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Research Article
Drug Interactions in Critical Patient with Multiple Pathology and Polymedication in a Surgery Hospital

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Abstract

Background and objective: Present guidelines tend to lead to polypharmacy in patients with multimorbidity. Studies have shown that hospital deaths caused by medication incidents are not infrequent in both developed and developing countries. Comprehensive medication management aimed at the development of guidelines and procedures so that drug therapy to be individually assigned, such as the medication to be both effective and safe for the patient. Therefore, this study aimed at exploring the drug-drug interactions (DDIs) in patients receiving simultaneously at least eight drugs, in a surgery hospital. **Methodology:** A group of 35 patients (54.3% women and 45.7% men) receiving eight or more drugs were investigated on the basis of their medical records. The hospitalized patients had diagnostics requiring surgery. All the patients received simultaneously 8-18 drugs, while the elders (over 65 years of age) received concomitantly 8-15 drugs. **Results:** The total number of identified DDIs was 177 with 1-11 DDIs simultaneous for the same patient. In terms of significance, the DDIs were 23% major, 46% moderate and 7% minor. Considering the mechanisms involved, 25% of the DDIs were due to the pharmacokinetic properties of the drugs, 53% to their pharmacodynamic profile, 12% were of a pharmacotoxicological nature and 10% were pharmacographic. No differences between the mechanisms and/or occurrence of DDIs could be noticed in elderly compared to younger patients. Examples of the most significant DDIs are discussed. **Conclusion:** The study showed that DDIs can appear in hospitalized patients subjected to surgical procedures, therefore, consulting the present therapy guidelines and warnings issued by FDA or EMA regarding DDIs is essential for the patient's benefit. An important feature of the therapeutic success is the engagement of the patient preferences, which is in close relation to the role of the clinical pharmacist.

Key words: Polymedication, drug interaction, critical patient, clinical pharmacy, surgery

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Present guidelines tend to lead to polypharmacy in patients with multimorbidity, without indicating how to correctly line up recommendations for patients in whom the treatment could develop to overwhelming issues. An adequate clinical judgment and also a meaningful engagement of the patient preferences are both needed for focusing on the patient's benefit[1]. Comprehensive medication management, represents a concept defined by the patient-centered primary care collaborative organization, tries to develop guidelines and procedures so that drug therapy to be individually set. This should be done in order to determine, which medication is appropriate for the patient, but also effective for his medical condition, safe (given the comorbidities and other prescribed medications) and thus enabled to be taken by the patient, as intended[1-3]. For example, a wide variation in the prescription of guideline-recommended medications were observed, with a measurable relationship to the mortality of elderly patients with congestive heart failure and diabetes[4].

While in countries with a developed health care system (such as USA or UK) less than 10% of all hospitalization and one out of 667 hospital deaths are caused by medication incidents[5], in less developed countries the incidence of such unwanted events is probably higher. As most of them seems to be preventable or ameliorable, a first step consists in managing polymedication is the identification of the relevant drug-drug interactions (DDIs)[5].

A present study performed by Baniasadi *et al*.[6] in an Iranian hospital, reveals that from 1780 administered drugs inside the hospital, 496 lead to major and contraindicated interactions originating from nine drug classes. According to this study, anti-infective agents caused clinically significant DDIs, followed by those acting on the Central Nervous System (CNS). A frequent pharmacological mechanism identified showed that azole antifungals, which intensely inhibit CYP3A4 substrate, involved in the metabolism of most drugs, reduces the plasmatic level and consequently the efficacy of the respective drugs[6]. Another study[7] showed that 38.1% of the patients receiving antimicrobial therapy were potentially exposed to an interaction caused by this class of drugs, fluoroquinolones and azoles being the most frequently involved.

The above lead to the idea that patients undergoing surgery and post-surgery treatment were more prone to suffer from unwanted effects linked to DDIs, as the surgery medication already includes minimum three drugs (anesthetic, antibiotic and analgesic). Therefore, the study aimed at exploring the DDIs in patients receiving simultaneously at least eight drugs in a surgery hospital.

MATERIALS AND METHODS

The study was retrospective and open, based on the medical records of 35 patients hospitalized in the Intensive Care Unit (ICU) of the Bucharest Emergency Clinical Hospital within three months, undergoing surgery and having been prescribed eight or more drugs. Patients with HIV were excluded. The patients were hospitalized for 3-108 days, with an average of 24 days.

