

Article

Incompatibilities and Interactions Drugs-Artificial Enteral Nutrition in a Hospital Institution in Cartagena/Colombia

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Abstract: Artificial enteral nutrition (AEN) is defined as the delivery of nutrients through feeding tubes for special medical purposes. Patients usually suffer from chronic or critical illnesses and are generally polymedicated, which represents a high probability of interactions and incompatibilities with the AEN that can cause adverse events and loss of effectiveness of pharmacological treatment. This study aimed to determine the potential incompatibilities and drug-enteral nutrition interactions in patients hospitalized in a clinic in the city of Cartagena. A retrospective cross-sectional study design was used, in a sample of 218 patients with a stay of at least three days, who were prescribed at least five medications and AEN. The data was collected from medical records. The information was screened with the CheckTheMeds software, using the APPs: drug-interactionchecker and <https://www.rccc.eu/ppc/Drogas/DrogasxSNG.htm>. A prevalence of pharmaceutical type incompatibilities of 50% and physicochemical type of 31.65%, interactions of pharmacokinetic type 10.55% and physiological type of 6.42% was revealed. The adverse events identified were tube obstruction 54.78% (n=126), mobility disorders and/or gastric emptying disorders 22.61% (n=52), diarrhea 12.51% (n=29), mesenteric ischemia with 0.87% (n=2) and seizures 6.96% (n=16). The p and OR values were variable according to the interaction and/or incompatibility vs. adverse events. Drugs-AEN incompatibilities and interactions were frequent, which is why active pharmacovigilance is necessary to intervene in the safety, quality and cost-effectiveness of the care provided in the different care services.

Keywords: Incompatibility; interaction; enteral nutrition; complication

1. Introduction

Artificial enteral nutrition (AEN) is defined as the delivery of nutrients through feeding tubes for special medical purposes. It must be administered to patients with at least a partially functioning intestine, whose energy and nutrient needs cannot be met by regular intake (1). AEN is an active therapy that attenuates the body's metabolic response to stress and modulates the immune system. It is less expensive than parenteral nutrition and is preferred in most cases due to fewer complications and better patient outcomes, including hospital cost and length of stay (2). The beneficiaries are usually patients with chronic or critical illnesses who are going to be subjected to aggressive diagnostic and treatment techniques, not being possible, in most cases, to maintain an adequate supply of nutrients through oral feeding, with an imbalance between the contributions and nutritional requirements (3,4). Generally, hospitalized patients are polymedicated and this characteristic is important due to the probability of interactions between drugs and interactions with the AEN that can cause obstruction of the tube, loss of effectiveness of the pharmacological treatment, and incompatibility and appearance of adverse reactions or altered nutritional status (5). Therefore, the appearance of interactions between drugs and nutrients depends on the characteristics of the patient, the drug and the nutritional support, which often leads to the need to modify the pharmaceutical form for administration by tube or enterostomy, which could increase the risk of appearance of interactions (6). Interactions between drugs and AEN can occur quite frequently and are very present in daily clinical practice (7). On the contrary, health personnel are not often aware of this problem, possibly due to lack of knowledge (5,7). On the other hand, drug-AEN interactions and

incompatibilities can interfere with the quality and cost-effectiveness of care in the intensive care unit, so it is essential that the health team is aware of them (8). The administration of drugs and AEN represents a challenge for patient safety in hospitalization units, so this study is a starting point to monitor therapeutic response and, when necessary, adjust in nutritional or pharmacological therapy and to achieve desirable clinical results, identify interactions and incompatibilities and be able to develop action plans through pharmacovigilance and guarantee the efficacy of enteral and pharmacological therapy.

