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RESEARCH ARTICLE

The Possibility of Therapeutic Drug Monitoring of the Most Important Interactions in Nursing Homes

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Abstract: ***Background*:** Therapeutic drug monitoring is a relevant tool in drug treatment of elderly patients. The aim of this study was to assess the possibility of therapeutic drug monitoring of the most important potential interactions in nursing homes.

***Methods*:** A material of prescribed drugs to 446 patients in three nursing homes in Bergen, Norway from a single day in March 2016 was analysed. Clinically relevant drug interactions (pharmacodynamic or pharmacokinetic) were identified and classified with Stockley`s Interaction Alerts. The most important interaction among several in each patient were ranked by recommended action > severity > evidence according to Stockley`s. The possibility of therapeutic drug monitoring of drug combinations involved in the most important interactions was retrieved from a database of all laboratories performing clinical pharmacology in Norway (the Pharmacology Portal).

***Results*:** Two or more drugs were used by 443 (99.3%) of 446 patients. Three-hundred and eighty-four patients (86.1%) had ≥ 1 interaction. About 95% of the most important interactions were pharmacodynamic. In 280 (72.9%) of these interactions, Stockley`s recommended adjust dose or monitoring. Among the 384 most important interactions, 93% involved one drug and 41% involved two drugs available for therapeutic drug monitoring.

***Conclusion*:** In this pilot study, therapeutic drug monitoring was possible in the majority of the most important interactions in Norwegian nursing homes. This option is of importance since adjust dose or monitoring were frequently recommended actions associated with these interactions.

Keywords: Databases, drug interactions, elderly patients, nursing homes, pharmacotherapy, therapeutic drug monitoring.

1. INTRODUCTION

A consequence of comorbidity is that elderly patients are treated with several concurrent drugs. A European survey found that almost one out of four nursing home residents had excessive polypharmacy (≥ 10 drugs) while polypharmacy (5-9 drugs) was observed in about 50% of the patients [1]. Acutely ill older patients who are prescribed more than five drugs are over three times more likely to receive an inappropriate prescription than those who received five or fewer drugs according to an Irish study [2].

With an increasing number of drugs, the risk of drugs affecting each other (drug interactions) increases proportionally. Elderly are especially prone to adverse drug reactions (ADRs) due to physiological changes like reduced kidney, cognitive and sensory function. Furthermore, the elderly are associated with altered pharmacokinetics and pharmacodynamics [3]. Polypharmacy and interactions among elderly patients due to comorbidity increases the risk of ADRs [4, 5].

A promising tool to avoid ADRs in elderly patients is therapeutic drug monitoring (TDM). TDM uses analytical measurements of drugs (and active metabolites) in blood to provide clinicians with decision support in pharmacotherapy [6, 7]. TDM can provide dosing strategies when a drug is added to or removed from a drug regime. It can also be useful when an inappropriate combination of drugs has to be continued. Dosing strategies with the use of TDM are related to defined therapeutic ranges that reflect optimal efficacy and safety, or reference ranges that reflect expectations of drug concentrations for a given dose [8]. Adherence is an

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increasing indication for TDM, in particular associated with chronic treatment of psychiatric diseases and hypertension [9].

TDM is underused among Norwegian nursing homes patients. A study of 6030 patients in a TDM database revealed that the use of TDM for antidepressants was significantly lower in patients older than 60 years compared to the younger patients [10]. There was a 3-fold difference between the oldest (> 90 years) and the youngest (10-19 years) patients in the use of TDM.

The Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrielists lists in their consensus guideline advanced age as a typical indication for TDM [11]. TDM of elderly patients in nursing homes could be of particular importance during clinical follow up of patients due to the risk of drug interactions and ADRs.

In the present pilot study, we assessed the possibility of TDM of drugs involved in the most important potential clinically relevant drug interactions among nursing home patients. This was achieved by performing an audit of drug use among patients in three Norwegian nursing homes, identify and classify the most important potential interaction in each patient, and then assess the possibility of TDM of the drug combinations involved.

2. METHODS

2.1. Study Material

Three nursing homes in Bergen, Norway took part in the study. The material contained no clinical or personal information besides age, gender and drug use among patients. Furthermore, no information about physicians, other staff, or details concerning organisation of the nursing homes was provided. Besides, information about the patients`nursing home was not given in the material. The collection of the material was approved by the head physician responsible for all the nursing homes in Bergen municipality based on a formal application. The Regional Ethics Review Board stated in 2018 that no approval was necessary for the material since it was anonymous. The three nursing homes in 2016 included regular units that provide long-term care as well as units for short-time care. They also included special care units that provide sheltered care for patients with dementia and psychogeriatric diseases.

