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Original Article

Implications of antibacterial scheduling in newborns in clinical nursing practice

Implicações dos aprazamentos de antibacterianos em recém-nascidos na prática clínica do enfermeiro

Implicaciones de los aplazamientos de antibacterianos en recién nacidos en la práctica clínica del enfermero

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Objective: to identify drug associations related to the scheduling of antibiotics in the neonatal unit which may cause drug interactions. **Methods:** a retrospective documentary study using medical records of newborns admitted into the neonatal unit. The sample was composed of 92 newborn medical records. Data were collected through forms and presented in tables and figures. **Results:** associations in drug scheduling leading to pharmacokinetic interactions were found in 24 medical records, highlighting associations between amikacin and ampicillin, cefepime and furosemide, and vancomycin and furosemide. **Conclusion:** the scheduling of drugs at the same time represents a risk to newborn's health due to the possibility of drug interactions.
Descriptors: Infant, Newborn; Nursing; Anti-Bacterial Agents.

Objetivo: identificar associações de medicamentos relacionadas aos aprazamentos de antibióticos em unidade neonatal que podem acarretar interações medicamentosas. **Métodos:** estudo documental, retrospectivo, utilizando prontuários de recém-nascidos internados em unidade neonatal. Amostra composta por 92 prontuários de recém-nascidos. Dados coletados por meio de formulário e apresentados em tabelas e figuras. **Resultados:** foram encontradas em 24 prontuários associações nos aprazamentos, que acarretaram interações farmacocinéticas, destacando-se associações amicacina e ampicilina, cefepime e furosemida, vancomicina e furosemida. **Conclusão:** aprazamento de fármacos no mesmo horário representa risco de agravo à saúde do recém-nascido, pela possibilidade de interação medicamentosa.
Descritores: Recém-Nascido; Enfermagem; Antibacterianos.

Objetivo: identificar asociaciones de fármacos relacionados a los aplazamientos de antibióticos en unidad neonatal que pueden causar interacciones entre medicamentos. **Métodos**: estudio documental, retrospectivo, utilizándose registros médicos de recién nacidos ingresados en unidad neonatal. Muestra compuesta de 92 registros médicos de recién nacidos. Datos recogidos por medio de formulario y presentados en tablas y figuras. **Resultados**: se encontraron en 24 fichas asociaciones en los aplazamientos, que resultan en interacciones farmacocinéticas, especialmente amikacina y ampicilina, cefepima y furosemida, vancomicina y furosemida. **Conclusión**: aplazamiento de medicamentos al mismo tiempo representa riesgo de lesiones para salud del recién nacido, por la posibilidad de interacciones medicamentosa.
Descriptores: Recién Nacido; Enfermería; Antibacterianos.

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Introduction

The administration of medication requires nurses' knowledge and skills for the safe administration in newborns admitted into neonatal intensive care units, and for this reason medications are used in clinical practice in order to meet the needs of pathological processes, in particular infectious diseases requiring the use of antibiotics.

The combination of at least two antimicrobials with action spectrums against gram-positive and negative microorganisms is common in hospitalized newborns with a diagnosis of infection. These regimens are proposed by hospital infection control committees of the institutions after assessing the results of blood cultures.

The simultaneous administration of medications can alter their action by modifying their pharmacological effects or by changing the concentration. Thus, the use of multiple medicinal products represents a risk for the development of adverse reactions, such as the results of interactions and incompatible medications administered at the same time, which may cause imbalance in the hemodynamic status of newborns.

Medications may compete with each other for the same receptor when administered simultaneously, but only one can bind to a molecule at a time[1]. Therefore, nurses' knowledge regarding pharmacokinetic aspects that encompass the body`s actions due to medications is essential.

Organic alterations related to system maturation occur in newborns and infants in the first months of life. To minimize treatment complications, it is important to understand these physiological aspects. It is known that blood flow in newborns affects the regulation of drug absorption, pH variation of the gastric contents, distribution of total body water, plasma protein organization, reduction of cytochrome P450 enzymes and reduced glomerular filtration rates[2].

