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Original Article

Drug interactions resulting from scheduling and errors in the preparation of antibacterials

Interações medicamentosas induzidas pelo aprazamento e os erros no preparo de antibacterianos

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Objective: to identify drug interactions resulting from scheduling and errors in the preparation of antibacterials. **Methods**: observational and cross-sectional study carried out in medical clinics of a sentinel hospital. Data were collected through the observation of prescriptions and the preparation of 265 doses of antibacterials with the use of a check list. **Results:** the administration of Piperaciclina and Tazobactan prevailed, with 51 doses. The scheduling of antibacterials with another drug occurred predominantly in the morning. Interactions with injectable anticoagulants and between antimicrobials of different classes stood out. The scheduling was associated with the lack of availability of printed guidelines on medication administration (p=0.003). The main error was the dose (32.5%). **Conclusion:** the scheduling of antibacterials in the medical clinic may potentiate possible drug interactions and dose errors have been identified in the administration of drugs.
Descriptors: Anti-Bacterial Agents; Medication Errors; Hospital Units; Drug Interactions; Medical-Surgical Nursing.

Objetivo: identificar as interações medicamentosas induzidas pelo aprazamento e os erros no preparo de antibacterianos administrados. **Métodos**: estudo observacional e transversal, realizado em clínicas médicas de hospital da rede sentinela. A coleta de dados ocorreu por meio da observação das prescrições e do preparo de 265 doses de antibacterianos com a utilização de um *check-list*. **Resultados:** prevaleceu a administração da Piperaciclina e Tazobactan, com 51 doses. O aprazamento de horário dos antibacterianos com outro medicamento ocorreu prevalentemente no período matutino, destacando-se interações com anticoagulantes injetáveis e entre antimicrobianos de classes diferentes, e se associou com a não disponibilização no setor de orientações impressas acerca dos cuidados com a administração do medicamento (p=0,003). O principal erro encontrado foi o de dose (32,5%). **Conclusão:** o aprazamento de antibacterianos em setor de clínica médica pode potencializar possíveis interações medicamentosas e os erros de dose são identificados na administração dos medicamentos.
Descritores: Antibacterianos; Erros de Medicação; Unidades Hospitalares; Interações de Medicamentos; Enfermagem Médico-Cirúrgica.

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Introduction

The use of antibacterial agents occurs on a large scale, corresponding to about 30.0% of drug costs in health institutions. This high utilization has been associated with increased health care costs and the emerging bacterial resistance to these drugs[1-3].

Antibacterials are the most prescribed class of medication in hospitals due to the destruction of bacteria, and the administration errors of these drugs have reached 27.4%. When considering that 20 to 50.0% of antimicrobials are used inappropriately in the hospital environment due to incorrect administration, among other causes, the importance of monitoring the use of these drugs is highlighted[4]. In this context, in order to improve the quality of antibacterial treatment and reduce the costs related to its adverse events, initiatives investigating the stages of prescription, preparation and administration are pertinent to the health environments[5].

Prescriptions present, simultaneously, several medicines that may have drug interaction and even contraindication of simultaneous administration. Potential drug interactions may have positive results (increased effectiveness), however, most of the time, effects are negative (decreased effectiveness and toxicity). A study carried out in Intensive Care Units pointed out this phenomenon can occur in up to 71.0% of patients and that, among other factors, it can be caused by the scheduling of administrations[6].

Safe and precise scheduling is the nurse' responsibility who, from fixed hours of routine, records the times in which the medicines should be administered. However, the distribution of schedules in standardized and fixed moments contributes to the simultaneous administration of several drugs in the same patient, which increases the chances of accidental drug interaction[7].

Another important step for safe administration of medication is the preparation. Although this step is often neglected, errors made during it may compromise the safety and efficacy of the drug therapy. Studies found in national databases, carried out in the last decade, have addressed the administration of medications and the post-administration effects, but the scheduling (focusing on the drug interaction induced by the determination of schedules for drug administration) and the preparation of antibacterials have been little explored in the literature.

The stages of scheduling and preparation of antibacterials are predominantly attributed to nursing. It is relevant to investigate the errors related to these stages in view of the need for scientific evidence to corroborate the reduction of the probability of error and to support the planning of continuing education and training of nursing professionals.

In view of the above, the present study aimed to identify drug interactions resulting from scheduling and errors in the preparation of administered antibacterials.

