

**DRUG-NUTRIENT INTERACTION IN OLDER ADULT PATIENTS USING
ENTERAL NUTRITION FROM AN INTENSIVE CARE UNIT OF A
UNIVERSITY HOSPITAL IN CENTRAL BRAZIL**

ABSTRACT

Drug-nutrient interaction is defined as changes in the pharmacodynamics or pharmacokinetics of the drug in relation to physical, chemical, physiological, or pathophysiological interactions between a drug and a nutrient.

Objective: To report the possible drug-nutrient interactions and identify the Subjective Global Assessment of older patients admitted to an intensive care unit using enteral nutrition.

Methods: This is an observational, descriptive, and retrospective study of non-probabilistic sampling of older patients at a University Hospital in the Central Region of Brazil. The possible interactions of drugs with nutrients were searched in the UpToDate software database with the risk classification of each possible interaction. **Results:** This study analysed the data of 50 older patients, comprising 29 (58%) males and 21 (42%) females. We identified 75 drugs that use the digestive tract, with 26 (34.66%) having the potential to interact according to the UpToDate software, totalling 47 types of interactions that were related to pharmacokinetics. Most of these interactions involved the food and/or nutrient reducing the therapeutic effect of the drug or the drug reducing the serum amount of the nutrient, totalling 24 (51.06%) types of interactions. The average number of interactions was higher in patients who died (1.5 ± 1.64) than in those who were discharged (1.19 ± 1.44); when statistically analysed through the t test (bilateral CI of 95%), it was possible to verify that there was no statistical difference between the samples, with a p-value >0.99 .

Conclusion: The study findings suggest that attention should be paid to the occurrence of possible drug-nutrient interactions, as their consequences may negatively impact the patient.

Keywords: pharmacovigilance; enteral nutrition; older adult health

INTRODUCTION

Hospital malnutrition in the older adults can reach up to 75% of cases, resulting in negative clinical and economic consequences. One instrument used to monitor hospital malnutrition is the Subjective Global Assessment (SGA), a questionnaire-based tool that was proposed and validated by Detsky et al [1,2].

Enteral nutritional therapy (ENT) is a strategy used to combat malnutrition, and its usage in addition to drugs can cause some complications, such as drug-nutrient interactions, which are defined as changes in the pharmacodynamics or pharmacokinetics of a drug due to physical, chemical, and physiological interactions between a drug and a nutrient. These interactions can change the effectiveness of both drug and nutrients, impact nutritional status, and interfere with the absorption of drugs and nutrients [3,4,5].

Interactions are classified into four types. Type I is bioactivation, which occurs through biochemical and physical reactions between substances. Type II affects absorption by impacting bioavailability through changing enzymatic functions via cytochrome P450 or transport mechanisms. Type III changes systemic or physiological disposition, leading to changes in drug or nutrient distribution. Type IV can cause changes in the elimination of drugs or nutrients [6].

After being absorbed, drugs and nutrients are simultaneously distributed throughout the body, and they compete for the same plasma proteins, with albumin being particularly highlighted. Older, critically ill patients who do not interrupt enteral nutrition for drug administration, as well as malnourished and obese individuals, are more susceptible to these interactions [7].

Knowledge about drug interactions can contribute to a safer therapeutic approach, allowing for early interventions with monitoring processes, screenings, protocols, and other practices that can be included in the hospital routine.

In light of this information, this study aims to report the possible interactions between drugs and nutrients and to identify the Subjective Global Assessment of older patients admitted to the intensive care unit with the use of enteral nutrition.

METHODS

This is an observational, descriptive, and retrospective study that used non-probabilistic sampling to collect sociodemographic and clinical data of older patients admitted to the intensive care unit of a University Hospital in the Central Region of Brazil from 2019 to 2020. The study was developed following the technical criteria defined by Resolution No. 466/2012 of the Health Council for the development of research in humans, and it was approved by the Ethics Committee of the Júlio Muller University Hospital (CEP-HUJM) with the approval number CAAE 5,214,651.

