Referência
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RESEARCH ARTICLE (ORIGINAL)

Patient safety: potential drug-drug interactions caused by the overlapping of medications agreed by the nurse

Segurança do doente: potenciais interações medicamentosas favorecidas pela sobreposição de medicamentos programados pelo enfermeiro

Seguridad del paciente: potenciales interacciones de los medicamentos favorecidas por la superposición de los medicamentos programados por el enfermero

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Abstract

Background: Hospital drug therapy has the potential for incidents, thus it is necessary to identify situations that may compromise patient safety.

Objective: To investigate potential drug-drug interactions caused by the overlapping of medications planned by nurses in the patients' prescriptions at a hospital inpatient unit.

Methodology: Descriptive, cross-sectional study of documentary analysis with a quantitative approach, of 260 prescriptions for adult patients. Potential drug- interactions were identified using the Drug Interaction Checker (Medscape®).

Results: A total of 3066 doses were analyzed, with a concentration of 4 schedules, showing an institutional standardization of schedules. The omission error rate was 5.44%. Drug-drug interactions of moderate severity were more frequent, especially lopinavir/clonazepam and diazepam/tramadol combinations.

Conclusion: Omission errors and interactions can be minimized with tools to support clinical decision and reconfiguration of the work process.

Keywords: patient safety; medication errors; drug interactions; medication systems, hospital; nursing

Resumo

Enquadramento: A terapêutica medicamentosa hospitalar possui potencial para incidentes e, neste sentido, é preciso intercetar situações que possam comprometer a segurança do doente.

Objetivo: Investigar as potenciais interações medicamentosas favorecidas pela sobreposição de medicamentos programados por enfermeiros nas prescrições de doentes numa unidade de internamento hospitalar.

Metodologia: Estudo descritivo, transversal, de análise documental com abordagem quantitativa, de 260 prescrições medicamentosas de doentes adultos. As potenciais interações medicamentosas foram identificadas por meio da ferramenta Drug Interaction Checker (Medscape®).

Resultados: Foram analisadas 3066 doses, com concentração de 4 horários, evidenciando uma padronização institucional de horários. A taxa de erros de omissão foi 5,44%. As interações medicamentosas com gravidade moderada foram as mais frequentes, destacando-se as combinações de lopinavir/clonazepam e diazepam/tramadol.

Conclusão: Os erros de omissão e as interações podem ser minimizados com ferramentas de apoio à decisão clínica e reconfiguração do processo de trabalho.

Palavras-chave: segurança do paciente; erros de medicação; interações de medicamentos; sistemas de medicação no hospital; enfermagem

Resumen

Marco contextual: El tratamiento farmacológico hospitalario tiene el potencial de provocar incidentes y, por ello, es necesario interceptar las situaciones que puedan comprometer la seguridad del paciente.

Objetivo: Investigar las posibles interacciones de medicamentos favorecidas por la superposición de los medicamentos programados por los enfermeros en las recetas de los pacientes en una unidad hospitalaria.

Metodología: Estudio descriptivo, transversal, de análisis documental, con enfoque cuantitativo, de 260 recetas de medicamentos de pacientes adultos. Se identificaron posibles interacciones entre los medicamentos mediante la herramienta Drug Interaction Checker (Medscape®).

Resultados: Se analizaron 3066 dosis, con una concentración de 4 horarios, lo que mostró una estandarización institucional de los horarios. La tasa de errores de omisión fue del 5,44%. Las interacciones de medicamentos de gravedad moderada fueron las más frecuentes, de entre las cuales destacaron las combinaciones de lopinavir/clonazepam y diazepam/tramadol.

Conclusión: Los errores por omisión y las interacciones pueden reducirse al mínimo con herramientas de apoyo a las decisiones clínicas y la reconfiguración de los procesos de trabajo.

Palabras clave: seguridad del paciente; errores de medicación; interacciones de drogas; sistemas de medicación en hospital; enfermería

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Introduction

Hospital drug therapy occurs in a setting with an increased probability of adverse events. Thus, it is even more challenging to identify situations that compromise quality care to offer risk-free benefits for patients (Al-Ramahi et al., 2016). Correct medication administration can be considered as a simple activity, but a nurse may administer more than 100,000 drugs throughout his/her career. Thus, it is difficult to imagine that no errors will occur, especially when there are no barriers or prevention systems (Duarte, Stipp, Cardoso, & Büscher, 2018). It should be noted that, in Brazil, the nursing team is composed of high- and middle-level professionals: nurses and nursing technicians, respectively. Both of them participate in the process of preparation and administration of medications. Forte et al. (2019) analyzed 112 news of errors reported by the journalistic media and found that the most common error was the medication error possibly caused by occupational conditions. The content of the news was not very explanatory, contributing to a negative image of healthcare professionals and making society insecure. Thus, it is a key topic and a public health issue whose discussion cannot be postponed due to its high magnitude and importance (Ministério da Saúde, 2014).

