to prevent tube occlusion.

Older patients or individuals with severe pathologies are possibly even more susceptible to such interactions. These factors converge to generate an increasing risk of adverse drug and food interactions in an environment of complex care.[22,34]

Table 3 - Enteral use of drugs and interactions with nutrients in daily enteral feeding practice

Knowledge of the type and location of the feeding tube
Stomach: choice for drugs that act on this site, such as antacids and ketoconazole
Duodenum: preferable route for drugs susceptible to gastric acidity (such as digoxin, carbamazepine, ciprofloxacin, and tetracycline)
Drugs that alter nutrients
Diuretics: hyponatremia, hypernatremia, hypokalemia, and dehydration
Steroids: changes in sodium, potassium, and glucose
Angiotensin-converting inhibitors: hyperkalemia
Amphotericin B: hypokalemia and hypomagnesemia
Calcium supplements: hypophosphatemia
Nutrients that affect drugs
Phenytoin: requires interruption of the diet for 1 to 2 hours
Quinolones: reduced serum levels when administered with food
Itraconazole: increased absorption with nutrients
Warfarin: decreased anticoagulation with vitamin K
Alendronate: decreased absorption with food

Table 4 - Precautions for drug administration via feeding tubes

Determine the type, caliber, and location of the distal end of the tube
Whenever possible, the administration of liquid medication is preferable
Whenever possible, choose a gastric tube instead of a duodenal tube
Avoid crushing drug capsules or programmed- or extended-release drug formulations
Administer each drug separately
Administer the entire programmed dose (bolus)
Do not mix drugs and nutrients. Breaks should be determined
Dilute viscous or hyperosmolar solutions with 60-90 mL of water
Rinse the probe with 30 mL of water before and after drug administration
Participate in continuous training

One of the most unwanted consequences of using the wrong practices for drug administration in tube-fed patients is obstruction of the enteral feeding tube (Table 4), which may interrupt the nutritional supply and impair the drug administration. Such obstruction occurs in 8.3% of cases, but a training protocol can reduce this incidence.[6] There are also reports of drug administration via an exclusive port in the feeding tube, which decreases the interaction between drugs and food.[35] To prevent enteral tube clogging caused by the administration of drugs, it is recommended that a pharmacist participates and follows the protocols for administering drugs via enteral feeding, thereby ensuring the overall effectiveness. Furthermore, the importance of using the appropriate protocol should be emphasized to the entire staff, with respect to all types of drug dilution, the requirement for temporary suspension of enteral feeding, the types of tubes, and the use of alternative routes.[6]

Specific drug-nutrient interactions

The interactions that interfere with the absorption and distribution of drugs or medications are well known and described. A good example is the interaction between the antiparkinsonian agent and a high protein diet. It is established that a high protein diet may prevent the absorption of levodopa/carbidopa, causing loss of efficacy and fluctuations of Parkinson's disease symptoms. Amino acids in the diet may compete with levodopa for absorption in the intestine.[13,14] Many studies have demonstrated interactions between a high protein diet and levodopa, but there are few reports about the interaction between enteral nutrition and levodopa.[13] Scheduling the feeding time is one strategy that might be adopted to administer a high protein content in the evening. In parkinsonian patients undergoing enteral nutrition, three strategies have been reported to decrease the potential interaction between enteral nutrition and levodopa. The first method consists of separating protein sources from the drug administration; the second method involves limiting the total daily protein intake (which may be disadvantageous in terms of the quality of the protein supplied to the patient); the third available method is to increase the dose of levodopa. In this case, drugs should be administered between 30 minutes and 2 hours before enteral nutrition or 2 hours after administration of the supplements. For critically ill patients with Parkinson's disease, who may exhibit high metabolic catabolism, protein restriction may be contraindicated and might cause malnutrition, prolonged hospitalization, or other associated complications.[14,36]

Another good example of the interaction between drugs and nutrients is observed with the anticonvulsant levetiracetam, whereby the use of this drug in patients undergoing enteral nutritional therapy correlates with a slight reduction in their serum drug levels.[8] Interestingly, intravenous administration to patients undergoingenteral nutrition is associated with higher bioavailability of the drug.[3] The opposite is demonstrated with the antibiotic gatifloxacin; intravenous administration of this antibiotic is not affected by enteral feeding, which occurs when the drug is administered via a feeding tube, thereby decreasing its serum levels. Thus, the potential advantage in terms of drug-savings by cost reduction through changing the drug route (e.g., intravenous to the enteral route) can be lost during maintenance of the intravenous route and, consequently, be less effective.[9]

The interactions between warfarin and nutrition are well established and described. Achieving therapeutic levels of this drug may be difficult because of its wide range of interactions with food.[15] Resistance to warfarin associated with food intake was originally attributed to the large amounts of vitamin K present in the formulations.[19] The initial administration of the usual dose of warfarin (5 mg)

did increase the international normalized ratio (INR) when the drug was administered simultaneously with continuous enteral nutrition. After increasing the warfarin dose to 7.5 mg per day, the INR increased to almost therapeutic levels. Thus, the authors suggested an adjustment in the drug administration with a 1-hour break before and after warfarin administration, which improved the INR.[19] The mechanism of interaction, in addition to the obvious administration of vitamin K (antidote for the drug), occurs because the constituents of the enteral diet reduce the absorption of warfarin via a protein-binding mechanism.[11,15] Another possibly related mechanism involves elevated levels of albumin caused by a high protein diet, which increases binding of the drug to these proteins and reduces the therapeutic effect.[11,37]