Due to the impossibility of obtaining the Informed Consent Form (ICF) from the older patients, the data were collected with the authorisation of the person in charge of the intensive care unit at the Júlio Müller University Hospital for the use and handling of electronically archived medical records. The project includes a waiver of the ICF.

We collected 50 medical records of patients, aged older than 60 years who were admitted to the intensive care unit and undergoing any pharmacological treatment with exclusive or non-exclusive enteral nutritional therapy. We excluded patients on a zero diet and those on enteral nutrition for less than 3 days of administration. The nutritional condition was assessed using the Subjective Global Assessment (SGA), which was proposed and validated by Detsky et al [2].

In the pharmacological treatment, the drugs administered via the digestive route were observed because it is the same route as food intake. This was done to identify possible interactions. The route of administration of the drugs was also considered, and in cases where drugs were administered via an enteral feeding tube, the pharmaceutical form in which they were presented was observed as well.

Furthermore, the following variables and relevant information were collected through the medical records: gender, age, length of hospital stay, drugs used, the Global Subjective Assessment (GSA) nutritional assessment tool, comorbidities, timing of initiation of enteral nutrition, length of hospitalisation, and final outcome.

After collecting the data, searches were conducted in the UpToDate[®] software database (Brazil, version 0.4.0 - 0.5.0 and its updates, 2022), which is an electronic clinical resource tool for healthcare professionals to describe and analyse possible interactions between drugs and food and/or nutrients. The aim was to provide safe and evidence-based answers. Access to the database was provided by the Brazilian Hospital Services Company (Ebserh).

The research on interactions through the software was conducted in the drug interactions tab. By adding the name of the desired drug to investigate, the system generates all possible drug interactions, not only between drugs, but also with medicinal plants, food, and/or nutrients. All interactions were supported by scientific evidence, with references at the end of each page. Furthermore, for each possible interaction, the software suggests the appropriate management for the patient for better outcomes.

One relevant data provided by the UpToDate[®] software was the risk classification of each possible interaction with suggested resolution, being classified as: low severity B: no action necessary; moderate severity C: monitor therapy; moderate severity X: avoid combination and higher severity; D: consider therapy modification.

The data analysis was performed using the Excel programme Microsoft[®] Office 2016 (USA) and OpenEpi (Andrew G. Dean and Kevin M. Sullivan, Atlanta, GA, USA), where the necessary statistical calculations, including mean, standard deviation, and t-test for some variables were performed.

RESULTS

We analysed the medical records of 50 patients. Most of the individuals were male, accounting for 58% (n=29), with a mean age of 68.27 ± 6.78 years. Among the female participants, who made up 42% of the sample (n=21), the mean age was 73.90 ± 9.97 years. Primary education was the predominant education level, accounting for 48.48% (n=16). Regarding comorbidities, we found that arterial hypertension was predominant among the individuals, accounting for 34.11% (n=29). In terms of hospitalisation duration, 48% (n=24) stayed in the ICU for more than 31 days. In terms of clinical outcome, 52% (n=26) were discharged to the general ward.

Regarding the timing of initiation of enteral nutrition, 36% (n=18) of patients took 8 or more days to begin the diet. This was followed by 28% (n=14) within the first 24 hours, 22% (n=11) between 2 to 3 days, and 14% (n=7) between 4 to 7 days.

Regarding the nutritional status of the older patients, a prevalence of 52% (n=26) of severe malnutrition was observed, followed by 26% (n=13) of patients with no reports in the medical records, and 22% (n=11) in moderate malnutrition.

Regarding the quantity of drugs offered during 3 days of enteral nutritional therapy, we found an average of 15.5 ± 5.03 drugs administered per day per individual. The most common method of administration was intravenous infusion at 63.10% (n=578), followed by subcutaneous administration at 10.59% (n=97), oral administration at 10.59% (n=97), enteral tube administration at 9.50% (n=87), inhalation at 5.79% (n=53), and rectal administration at 0.44% (n=4).

