



## Revisión

# Interactions between drugs and drug-nutrient in enteral nutrition: A review based on evidences

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### Abstract

**Introduction:** Enteral nutrition (EN) provides calories, macronutrients and micronutrients in adequate quantity and quality to meet the patient's needs. Some drugs when crushed and diluted may have their properties altered, including the reduction of bioavailability causing the reduction of the serum concentration of the drug; tube obstruction; drug-drug interaction or drug-nutrient interaction.

**Methods:** The study was conducted through review of submitted articles in the databases of the Virtual Health Library (VHL): MEDLINE (National Library of Medicine, USA), Lilacs (Latin American and Caribbean Literature on Health Sciences) PUBMED - NCBI (National Center for Biotechnology Information) and COCHRANE.

**Results:** For this survey, 42 articles were identified during database searching. After applying the inclusion and exclusion criteria, 08 articles were selected, obtained from the MEDLINE and Lilacs.

**Discussion:** Some interactions were found such as the aluminium hydroxide and lactulose with the enteral nutrition, which may result in a precipitation and reduction of drug bioavailability. Mineral oil will alter the absorption of fat-soluble vitamins and reduces the tube light. Others results were found as phenytoin, warfarin, captopril and furosemide with enteral nutrition may reduce the maximum serum concentration.

**Conclusion:** Drug interactions are more common in day-to-day activities than health professionals may suppose. Knowledge on the matter may also assist in reducing cases of obstruction of tubes, through which enteral nutrition and medications are administered. Thus, the multidisciplinary team, acting together, may have more beneficial effects to the patient.

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Key words: *Enteral nutrition. Drug interactions. Food interactions. Food-drug interactions.*

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### INTERACCIONES ENTRE FÁRMACOS Y ENTRE FÁRMACOS Y NUTRIENTES EN LA NUTRICIÓN ENTERAL: UNA REVISIÓN BASADA EN EVIDENCIAS

#### Resumen

**Introducción:** La nutrición enteral (NE) aporta calorías, macronutrientes y micronutrientes en una cantidad y cualidad adecuada para cubrir las necesidades del paciente. Algunos fármacos, al ser aplastados y diluidos, pueden ver sus propiedades alteradas, incluyendo la reducción de su biodisponibilidad que da lugar a una reducción de la concentración sérica del medicamento, obstrucción de la sonda, interacción con otros fármacos o interacción entre el fármaco y los nutrientes.

**Métodos:** El estudio fue llevado a cabo mediante revisión de artículos enviados a las bases de datos de la Biblioteca virtual de la Salud (*Virtual Health Library -VHL*): MEDLINE (Biblioteca Nacional de Medicina, EE. UU.), Lilacs (Literatura Latino Americana en Ciencias de la Salud) PUBMED – Centro nacional para la información sobre biotecnología (*NCBI -National Center for Biotechnology Information*) y COCHRANE.

**Resultados:** Para este estudio, fueron identificados 42 artículos en la búsqueda en las bases de datos. Después de la aplicación de los criterios de inclusión y exclusión, se seleccionaron 08 artículos, procedentes de MEDLINE y de Lilacs.

**Debate:** Se encontraron ciertas interacciones como la del hidróxido de aluminio y lactulosa con la nutrición enteral, lo que podría dar lugar a una precipitación y reducción de la biodisponibilidad del fármaco. El aceite mineral altera la absorción de vitaminas liposolubles y reduce la luz del tubo digestivo. Se encontraron otros resultados como que la fenitoína, warfarina, captopril y furosemida con la nutrición enteral podrían reducir la máxima concentración sérica.

**Conclusión:** Las interacciones farmacológicas son más comunes en las actividades cotidianas de lo que los profesionales de la salud podrían suponer. El conocimiento de la materia también podría ayudar a reducir casos de obstrucción de las sondas que sirven para la nutrición enteral y también para la administración de medicación. Así, el equipo multidisciplinar, actuando en conjunto, resultaría una estrategia más beneficiosa para el paciente.

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Palabras clave: *Nutrición enteral. Interacciones farmacológicas. Interacciones de los alimentos. Interacciones entre fármacos y alimentos.*

## Introduction

Nutritional therapy constitutes a set of procedures aimed at maintaining or restoring the nutritional status of the patient by administering food artificially. The critically ill patient requires the use of nutritional therapy (enteral or parenteral), mainly to minimize the reduction of physiological stress and adverse effects of protein catabolism<sup>1,2</sup>.