Moreover, one should consider medication pharmacokinetics in determining the scheduling of medicines, since they are influenced by the physiological processes in the first months of life. Thus, nurses need to have pharmacology knowledge to minimize the occurrence of adverse effects related to medication associations[3].

Advocating for newborn health is important in reducing child mortality in Brazil, which is still at high levels. Neonatal age is a very vulnerable period in the life of newborns because biological, environmental, socioeconomic and cultural risks are intensified and many comprehensive care actions are needed[4].

The use of antibacterials may cause potential complications early in life, being that all the child`s systems involved may not be completely mature, potentially resulting in acute renal failure, nephrotoxicity and ototoxicity[2-5]. Therefore, nurses have an important role in monitoring antibiotic therapy, since changes in drug scheduling can interfere with quality of care[6].

For appropriate therapeutic pharmacology knowledge, encompassing aspects related to drug type, actuation mechanisms in organic systems, knowledge of semiotics and physical examination techniques, and clinical evaluation of patient's health is crucial[7].

The administration of medication is an activity performed by nurses in health services; it begins with planning, preparation, administration and monitoring of side effects. Nursing technicians also prepare and administer drugs.

If not planned properly, the scheduling of medications can cause side effects. It is necessary for nurses to assess the drugs contained in the pharmacotherapeutic plan, demonstrate knowledge about related drugs and the variety and proper way of using the medications[8].

Antibacterials are the most used drugs in neonatal units, and their use requires care starting with the scheduling, as the organs in newborns which are responsible for absorption, distribution, metabolism and excretion of drugs are still immature.

Nurses must perform scheduling considering the pharmacokinetic aspects to minimize the risks that may be related to the administration.

The interest in conducting this study was based on observations made in the medical records of newborns who were in the neonatal unit. Antibacterials are frequently prescribed medications that require attention, starting with planning their scheduling up to their administration.

Given the above, this study aimed to identify the drug associations related to the scheduling of antibiotics in the neonatal unit which may induce medication interactions.

Method

This is a retrospective, descriptive and documentary study with a population consisting of 390 medical records of infants from zero to 28 days of age, who were admitted into the neonatal intensive care unit of a tertiary hospital in Fortaleza, Ceará. The period of data collection was from August to October 2010. The records were made available by the Service of Medical and Statistics Files of the institution.

The inclusion criterion consisted of the prescription of at least two antibiotics during the first week of hospitalization, regardless of gestational age. The association between antibiotics or between the antibiotic to another drug class was analyzed. Thus, the study consisted of a convenience sample of 92 medical records of newborns admitted to the neonatal intensive care unit.

The variables studied were: gestational age, weight, height, length of hospitalization, type of access (peripheral or central catheter peripherally inserted), type of antibacterial and scheduling time of drug administration. The selection of antibiotic regimens is determined by the Hospital Infection Control Commission, together with the recommendations provided by the Brazilian Society of Pediatrics.

An instrument designed by the researchers was used for data collection. The form was divided into two parts; the first consisting of the identification of the newborns, and the second on medication administration, type of antimicrobial, administration method and scheduling.

Interactions and incompatibilities were evaluated through literature and by Micromedex software, which features systematic review of clinical trials and drug information, such as the benefits, toxicity and interactions. The software is anchored on the periodical platform of the Higher Education Personnel Improvement Coordination (Coordenação de Aperfeiçoamento de Pessoal do Nível Superior).

Interactions were classified according to severity: contraindicated, when medications were contraindicated for concomitant use; serious when the interaction can cause risks to the patient's life and requires immediate medical intervention; moderate, when the interaction may result in exacerbation of the clinical condition of the patient or requires alteration to the therapy; light, when the interaction may have limited clinical effects, without demanding alterations in the drug therapy; and unknown when there is no definition to the degree of seriousness[1-2].

Data were organized in Microsoft Office Excel 2010 spreadsheets, then analyzed using descriptive statistics and presented in tables and figures.

The project was approved by the Ethics Committee from the General Hospital Research Fortaleza, according to the protocol 060810/09, in effecting Resolution No. 196/96, repealed by Resolution number 466/12, which points to the Guidelines and Norms Regulating Research Involving Beings Humans.