Methods

This is an observational and cross-sectional study conducted between August and December 2014 in the medical clinics of a teaching hospital belonging to the Sentinel Network of the National Sanitary Surveillance Agency, located in Fortaleza, Ceará, Brazil. In the period of data collection, the medical clinics of the referred hospital were divided into two nursing posts, A and B, which included assistance to 114 beds of the following specialties: Dermatology, Cardiology, Medical Clinic, Endocrinology, Gastroenterology, Pneumology, Neurology, Nephrology, Hematology and Rheumatology.

For the sample calculation from the definition of the total doses to be observed, we requested from the hospital pharmacy service of the Institution the amount of doses of antibacterials, divided by shifts, dispensed for Clinics A and B in a period of 30 days before the beginning of data collection, which was 270 and 420 doses for Clinics A and B, respectively, totaling 690.

Thus, the sample group of the present resear-

ch was composed of 40.0% of the doses reported by the pharmacy service, that is, 276. This sample percentage was calculated based on the average errors of preparation and administration of antimicrobial medication present in another Brazilian study[8], considering a sample error of 5% and a 95% confidence level. Thus, 157 observations were made at Medical Clinic B: 67 in the morning; 30 in the afternoon; and 60 in the night shift. In Clinic A, 108 doses were observed: 44 in the morning; 22 in the afternoon; and 42 in the night shift. It should be noted that the final sample was 265 doses, since the first 11 doses observed were discarded due to the Hawthorne effect.

Data collection was conducted in randomly sorted days by the researchers. On these specific days, the three shifts were contemplated by the observation of errors, regardless of weekends or holidays. The number of doses observed at each shift varied according to the availability of antibacterials due for each period.

At first, researchers read the medical prescription to identify the medication used and the scheduling. Pharmacological classification and verification of possible drug interactions were performed according to the Anatomical Therapeutic Chemical System of the Collaborating Center for Drug Statistics Methodology, used by the Collaborating Center for the International Monitoring of Medicines[9].

Data collection was performed by two independent researchers who, after previous training to standardize their conducts, observed the same preparation situations. The information collected by them was compared by double checking the instrument and by discussing the observed situation in order to avoid discrepancy in the data collection. To avoid the Hawthorne effect, common in observational studies, which comprises drastic changes in the performance of certain tasks by the subjects when they know they are being observed by people who are not part of the routine of the workplace, the observations made in the first month of data collection were not considered for analysis.

A check-list type instrument was used, with the following variables: drug classification, time used for preparation, availability of printed instructions on medication administration and preparation error in the sector. In addition, the errors were categorized according to the taxonomy used for international research in dose errors, time errors (preparation time) and wrong choice of medication, characterized by incorrect selection of the prescribed medication at the time of preparation[10].

The data were grouped into the database using the Statistical Package for Social Science 19.0 software for statistical judgment. The chi-square test was performed to identify the associations between the variables raised and the medication errors. A significance level of 5% was used.

The study complied with the formal requirements contained in the national and international regulatory standards for research involving human beings.

Results

Of the 265 observations, the classes of antibacterials most used in the Clinics were: penicillins 112 (42.3%), glycopeptides 68 (25.7%), cephalosporins 47 (17.7%), quinolones 22 (8.3%) and imidazole 16 (6.0%). Levofloxacin was the least used antibacterial, at a frequency of four times, as Table 1.

Regarding the medication scheduling, which was performed entirely by nurses, doses were administrated predominantly in the morning and night periods. These were the shifts in which there was a greater amount of scheduling of antibacterials for simultaneous administration with other drugs that had potential drug interactions. At Medical Clinic A, there were 15 scheduling situations that induced drug interactions in the morning and eight during the night shift, while in Clinic B, 39 occurred in the morning and 22 in the night shift.