In the United States of America, it is estimated that medication errors cause at least one death every day, involving about 1.3 million people annually. In underdeveloped countries, the impact is estimated to be twice as much in terms of the number of years of healthy life lost. The cost associated with these errors has been estimated at US$ 42 billion annually or almost 1% of total global health expenditure (Organização Pan-Americana da Saúde [OPAS], 2017).

This study is justified by the fact that the World Health Organization (WHO) has recently addressed the high number of medication errors, launching in 2017 the Third Global Patient Safety Challenge: Medication without Harm with the overall objective of reducing severe, avoidable medication-associated harm in all countries by 50% over the next 5 years (OPAS, 2017).

This Global Challenge foresees actions focused on four areas: a) patients and the public; b) healthcare professionals; c) medicines as products; and d) systems and practices of medication so that the medication system can make improvements in each stage, including prescribing, dispensing, administering, monitoring, and use. In this way, WHO provides strategies, plans, and tools to ensure patient safety in the healthcare facilities (OPAS, 2017).

Therefore, the general objective of this study is to investigate potential drug-drug interactions caused by the overlapping of medications planned by nurses in patients' prescriptions at a hospital inpatient unit.

Background

James Reason, a British psychologist, developed the Swiss Cheese Model by analyzing several accidents in the aviation and nuclear power industries, where complex aviation and nuclear power plant systems predict the facts and anticipate themselves by recognizing human error as possible. Reason noted that only one error in the final phase of a process is enough to generate damage and that it can be the result of a cascade of latent errors in the system stages that culminate in an active error (Ministério da Saúde, 2014).

The association between the swiss cheese holes and the errors occurs when these failures (holes) are aligned, leading to a trajectory that, without interruption or identification of potential damage, may increase the likelihood of an error. Both the professionals and the patients are victims because latent errors become active when they are made on the front line (Ministério da Saúde, 2014).

This systemic approach focuses on the analysis of each phase of the process, identifying conditions with potential for error so that it does not materialize. Therefore, the human factor is no longer the *a priori* reason and so knowing who made the error falls into the background. Those individuals who make up the health institutions should know how to react and manage the consequences of the question: who was it? (Correia, Martins, & Forte, 2017; Duarte et al., 2018).

When revealed within a systemic approach, which looks at the medication process as a system composed of stages, the managers are shifting from a punitive to a pedagogical perspective of errors, providing an environment for intellectual growth (Ministério da Saúde, 2014).

The majority of errors are associated with system failures, but it should be noted that the professionals' characteristics pose risks to the patients, influencing the occurrence of adverse events. In the case of an iatrogenic event, a systematic analysis is required to understand its flaws, without neglecting the behavioral relationship between the individual and the situation. Thus, a non-punitive environment does not represent tolerance to intentional risk actions, where professionals do not comply with the safety regulations in an intentional and/or recurrent manner (Duarte et al., 2018).

Research question

What are the potential drug-drug interactions caused by the overlapping of medications planned by nurses in patients' prescriptions in a hospital inpatient unit?

Methodology

This is a descriptive, cross-sectional study of documentary analysis with a quantitative approach aimed to outline the profile of medication schedules planned in inpatient units of a university hospital, with a view to identifying the overlapping of medications.

This study was carried out in two inpatient units of a university hospital located in Rio de Janeiro, with a total of 26 beds. The clinical-epidemiological profile of these units includes infectious diseases, chronic non-commu-

nicable diseases, and oncological diseases. This hospital uses the following single-dose medication process: the physician prescribes the medication using a pre-typed prescription (computer-generated and printed), two copies, until 10 a.m., and delivers it to the nurse in the unit. One copy is forwarded to the pharmacy and another one is used by the nurse to manually plan the schedules based on the standardized institutional routine: 2 p.m., 10 p.m., 6 a.m., and 12 a.m., 6 p.m., 12 p.m., and 6 a.m. for medications every 8 and 6 hours, respectively. It should be noted that it is common practice in this scheduling to use the previous prescription but each nurse can change the schedules according to the patient's need, except in situations where the prescriber establishes the medication administration time. At the nursing station, after scheduling, the nursing technician separates the medications on a tray, by schedule, and then the nurse administers them to the patient, monitoring the therapeutic effects.

