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Potential nutrient-drug interactions in pediatric patients from a University Hospital

Potenciais interações fármaco-nutriente em pacientes pediátricos de um Hospital Universitário

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ABSTRACT
The drug-nutrient interaction has aroused interest in research in the area of nutrition in order to avoid unwanted responses to nutritional therapy. In children, the failure to provide adequate nutrients can adversely affect both weight development and growth. To investigate the potential drug-nutrient interactions that occur in hospitalized pediatric patients. Descriptive and cross - sectional study with non - probabilistic sampling for convenience. The research was carried out by consulting the medical records and information of the nutrition service of the pediatrics sector of the University Hospital of the Federal University of Maranhão, in the Maternal and Child Unit, from August to November 2018. For the identification of potential interactions the website www.interacoesmedicamentosas.com.br and relevant scientific literature were used. A descriptive analysis of the results was performed, being presented by means of percentages and frequency distribution of the variables involved. The prescriptions of 76 patients were verified, with a mean of 28.3 ± 37.2 months. Of these, 50% were males. The mean number of prescriptions was 5.98. Among the 76 individuals, 60 (78.9%) observed possible interactions, and one patient presented five and four patients presented four. The results presented in this study reinforce the need for future research that may guide patient care aiming at the standardization of drug administration simultaneously to enteral nutrition to avoid drug-nutrient interactions in order to obtain the desired clinical results.
Keywords: Children. Drug Interactions. Nutrition Therapy.

RESUMO
A interação fármaco-nutriente tem despertado interesse em pesquisa na área da nutrição a fim de evitar respostas indesejadas à terapia nutricional. Em crianças, a falha em proporcionar adequados nutrientes, pode trazer prejuízos tanto sobre o desenvolvimento ponderal quanto sobre o crescimento. Investigar as potenciais interações fármaco-nutriente que ocorrem em pacientes pediátricos hospitalizados. Estudo descritivo e transversal com amostragem não probabilística por conveniência. A pesquisa foi realizada por meio de consulta ao prontuário e de informações do serviço de nutrição do setor de pediatria do Hospital Universitário da Universidade Federal do Maranhão, na Unidade Materno Infantil, no período de agosto a novembro de 2018. Para a identificação das potenciais interações foram utilizados o site de interações medicamentosas e a literatura científica pertinente e literatura científica pertinente. Foi realizada a análise descritiva dos resultados, sendo apresentados por meio de porcentagens e distribuição de frequência das variáveis envolvidas. Foram verificadas as prescrições de 76 pacientes, com média de 28,3 ± 37,2 meses. Destes, 50% eram do sexo masculino. A média de medicamentos prescritos por pessoa foi de5,98, configurando polifarmácia. Dentre os 76 indivíduos, em 60 (78,9%) foram observadas possíveis interações, sendo que um paciente apresentou cinco interações e quatro pacientes apresentaram quatro. Os resultados apresentados neste estudo reforçam a necessidade de pesquisasfuturas que poderão orientar a assistência ao paciente visando a padronização na administração de medicamentos simultaneamente à nutrição enteral para evitar interações fármaco-nutriente afim de se obter os resultados clínicos desejáveis.
Palavras-chave: Crianças. Interações de Medicamentos. Terapia Nutricional.

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INTRODUCTION

Drug-nutrient interaction is the modification of pharmacological or clinical response of a medication due to previous or simultaneous administration with a nutrient or the alteration of the nutrient activity because of previous or concurrent administration with a drug, involving pharmacokinetic and pharmacodynamic processes[1]. The nutrients may be food or dietary supplement components such as the ones used in enteral nutritional therapy. Therefore, interaction can occur when drugs and enteral nutrition are used concurrently[2,3].

Concerning classification, the drug-nutrient interactions can be divided into four types: I: Bio-inactivation; II: Absorption; III: Physiologic action and IV: Elimination, and patients receiving enteral feeding have a higher risk of presenting interactions types I and II. The interaction type I is the one given between drug and nutrient through biochemical or physical reactions. Type II interaction affects drug and nutrient absorption, administered by mouth or enteral, causing the increase or decrease of bioavailability[4,5].

The decrease in the anticoagulant effect of warfarin with diets rich in K vitamin can be pointed out as an example of interaction, increasing the risk of thromboembolic events and myocardial infarction; the decrease of antimicrobials absorption, such as tetracyclines and certain quinolones, due to the chelating effect with cations of the diet, which can also result in the development of bacterial resistance and complications arising from nutritional deficiencies caused by drugs[6].