Table 1 – Distribution of antibacterial types and amount of drug interactions (n=265)

Antibacterials	Shift						Total
	Morning		Afternoon		Night		
	Yes	No	Yes	No	Yes	No	
Medical clinic A							
Ciprofloxacin	2	6	0	0	0	10	18
Piperacillin + Tazobactam	4	4	4	7	1	10	30
Sulbactam + Ampicillin	3	7	5	6	2	6	29
Teicoplanin	3	6	0	0	0	0	9
Vancomycin	3	6	0	0	5	8	22
Total	15	29	9	13	8	34	108
Medical clinic B							
Cefepime	5	3	2	5	4	7	26
Ceftriaxone	12	0	0	5	1	3	21
Levofloxacin	0	3	0	1	0	0	4
Metronidazole	0	0	1	6	6	3	16
Oxacillin	2	4	1	4	5	8	24
Piperacillin + Tazobactam	8	2	0	4	6	1	21
Sulbactam + Ampicillin	2	5	0	1	0	0	8
Teicoplanin	9	0	0	0	0	7	16
Vancomycin	1	11	0	0	0	9	21
Total	39	28	4	26	22	38	157

It is important to note that 23 doses of Piperacillin + Tazobactam were administered combined with other medications, such as Lithium and Furosemide. Metronidazole and Teicoplanin also stood out in this aspect, with approximately half of the doses administered under potential drug interaction. The drug-drug interaction was the most frequent; concomitant administration with injectable anticoagulants, such as low molecular weight Sodium Heparin, and the association between cephalosporins with penicillins (oxacillin) were frequent.

Some drugs had printed guidelines about the administration available in the sector: in Clinic B, the guidelines for Piperacillin and Tazobactam were present, while in Clinic A, information was available about Teicoplanin, Sulbactam and Ampicillin.

Table 2 presents the data related to the drug interaction induced by scheduling associated with the existence of printed guidelines about administration in the sector. It is noteworthy that in Clinic B there was less availability of printed information and statistical association with greater number of scheduling that induced interactions (p=0,003).

Table 2 – Association between drug interaction induced by scheduling and availability of printed guidelines on antibacterial administration (n=265)

Drug interaction induced by scheduling	Availability of printed guidelines on antibacterial administration		Total	p*
	Yes	No		
Medical clinic A				
Yes	20	12	32	
No	39	37	76	0.286
Total	59	49	108	
Medical clinic B				
Yes	16	49	65	
No	7	85	92	0.003
Total	23	134	157	

*Chi-square test

Regarding the types of errors observed, the wrong choice of medication occurred in 29 (11.6%) preparations and dose errors occurred in 81 (32.5%), with a tendency to subdose. Regarding the time, the preparation time was prolonged in some situations, which may influence the pharmacological stability of the medicines and, therefore, configure an error.

Among the erroneously chosen drugs, the similarity in the names of the antibacterials may have generated some confusion or mistake in the selection of the drug to be prepared, such as those of the class of cephalosporins (Ceftriaxone, Cefemipe and Cefazolin).

As regards the preparation time of the medicatiob, Table 3 shows that the mean time ranged from 14

to 30 minutes. It was observed that Sulbactam, Ampicillin and Cefepime were the drugs with the highest preparation time, 60 and 72 minutes, respectively. While the highest mean, 30 minutes, was seen in Levofloxacin. On the other hand, a finding that requires attention was the minimum time of 4 minutes for the preparation of Piperacillin and Tazobactam in Clinic B.

Table 3 – Distribution of preparation time of antibacterials in Clinics A and B (n=265)

Antibacterials	Preparation time (minutes)							
	Medical clinic A				Medical clinic B			
	n	Mean	Minimum	Maximum	n	Mean	Minimum	Maximum
Ciprofloxacin	18	15	7	28	-	-	-	-
Piperacillin + tazobactam	30	21	10	44	21	17	4	34
Sulbactam + ampicillin	29	26	7	72	8	14	7	26
Teicoplanin	9	26	12	38	16	16	5	31
Vancomycin	22	14	5	48	21	18	6	33
Cefepime	-	-	-	-	26	22	7	60
Ceftriaxone	-	-	-	-	21	17	7	30
Levofloxacin	-	-	-	-	4	30	10	50
Metronidazole	-	-	-	-	16	22	10	31
Oxacillin	-	-	-	-	24	22	10	40

In situations where the preparation time was more than 30 minutes, the cause of the delay was the interruption to perform other activities.

Discussion

The present study presents as a limitation the investigation in a specific scenario, which may differ from the reality of other medical clinics. In addition, the data obtained refer to the scheduling and preparation of antibacterials, so that other pharmacological classes may have different results.

Antibiotics are often used to treat diseases related to bacterial infection due to the efficient action and clinical urgency of solubility. Drug interaction as a result of drug antagonism may weaken the antibiotic action, and ineffective treatment of infections may lead to worse prognosis and death of the patient[1,11]. In view of the use of multiple drugs in the hospital context, interactions may occur and impaired antibiotic efficacy may contribute to the development of bacterial resistance to antibiotics[12-13].