Enteral nutrition (EN) is performed by means of a nasogastric tube or ostomies, through which calories and nutrients are provided in adequate quantity and quality, according to the patient's needs. This nutritional therapy is indicated when oral food intake is undesirable or insufficient to maintain the nutritional status, so as to prevent the patient from malnutrition process<sup>1-4</sup>. Enteral nutrition is regulated by Resolution 63/2000 of the Brazilian Health Surveillance Agency (ANVISA)<sup>1</sup>.

The medication administration by tubes is a common practice in the hospital routine, which should be taken into account in order to choose the best pharmaceutical form of drug administration or to select or the drugs which may be crushed, given the high incidence of patients who use multiple medications. Some drugs when crushed and diluted alter some of their effects, including the reduction of bioavailability causing the reduction of the serum concentration of the drug; tube obstruction; the drug-drug interaction when there are simultaneous administration of two or more drugs; or the drug-nutrient interaction<sup>5,6</sup>.

Insofar as changes occur, there may be an interference in the therapy proposed to the patient, since many drugs have pharmaceutical forms which permit a slow release in the body, or whose formulation is intended to be release in another portion of the gastrointestinal tract other than the stomach. Some drugs may alter the absorption of nutrients; even to the point of inhibiting the metabolic process of the latter, as well as the concomitant intake of food may affect the bioavailability of the drug through interactions<sup>6,7</sup>.

Aiming for the promotion of rational and safe use of medications concomitant to enteral and parenteral nutritional therapy, the formation of a multidisciplinary team of Nutritional Therapy (MTNT) became mandatory in Brazilian hospitals, composed mainly by nurse, pharmaceutical, physician, nutritionist, and other professionals<sup>1</sup>.

For the professional nurse, in the condition of responsible for the supervision and/or administration of drugs via enteral feeding tubes, it is important to hold knowledge about those interactions, conduct training with the team for the correct administration of drugs, provide protocols to be followed and thus support the decisions for a safe patient care<sup>8-10</sup>.

The objective of this study was to analyze clinically relevant possible interactions, between drugs and nutrients in enteral nutrition in order to increase safety and in the concomitant administration medications with nutritional therapy.

## Methods

The study was conducted through the review of submitted articles in the databases of the Virtual Health Library (VHL): MEDLINE (National Library of Medicine, USA), Lilacs (Latin American and Caribbean Literature on Health Sciences), PUBMED - NCBI (National Center for Biotechnology Information) and COCHRANE.

Health sciences descriptors were used - DECS and MeSH (Medical Subject Headings) in Portuguese: “*nutrição enteral*”, “*interações medicamentosas*”, “*interações medicamentos e interações medicamentos/alimento*”; in Spanish: “*nutrición enteral*”, “*interacciones medicamentosas*”, “*interacciones farmacológicas y interacciones entre medicamentos y alimentos*” and in English: “*enteral nutrition*”, “*drug interactions*”, “*drug/food interactions*”.

The inclusion criteria, included original and review articles related to medications use in hospitalized and/or household patients with enteral nutrition. Published articles from January 1990 to April 2013 with the following study designs were selected: literature review, prospective, retrospective, analytical and descriptive. Articles characterized as letters to the editor, reports or case series and sketches were excluded from the survey.

## Results

For this survey 42 articles were identified during database searching. After applying the inclusion and exclusion criteria, 08 articles were selected, obtained from the MEDLINE and Lilacs. These were about those topics: drug-drug interactions, drug nutrient interactions, changes that occur when a new item is added and the stability of enteral nutrition. Table 1 presents the selected studies emphasizing the reference, the method, the casuistry, if drugs were added the observed chemical interactions and the observed clinical results.