2. Materials and Methods

A retrospective cross-sectional study was carried out in a hospital institution of the III level of complexity in Cartagena/Colombia. Patients who were hospitalized between January 1, 2018, and January 1, 2019, were selected. Their medical records were reviewed, the data was recorded from the institution's management software, guaranteeing confidentiality. The Statement of Strengthening Reports of Observational Studies in Epidemiology (STROBE) was used to report the data. The sample size was 218, which was calculated based on the formula for a finite population, with a confidence level of 95% and a margin of error of 5%. Patients older than 18 years of either sex, hospitalized for any reason, with a stay of at least three days, with a prescription for at least five drugs consumed simultaneously during the study period and enteral nutrition administered through feeding tubes were included. Patients who received only parenteral nutrition formulations were excluded. The daily prescriptions were evaluated in search of potential drug-enteral nutrition interactions and incompatibilities, and the presence of a correlation between the potential interactions and incompatibilities with the identified adverse events was established. The information obtained was evaluated with the help of the CheckTheMeds v.3.6.4 program, the use of the APPs: drug-interactionchecker and <https://www.rccc.eu/ppc/Drogas/DrogasxSNG.htm>

2.1. Statistical Analysis

Data analysis was performed with the statistical package SPSS version 26. (IBM Corporation, Armonk, NY, USA). Descriptive statistics (frequencies, mean and standard deviations) were used to characterize the study sample. The prevalence of enteral nutrition medication interactions and incompatibilities was determined and a correlation analysis was performed using the χ^2 test. The odds ratio (OR) was calculated and a value of $p < 0.05$ was considered significant.

2.2. Ethical Considerations

The study was approved by the ethics committee of the hospital institution and was carried out in accordance with article 11 of the resolution of the Ministry of Health of Colombia No. 008430 of 1993. The management of the data obtained from the medical records was It will be carried out under strict reserve and confidentiality according to the provisions of Law 23 of 1981 of the Colombian Congress and Resolution 1995 of 1999 of the Ministry of Health.

3. Results

In the 218 patients, the average age was 75 ± 16.3 years, 44.03% ($n=96$) were men and 55.97% were women ($n=122$), who were hospitalized in different services such as , ICU (55.96%), intermediate care (27.06%) and general hospitalization (16.97%), with an average length of stay of 12.8 ± 7.47 days; the main causes of hospital admission were pulmonary disease (26.61%), cardiovascular disease (24;77%) and neurological disease (22.48%). Table 1 summarizes the characteristics of the sample.

Table 1. Characterization of the studied sample ($n=218$).

Variable		Measure
Gender	n (%)	218

	male	96 (44,03%)
	femenine	122 (55,97%)
Age	(years) (mean \pm SD)	75 \pm 16,3
Length of stay (days)	(media \pm DE)	12,8 \pm 7,47
stay service	n (%)	
	intensive care unit	122(55,96%)
	Intermediate care unit	59 (27,06%)
Diagnostic groups	hospitalization	37 (16,97%)
	n (%)	
	Pulmonary	58 (26,61%)
	Cardiovascular	54 (24,77%)
	Neurological	49 (22,48%)
	metabolic	33 (15,14%)
	Renal	12 (5,50%)
oncological	4 (1,83%)	
	miscellaneous diagnoses	8 (3,67%)

Normocaloric and Normoprotein Polymeric nutrition was the most administered to patients 49.08% (n=107), followed by special specific nutrition for diabetics 26.15% (n=57) and special specific nutrition for respiratory patients with a 22.94% (n=50). The total number of days of AEN administered was 2794 with an average of 12.82 days of nutrition per patient, being those categorized as oncological and miscellaneous diseases those that required longer nutritional administration time and the type of tube for administration the most used. was the orogastric tube (70.64%). Table 2 summarizes these findings.