Results

Participants in the study of the neonatal intensive care units were more males (51-55.4%). The weight in 43 newborns (46.6%) ranged from 1501 to 2500 grams, the height for 53 (57.6%) of them was between 30-42 cm, and gestational age in 63 (68.5%) was between 32-37 weeks. Regarding length of

hospitalization, 36 (39.1%) remained in the neonatal intensive care units for more than 31 days. The most common type of access was the central catheter peripherally inserted in 59 (64.1%) newborns. There were more prescriptions without association of medication identified (68-74.0%) (Table 1).

Table 1 - Description of the characteristics of newborns participating in the study

Variables	n (%)	Mean±Standard Deviation
Gender		
Male	51 (55.4)	
Female	41 (44.6)	
Gestational age (weeks)		33 ± 3
24 – 31	16 (17.4)	
32 – 37	63 (68.5)	
38 – 40	13 (14.1)	
Weight (grams)		1.972 ± 791
500 – 1.500	30 (32.6)	
1.501 – 2.500	43 (46.6)	
> 2.501	19 (20.8)	
Height (centimeters)		42 ± 5
30 – 42	53 (57.6)	
43 – 56	39 (42.4)	
Duration of hospital stay (days)		30 ± 20
1 – 15	27 (29.3)	
16 – 30	29 (31.6)	
> 31	36 (39.1)	
Type of access*		
Peripherally inserted central cateter	59 (64.1)	
Umbilical access	42 (45.6)	
Peripheral access	19 (20.6)	
Drug schedule analyzed		
No associations	68(74.0)	
With associations	24 (26.0)	

*More than one type of access was considered

In Neonatology and Pediatrics, there is standardization for antimicrobial regimens to be used in infections. In the study, the first regimen of antibiotics considered was: penicillin (ampicillin and benzylpenicillin) and aminoglycoside (amikacin). The second regimen: penicillin (sodium piperacillin and tazobactam sodium in association with ureidopenicillin a β-lactamase inhibitor). The third regimen: glycopeptides (vancomycin and teicoplanin) associated with cephalosporins (cefepime). Other regimens: carbapenems (meropenem), quinolones (ciprofloxacin) and antibacterial (metronidazole). The result of the blood culture guides/directs the association of antimicrobials.

Table 2 - Description of antibacterial used in the treatment of newborns, according to gestational age.

Antibacterial	Gestational age			
	24 – 31	32 – 37	38 – 40	Total
	16 (17.4%)	63(68.4%)	13(14.2%)	92(100.0%)
Amikacin	14	54	13	81
Ampicillin	14	50	10	74
Piperacillin + tazobactam	8	34	7	49
Vancomycin	4	7	2	13
Meropenem	4	6	1	11
Cefepime	2	8	1	11
Crystalline penicillin	-	5	3	8
Teicoplanina	-	1	-	1
Ciprofloxacin	1	-	-	1
Metronidazole	-	1	-	1

The most frequently identified antibiotics for newborns with a gestational age of 32-37 weeks were amikacin, ampicillin and piperacillin + tazobactam (Table 2). These antibiotics are considered to be first and second regimens according to the guidelines of the Commission of Control and Hospital Infection of the institution.

In Figure 1, 24 medication associations administered at the same time were identified from a total of 97 doses. The antibacterial with the most associations was ampicillin, with 43 doses administered at the same time, and the association with ranitidine was the most frequent.

Association of antibiotics with other drugs	Nº of doses scheduled at the same time
Ampicillin x Ranitidine	18
Ampicillin x Dopamine	5
Ampicillin x Fentanyl	5
Ampicillin x Dipyrone	1
Amikacin x Ranitidine	3
Amikacin x Fentanyl	1
Meropenem x Furosemide	8
Meropenem x Ranitidine	2
Penicillin x Ranitidine	2
Piperacillin + tazobactam sodium x Ranitidine	17
Piperacillin + tazobactam sodium x Aminophylline	9
Piperacillin + tazobactam sodium x Dopamine	3
Piperacillin + tazobactam sodium x Fentanyl	3
Piperacillin + tazobactam sodium x Furosemide	1
Vancomycin x Phenobarbital	12
Vancomycin x Fentanyl	2
Vancomycin x Midazolam	1

Figure 1 - Description of antibiotic associations with other drugs administered at the same time that did not show any incompatibility

Three possible drug interactions were identified in Figure 2: amikacin and ampicillin, cefepime and furosemide, and vancomycin with and furosemide; and five physical incompatibilities characterized by precipitation and color change of the solution: amikacin and dobutamine, cefepime and phenytoin, piperacillin/tazobactam and dobutamine, aminophylline and vancomycin, and vancomycin and furosemide.