Subjects were divided into two classes: 27 patients (78%) were aged above 65 (Elder Patients-EP) and represented the main focus of this study and the second class consisted in 8 Adult Patients (AP) (22%). Patients were provided drugs from the hospital pharmacy and were able to continue the drug therapy previously prescribed. The study was approved by the Hospital Ethics Committee and the patients and/or their relatives gave their written consent to participate in the study.

In order to achieve as much data as possible, the diagnosis-treatment coherence was evaluated; the possible DDIs were identified, classified and quantified, then, the Clinical Significance (CS) of each DDI and the corresponding therapeutic attitude, which the clinical pharmacist would have had for each of the DDIs with CS was established.

RESULTS

The patients were 54.3% women and 45.7% men. The hospitalized patients had the following diagnosed pathologies categories: Cranial-cerebral, cardiovascular and pulmonary, tumors, orthopedic and other surgery-needing disorders (Fig. 1). Patients also suffered from associated pathologies, such as: Psychiatric disorders, anemia, liver failure, chronic obstructive pulmonary disease, renal failure, diabetes mellitus, obesity and dyslipidemia and cardiovascular diseases (Fig. 2).

All the patients received simultaneously 8-18 drugs, while EP received concomitantly 8-15 drugs. The total number of identified DDIs was 177, with 1-11 DDIs simultaneous for the same patient. In terms of significance, the DDIs were 41 major, 81 moderate and 12 minor. Considering the mechanisms involved, 22 of the DDIs were due to the pharmacokinetic properties of the drugs, 46 to their pharmacodynamic profile, 10 were of a pharmacotoxicological nature and 9 were pharmacographic (Fig. 3).

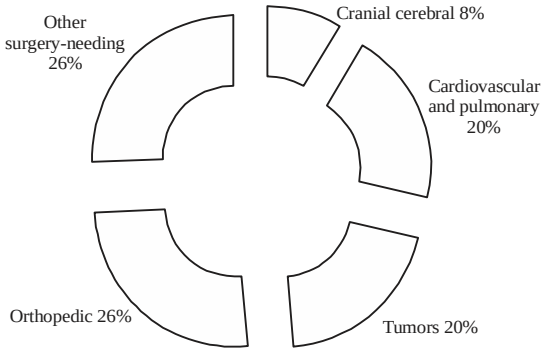

Fig. 1: Main pathologies of the patients under study required cranio-cerebral (8%), cardiovascular and pulmonary (20%), tumors (20%), orthopedic (26%) surgery and other surgery-needing pathologies (26%)

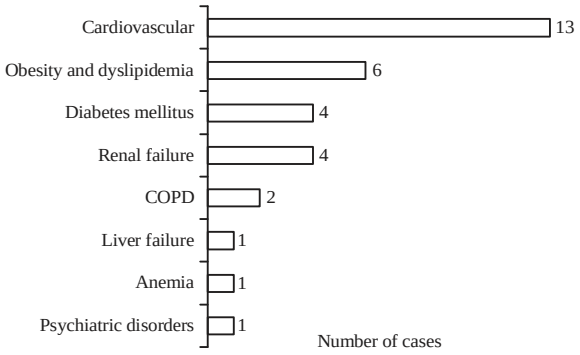

Fig. 2: Associated pathologies of the patients under study, requiring specific medication, included one ore more diseases from the following: Cardiovascular, obesity, dyslipidemia, diabetes mellitus, renal failure, chronic obstructive pulmonary disease, liver failure, anemia, psychiatric disorders

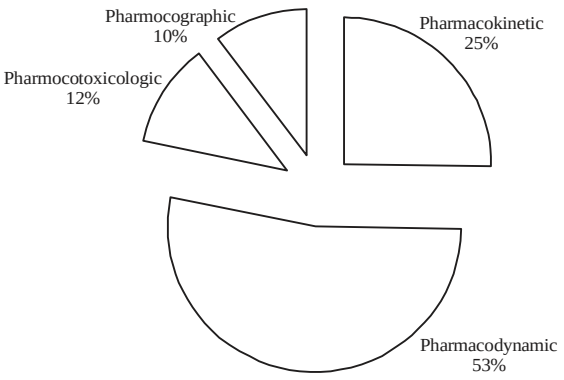

Fig. 3: Identified possible drug-drug interactions were 53% pharmacodynamic, 25% pharmacokinetic, 12% pharmacotoxicologic and 10% pharmacographic. One or more drug-drug interactions could be identified in the treatment of a patient