This type of interaction has aroused interest in research on the field of nutrition aiming to avoid unwanted responses to nutritional and/or drug therapy; once such interactions can bring about some damage to patients, increasing their hospital stay or leading to modifications/adjustments of their drug therapy. In addition, there may be disorders in the nutritional status of patients, especially in the elderly, children or those undergoing chronic and prolonged treatments[7].

In infants and children, the fact that rapid growth rates are accompanied by marked changes in the development, function and composition of organs makes the failure to provide adequate nutrients in this period increase the likelihood of negative effects both on weight development and growth[7].

In addition to altering the pharmacological effect of the medication and compromising nutritional status, interactions can lead to obstruction of feeding tubes. These factors can impact the increase in morbidity and hospitalization time; as well as rising health costs[8].

Drug-food interactions are potentially critical, especially regarding the use of drugs with a low therapeutic index, and the number of studies investigating them is limited considering the number of drugs currently available[9,10]. In this context, the importance of identifying potential drug-nutrient interactions in hospitalized children through the analysis of medical and nutritional prescriptions is justified, corroborating for later interventions for the control, management, preventive measures and early identification of these possible interactions.

METHOD

This is a descriptive cross-sectional exploratory study with a quantitative approach with non-probability sampling for convenience. It was performed in the pediatrics sector of a public hospital - University Hospital of the Federal University of Maranhão, Maternal and Child Unit (HUMI).

Sampling consisted of all secondary data available in the medical records of children admitted to the pediatric sector at the University Maternal and Child Hospital from May to June 2018.

The study included patients admitted to the pediatric sector aged between 1 month and 10 years, who were submitted to some pharmacological treatment by any route of administration and received a complete enteral nutrition or infant formula via enteral route. Patients who were exclusively fed orally were excluded from the study.

Data were collected through analyzing medical records in the pediatrics unit as well as information regarding nutrition service about diet composition and administration times. Data concerning the pharmacologic treatment (drug, time and administration route) were collected in the medical prescriptions. The nutrition service provided patients' diets, as well as times and administration route.

Administration times of the diet and prescribed drugs were compared. The verification of potential drug-nutrient interactions was carried out through checking the database Micromedex®, Drug Interaction Checker (drugs.com) and Food and Drug Administration (fda.gov), and the website: www.interacoesmedicamentosas.com.br[11]. Regarding knowledge about the composition of diets, the nutrition fact sheet was consulted *in grams) containing information such as: energy value, amount of total fats, saturated fats, monounsaturated fats, proteins, carbohydrates, lactose, dietary fiber, vitamins (vitamin A, C, D, E, K, and others) and minerals (copper, chromium, manganese, zinc, among others). A descriptive analysis of the results was carried out, being presented by means of percentages and frequency distribution of the variables involved. Data were tabulated using Microsoft Excel 2010[12].

This research is in accordance with Resolution No. 466/2012 of the National Health Council and is approved by the Research Ethics Committee (CEP) of the Presidente Dutra University Hospital, of the Federal University of Maranhão, under the attached statement number 2,830. 354.

RESULTS

Seventy-six patients with a minimum age of one month and a maximum age of 120 months (10 years) were included in the study. Among them, 38 (50%) were male. Regarding the hospitalization sector, neurology prevailed with 22 (28.9%), followed by medical clinic with 27 (35.5%), surgical clinic 18 (18.4%), infectious and parasitic diseases (PID) 7 (9.2%) and ICU 6 (7.8%) (Table 1).

Table 1. Characterization of pediatric patients admitted to a referral hospital in São Luís (MA), Brazil, 2018

Variables	n	%
Gender		
Female	38	50
Male	38	50
Age (months)		
Minimum	1	11,8
Maximum	120	2,6
Mean	28,3±37,2	
Inpantient sector		
Neurology	22	28,9
Medical Clinic	27	35,5
Surgical Clinic	14	18,4
PID	7	7,8
ICU	6	9,2
Most frequent diagnosis		
Hydrocephalus	12	15,7
Heart disease	8	10,5
Biliary atresia	4	5,2
Brain tumor	3	3,9
Convulsive seizures	3	3,9
Cerebral palsy	3	3,9
Total prescribed drugs		
<5	34	44,7
5 a 10	37	48,7
>10	5	6,6

As for the children's diagnosis, the most frequent ones were hydrocephalus 12 (15.7%), heart disease 8 (10.5%), biliary atresia 4 (5.2%), brain tumor 3 (3.9%), seizures 3 (3.9%) and cerebral palsy 3 (3.9%). The diagnoses of esophageal atresia, respiratory failure, pneumonia, cow's milk protein allergy (CMPA) and liver disease were identified in 2 (2.6%) patients each.

The number of different types of drugs administered was 79 and the total number of drugs administered to all patients was 455. The minimum number of drugs prescribed per patient was 2 and the maximum number 16, being 5.98 per person on average, characterizing polypharmacy.