## Discussion

Studies about drug-nutrient and drug-drug interactions, have been growing in number and collaborating to increase effectiveness therapy. As REIS et al. 2010 showed in their study of descriptive nature, exploratory field with qualitative approach, in which the prescriptions of 24 hospitalized patients were analyzed, 62.5% used enteral nutrition for more than 10 days and 42% were using more than five drugs per day. The most commonly prescribed drugs were: mineral oil in liquid form; dimethicone, dipyrrone and paracetamol; in solid form: folic acid, pyrimethamine and sulfadiazine acid. Regarding to drugs which are administered concomitantly with enteral nutrition, the changes that occur are the following: (a) ciprofloxacin

- there is a reduction in the bioavailability of the drug, (b) chlorpromazine – there is precipitation and reduction in bioavailability of the drug, (c) phenytoin - the decrease in bioavailability is 50-75%, (d) aluminum hydroxide leads to the precipitation and reduction of the bioavailability of the drug, (e) lactulose - generates precipitated particles and reduction of absorption of nutrients, and (f) mineral oil – alters the absorption of fat-soluble vitamins, adheres to tube reducing the light even when washing with water there are no great results because they have different polarities. Omeprazole comes in capsule form and its release is gastric, and differentiated administration is required. The ferrous sulfate due to its viscosity may cause tube obstruction<sup>7</sup>.

The inclusion of interactions in the matter of drug administration and nutrition, motivate the management of recommendations for their effectiveness of the treatment proposed to the patient. Given this situation, the authors suggest some recommendations, such as to take into account the nutritional status of the patient, to avoid over or underestimation in nutrient retention and pay attention to the prescriptions, to prevent unexpected therapeutic response. With regard to medicines and nutrition, they advise stopping the administration of the diet one hour before and two hours after drug therapy to avoid the afore said changes, paying attention to the rhythm of dripping after restarting no as to administered the full volume and proposal energy<sup>7</sup>.

In vitro studies are conducted in order to promote greater confidentiality to what is already known on the clinical and laboratory evaluation. SILVA and LISBOA 2011, in their integrative literature review identified an in vitro study and clinical studies with warfarin, which showed the reduction in bioavailability of the drug when administered in conjunction with enteral nutrition. As recommendations, they suggest that attention to the possible risks in prescribing and administering medicines. The nurse, in the condition of responsible for the nursing staff, should be aware of these risks and always promote continuing education. Another study demonstrated the role of the pharmaceutical with the team evaluating the medical prescriptions, which resulted in the change of presentation of medicines, leading to decreased interactions and incompatibilities between drugs and enteral nutrition<sup>9</sup>.

SILVA et al. 2010, conducted a literature review, and selected seven out of 62 articles. The authors divided the drugs into three categories: antiepileptic drugs, antibiotics and anticoagulants. Among the antiepileptic drugs, there was the phenytoin whose serum levels are reduced when administered with enteral nutrition. In the antibiotics group, the moxifloxacin has its serum levels reduced by 5 % when crushed and administered by the tube, and by 12% when administered with nutrition; likewise, the ciprofloxacin reduces the maximum serum concentration, but the minimum serum concentration is similar intravenously. In the class of anti-

coagulants, in a study with warfarin, it was revealed that when there was no interruption of nutrition, INR (international normalized ratio - one of the parameters for evaluating the clotting) decreased by 73 % in comparison with the period nutrition was interrupted for the drug administration. It was suggested, therefore, enhancing the knowledge of the subject by the nursing staff and the proposition of management protocols ensuring an effective treatment<sup>11</sup>.

GORZONI et al. 2010, through their retrospective observational study where medical prescriptions of patients were analyzed, with the inclusion criteria of patients undergoing enteral nutrition for more than 48 hours and the objective of defining the prevalence in the use of drugs that are incompatible with the tube used in the feed. 57 patients were selected in use of feeding tubes, with an average of 5.7 drugs administered by this means per patient. The most commonly prescribed medications, but with contraindications to be crushed for their administration are: captopril, clonidine, digoxin, spironolactone, phenytoin, furosemide, haloperidol, midazolam, prednisone, propranolol, and ranitidine. The location of drug release also alters the desired effect, for example, the drugs which are prepared for action in the stomach are not suitable for the tubes whose distal end is located in the small intestine, since there is an increase of bioavailability of the drugs with extensive first-pass metabolism by the liver. The study proposes specific cares while administering because some medications when crushed may release airborne particles and intoxicate those who are manipulating them. It is also important not to mix medications in the same dilution and to wash the tube before and after the completion of the medication<sup>12</sup>.

