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Pharmacological Interactions in Patients with Epileptic Crisis Hospitalized in a Public Institution

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ABSTRACT

Objective: The present study was carried out to evaluate the potential pharmacological interactions in a group of adult hospitalized patients due to an epileptic crisis.

Methodology: Descriptive-analytical study. Data was obtained from medical records of hospitalized patients during the investigation period.

Results: 937 patients were enrolled in the study, 143 different drug interactions were detected in 35 patients, which involved 46 medicines administered. The interactions were classified according to their theoretical relevance in serious (18.88%), significant (51.04%) and minor (30.07%). 48.57% of patients presented drug interactions with nutrients.

Conclusion: The intervention of a multidisciplinary team is necessary for the management of these patients, which includes nutritionists specially trained in aspects of pharmacokinetics and pharmacodynamics, in order to minimize the incidence of pharmacological interactions.

Keywords: Pharmacological interactions, Nutrients, Hospitalization

INTRODUCTION

The term drug interactions (DI) refer to a clinical situation in which the action of a drug is altered by the presence of another drug or food, with neutral, beneficial or malefic consequences [1]. The risk of its occurrence and severity is due to factors related to the patient, the medicines themselves and the medical prescription [2]; they can end either in a therapeutic failure or in the appearance of adverse effects. There are some illnesses that due to their characteristics or type of medications used have a higher risk of interactions. This is the case of patients diagnosed with epilepsy. Epilepsy is one of the most common neurological diseases, with more than 50 million people affected around the world and of which about 80% come from developing regions. It is estimated that about 5 million people suffer from the disease in Latin America and the Caribbean countries [3]. Epilepsy is characterized by recurrent seizures, which are brief episodes of involuntary movements that can affect a part of the body (partial seizures) or its entirety (generalized seizures) and are some cases accompanied by loss of consciousness. Pharmacological treatment for epilepsy manages to control epileptic seizures in up to 70% of patients, some of them severe that need hospital admission [3].

The objective of this work is to identify the possible drug interactions in hospitalized patients due to epileptic seizures; in order to optimize their health care.

MATERIALS AND METHODS

Type of study

Descriptive-analytical, retrospective study.

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Institution

The present work was developed in a Public Hospital Specialized in Burns, located in the city of Asunción, Republic of Paraguay.

Population

Adult patients >18 years hospitalized for burn injuries for more than 48 h as a result of epileptic seizures, who entered the boarding school unit in the period from January 2015 to December 2017.

Data collection instrument

Review of medical records of hospitalized patients. Pharmaceutical records of dispense record.

Instrument for identification and classification of interactions: Medscape Interaction Checker (WebMD, LLC).

Variables

Date of admission, date of discharge, age, sex, origin, number, type, dose of medicines dispensed and type of administration, type of food and nutritional supplements administered and type of intake.

STATISTICAL ANALYSIS

The statistical analysis was performed with the EPI INFO statistical software, each variable was coded for the programme management, with its description and its categories. This software allows expressing the results in frequency and percentage of each study variable.

ETHICAL ASPECTS

This work was carried out according to international standards for biomedical research in human beings proposed by the Council of International Organizations of Medical Sciences (CIOMS) where the confidentiality of data obtained from patient records is respected, for this; the project was presented to the Research Ethics Committee of the Faculty of Chemical Sciences, National University of Asuncion (UNA) Paraguay Republic and each patient was asked to sign an informed consent for this purpose.

RESULTS

A total of 937 adult patients entered the Burns boarding room unit during the study period, 35 patients of whom suffered burns due to epileptic seizures, which represent 3.73% of all admissions. 62.86% of the patients belong to the female sex. The age range is between 18 to 74 years, with an average of 40 years and a standard deviation of 16.5. 65.71% of patients come from rural areas **(Table 1)**.