Association of antibiotics with other drugs	Nº of doses scheduled at the same time	Drug interaction/compatibility
Amikacin x Ampicillin	5	Incompatibility: aminoglycosides can be inactivated by penicillins.
Cefepime x Furosemide	7	Pharmacodynamic interaction (synergism): nephrotoxicity.
Vancomycin x Furosemide	10	Physical and chemical incompatibility: preciptation
Vancomycin x Aminophylline	2	Physical incompatibility: change of color the solution.
Ampicillin x dobutamine	5	Physical and chemical incompatibility: precipitation.
Piperacillin + tazobactam x dobutamine	1	Physical incompatibility: change of color to a milky solution.
Cefepime x phenytoin	1	Physical incompatibility: precipitation.

Figure 2 - Description of antibiotic associations with other drugs administered at the same time, and record of the most serious pharmacokinetic interactions found according to *Micromedex Solutions*

Discussion

The use of antibiotics in premature newborns is frequent, as their immunological immaturity favors the acquisition of infectious diseases. This therapy requires caution, due to complications related to antibiotics, such as multidrug-resistant microorganisms and side effects caused by this group of drugs.

The survival of premature newborns depends on invasive procedures such as assisted ventilation or oxygen supplementation within the first 24 hours, use of parenteral nutrition, and intravenous catheterization. Inadequate perinatal conditions favor hemodynamic changes and risk of neonatal sepsis. Nurses in the neonatal intensive care units are often the ones who notice the first signs and symptoms of infection since they are the professionals who care for newborns for a longer period of time[9].

Low birth weight and gestational age are

risk factors for nosocomial infections. Newborns are subjected to many invasive procedures during hospitalization, favoring the acquisition of hospital infection that culminates in long stays in neonatal units.

Neonatal intensive care units are closed spaces with immunocompromised newborns, patients with severe pathologies, undergoing invasive procedures and with long hospitalization, increasing the risk of acquiring and spreading multi-resistant agents. This group of patients stays longer in these units, increasing susceptibility to new infections with different micro-organisms, requiring the association of different classes of antibiotics for drug treatment.

A common practice in neonatal units is implanting catheters for venous access, and peripherally inserted central catheters are one of the most used in admitted newborns for the administration of antibiotics, other medications and parenteral solutions.

This type of catheter has many advantages, such as preserving the venous network, avoiding frequent venipuncture, thereby allowing less manipulation of newborns and ensuring less risk of complications[10].

Among central venous catheters, peripherally inserted central catheters are more cost-effective, have lower cost and less risk when compared to venous dissection. They can be inserted into/placed on the edge of the bed of the inpatient unit, being suitable for extreme intravenous treatments such as pH and osmolarity. After the procedure, a simple X-ray should be done to confirm its location. Medications and prescribed solutions are administered through these catheters[11].

Medications administered to newborns are mostly antibiotics, since newborns present a condition of clinical infections. Infections can come from the environment, the material used, the lack of proper hand hygiene of the professional multidisciplinary team who provide assistance or may have been acquired at birth.

Therefore, effective antibiotics for gram-positive and gram-negative micro-organisms are needed for treating neonatal infections. The organization of treatment schedules considers the potency of the product. The first line consists of an aminoglycoside and broad spectrum penicillin. The second line is usually an antipseudomonal penicillin. The third line are cephalosporins and glycopeptides[12]. The combination of several classes of antibiotics is common, and administered according to the needs of newborn, since certain antibiotics combat gram-negative or gram-positive bacteria.