Table 2. AEN administered according to diagnosis and type of tube

Diagnosis	Type of AEN n= 218					Type of tube			
	Specifies special (respiratory)	Specifies special (diabetes)	Specific special (kidney disease)	Normocaloric and Normoprotein polymeric	total, patients by diagnosis	days of AEN (mean)	Orogastric Tube	Nasogastric Tube	Gastrostomy Tube
Pulmonary	24	14	1	19	58	783 (13,5)	46	2	10
Neurological	7	10	1	31	49	646 (13,18)	32	0	17
Cardiovascular	5	6	2	41	54	586 (10,85)	35	8	8
metabolic	3	24	0	6	33	459 (13,9)	24	1	8
Renal	6	2	0	6	14	148 (10,57)	12	0	2
oncological	0	1	0	3	4	78 (19,5)	1	3	3
miscellaneous diagnoses	5	0	0	1	6	94(15,66)	4	2	0
total	50(22,94%)	57 (26,15%)	4 1,83%	107 49,08%	218	2794 (12,82)	154 (70,64%)	16 (7,34%)	48 (22;02%)

In the Check the Meds and drug-interactionchecker programs, different drug interactions were identified, which were classified as major severity (30.85%) and moderate severity (69.15%). Table 3 identifies the types of drug interactions. The most frequent being opioids/benzodiazepines (40.43%) and anticonvulsants/benzodiazepines (19.15%).

Table 3. Main drug interactions.

Major Gravity	n	%	Interaction type
Phenytoin/Midazolam	18	19,15	Inhibition
Fluconazole/Fentanyl	5	5,32	Induction
Metoclopramide/Haloperidol	3	3,19	Induction
Haloperidol/Fentanyl	2	2,13	Synergism
Clarithromycin/Fentanyl	1	1,06	Synergism
Subtotal	29	30,85	
Moderate Severity			
Fentanyl/Midazolam	38	40,43	Synergism
Omeprazole/Losartan	15	15,96	Induction
Fentanyl/Furosemide	10	10,64	Inhibition
Fentanyl/Morphine	2	2,13	Synergism
Subtotal	65	69,15	
Total	94	100	

built from Check the Meds and drug-interactionchecker.

With the use of the APP: <https://www.rccc.eu/ppc/Drogas/DrogasxSNG.htm>. 215 drug-AEN interactions and incompatibilities were identified. 50.70% corresponded to incompatibilities of a pharmaceutical type and 32.09% of a physical-chemical type. Among the interactions, it was found that 10.70% were pharmacokinetic, and 6.51% physiological. Among drug-AEN interactions and incompatibilities, the most frequent was omeprazole capsules (26.05%), followed by opioids (22.33%), which showed incompatibility of a pharmaceutical type, metoclopramide syrup 11.16%, which confirmed incompatibility of physicochemical type and erythromycin suspension 10.23% that showed interaction of physiological and pharmacokinetic type.

In the same way, the AEN that was most related to incompatibilities and/or interactions was the polymeric, normoprotein and normocaloric with a frequency of 38.60%, followed by the specific special AEN for diabetics and respiratory patients with 25.58% and 24.65% respectively. All these findings are summarized in Table 4.

Table 4: Drug-AEL interactions and incompatibilities

cases: 215	Incompatibility		Interaction				Nutrition	
	Physicochemical	Pharmaceutical	Physiological	Pharmacokinetics	Specifies special (respiratory)	Specifies special (diabetes)	Specific special (kidney disease)	Normocaloric and Normoprotein polymeric
Atorvastatin	10 (4,65%)	0	0	0	0	10	0	0
Metoclopramide solution	24 (11,16%)	0	0	0	6	10	0	8
Fluoxetine	0	2 (0,93%)	1 (0,47%)	1 (0,47%)	2	0	0	2
Omeprazole capsule	0	56 (26,05%)	0	0	15	12	9	20