LOPES et al. 2010, through an exploratory descriptive study of direct observational quantitative approach, conducted an analysis of the possible interactions between nutrients and drugs prescribed, through a list of medications with food, in order to make recommendations in their research. The intake of some drugs with food in some cases is recommended (for example, carvedilol, nifedipine, propranolol and diclofenac) but not in others, due to interferences both in the absorption of the drug as in the absorption of vitamins and minerals (for example, acetylsalicylic acid, omeprazole, ranitidine, mineral oil, aluminum hydroxide, spironolactone, laxatives and captopril). From the analysis performed in the study, a large number of interactions between foods and nutrients may be verified, which leads to an increase of interferences in the treatment or even an improvement in the therapeutic process, which requires the evaluation of each case individually.

SEHN et al. 2003 analyzed the prescriptions of patients of a hospital, in order to conduct the survey on drugs prescriptions and interactions. 81 varieties of drugs were found and 54 interactions were identified. From the prescriptions, 65 % had at least one potential drug interaction. The most frequent drug-drug inter-

actions were: furosemide / paracetamol, furosemide / captopril, dipyron / captopril, digoxin / metoclopramide, digoxin / captopril, digoxin / furosemide and acetylsalicylic acid / captopril. Regarding the serious interactions, were found: digoxin / amiodarone, digoxin / verapamil, furosemide / potassium chloride and sulfamethoxazole + trimethoprim / cyclosporine. Given those findings, the conclusion was in favor of the use of computer programs to identify the interactions and assess the profile of prescriptions, as well as in favor of the continuing education of professionals, which demonstrate being important to reduce the interactions<sup>14</sup>.

LIMA and CASSIANI 2009 conducted an exploratory descriptive study with cross-sectional design, by investigating the prescriptions of patients who were hospitalized for six or more days in an intensive care unit at the University Hospital of Ceará. 102 patients were included in the study, by meeting the inclusion criteria. Among the patients, those who received nine or more drugs in the first and sixth day of hospitalization showed a higher number of drug interactions. Midazolam was the most frequent drug among the potential interactions identified. Among the pair of drugs that interacted more, fentanyl and midazolam were the ones more frequently identified. Actions that can be taken in order to minimize those interactions are as follows: observe signs and symptoms, monitor therapy response, adjust the timing of medications and avoid the combination. It is also important that health professionals learn how to identify, classify, be acquainted with the clinical management, so that the interactions may be avoided<sup>15</sup>.

MARTINS et al. 2013, through their descriptive, exploratory and quantitative study, analyzed the prescriptions from three ICUs within one month. As a result, some of the drugs with restrictions to be administered by tube were highlighted: *amiodarone* – to be avoided due to lack of study, *atenolol* - reduces the drug absorption when administered with nutrition, *phenobarbital* – to be avoided due to lack of specific data on administration by tubes. *Hydrochlorothiazide* - with nutrition, there is a reduction in the drug absorption, *hydroxyurea* - cytostatic, care with the handler, *nifedipine retard* – it should not be crushed so that not to lose the slow release or block the tube, *nimodipine* - reduces absorption of the drug with the nutrient. The recommendations the study proposes are: interruption of nutrition one hour before and two hours after for administration of the drugs that have interaction with nutrition; readjustment of the infusion pump when it is paralyzed for total caloric intake, rinsing the tube before and after administering medications, and avoiding grinding the drugs that have toxic effects on handler<sup>17</sup>.

Most studies relate the interactions present between drugs and enteral nutrition. It is important to understand those interactions, because the enteral feedings are administered continuously in the most of the cases,

and during this process medications are administered via tube without paralyzing the process of dieting, which is one of the main reasons to conduct studies related to this topic. Studies that evaluate the preparation and administration of medication are insufficient. It was also observed that all selected studies were performed by Brazilian authors in hospitals in Brazil.

## Conclusion

From the evidence demonstrated in the chosen studies, it may be concluded that drug interactions are closer and more present in the day-to-day than health professionals could expect. The knowledge about this issue, especially when it comes to drugs that are given often to patients in such a hospital sector (ICU), is vital for the appropriate therapy to the patient and all staff involved in the process of nutritional therapy should be aware of the risks of interaction, from the time of prescription to the time of drug administration. Such knowledge may also assist in reducing cases of tube obstruction, through which enteral nutrition and medications are administered. Thus, the multidisciplinary team (doctor, nurse, pharmaceutical and nutritionist), acting together, may bring about more beneficial effects to the patient.