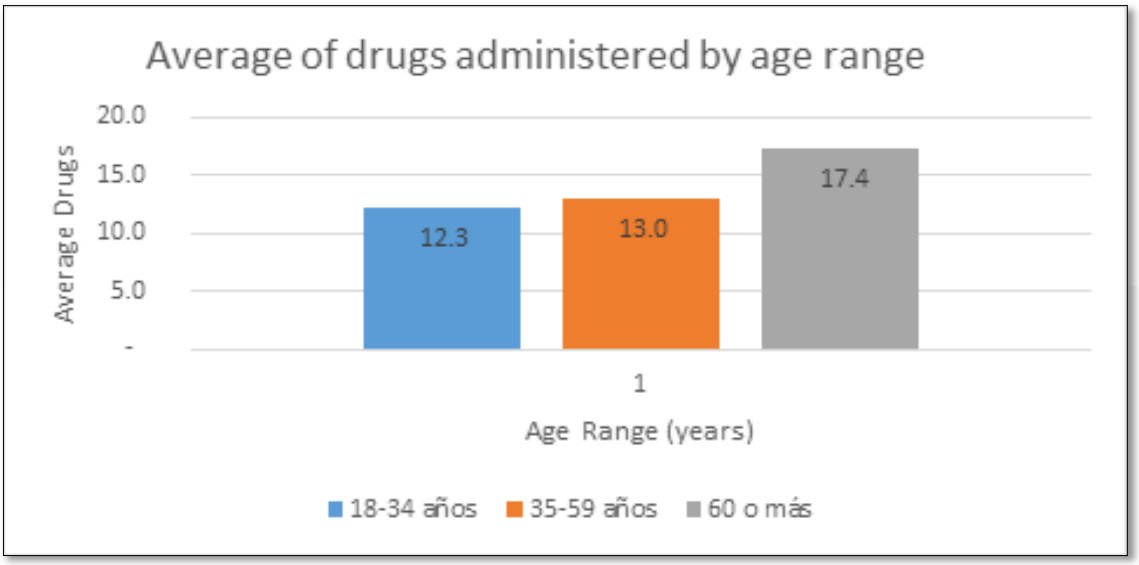
Table 1. Characteristics of the patients included in the study.

	Variables	Frequency	Percentage
GENDER	Male	13/35	37,14%
	Female	22/35	62,86%
AGE (YEARS)	18-34	12/35	34,29%
	35-59	18/35	51,43%
	60 or more	5/35	14,29%
CITY	Urban versus Rural	12/35	34,29%
	Other	23/35	65,71%

The administration of registered and dispensed medicines allowed us to identify that the patients enrolled in the study received between 5 and 28 medications throughout the day of hospitalization (29 ± 8), with an average of 12 medicines per patient **(Figure 1)**.

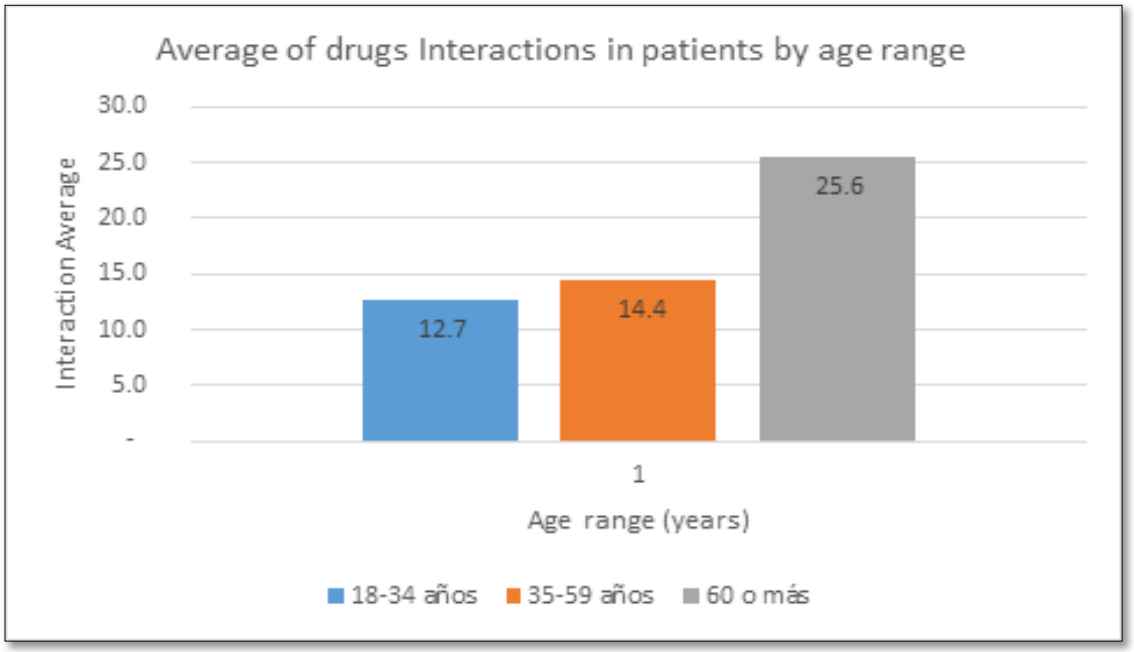
It was found that patients with ages over 60 years have a tendency to receive a greater quantity of medicines **(Figure 2)**, which is directly related to the risk of possible pharmacological interactions in patients with that age range.