Erythromycin suspension	0	0	11 (5,12%)	11 (5,12%)	13	0	0	9
Loperamide solution	0	0	1 (0,47%)	1 (0,47%)	0	0	0	1
Fluconazole	0	0	1 (0,47%)	1 (0,47%)	0	1	0	0
Opioids	0	48 (22,33%)	0	0	15	12	5	16
Cholinesterase Inhibitors	0	1	0	0	0	0	0	1
Phenytoin	17 (7,91%)	0	0	0	0	7	0	10
Phenobarbital	13 (6,05%)	0	0	0	0	1	0	12
Antipsychotics	0	0	0	7 (3,26%)	0	2	4	0
Prednisolone	1 (0,47%)	0	0	0	0	0	1	0
Spirolactone	0	2 (0,93%)	0	0	0	0	2	0
Levothyroxine	4 (1,86%)	0	0	0	0	0	0	4
Vasoactive	0	0	0	2(0,93%)	2	0	0	0
TOTAL	69 (32,09%)	109 (50,70%)	14 (6,51%)	23 (10,70%)	53 (24,65%)	55 (25,58%)	21 (9,77%)	83 (38,60%)

The prevalence of pharmaceutical incompatibilities was approximately 50% and physicochemical 31.65%; in the case of interactions, the pharmacokinetic type was 10.55% and the physiological type was approximately 6.42%. All these findings are summarized in Table 5.

Table 5: Prevalence of incompatibilities and interactions.

Type Incompatibility and Interaction	number of cases	Prevalence (%)
Physicochemical	69	31,65
Pharmaceutical	109	50
Physiological	14	6,42
Pharmacokinetics	23	10,55
n	218	

Adverse events related to incompatibilities and interactions identified were tube obstruction in 54.78% (n=126), mobility disorders and/or gastric emptying disorders in 22.61% (n=52), diarrhea 12.51% (n=29) identified mesenteric ischemia in 0.87% (n=2) and seizures in 6.96% (n=16) as an important finding. Summary of adverse events in Table 6.

Table 6: Adverse events / AEN.

Adverse events						
tube obstruction	Diarrhea	Abdominal pain	Decreased motility or rate of emptying	seizures	hypokalemia	mesenteric ischemia*
126 (54,78%)	29 (12,61%)	3 (1,3%)	52 (22,61%)	16 (6,96%)	2 (0,87%)	2 (0,87%)

*Deceased patients.

Correlation analysis and risk analysis revealed (Table 8). that there is a statistically significant correlation between drug administration incompatibilities and interactions/AEN with adverse events. See Table 7.

Table 7: Correlation Analysis: Interactions and Incompatibilities / Adverse Events

EVENTO	Fisicoquímica		Farmacéutica		Fisiológica		Farmacocinética	
	P	OR	P	OR	P	OR	P	OR
Obstrucción de sonda	<0.001	2.614	<0.001	6.841			<0.001	0.062
Diarrea	0.026	0.305	0.032	0.409	<0.001	24.342	<0.001	45.292
Dolor Abdominal							<0.001	0.857
Disminución de la motilidad o velocidad de vaciado			<0.001	16.180				
Convulsiones	<0.001	0.768						
Hipokalemia							0.052	9.800
isquemia mesentérica							<0.001	0.905

4. Discussion

AEN is an increasingly widespread technique when nutritional support for critically ill patients is considered (9). One of the non-nutritional purposes of its use is to maintain the integrity and function of the intestinal barrier (10). Despite the above, there are still several complications with AEN that, due to their frequency, need to be identified and minimized, especially those that are related to the administration of drugs-AEN when the route of administration of ambassadors is through catheters (10,11).

In this study, the sample corresponded to older adult patients who required AEN due to being hospitalized in different services and who mainly presented diseases of pulmonary origin, cardiovascular and neurological disease, all of whom had been assessed by a clinical nutritionist who previously determined the need for AEN and ruled out the absolute contraindications of these. According to authors such as Artiga, Moragas et al; Whenever AEN is administered, a fundamental requirement is the existence of a functioning digestive system and bearing in mind the absolute contraindications (12,13).

The polymeric, normocaloric and normoprotein type AEN and those specific for diabetics and respiratory pathologies were the most supplied, which allows us to infer that 49.08% of the patients in the sample required volume restriction, as it is in cases of renal insufficiency or decompensated liver cirrhosis or heart failure, this is related to the findings in Table 1 where 24.77% of patients have cardiovascular disease and 5.5% kidney disease and it should also be taken into account that when choosing this type of formulas it is important to verify the metabolic status and the presence of other pathologies as indicated by the ESPEN guide (11). When considering the number of days of nutrition, it is notable that the patients categorized as oncological and miscellaneous diseases were the ones that required the longest time of nutritional administration with averages that could indicate a greater degree of clinical compromise.