The physical form of drugs administered through enteral feeding tubes was predominantly in liquid form at 50% (n=44), followed by solid form at 31.82% (n=28), powder form at 3.41% (n=3), and not described in medical records at 14.77% (n=13).

Regarding the possibilities for drug-nutrient and/or food interactions, we found 75 drugs that use the digestive route. Out of these, 34.66% (n=26) were found to have the potential for interactions according to the UpToDate software, resulting in a total of 47 types of interactions (Table 1).

Table 1. Listing of some drugs that potentially interact with nutrients and/or food according to the UpToDate software and that were administered to older adults admitted to the Intensive Care Unit of a university hospital in Cuiabá - MT.

| ACETYL SALICYLIC ACID - ASPIRIN | | | |
|---|---|---|--|
| PHARMACOLOGICAL CLASS: Cardiovascular antiplatelets; Nonsteroidal anti-inflammatory. Salicylates. | | | |
| FOOD/NUTRIENT | POSSIBLE INTERACTIONS | MANAGEMENT | RISK CLASSIFICATION |
| Fish oil | It can enhance the antiplatelet effect of the drug. | Monitor patients for signs and symptoms of bleeding. | Moderate Gravity C: Monitor the therapy. |
| Vitamin E | It can enhance the antiplatelet effect of the drug. | Monitor patients for signs and symptoms of bleeding. | Moderate Gravity C: Monitor the therapy. |
| Vitamin C | Aspirin can decrease the serum concentration of Ascorbic Acid | This interaction was only demonstrated with doses of aspirin of 600 mg or more. | Low Gravity B: no action required. |
| HYDROCHLOROTHIAZIDE | | | |
| PHARMACOLOGICAL CLASS: Anti-hypertensive; Diuretic and Thiazide. | | | |
| FOOD/NUTRIENT | POSSIBLE INTERACTIONS | MANAGEMENT | RISK CLASSIFICATION |

| | | | |
|-----------------------|--|---|--|
| Vitamin D and Calcium | Possibility of increasing the hypercalcaemic effect. | Monitor evidence of calcium-related toxicities and its serum concentration, as well as the response to vitamin D in patients. | Moderate Gravity C: Monitor the therapy. |
| Papaya | Reduction in drug absorption. | No action required beyond standard care measures. | Low Gravity B: no action required. |

OMEPRAZOLE

PHARMACOLOGICAL CLASS: Proton Pump Inhibitor

| FOOD/NUTRIENT | POSSIBLE INTERACTIONS | MANAGEMENT | RISK CLASSIFICATION |
|---------------|-------------------------------|---|------------------------------------|
| Iron | Reduction in iron absorption. | No action required beyond standard care measures. | Low Gravity B: no action required. |

SIMVASTATIN

PHARMACOLOGICAL CLASS: Antilipemic Agent

| FOOD/NUTRIENT | POSSIBLE INTERACTIONS | MANAGEMENT | RISK CLASSIFICATION |
|------------------|---------------------------------------|-----------------------------------|--|
| Grapefruit juice | Increase in serum drug concentration. | Avoid consuming grapefruit juice. | Moderate Gravity X: Avoid combination. |

All possible interactions were related to pharmacokinetics, as they influence the absorption of substances. Among them, we observed that the majority occurred when food and/or nutrients reduced the therapeutic effect of the drug or when the drug reduced the serum concentration of the nutrient, totalling 51.06% (n=24) of the interactions.

Although the average number of interactions was higher in patients who died (1.5 ± 1.64) compared to patients who were discharged (1.19 ± 1.44), a t-test with a bilateral 95% confidence interval was conducted to statistically analyse the data showing that there was no significant difference between the samples, with a p-value > 0.99.