Among the study participants, 60 (78,9%) possible drug-nutrient interactions in children were verified, and there were 133 possible interactions, considering the fact that many drugs are repeated among participants. One patient presented five potential interactions concurrently and four patients presented four possible interactions.

The most frequent potential interactions, as well as the effects and recommendations are described in Table 2.

Table 2. Analysis of the possible interactions between nutrients and medications prescribed to pediatric patients hospitalized in a referral hospital in São Luís (MA), Brazil, 2018

(Continua)

Drugs	Nutrients	Effects	Recommendations	Nº of cases of possible interactions
Anti-ulcer medication				
Omeprazole	Enteral nutrition. Fe and B12*	The diet inactivates the drug because it increases stomach pH. Drug reduces the absorption of Fe and Vit B12*	Administer pills on an empty stomach, 30 to 60 minutes before breakfast. It may require supplementation of these nutrients with long-term use.*	28
Ranitidine				22
Anti-inflammatory				
Ibuprofen	Any food	Positive interaction with food, reduces irritation and risk of gastrointestinal bleeding.	Take with food	2
Diuretic				
Furosemide	Zn, Na, K, Ca, Mg, Cl, Vit B1	Depletes Zn, Na, K, Ca, Mg, Cl and Vit B.	Supplementation of these nutrients may be necessary. Administer before or after meals.	13
Spironolactone	Any food †	Positive interaction with food, increases absorption.†	Take with food to avoid GI irritation and increase absorption. †	
Carvedilol				3
Antibiotics				
Vancomycin	Enteral nutrition. Vitamin K and B12‡	The enteral nutrition reduces the bioavailability of this drug (slows down absorption). Affects microbiota reducing the availability of vitamin K and B12‡	Take one hour before or two hours after meals. Supplement pre and probiotics ‡	2
Cephalexin				2
Piperacillin and Meropenem				3
Ceftriaxone				6
Oxacillin				10
Psychotropic/ Tranquilizer				
Phenytoin	Enteral diet	Enteral nutrition reduces its absorption, and its serum level from 50 to 75%, consequently.	Interrupt the diet for 1 to 2 hours before and restart it 1 to 2 hours after administering the medication and wash the probe with 60 ml of water before and after. It can be crushed	9
Anticonvulsant				

(Conclusão)

Drugs	Nutrients	Effects	Recommendations	Nº of cases of possible interactions
Phenobarbital	Vit D, Ca, B12 and Folate	Deplets Vit D, Calcium, B12 and folate	You may need to supplement these nutrients with long-term use.	11
Glucocorticoid/ Immunosuppressants				
Methylprednisolone	Ca and Mg food‡	Deplets Ca and Mg	You may need to supplement these nutrients with long-term use.	4

* Pertinent to Omeprazole and Ranitidine

†Pertinent to Spironolactone and Carvedilol

‡Pertinent to all antibiotics.

DISCUSSION

Patients admitted to the University Hospital Maternal and Child Unit receive adequate feeding and medication for each case. However, as there is a great demand from patients, the possible interaction that may happen between enteral nutrition and administered drugs are not taken into account. Patients with prolonged hospital stay usually receive a high number of drugs, increasing the risk of drug-nutrient interactions. The number of prescribed drugs in patients in ICU, for instance, can vary from 11 to 13 drugs per day, enabling the risk of adverse events[13].

The presence of food in the digestive tract can reduce drug absorption. This alters gastric motility and gastrointestinal pH, and provides substances for chelating and adsorbing drugs and nutrients. Usually, when food is present in the stomach, medicines are absorbed more slowly; many times these interactions can often be avoided by taking the drug 1 hour before or 2 hours after ingestion. This is the appropriate management to avoid the interactions found with antibiotics, which had a high number in this study[14].

In the study by Reis et al.[15] and Rodrigues et al.[16], regarding gender, they identified a higher prevalence of female 61.6% and male 56%, respectively. In this study, the prevalence was 50% for both genders. For Rodrigues et al.[16] the main hospitalization sector was Neurology (26.7%), similarly to what was found in this research. This finding can be explained by the fact that most patients with neurological diseases have sequelae and do not eat orally, therefore receiving an enteral nutrition, which was an inclusion criterion in the present study.

In their research, Lisboa, Silva and Matos[17] found that there was no pause in feeding in 116 doses of medications that needed relative fasting as they presented possible interactions with the enteral nutrition, being the most prevalent captopril, warfarin, levothyroxine, digoxin and phenytoin. In this study it was found that there were 71 administrations of antibiotics and there was no pause between the administration of the medication and the infusion of the enteral nutrition in 30 of them. This way, these drugs absorption speed may have been reduced, also decreasing their half-life, that is the time taken for the plasma concentration of a drug in the body to be reduced by half. Such alteration can cause bacterial resistance, therapeutic failure and/or prolonged hospital stay.