Authors such as Magnuson and Beckwith point out the importance of clinical nutritional evaluation depending on the underlying disease both for the selection of the formula, type of tube and medications to be administered to avoid or reduce the risk of incompatibilities and interactions in severely compromised patients where the administration of AEN and medications through tubes is the only option (14,15).

In this study, the most prescribed medications were antibiotics, antihypertensives, proton pump inhibitors, opioids and anticoagulants, which, when analyzed in the program and APP used, drug interactions were found, which is of clinical importance considering that these were both of major severity and of moderate severity, an aspect that coincides with the study carried out in Colombia by Hernández, Tribiño et al, who point out that in intensive care units, interactions of moderate severity are common, followed by those of greater severity, being the most frequent. frequent: opioid/benzodiazepine, classified as a pharmacodynamic interaction with a synergistic effect (16). The foregoing

is also pointed out by Erazo and Gómez et al, who state that pharmacodynamic interactions represent 71.8% of the total interactions that occur in adult hospitalization services, the most frequent being those of synergism with potentiation and they recommend to the institutions that establish control measures (17). However, the previous authors do not say anything about drug-AEN interactions.

In this study in relation to drug-AEN interactions and incompatibilities, it was found that omeprazole capsules and opioids showed pharmaceutical incompatibility. Syrup metoclopramide showed physicochemical incompatibility, erythromycin suspension showed physiological type interaction and anticonvulsants such as phenytoin and phenobarbital showed physicochemical incompatibility and likewise the most frequent AEN related to incompatibilities and/or interactions was polymeric type, normoproteic and normocaloric.

In accordance with the above finding, authors such as Boullata and Sack point out that in the studies carried out on the compatibility of enteral nutrition products with drugs, the factors related to enteral nutrition (type and concentration of protein, mineral and fiber content of the formulation) and drug-related characteristics (such as pH, viscosity, osmolarity, and mineral content of the drug solution) are considered factors causing incompatibility, and only a few studies evaluate the stability of enteral nutrition and those evaluations they are often limited only to visual inspection and changes in chemical (such as pH) or physical (such as osmolarity) properties (18,19).

Moreira et al; highlight that the most frequent drug-AEN interactions were phenytoin-AEN, levothyroxine-AEN, warfarin-AEN and affirm that these interactions can interfere with the quality of care in hospital services, especially in the intensive care, so it is essential that the team of health is aware of it (8). Although the most frequent incompatibility was associated with the use of omeprazole capsules, the studies related to this are only limited to tube obstruction, while drugs such as phenytoin have been extensively studied in terms of compatibility and interactions with enteral nutrition preparations. ; thus, for example, Bauer studied 20 neurosurgical patients to whom a phenytoin suspension was being administered and observed that the plasma levels of the drug were lower (70-80% reductions) when it was administered with enteral nutrition, although they increased when the suspension was administered. Nutrition administration was interrupted 2 hours before and up to 2 hours after drug administration (20). Other authors point out that those formulas with a high protein content show an important interaction with phenytoin, so this interaction can seriously compromise its therapeutic action (21).

In this study, the prevalence of drug-AEN interactions and incompatibilities was higher for those of a pharmaceutical and physicochemical type and lower for interactions of a pharmacokinetic and physiological type. When contrasted with the literature, it is found that Moreira determines a prevalence between 6.6 % - 7.6% of possible drug-enteral nutrition interactions but does not establish the differentiation shown here (8). Regarding the related adverse events, the most common were tube obstruction, mobility disorders and/or gastric emptying disorders, diarrhea, and mesenteric ischemia and the development of seizures stand out as important data.