For the risk ratings of possible interactions, a prevalence of 40.42% (n=19) was observed for low severity B (no action required), followed by moderate severity C

(monitor therapy) at 36.17% (n=17), higher severity D (consider therapy modification) at 17.02% (n=8), and finally moderate severity X (avoid combination) at 6.38% (n=3).

DISCUSSION

Considering the data presented here, it is possible to observe that the occurrences of interactions may be correlated with nutritional status, due to a decrease in serum levels of certain nutrients and/or inefficiency in the therapeutic response of the drug. These factors can lead to negative outcomes and have an impact on the healthcare system.

When we analyse the findings critically, we find that males are the slight majority in the Intensive Care Unit (ICU). In the study by Roland et al (2021), which evaluated anthropometric parameters to predict mortality risk in older patients admitted to the ICU, we also observed a predominance of males in hospitalisation, similar to the present study. A likely explanation for these findings could be that the female population pays more attention to their own health compared to males [8].

In the study conducted by Bini et al (2018) at the University General Hospital of Cuiabá, which evaluated the length of stay of older patients in the ICU, the average length of stay was 13 days. This result was significantly lower compared to the length of stay in the present study. Despite having a similar population profile in terms of age range and hospital unit, there may be differences in the clinical profile and therapeutic approaches of the individuals [9].

When evaluating the timing of initiation of enteral nutrition (EN), a study conducted at the Regional Hospital of Mato Grosso do Sul found that 52.4% of hospitalised patients received early enteral nutrition within the first 24 hours of admission. This contrasts with the findings of the present study, where it was common for EN to initiate after 8 days or more. However, it is important to note that not all patients were fasting during this time, as they may have been receiving other forms of nutritional support until the initiation of EN [10].

Regarding the nutritional status, it was observed that more than half of the individuals were severely malnourished. This contrasts with the findings of Vargas et al. (2018), who evaluated the profile and nutritional status of hospitalised patients using

TNE and observed a diagnosis of severe malnutrition in only 24.24% of the sample. One possible explanation for this difference is that in Vargas' study, the population studied did not consist solely of older individuals. [11].

When investigating the prevalence of drug-nutrient interactions in hospitalised patients undergoing TNE (transnasal endoscopy), Kampa et al. (2020) found that 28.57% of the drugs had potential drug-nutrient interactions, which is a lower result compared to the present study. Although both studies used TNE, Kampa et al. did not solely focus on older individuals, which reinforces the hypothesis that older individuals have a higher chance of experiencing interactions [3].

Almeida and Genaro (2019), who also investigated drug-nutrient interactions but did not use software, observed that acetylsalicylic acid can reduce the absorption of vitamin K, B1, and folic acid, and that carbohydrates reduce the drug's absorption time. Hydrochlorothiazide, in turn, can have its absorption reduced by food, making it necessary to pause the diet before administering the drug. The difference in the scientific basis used in investigative methods may be the reason for the divergences in the information [12].

Regarding the interactions investigated in other studies that were not mentioned by UpToDate, a randomised clinical trial conducted in Spain evaluated the influence of food on the pharmacokinetic parameters of omeprazole, rabeprazole, and pantoprazole. It was observed that consuming food before taking omeprazole delayed the average Tmax of the drug by approximately 3 hours, reinforcing the recommendation to take it on an empty stomach [13].

This study has certain limitations. First, limitations were observed in data collection, as it relied on retrospective medical records, thereby using information that was not gathered by the researchers in real-time. Second, limitations were present in the potential annotations made by the software used. Therefore, these limitations can be overcome in future studies, that is, suggest the scope for future research in that field.

CONCLUSION

The study findings suggest that the occurrence of possible drug interactions deserves attention, as their consequences can negatively impact the patient outcome. We found that a large portion of the patients were severely malnourished, which increased

the risks for negative outcomes. In enteral nutrition, we can rely on concentrated formulas as a strategy to minimise the risks of malnutrition and unwanted interactions with drugs. This is because they allow for the provision of nutrients in a smaller volume, shorter infusion time, and more time between drug and nutritional intake.

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