At the pharmacy, the pharmacist sorts out the medications to be sent, and the pharmacy technician separates and distributes the single doses in their original packages, separated by patient, in a specific organizer that is delivered to the units at 2 p.m. for the 24-hour period.

Generally, nurses check each patient's medications, dose by dose, and, when they cannot perform this task for any reason, such as workload, they delegate it to a nursing technician. Any discrepancies, that is, missing, extra, or changed medications, found during the verification process or at any time should be reported to the pharmacy.

The sample consisted of drug prescriptions, in which the unit of analysis was the planned medication schedules. The sample for this study was calculated based on the total number of existing beds (26) and the low patient turnover (100% of the occupied beds). The statistical calculator of Epi Info 7, version 1.3.4, was used for finite population sampling. A confidence level of 95% was used, resulting in 257 prescriptions. The sample was selected by convenience.

Data were collected through a semi-structured form with the following variables: gender; inpatient unit; date of admission; diagnosis; medication; route of administration; total number of prescribed medications; number of medications; frequency of dose omission; reason for dose omission; total number of suspended medications; reasons; erasures on schedule planning; erasures on the prescription; presence of the nurse's signature; presence of the nurse's stamp; and type of prescription.

The visits took place over 12 days. The prescriptions that were active on the day of data collection were not considered because they could still be changed. Therefore, the target prescription was that of the day before the date of data collection because it was available in the medical records and had already been evaluated by the team.

Data were analyzed using descriptive statistics: frequency, mean, and standard deviation. Microsoft Excel® software, version 2010, was used to consolidate the variables, creating a database presented through charts and tables.

Potential drug-drug interactions were identified based on combinations of planned overlapping drugs, that is, administered on the same schedule, using the Drug Interactions Checker, available on the Medscape® database.

This study was approved by the hospital's Research Ethics Committee, with the Certificate of Presentation for Ethical Consideration (CAAE) no. 16581119.0.0000.5258. Data were collected only after the research was approved and the Informed Consent form was applied.

Results

This study analyzed 260 medical prescriptions, in a total of 3066 doses, which were evenly distributed between shifts. However, there was a concentration of four schedules (10 a.m., 6 p.m., 10 p.m., and 6 a.m.), revealing an institutional standardization of schedules.

The oral route was the predominant route (74%), followed by the intravenous route (21%). In these prescriptions, 189 omitted doses were found.

The reasons for dose omission were: no reason in 60.3% ($n = 114$); the drug was missing or unstandardized in 22.8% ($n = 43$); and the schedule was absent in 5.3% ($n = 10$). After application of the equation for calculating the medication error rate (no. of medications administered with omission errors (167) / total number of administered medications (3066) x 100 = 5.44) suggested by the National Patient Safety Program (Portaria n. 529, 2013), an error rate of 5.44% was found.

Regarding the type of prescription, there was a predominance of pre-typed prescriptions ($n = 194$, 74.61%), only three (1.15%) were handwritten, and 63 (24.23%) were mixed (both typed and handwritten).

The following potential drug-drug interactions of mild risk should be highlighted: valproic acid/isoniazid and calcium carbonate/aspirin, both with 19.7% ($n = 12$).

As regards those of moderate risk, there was a predominance of lopinavir/clonazepam (11.9%; $n = 26$) and diazepam/tramadol (7.3%; $n = 16$).

Finally, the potential drug-drug interactions with severe risk were isoniazid/omeprazole (12.3%; $n = 44$) and rifampin/dexamethasone (2.8%; $n = 10$).

A total of 342 drug combinations with the potential to induce drug-drug interactions were found. Table 1 shows the analysis of the most prevalent drug combinations with the potential to induce drug-drug interactions of mild, moderate, and severe risk.

Table 1

Distribution of the major potential drug-drug interactions, classified as mild, moderate, and severe risk

Risk	Medication I	Medication II	*n*	%
Mild (*n* = 61)	Isoniazid	Valproic acid	12	19.7
	Calcium carbonate	Aspirin	12	19.7
Moderate (*n* = 201)	Lopinavir	Clonazepam	26	12.9
	Diazepam	Tramadol	16	8
Severe (*n* = 80)	Isoniazid	Omeprazole	44	55
	Rifampin	Dexamethasone	10	12.5

Discussion

The concentration of doses in four schedules is a deleterious pattern for quality nursing care because it hinders the monitoring of undesired reactions, delays infusion, and increases preparation time, environmental exposure, the likelihood of drug-drug interactions, the number of medication errors, and work overload. The schedules with a higher number of doses at the beginning (10 a.m. and 10 p.m.) and the end (6 p.m. and 6 a.m.) of the shifts, established by the institutional routine in a standardized way, are the same in several studies (Henrique et al., 2017).