Antibiotic administration requires rigorous time scheduling, as well as dilutions and intervals between doses, so that the effect of the maximum peak of action and the minimum level required for killing bacteria is achieved with therapy, making it effective in minimizing the selection of resistant organisms[2]. Thus, changes in antibacterial scheduling should be avoided.

Among drug associations evaluated in this study, amikacin and ampicillin stand out due to their higher frequency. Simultaneous administration of these drugs leads to physical and chemical incompatibility[13]. Thus, reconstitution into a single solution is not recommended, and to avoid administrations at the same time because of the risk of precipitation among the medications[14].

Regarding drug incompatibilities, the following associations with antibiotics were identified by determining physical characteristic incompatibilities with risk of precipitation and change of color: cefepime and phenytoin, piperacillin and dobutamine, aminophylline and vancomycin, and vancomycin and furosemide.

The instability of cefepime solution in combination with phenytoin was confirmed in a study with intravenous infusion solution[15]. Vancomycin solutions and their use in continuous infusion is safe for stability, but requires attention as to its incompatibility with other medicinal products (including all

β-lactams), requiring separate intravenous routes or appropriate procedures to prevent unauthorized contact[16]. When piperacillin+tazobactam and dobutamine are administered simultaneously, there may be physical-chemical incompatibility, resulting in a color change of the solution and organoleptic characteristics[17].

Procedures to prevent and address drug interactions are: patient monitoring, dose adjustments, exchange or suspension of one of the drugs, and change of administration times, among others. Thus, the detection of changes in the plasma concentration of the drugs, for example, leads to dose adjustment, replacement or interruption of medication, or other methods to prevent damage to the health of the patient[18].

Adverse reactions to antibiotics is not unusual, and in some cases can be quite severe; the overuse of antibiotics interferes in the diagnosis of potentially serious bacterial diseases, prevents the growth of agents in cultures, increases the cost of medical treatments, and promotes the growth and spread of bacterial strains resistant to antibiotics[19].

From searching the literature, there are not specifications on drug interactions, or an expected start time of the adverse effects related to this interaction. However, when two drugs are administered simultaneously, it is crucial to advise that the patient is properly monitored post-position in an intensive care unit[20].

By analyzing the scheduling of medication prescriptions, it is clear that nurses need to improve their knowledge regarding the clinical management of these drug interactions, as antibacterials are often used to treat infections in newborns.

Drug interactions can be minimized with the proper planning of schedules when there is concomitant use of other drugs. Therefore, one must consider the interval between doses, the type of venous catheter used, the route of administration, and the venous conditions of newborns. Administration of safer drugs requires from nurses broad view of context.

Therefore, it is necessary that nurses avoid scheduling drugs at the same times, since the concomitant administration increases the risk of interactions by altering drug pharmacokinetics. Careful administration of drugs provides better quality drug therapy for newborns.

Therefore, it is necessary to provide training directed to the area of drug therapy so that nurses carry out trials and appropriate clinical evaluations before simultaneous administration of certain medications. Knowledge of these interactions is of great importance so that it can prevent complications in the clinical picture of newborns.

Conclusion

Antibiotics are frequently prescribed for newborns in order to treat neonatal infections. Among the most popular drugs, penicillins and aminoglycosides are the first choice in these units.

Associations of antibiotics occur as a result of health problems of newborns, particularly premature infants, who are more susceptible to infections. The scheduling of drugs at the same time represents a risk to the health of newborns due to the possibility of drug interactions. In addition to antibiotics, other drugs are prescribed and administered by virtue of a complex clinical condition of these patients.

The scheduling of drugs at appropriate times is important to minimize drug interactions. This is a complex aspect in clinical practice since it is necessary to increase the knowledge of nurses in pharmacokinetics. So it is up to the nurse to schedule medication prescriptions based on the complexity presented.

As limitations of the study, we cite the lack of information in the records as the reasons for changes in the medication scheduling used in newborns.

Collaborations

Silva WM and Dodt RCM contributed to the project design, data collection, analysis and interpretation of data. Carvalho REFL, Nogueira AO, Farias LGO and Chaves EMC contributed to the design, drafting and final approval of the version to be published.

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