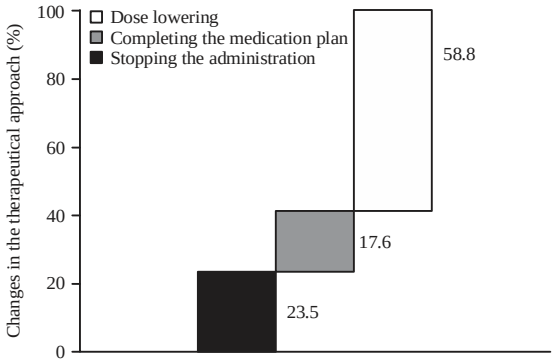

Fig. 4: Clinician pharmacist acted in the therapeutical approach in 51 of the identified possible drug-drug interactions, by dose lowering (58.8% of all changes), completion of the medication (17.6%) and cessation of administration for one or more drugs (23.5%)

The occurrence of DDIs according to their categories were the same in both EP and AP classes considered in the analysis.

The clinician pharmacist acted in 51 of the identified DDIs. The action consisted in dose lowering, completion of the medication plan with other drugs or cessation of certain drug administration (Fig. 4).

DISCUSSION

Pharmacokinetic DDIs represented 15.11% of all DDIs occurred in elders. For instance, the omeprazole-clopidogrel association was prescribed. Omeprazole strongly inhibits CYP2C19 involved in the biotransformation of clopidogrel[8,9], so its antithrombotic effect is reduced, thus increasing the risk for cardiovascular complications, such as cerebral vascular accident or myocardial infarction. The FDA issued a warning in November, 2009 and revised it in October, 2010[10,11] concerning the specific use of omeprazole from all Proton Pump Inhibitors (PPI), in combination with clopidogrel. Further studies revealed that, despite this warning, this specific combination was still prescribed to one third of the patients having the indication of clopidogrel and a PPI. Pantoprazole or lansoprazole were recommended as substitutes for omeprazole and pantoprazole being available on the national pharmaceutical market also in generic products[9]. Omeprazole was also involved in a DDI with theophylline; as omeprazole is an inductor of CYP1A2 and an inhibitor of CYP3A4[9], the plasmatic concentration of theophylline administered parenterally may decrease or increase, which leads respectively to a poor control of the breathing status of the asthmatic patient, or to a gastric irritation and even hemorrhage. The recommendation for

replacing omeprazole from this association was for pantoprazole, as its enzymatic influence is negligible.

Another relevant pharmacokinetic DDI was carbamazepine-amlodipine, as a result of the enzymatic induction of CYP3A4 caused by carbamazepine and hypertension crises may occur when lowering the plasmatic concentration of amlodipine[12]. Valproate or lamotrigine were considered as valid antiepileptic treatment alternatives for carbamazepine.

Pharmacodynamic DDIs included 26.74% of all DDIs that appeared in elders. One of these was morphine-midazolam, which may lead to CNS impairment and withdrawal syndrome because of their synergistic effect. When administered to young adults in clinically relevant sub-anesthetic doses, this combination leads to pharyngeal dysfunction and affects breathing-swallowing coordination, eventually compromising airway protection and increased risk of aspiration[13]. As elders are even more susceptible to the pharmacotoxic profile of the drugs and to DDIs, these side effects are even more probable in this age category. Another DDI encountered was dalteparin prescribed together with clopidogrel, their anticoagulant added effect is very likely to increase the risk for hemorrhage at various levels. Studies from different European countries have revealed that a frequent mistake made when dosing Low Molecular Weight Heparin (LMWH) was not weighing the patients, or to miscalculate doses without taking into account their weight and renal clearance. In this direction, it was recommended to build a routine dosage of LMWH for patients with renal failure aged over 75[14].