2.2. Drugs

The prescribed medications started before 15.03.2016 were analysed for potential drug interactions. This included all the drugs the patients used (regularly prescribed and additional drugs as needed). Drugs were classified according to the Anatomical Therapeutic Chemical (ATC) classification system (WHO Collaborating Centre for Drug Statistics Methodology) [12]. The ATC-system allocates drugs to different groups according to the organ or system on which they act, which are based on their therapeutic, pharmacological and chemical properties. Active substances are classified in a hierarchy with five different levels, and the 5^{th} level is the chemical substance (*e.g.* A10B A02 = metformin) [11]. Drug data represented a one-day, point-prevalence in the institutions and drug use (5^{th} ATC-level) for each patient was listed orderly. Polypharmacy was defined as $\geq$ 5 concurrent drugs.

2.3. Classification of Drug Interactions

Classification of drug interactions was collected from the subscription interaction database Stockley`s Interaction Alerts (SIA) [13]. SIA provides a consistent but brief information on drug interactions compared to Stockley's Drug Interactions, and SIA also provides information on the clinical relevance of a drug interaction. A clinically relevant drug interaction is classified with regard to recommended action ("informative", "monitor", "adjust dose", or "avoid"), severity ("mild", "moderate" or "high") and evidence ("theoretical", "case", "study" or "extensive"). All drug interactions were categorized as either pharmacodynamic or pharmacokinetic based on the description of the interaction outcome in SIA. The description of the interactions in SIA was inspected for this purpose by PS with consultation with JS (clinical pharmacologist) if needed. If there were any changes in drug plasma levels of one or either drug, the interaction was described as pharmacokinetic. If there were no changes in drug plasma levels, the interaction was described as pharmacodynamic. Due to the high prevalence of several and concurrent drug interactions in each patient, the most important interaction was ranked for further analysis. Ranking was done in the following order; recommended action (avoid > adjust dose > monitor > informative), severity (high > moderate > low) and finally evidence (extensive > study > case report > theoretical). Drug interactions that were described as not clinically relevant in SIA (*e.g.* "No interaction or no interaction of clinical significance") were excluded from the study. The number of concurrent clinical drug interactions in each patient were registered.

2.4. Availability of TDM

We used the Pharmacology Portal to see which drugs could be monitored by measuring plasma levels. The Pharmacology Portal is a Norwegian website where all the clinical pharmacological laboratories in Norway provide their analytical repertoire [14]. Only drugs from the most important drug interactions in each patient were examined for the possibility of TDM. The possibility of TDM was described into the following three categories; "none of the drugs could be monitored", "one drug could be monitored" or "both drugs could be monitored".

2.5. Statistics

IBM® SPSS® Statistics for Windows, Version 24.0. Armonk, NY, USA; IBM Corp was used for data analysis. Data are presented as numbers (n) and percent (%). Student t-test was used to compare age, while Mann–Whitney U test was used to compare the number of drugs and interactions. Spearman`s rank correlation was used to examine the correlation between the number of drugs and interactions. All tests conducted were two-sided. The general significance level was set to $p < 0.05$.

3. RESULTS

3.1. Demographics

Four hundred and forty-six patients from three nursing homes took part in the study. Among them 65.5% were women and 34.5% were men. The youngest patient was 23

Table 1. Drugs and interactions.

Characteristic	Patients n = 446	% of those with ≥ 2 drugs	% of those with ≥ 1 drug interaction
≥ 1 drugs	446	-	-
≥ 2 drugs	443	100.0	-
≥ 5 drugs	412	93.0	-
≥ 1 drug interaction	384	86.7	100.0
PD	366	82.6	95.3
PK	18	4.0	4.7

Interactions identified and classified among 446 patients from three Norwegian nursing homes with [13]. Polypharmacy defined as ≥ 5 drugs. PD = pharmacodynamic, PK = pharmacokinetic.

years old and the oldest patient 103 years old. The number of patients younger than 65 years was 30 (6.7%). Mean age of 446 patients was 82.2 years, while median age was 84.0 years. The mean age (standard deviation, SD) was significantly higher among women than men (83.9 ± 11.0 vs 78.9 ± 11.6, $p < 0.001$).