Figure 1. Distribution of the average of medicines administered according to the age range of the patients.



It was found that patients with ages over 60 years have a tendency to receive a greater quantity of medicines **(Figure 2)**, which is directly related to the risk of possible pharmacological interactions in patients with that age range.

Figure 2. Distribution of the average of possible interactions according to the age range of the patients.



Of a total of 46 medicines that were detected in the interactions, the most prescribed correspond to group N (Drugs that act on the Nervous System) according to ATC.

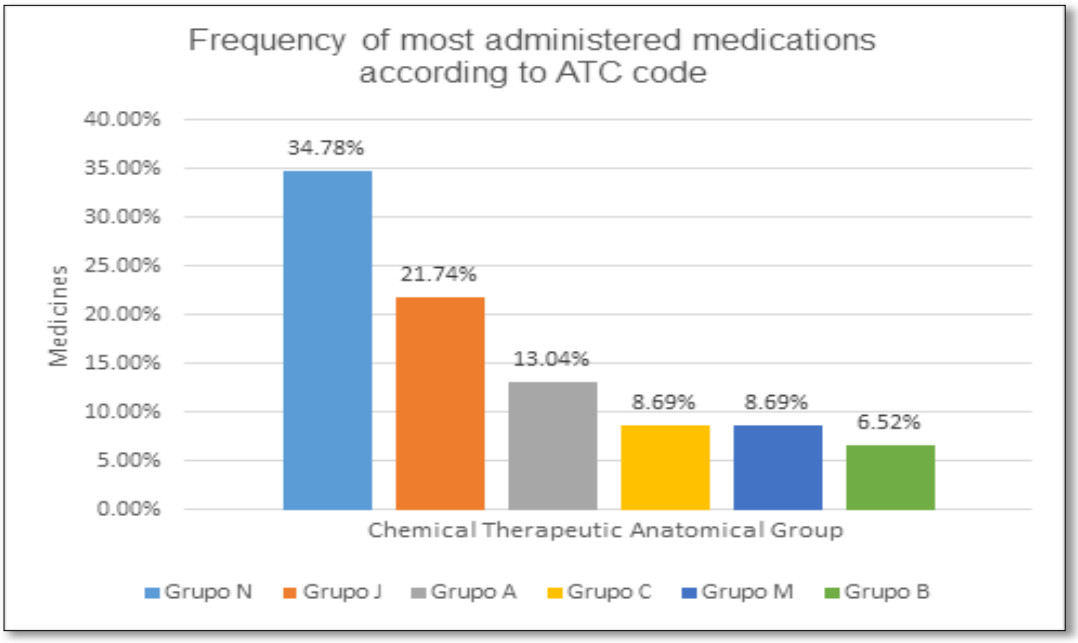
Phenytoin was the most prescribed and administered medicines, with a frequency of 71.43% of the total patients.

Then they are followed by those of group J, anti-infective drugs for systemic use, in which ciprofloxacin corresponds to the most administered medicines within the group, with a frequency of 45.71% **(Table 2 and Figure 3)**.

Table 2. Classification of the most frequent medicines administered.