According to a study that analyzed 53 cultures for antibiogram of patients with hospital infection admitted in the Intensive Care Unit, the major bacterial resistances were related to cephalosporins and glycopeptides[5]. These classes corresponded to 43.4% of the antibacterials administered in the Medical Clinics investigated in this study. The wide use in the medical clinic, added with the bacterial resistance detected in another study, alerts the nursing staff to pay extra attention with the scheduling of such drugs.

International study results on errors in drug administration in an emergency unit confirm that incongruities in scheduling are the most common errors in this stage[14]. When considering that the administration schedule depends on the time invested in the drug preparation, the relevance of the results of this study, which point out the duration of 72 minutes in the preparation of some antibacterials, is highlighted.

Delay in the preparation can cause delay of the infusion, which is an error with serious consequences, since the prescription and the delay meet the need of maintaining the plasma levels for action of the medicine that consider its half-life and elimination. So, when these levels are not maintained by a new infusion, the microorganism can develop mechanisms of adaptation and become resistant to that active principle[2]. In addition, long-term preparation may promote environmental exposure of the drug and promote contamination of the devices used in the preparation and administration[15].

The types of errors included the wrong choice of drug and the dose errors. These types of errors are worrisome because there is a consensus for the indication of the antibacterial to occur according to the biological characteristics of the cell wall of the bacte-

rium, otherwise there may be considerable difficulty for penetration of the active principle into the microorganism. Thus, when there is wrong selection of the drug in the preparation or administration, the patient may be exposed to an ineffective and pharmacodynamically incompatible substance to that bacterium[13].

The frequency of dose errors found in this study coincides with that shown in a national assessment of 3,500 records of medication errors, of which 11.4% were dose errors[4]. In this case, the wrong dose of antimicrobial may compromise the bioavailability, efficacy and therapeutic effect of the active principle, culminating, in some cases, with potentiated toxicity and/or increased bacterial resistance.

It was observed that the unavailability of guidelines on the administration of medications was statistically related to the scheduling of drugs with drug interaction to be administered at the same time. Such a finding suggests that nurses responsible for scheduling tend not to make mistakes if written instructions are available, which raises awareness on the relevance of the availability of printed instructions on the subject for consultation of professionals.

In this context, it is relevant that such instructions have enough information to support safe use by nurses, which must include: name of the drug, route, indication, contraindication, presentation, dosage, dilution/reconstitution technique, stability, adverse reactions, infusion and potential drug interactions[16]. In addition, it is important to provide training and raise awareness of the professionals so that the use of the materials occurs correctly and they feel stimulated to adhere to the available resource[17].

The administrative and organizational structure of health institutions motivates the nursing staff to follow institutionally standardized schedules, and such standardization requires a lot of attention from the nurses responsible for the scheduling so that the possibility of potential drug interaction is considered in the drug scheduling of each patient[18]. In order to avoid drug interaction resulting from scheduling, we highlight the computerization of the medical prescription and nursing scheduling associated to some tool in the computerized system that prevents the scheduling of medicines with drug interaction for the same time as a strategy that can be effective.

We expect that this study may contribute to alert nursing professionals to the need to organize medication administration schedules taking into account pharmacokinetic and pharmacodynamic principles in order to guarantee greater effectiveness regarding the active principle used and to avoid interactions. In addition, the findings lead to a reflection on the need for the rational use of antimicrobials and, finally, it is a set of indicators that can support the planning of training and improvement in nursing education.

Conclusion

The potential drug interactions resulting from the scheduling of antibacterials together with another drug occurred with a higher prevalence in the morning shift (Piperacillin + Tazobactam administered in combination with Lithium and Furosemide, Metronidazole and Teicoplanin; and drug-drug interaction with injectable anticoagulants, and the association between cephalosporins and penicillins (oxacillin)), and were associated with the lack of availability of printed guidelines on drug administration in the sector. This way, the scheduling of antibacterials in the medical clinic sector may potentiate possible drug interactions, and dose errors are identified in the administration of drugs.

Collaborations

Pereira FGF contributed to the concept and design or analysis and interpretation of data. Melo GAA and Galindo Neto NM contributed to the essay writing and relevant critical review of intellectual content. Carvalho REFL, Néri EDR and Caetano JA contributed in the writing, critical review of the intellectual content and final approval of the version to be published.

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