Pereira et al. (2018) highlight that the administration of multiple medications at the same schedule can significantly increase the time of preparation and administration, compromising pharmacological stability. Another problem is the increase of environmental exposure, with the possibility for contamination of the inside of these devices. In the case of antibiotics, the delay in infusion caused by the excessive number of medications administered at the same schedule may compromise efficacy and increase the microorganism's resistance to the active principle because the prescribed dosage takes into account the elimination half-life for the maintenance of plasma levels until the next dose is administered (Pereira et al., 2018).

It is also estimated that the concentration of medications at the same schedule increases the probability of errors during the preparation and administration of medications (Pereira et al., 2018) and makes it difficult to verify information on care during the preparation and administration of medications. A study found a positive association (*p* = 0.003) between the lack of printed guidelines and the standardization of the same schedules with drug-drug interactions (Pereira et al., 2018).

Magalhães et al. (2015) add that the nursing team spends a considerable amount of time in the preparation of medications. It is estimated that the nursing teams in inpatient units spend 40% of their working hours in the administration of medications. Therefore, both the high amount of time spent on drug therapy and the high demand for other tasks have a negative impact on compliance with the planned schedules and the records of events after medication administration.

The 114 omitted doses (60.3%), without any record or reason for non-administration, may induce other potentially severe errors, such as duplicate medication and misinterpretation of the therapeutic action expected for each drug, compromising patient safety.

The lack of a verification record can mean two things: the drug was not administered or the drug was administered but no record was made. A study analyzed 51 incidents at a private hospital in São Paulo and found that the most common errors were omission errors, occurring in 31.5% of reported incidents (Teixeira & Cassiani, 2014).

Another situation of incomplete drug therapy, other than record omission, was the 10 doses (5.3%) found with a missing schedule. Despite being in an intensive care unit, Ribeiro et al. (2018) found similar results when analyzing 362 prescriptions, 80.5% of which had incomplete scheduling.

In this study, 43 doses (22.8%) were not administered due to a lack of the medication in the pharmacy and/or because they did not belong to the hospital's standardized list. The analyzed prescriptions were from the day before data collection, which meant that 24 hours had passed since their validity and the issue was not resolved. There are clinical situations in which it is possible to replace the drug of first choice with another one with a similar mechanism of action, when the former is considered a non-standard drug at the institution. Teixeira and Cassiani (2014) found that 6.9% (*n* = 119) of medications were not administered because they were lacking in the pharmacy.

Whenever it is impossible to distribute the prescribed medication, it is required effective verbal and/or written communication among the interdisciplinary team involved in the medication process. If there is a shortage of a medication in the pharmacy, the pharmacist should inform both the nursing and the medical teams, and these professionals should clarify the pharmacists' doubts about the medication already prescribed or to be prescribed. A study analyzed the communication among 22 professionals (pharmacy and nursing, randomly) regarding safe drug administration at a private hospital in Bahia and found that 64% of them did not analyze the prescription dispensed and, when doubts emerged about medications, only 50% of them turned

to the pharmacist (Oliveira, Oliveira, Portela, & Soares, 2017).

Omitted doses are an important indicator of organizational failure, whether in the transition of care, when a drug that the patient was taking prior to admission is not prescribed, or in the pharmacy, with errors in the distribution (delays, lack of the medication in the institution, understaffing, etc.) or the administration of medications (the patient is not in bed, lack of professionals in the team, unclear instructions on the prescription that lead to misinterpretation or delay in the search for information; Ministério da Saúde, 2014).

The medication error rate in this study was 5.44%, which can be considered low when compared to other studies in which the medication error rate ranged from 14.8% to 17.31% (Teixeira & Cassiani, 2014).

Regarding the structure of the prescriptions, a study found that the type of prescription influences the prescription errors. The potential for prescription errors was more frequent in handwritten (2.96 times) and mixed (2.5 times) prescriptions than in electronic prescriptions. The use of the electronic prescription system seems to be associated with the reduction of risk factors for medication errors, such as illegibility, use of a brand name, and essential items that provide a more effective and safe prescription (Volpe, Melo, Aguiar, Pinho, & Stival, 2016).