In a study using 90 medical records of inpatients, antimicrobials had a significant frequency in relation to all interactions, with ceftriaxone standing out, with 41 possible interactions. In this study, the antibiotics that had the greatest number of interactions were Oxacillin, Ceftriaxone and Piperacycline. As antibiotics affect the intestinal microbiota and these bacteria are responsible for the synthesis of vitamin K and B12, there is a reduction in the availability of vitamins. So, as shown in Table 2, to minimize the losses resulting from the lack of these vitamins, it is necessary to supplement or administer diets that already contain probiotics and prebiotics[7].

Twenty-eight administrations of Omeprazole were found at the same time as the diet and 22 of Ranitidine. Guidance for anti-ulcers is fasting, at least 30 to 60 minutes before breakfast. Food increases the stomach pH and these drugs are inactivated at neutral pH. In addition, this medication reduces the absorption of Iron and Vitamin B12. Assessing the need for supplementation of these nutrients to prevent anemia and symptoms such as fatigue or numbness in the extremities of the lower and upper limbs, which are related to vitamin B12 deficiency[17].

Regarding diuretics, Furosemide was administered 13 times with the diet, when the recommendation is to take it before or after a meal. This medication leads to depletion of micronutrients such as zinc (Zn), sodium (Na^+), potassium (K^+), calcium (Ca^{+2}), magnesium (Mg^{+2}), chloride (Cl^-) and Vitamin B1, which can lead to changes in physiological functions due to their deficiency. Therefore, it is important to frequently analyze laboratory tests for these nutrients to assess the need for supplementation.

Moreira Reis et al.[3] investigated the prevalence of interactions in Intensive Care Units in 1,124 records, and identified that 320 were patients with 24 hours of hospitalization who were using enteral nutrition. Twenty patients (6.3%) presented drug-enteral nutrition interaction. In this study, only 6 (9.2%) children were admitted to the ICU, five were had polypharmacy and all of them had one to three possible interactions.

The practice of polypharmacy is directly related to maximizing the risk and severity of adverse drug reactions, medication errors, drug interactions and low adherence to treatment. It has also been associated with an increase in hospitalizations and mortality. Regarding mortality, the data are conflicting, since the reason for death is not necessarily the medication, and there are other reasons that explain what happened[18].

According to Péter et al.[2] the notification of adverse effects and drug-food interactions in clinical practice must be encouraged. Other strategies should include the development of protocols review, evaluation and information sharing between the pharmacy and nutrition service of hospitals. Furthermore, it is important to raise greater awareness among physicians about the potential interactions, for instance, integrating this topic into the continuing education plan.

Several actions to reduce the risk of interaction should be adopted in the clinical practice, such as pause of diet at the moment of drug administration, however, this interruption may cause lack of calories and nutrients supply, and reduction of the time of diet administration, which can lead to patient's intolerance to increased infused volume. Therefore, the team must evaluate the risk of each interaction and the necessity to interrupt the diet aiming at the best for the patient[13].

Limitations: This study reports the potential of drug and food interaction in a population of children assisted specifically at the University Hospital of the Federal University of Maranhão, Maternal and Child Unit (public hospital), thus not reflecting the reality of other Hospital Institutions that assist children in the Capital city São Luís/MA. Thus, these data cannot be extrapolated to the general population, although some results are in agreement with other research in this field. In addition, when a sample consists of selection procedures for the convenience of the participants, the representativeness of the results cannot be guaranteed in relation to the target population. However, the non-representativeness of the sample does not necessarily mean that the results are invalid, but it cannot be stated statistically.

Strengths: this study revealed an important number of potential drug-nutrient interactions in a university hospital, which deserves careful reflection by health professionals. When not detected, this phenomenon can trigger adverse reactions to medications, nutritional deficiencies, therapeutic failures, as well as increased hospital stay and health costs. Therefore, knowledge about these interactions effectively contributes to patient safety.

CONCLUSION

There was, therefore, a high rate of potential drug-nutrient interactions in the studied sample. Being more frequent with Anti-ulcer medications, Diu-

retics, Antibiotics and Anticonvulsants. Throughout the development of this study, issues were identified that would allow the development of other studies to broaden the understanding of the potential drug-nutrient interaction, or to seek confirmation of the results obtained, with higher sample number and locations (public and private hospital units) of data collections. In addition, the interprofessional analysis of these interactions could contribute to professional training/qualification and better patient care.

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