Reduced drug absorption characterizes certain interactions, such as those observed with the antifungal voriconazole or the hormone levothyroxine. Enteral administration of voriconazole should be avoided in patients with concomitant enteral feeding because this situation causes a significant reduction in the serum drug levels.[12] The hormone levothyroxine displays two types of interactions: reduced absorption caused by loss of the drug along the walls of the feeding tube and competition from the food administered through the enteral tube. The losses during drug crushing and administration are secondary to the presence of diet residue and gastric fluid in the stomach when the drug is administered. Levothyroxine absorption increases during fasting and decreases in congestive heart failure, malabsorption syndromes, and diarrhea. High-fiber foods decrease the absorption of levothyroxine.[5] Last but not least important, we must record the action of drugs that structurally or functionally modify the digestive system, thereby impairing the digestive process quality. This scenario is more evident when we observe the constipating effects of analgesic opioids and diarrhea caused by elixirs with high osmolarity or due to dysbiosis secondary to the use of antibiotics and anti-inflammatory agents, which cause erosion or other important alterations in the structure of the digestive epithelium. A protocol with standard procedures for reducing the unwanted effects of drug and nutrient interactions should address these possibilities.[21,31]

Interactions between drugs and parenteral nutrition

Several interactions between intravenous medications and enteral nutrition have already been explored in the previous section. However, interactions between drugs and PN have been even less studied and therefore less known. Some investigations have demonstrated the absence of significant changes in the plasma concentrations of the antibiotic netilmicin in children fed by PN.[4]

Anticonvulsants have been the most studied in this context. Researchers have demonstrated increased serum concentrations of free fatty acids, which cause an increase in the free fraction of valproic acid.[16] The plasma-protein binding of valproic acid ranges from 90 to 95% and occurs mostly with albumin. The phenytoin protein binding has been observed to be significantly decreased. Therefore, the free fatty acids from the fat emulsions in the PN may displace drugs, such as phenytoin, from the albumin-binding sites.[16] An *in vitro* study that assessed the interaction between anticonvulsants (carbamazepine, phenytoin, phenobarbital, procainamide, quinidine, and valproic acid) and theophylline in human serum with five types of PN fluids revealed that five drugs (phenobarbital, phenytoin, procainamide, quinidine, and valproic acid) exhibited greater binding to human serum than to the PN components. Carbamazepine exhibited greater binding to the PN components, whereas for theophylline, the binding to the PN and to the serum was similar. Thus, it was concluded that PN administration may significantly alter the free fraction of certain therapeutic drugs.[10] Alterations in the drug free fraction caused by the co-administration of PN fluids may be clinically significant and require a careful reevaluation of drug dosages in patients receiving these treatments. Monitoring the free-drug concentrations may be useful, particularly for those drugs that are tightly bound to proteins. These interactions should be studied prospectively *in vivo*.[10]

CONCLUSIONS

Studies assessing the clinical impact of the interactions between drugs and nutrients are limited, and the recommendations are based on weak evidence. Therefore, clinical trials with appropriate designs and samples are urgently needed to create solid recommendations. The standardization of drugs administered simultaneously with enteral nutrition or PN, in addition to development of methods for monitoring, is important for preventing drug-nutrient interactions. Most likely, a drug-nutrient interaction consortium of multidisciplinary professionals (i.e., pharmacists, nutritionists, nurses, physicians, and other professionals involved in this process) may obtain better and safer results in this area, which merits further study.

RESUMO

Objetivo: Descrever as interações entre fármacos e nutrientes e sua frequência nas unidades de terapia intensiva bem como avaliar o grau de consciência a esse respeito por parte da equipe de profissionais.

Métodos: Foram revisados, na base de dados eletrônica PubMed, especificamente no MeSH, os unitermos: "drug interactions" e "nutrition therapy". Os estudos foram sistematicamente revisados para a descrição de tipos de interações entre fármacos e nutrientes, suas frequências e consequências.

Resultados: Foram encontrados 67 artigos. Dentre estes, 20 artigos estavam adequados à metodologia adotada e atingiram os objetivos do estudo. Destes, 14 artigos descreviam interações entre fármacos e nutrição enteral, 3 descreviam interações entre fármacos e nutrição parenteral, e 3 descreviam a importância e os cuidados para evitar tais interações.

Conclusão: A literatura referente a interações entre fármacos e nutrientes é escassa e sugere a fragilidade das equipes assistenciais em reconhecer o potencial para interações. Possivelmente a construção de um protocolo para avaliação de interação fármaco-nutriente aumente a segurança e eficácia dos processos terapêuticos.

Descritores: Preparações farmacêuticas; Nutrientes; Terapia nutricional; Terapia intensiva; Cuidados críticos; Interações de medicamentos

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