In the medical literature, the identification of possible complications and/or adverse events is highly relevant for clinical decision-making and the generation of management protocols and guidelines, for example, Boullata et. al, describes that the addition of drugs to enteral nutrition bags can cause tube occlusion, changes in the bioavailability of the nutrient or drug, or alteration of gastrointestinal function due to interactions of the drug with the enteral product and found that 23 of 24 different drug mixtures and incompatible enteral products resulted in tube occlusion (18).

On the other hand, sufficient gastrointestinal blood flow is required for the absorption and utilization of nutrition. Therefore, authors such as Galindo and Monares, supported by the ASPEN and ESPEN guidelines, warn that mesenteric ischemia and, on rare occasions, intestinal necrosis may occur. which has a high risk of mortality and therefore AEN administration should be avoided in patients requiring vasoactive agents (22). It is important to highlight that within the relevant data of this study, two cases of mesenteric

ischemia were presented, but the limitations of this study do not allow establishing that this condition is due, and it is left to the institution where this study was carried out to do the analysis of these cases.

Diarrhea is one of the most common manifestations that can occur in up to 45% and is produced by enteral nutrition products or for various reasons, such as sorbitol, and that can alter the absorption of the drug for the purposes of this study. this manifestation also it was among those commonly identified as well as gastric emptying alterations, which is related to what is reported in the literature (23). The development of diarrhea both in the case where there are incompatibilities and interactions can have statistical significance with p values less than 0.05 and, as referred to in the literature by authors such as Prieto and Navas, who show that this is one of the manifestations more frequent in patients treated in intensive care, who receive AEN with an incidence that varies between 5%-64%, and as expected, these patients are polymedicated in relation to the severity of their pathologies and comorbidities (24). However, it is very difficult to categorically state the relationship between the use of AEN and the appearance of diarrhea despite the statistical data shown here; because a strict follow-up would be needed, and this study is retrospective.

Regarding the presence of convulsions, these could be related to the phenomenon of physical-chemical incompatibility of phenytoin already explained, of which it has also been shown that the level of phenytoin in the blood is reduced by 72% when administered through of the feeding tube, but unfortunately for this work the measurement of serum levels was not contemplated within the methodology.

Regarding the other adverse events found, there are multiple studies that show the presence of these when AEL and medications are administered simultaneously, however, all of them carry out descriptive analyzes such as Sainz and Montejo where they describe the presence of gastrointestinal complications of enteral nutrition (9,25), the most frequent being those found and described in this article. However, Wanden-Berghe et al in 2019 determined the association between the administration modality of NEA and the presence of adverse events and although it was a study carried out in patients with home care, it is of great value because it is one of the few prospective multicenter studies and where it was shown that gastrointestinal events were the most frequent, but an adequate choice of the formula, route, feeding modality, number of doses, administration time and the volume of intake can greatly reduce the appearance of these, as well reports that specific modalities of AEN and use of nasogastric tube results in a lower risk of diarrhea compared to percutaneous endoscopic gastrostomy (OR = 0.4), but results in a higher risk of tube obstruction (OR = 7.4).). The other events had OR less than 1 (26). Although this study does not relate to the use of medications, it is considered a starting point for inferential statistical analysis.

Lastly, manifestations such as seizures and hypokalemia, the studies referred to carry out descriptive analyses here only, which indicates that it is necessary to continue conducting studies in hospitalized patients and undertake pharmacovigilance and continuing education actions for medical and paramedical personnel to avoid possible complications in patients.

5. Conclusions

From this study it is highlighted that there is a high prevalence between the interactions and incompatibilities identified due to the administration of NEA with some drugs and in the same way the correlated adverse events are identified, however it is not possible to offer accurate statistical conclusions because it was only carried out in a single health institution in addition to being a retrospective review of cases, but this can constitute a basis for conducting prospective pharmacovigilance studies that allow intervention in terms of safety, quality and cost-effectiveness of care provided to patients. patients hospitalized in the different care services in the city.

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