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## References

1. Marchini JS, Okano N, Cupo P, Passos NMRRS, Sakamoto LM, Filho AB. Nutrição parenteral – princípios gerais, formulários de prescrição e monitorização. *Medicina, Ribeirão Preto* 31: 62 – 72, jan./mar. 1998.
2. Kurihayashi AY, Caruso L, Soriano FG. Terapia nutricional parenteral em UTI: aplicação dos indicadores de qualidade. *O Mundo da Saúde*, São Paulo;33(4):480-487, 2009.
3. Souza FIS, Teske M, Sarni ROS. Nutrição parenteral no recém – nascido pré – termo: uma proposta de protocolo prático. *Rev Paul Pediatr* 26(3):278-89, 2008.
4. Vasconcelos MIL, Tirapegui J. Aspectos atuais na terapia nutricional de pacientes na Unidade de Terapia Intensiva (UTI). *Rev Bras de Cien Farmac* vol. 38, n. 1, jan/mar, 2002.
5. Hinrichsen SL, Vilela TAS, Lira MCC, Moura LCRV. Monitoramento do uso de medicamentos prescritos em uma unidade de terapia intensiva. *Rev enferm UERJ*, Rio de Janeiro, 17(2):159-64, abr/jun, 2009.
6. Zaban ALRS, Novaes MRCG. Perfil epidemiológico e aspectos econômicos da nutrição enteral domiciliar no Distrito Federal: uma análise histórica de 2000 a 2005. *Com. Ciências Saúde* 20(2):143-150, 2009.
7. Reis VGO, Cândido MF, Jesús RP, Mendes-Netto RS. Perfil de utilização de medicamentos administrados por sonda enteral en el hospital universitario. *Rev. Chil. Nutr* Vol. 37, nº 3, setembro, 2010.

8. Sánchez AIG, Almagro CGM, Aranzana MC, Continente AC, Hernández MAC. Atención farmacêutica em pacientes com nutrição enteral. *Farm. Hosp* 30:44-48, 2006.
9. Silva LD, Lisboa CD. Consequências da interação entre nutrição enteral e fármacos administrados por sondas: uma revisão integrativa. *Cogitare Enfermagem* Jan/Mar; 16(1):134-40, 2011.
10. Moura MRL, Reyes FGR. Interação fármaco-nutriente: uma revisão. *Rev. Nutr* Campinas, 15(2): 223-238, maio/ago., 2002.
11. Silva LD, Schutz V, Praça BFM, Santos MER. Interações fármaco – nutrição enteral: uma revisão para fundamentar o cuidado prestado pelo enfermeiro. *Rev. Enferm. UERJ* Rio de Janeiro, abr/jun; 18(2):304-10, 2010.
12. Gorzoni ML, Torre AD, Pires SL. Medicamentos e sondas de nutrição. *Rev. Assoc. Med. Bras* 56(1): 17-21, 2010.
13. Lopes EM, Carvalho RBN, Freitas RM. Análise das possíveis interações entre medicamentos e alimento/nutriente em pacientes hospitalizados. *Einstein* 8(3 Pt 1): 298-302, 2010.
14. Sehn R, Camargo AL, Heineck I, Ferreira MBC. Interações medicamentosas potenciais em prescrições de pacientes hospitalizados. *Infarma* v. 15, nº 9-10, set-out, 2003.
15. Lima REF, Cassiani SHB. Potencial drug interactions in intensive care patients at a teaching hospital. *Rev. Latino-am Enfermagem* 17(2), mar-abril, 2009.
16. Martins MR, Soares AQ, Modesto ACF, Carvalho RF, Melo VV, Duarte IP. Análise de medicamentos administrados por sonda em unidades de terapia intensiva em hospital de ensino. *Rev. Eletr. Enf* [Internet]. Jan/mar; 15(1):191-6, 2013. Available at: <http://dx.doi.org/10.5216/ree.v15i1.15848>.