3.2. Drugs, Interactions and TDM

The number of prescribed drugs in the study was 5 105 with 340 different preparations. The most frequent drug groups according to the ATC-system were analgesics (N02), psycholeptics (N05), drugs for constipation (A06) and psychoanaleptics (N06). The mean and median number of drugs were 11.5 and 11.0, respectively, among 446 patients. The range of drugs among patients was 1-28. Most patients used 8 to 14 concurrent drugs. Four-hundred and twelve patients (92.4%) had polypharmacy. There was no significant difference between men and women regarding the number of concurrent drugs ($p = 0.66$). There was also no difference between patients < 84 year or 84 years or older in relation to number of drugs ($p = 0.81$). Three hundred and eighty-four patients (99.3%) had a total of 2478 interactions. The mean number of interactions was 6.5 and the median number of interactions was 5.0. The range of interactions among patients was 1-37. Most patients had 1 to 6 concurrent interactions. There was no significant difference between men and women regarding the number of interactions ($p = 0.29$). There was also no difference between patients < 84 year or 84 years or older in relation to number of interactions ($p = 0.63$). A strong positive correlation was observed between the number of drugs and interactions ($rs = 0.68$, $p < 0.001$). Table **1** shows the use of drugs, number of patients with ≥ 1 interaction and categories of interactions among the most important interactions.

Table **2** shows the classification of the most important interactions according to SIA. Nearly seventy-three percent of the interactions recommended adjusting dose or monitoring as a recommended action. More than 75% of interactions had high severity, and nearly 50% were based on theoretical documentation.

Among the 384 most important drug interactions, 93% of the drug combinations involved at least one drug, and 41% involved two drugs available for TDM according to the Pharmacology Portal [14].

The three most frequent combinations of drugs among the most important interactions were olanzapine/oxazepam (n = 35), acetylsalisylic acid/paracetamol (n = 24) and furosemide/sodium picosulfate (n = 13). In the first two combinations, both drugs can be monitored, but none of the drugs in the last combination. The potential ADRs for the three combinations are sedation, gastrointestinal bleeding, and seizures due to electrolyte disturbances (hyponatremia and/or hypokalemia), respectively. All the 15 most frequent interactions were pharmacodynamic [13].

Table **3** shows the possibility of TDM of combinations that should be avoided (contraindicated) among 13 patients. The frequencies of the individual drug combinations were between one to three (*e.g.* three patients out of thirteen had the combination haloperidol/citalopram as the most important interaction).

Table 2. Classification of the most important interactions.

Classification	Interactions n = 384 (%)
Recommended action	
Avoid	13 (3.4)
Adjust	45 (11.7)
Monitor	235 (61.2)
Informative	91 (23.7)
Severity	
High	293 (76.3)
Moderate	88 (22.9)
Mild	3 (0.8)
Evidence	
Extensive	10 (2.6)
Study	96 (25.0)
Case report	94 (24.5)
Theoretical	184 (47.9)

Interactions identified and classified among 446 patients from three Norwegian nursing homes with [13].

The most frequent potential ADR among contraindicated interactions was the risk of QT-prolongation. The majority of the contraindicated interactions was pharmacodynamic.

Table 3. The possibility of therapeutic drug monitoring of drug combinations that should be avoided.

Drug Combinations*	Type	Potential ADR
Haloperidol/Citalopram	PD	QT-prolongation
Rosuvastatin/Ciclosporin	PK	Rhabdomyolysis
Selegiline/Bupropion	PK	Hypotension
Ondanseton/Escitalopram	PD	QT-prolongation
Ondansetron/Citalopram	PD	QT-prolongation
Selegiline/Escitalopram	PD	Serotonin syndrome
Haloperidol/Escitalopram	PD	QT-prolongation
Simvastatin/Ketoconazole	PK	Rhabdomyolysis
Hydroxyzine/Citalopram	PD	QT-prolongation

Interactions identified and classified among 446 patients from three Norwegian nursing homes with [13]. *Italics = the possibility of TDM of a drug in a drug combination. PD = pharmacodynamic, PK = pharmacokinetic. ADR = adverse drug reaction.

4. DISCUSSION

TDM was possible in the majority of the most important drug interactions in Norwegian nursing homes according to this small, preliminary study. This is of importance since adjusting dose or monitoring was a frequently recommended action associated with the interactions. An argument for TDM is the observation of extensive polypharmacy and several concurrent interactions among the patients in the material.