Drug-drug interactions have a mild risk when the interaction results in restricted clinical effects. Manifestations may increase the frequency or intensity of adverse effects, but generally do not require a major change in pharmacotherapy (Lima & Godoy, 2017; Drug Interaction Checker, 2019). The most prevalent mild interactions were valproic acid/isoniazid and calcium carbonate/aspirin, both with 19.7% (n = 12).

Valproic acid and isoniazid are highly associated with hepatotoxicity. A study conducted on VigiBase, the global database of the World Health Organization (adverse event reporting system), investigated the liver event reporting frequency of these medications in the presence of co-reported medications and concluded that they can modify drug hepatic safety (Suzuki et al., 2015). Isoniazid can cause hepatocellular injury due to metabolic and epigenetic factors that increase with aging, and valproic acid causes mitochondrial toxicity, particularly in infants and young children (Suzuki et al., 2015).

According to Medscape®, another drug-drug interaction of mild risk was calcium carbonate/aspirin because salicylate levels increase at moderate doses with this combination (Drug Interaction Checker, 2019). A retrospective cohort study evaluated 275 hemodialysis patients in the West Bank, Palestine, with a total of 930 potential interactions. Calcium carbonate/amlodipine (41.5%; n = 114 patients) was the most common combination, followed by calcium carbonate/aspirin (27.6%; n = 76 patients). This significant result of potential interactions is associated with the number of diseases, polypharmacy, and patient age (Al-Ramahi et al., 2016).

Drug-drug interactions of moderate risk mean that the interaction results in exacerbation of the patient's health problem and/or requires a change in pharmacotherapy (Lima & Godoy, 2017; Drug Interaction Checker, 2019). The The lopinavir/clonazepam combination was of moderate risk. The former increases the levels of the latter, affecting hepatic enzyme CYP3A4 metabolism with potential for increased toxicity and sedation. The recommendation is to reduce the dosage of benzodiazepine (Drug Interaction Checker, 2019).

Another combination with a moderate risk is the diazepam/tramadol combination, which are central nervous system depressants and whose interaction enhances sedation of the former and causes low blood pressure (Fuchs & Wannmacher, 2017).

Interactions with severe risk represent life damage and/or need for medical assistance to mitigate harmful effects, so their simultaneous use is not recommended (Lima & Godoy, 2017; Drug Interaction Checker, 2019).

In this study, the omeprazole/isoniazid and the rifampicin/omeprazole combinations were classified as having a severe risk. Omeprazole is a proton-pump inhibitor (H^+) and an inhibitor of the hepatic CYP2C19 and CYP3A4 isoenzymes in their biotransformation (Fuchs & Wannmacher, 2017). On the other hand, isoniazid is a weak inhibitor of the CYP2C19 enzyme. This inhibition is an acute and immediate process which increases the effect of omeprazole by influencing CYP2C19 metabolism. Clinically, the acute inhibitory effects of isoniazid on omeprazole can be avoided if the nurse administers the drug at an adequate interval (Xavier, Kumar, Sundaram, Francis, & Shewade, 2016).

Another severe drug-drug interaction was the rifampicin/dexamethasone combination because it accelerates the hepatic metabolism of the latter, reducing the pharmacological effect. The CYP3A4 expression in enterocytes can be induced by dexamethasone and rifampicin. This induction might affect the pharmacokinetics of concomitant drugs administered orally (Negoro et al., 2016).

One of the limitations of this study is that, despite the significant number of analyzed drug doses, the results cannot be generalized because they were obtained in only two inpatient units, and different results may be obtained in other realities. It is not possible to make inferences because it is a descriptive study and other variables have not been studied, such as food-drug interactions.

Conclusion

The results show a concentration of the 3066 doses in four schedules (10 a.m., 6 p.m., 10 p.m., and 6 a.m.), evidencing an institutional standardization of schedules. The medication omission error rate was 5.44%, which is a lower percentage than that found in other studies. Drug-drug interactions with moderate risk were the most frequent interactions in this study, namely the lopinavir/clonazepam and diazepam/tramadol combinations. The most frequent severe drug-drug interac-

tions were omeprazole/isoniazid and rifampicin/omeprazole.

Given the legal obligations and the importance of nursing in patient safety, it is possible to adopt strategies that contribute to patient safety. Thus, the nursing team should consider patient-centered care, adequate verbal and written communication among the healthcare professionals, and the use of databases as a tool to support clinical decision-making.

The following are recommended: avoiding medication overlap, planning schedules according to individual needs, including sleep preservation, double-checking of high-risk medications, preparing a manual for schedule planning within a private environment, and organizing a better work environment.

Author contributions

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