Pharmacotoxicological DDIs gathered the greatest proportion, 54.65% of the DDIs theoretically occurring in elders, according to the present study. A relevant case is the association of ketorolac and a LMWH such as enoxaparin or dalteparin. This might involve hemorrhage, since ketorolac was demonstrated to be one of the non-steroidal ant-iinflammatory drugs having a particularly high individual risk for upper gastrointestinal bleeding, even at low doses[15]. The suggestion targeted replacing it with ibuprofen, naproxen or meloxicam, if the cardiovascular condition of the patient allowed it. Another DDI called the attention, consisting in co-administering furosemide and ketorolac, with a consequent decreased effect of the diuretic and increased risk of renal impairment[16]. When the patient already has renal failure, although hypertension has to be overcome, great precaution must be taken when dosing furosemide, so that the kidney function would not be worsen. When cefuroxime or ceftriaxone were included simultaneously into therapy aside furosemide, nephrotoxicity was favored. Moreover, there was no pharmacological justification for administering two cephalosporins, since their spectra overlaid.

Of all pharmacotoxicological DDIs (occurred in patients of all ages), one can highlight important side effect-generating drug combinations, such as: Ketorolac and carbamazepine, involving a poor control of epileptic crises, duloxetine and tramadol leading to serotoninergic syndrome and also linezolid and mirtazapine that exposed the patient to the risk of serotoninergic syndrome. For the last one, FDA issued a warning in 2011[17].

The statistics for the AP group were very similar to the one corresponding to the EP group. Considering the data collected from the patient's records and the identified DDIs, three types of changes in the therapeutic attitudes were suggested: Stopping the administration, completing the therapeutic plan and lowering the doses.

Stopping the administration was admitted to be the fair change in 12 cases, from which the following were emphasized according to their clinical significance. Morphine associated with amitriptyline, escitalopram and mirtazapine raised the risk for CNS impairment and serotoninergic syndrome; in this case, one or two of the antidepressants had to be removed from the medication plan. When furosemide and amikacin were co-administered, the probability for cochlear lesions to occur was greater[18] and caused by multiple phamacokinetic mechanisms[19] for avoiding this event, amikacin was recommended to be replaced with another antibiotic (with similar Gram negative spectrum). Ketorolac taken concomitantly with enoxaparin might induce severe hemorrhagic diatheses, for hindering this effect, ketorolac was suggested to be replaced by a selective COX-2 nonsteroidal anti-inflammatory drug.

Completing the medication plan was requested in 9 cases. The benefit of this clinical attitude was assumed to be major in the ones selected below. When adding diclofenac to dexamethasone in pain treatment, patient was then exposed to great risk of gastric hyperacidity and gastric bleeding, this situation required a hyposecretion-inducing drug, as proton pump inhibitors or H_2-histamine receptor blockers. The same change is imposed by the administration of both ketoprofen and dexamethasone. When giving the patient multiple antibiotic therapy including ertapenem and linezolid, an antifungal drug, such as nystatin or azoles was needed in order to prevent candidiasis, that might installed as a result of the immunosuppression antifungal treatment had to be accompanied by constantly assessement of the hepatic function.

Dose lowering was appropriate in 30 cases, of which two are detailed below. Imipenem, colistin, piperacilin, doxycycline and vancomycin were all associated in an antimicrobial therapy, lower doses would have impeded the renal accumulation. Amiodarone might even double the digoxin plasmatic concentration when associated to it, leading to bradycardia, so a lower dose of amiodarone would decrease this risk.

Studies have demonstrated that improved adherence among patients with frequent chronic pathologies has reduced hospitalization rates with an overall reduction in total health care costs, as a result of the interventions of the clinical pharmacist[4]. It is strongly considered that engaging the pharmacist in the team in charge of setting the patient's drug therapy would remarkably increase his therapeutic benefit.

CONCLUSION

The present study included 35 hospitalized in view of surgical procedures subjects having at least 8 drugs administered concurrently, focusing on those above 65 years. In the specific case of patients undergoing surgery, diminishing the number of DDIs is even more challenging than for other elder patients, as the specific surgery medication already involves at least three drugs (anesthetic, analgesic and a bleeding control drug). Consulting the present therapy guidelines and warnings issued by FDA or EMA regarding DDIs is essential for the patient's benefit in terms of a minimum of side effects. An important feature of the therapeutic success is the engagement of the patient preferences, which corresponds to the clinical pharmacist role, as part of the multidisciplinary health professional's team.

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