TDM is of relevance irrespective of type of interaction (pharmacodynamic or pharmacokinetic) since most ADRs are dose-dependent. ADRs in nursing home patients can develop rapidly without warnings (*e.g*. arrhythmias or seizures) or more slowly (*e.g*. sedation, hyponatremia). Combination of psychotropic drugs and drugs for constipation could involve additive or synergistic effects. A diagnostic challenge is that ADRs can mimic worsening of existing conditions. The descriptions of the interactions in SIA often lack stratification to indication, age, dose or gender [13]. Thus, TDM could be a useful complementary tool to address alerts concerning potential interactions during clinical follow up of nursing home patients. In particular, it can be used to directly assess the relationship between dose and concentration. A Norwegian study of 32 126 serum concentrations from 17 930 patients found 1.5- to 2-fold higher mean concentration to dose ratios of most antidepressants in patients older than 65 years compared to patients younger than 40 years. Importantly, the increased concentration to dose ratios of most antidepressants in patients older than 65 years was found to be irrespective of a dose reduction of 10-30% [15]. Thus, altered pharmacokinetics among these patients was not compensated by sufficient dose reduction. A further argument to increase the use of TDM in nursing homes is that about 80% of patients in Norwegian nursing homes have dementia [16]. These patients are particularly vulnerable since many cannot communicate their experience of ADRs. In Norway, structured medication reviews at least once a year is now mandatory in nursing homes according to national regulations from 2017. We suggest that TDM could be a useful tool in medication reviews, but also in general clinical follow-up of patients in nursing homes.

Development of analytical methods in clinical pharmacology is based on a selection of drugs where TDM is regarded as useful [6-8]. TDM today are increasingly using mass spectrometry methods that include quantification of parent drug and active metabolite(s) which provide information about a patient `s pharmacokinetic phenotype [6-8, 14, 15]. In this respect, clinically relevant interactions or possible genetic variation that influences drug therapy can be detected. The development of analytical methods for several psychotropic drugs, frequently used in our material, is based on this argumentation [11]. The concept of the Pharmacology Portal encourages cooperation among clinical pharmacologic laboratories [14]. Besides, providing a tool for standardization of terminology and a user-friendly interface to share analysis repertoires, the portal has also facilitated further collaborative projects. For instance, the Norwegian Association of Clinical Pharmacology is presently working on joint reference ranges for therapeutic drug monitoring and mutually agreed upon explanatory texts for each substance. This will permit the portal to become a joint reference manual for the laboratories, providing clinicians with useful information on how and when tests are to be taken, and how test results are to be interpreted. Such functionality may partially or fully replace many reference manuals in the use throughout the country [14].

A limitation in this study is that a single person (PS) collected and categorized the data. However, strict definitions of categories from SIA were used, and a clinical pharmacologist (JS) was consulted in case of controversy. Only one drug interaction database was used for the classification of the drug interactions, and it is well-known that drug interaction databases lack consistency [17]. Furthermore, potential ADRs were described as presented in SIA, and was not further classified with medical terminology dictionaries like MedDRA or SNOMED CT [18, 19]. Only the most important interaction in each patient was studied, and the availability of TDM for the other drugs the patient used is unknown. Persons younger than 65 years are not uncommon in Norwegian nursing homes and typically suffer from chronic and neurological disorders with a high burden of care [20]. Thus, TDM could be useful in the clinical follow-up of these patients. Finally, our material was limited in the sense that there was no clinical information provided, and only three nursing homes were included. There was also no information whether the drugs where regularly prescribed or additional drugs as needed. For the purpose of examing potential drug interactions, all drugs were included. Only potential interactions were studied since clinical data was lacking. Physicians perception was not available, and it could be that they found the drug combinations appropriate.

CONCLUSION

TDM was possible in the majority of the most important drug interactions in Norwegian nursing homes according to this pilot study. However, TDM is still underused in nursing homes in our and probably other countries. This study relates selected drug combinations associated with potential drug safety among the patients to the possibility of TDM. The clinical impact of TDM regarding rational pharmacotherapy and avoidance of ADRs in these institutions should be assessed in future studies.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The collection of the material was approved by the head physician responsible for all the nursing homes in Bergen municipality based on a formal application. The Regional Ethics Review Board stated in 2018 that no approval was necessary for the material since it was anonymous.

HUMAN AND ANIMAL RIGHTS

All research procedures followed were in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national), and with the Helsinki Declaration of 1975, as revised in 2008 (http://www.wma.net/en/20activities/10ethics/10helsinki/).

CONSENT FOR PUBLICATION

All participants provided informed consent.

AVAILABILITY OF DATA AND MATERIALS

The data supporting the findings of the article is available after personal agreement with the consultant physician in the Department of Nursing Home Medicine, Bergen, Norway at https://www.bergen.kommune.no/omkommunen/avdelinger/sykehjem/enhet-for-sykehjemsmedisin, reference number Schjøtt 021216.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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