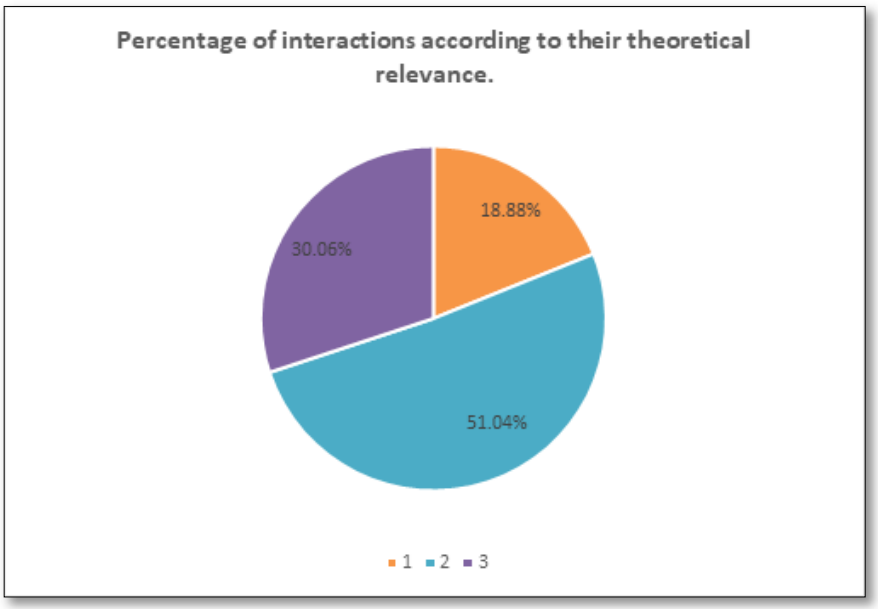
Nervous system. Group N			
Medicine	**ATC**	**n/N**	**Percentage (N=35)**
Phenytoin	N03AB05	25/35	71.43%
Propofol	N01AX10	16/35	45.71%
Diazepam	N01AX03	15/35	42.86%
Clonazepam	N03AE01	15/35	42.86%
Carbamazepina	N03AF01	12/35	34.29%
Fentanyl	N01AH01	11/35	31.43%
Anti-infective in general for systemic use. Group J			
Ciprofloxacin	J01MA02	16/35	45.71%
CeftazidDIe	J01DD02	13/35	37.14%
Amikacine	J01GB06	2/7	28.57%
Digestive system and metabolism. Group A			
Ranitidine	A02BA02	24/35	68.57%
Omeprazole	A02BC01	12/35	34.29%
Skeletal Muscle System. Group M			
Ibuprofen	M01AE01	19/35	54.28%
Ketorolac	M01AB15	16/35	45.71%
Blood and hematopoietic. Group B			
Heparin	B01AB01	14/35	40.00%

Figure 3. Chemical therapeutic anatomical classification of the most frequently used medicines.



The patients included in this study presented a total of 143 pharmacological interactions, which were classified according to their theoretical relevance in serious; which represent 18.88% of the interactions; 51.04% significant and 30.07% lower **(Figure 4)**. The lowest number of potential interactions presented by the patients was 4 and the highest was 44 interactions **(Tables 3-5)**.

Figure 4. Theoretical relevance of pharmacological interactions according to the Medscape Interaction Checker programme classification.



1. IF severe. 2. IF significative. 3. IF minors. Expressed as a percentage of the 143 potential Ifs

Table 3. More frequent serious drug interactions.

Medicine 1	Medicine 2	n/N	Percentage (N=110)	Potencial DAR
Ibuprofen	Ketorolac	9/143	6.29%	Ketorolac increases the toxicity of the other by pharmacodynamic synergism.
Propofol	Fentanyl	9/143	6.29%	One increases the effects of the other by pharmacodynamic synergism. Avoid or use alternative drugs. It can cause respiratory depression, hypotension, deep sedation, coma and/or death.
Cefazoline	Heparin	7/143	4.89%	Cefazolin increases the effects of heparin by pharmaco dynamic synergism. Avoid or use alternative drugs.
Cefazoline	Enoxaparin	7/143	4.89%	Cefazolin increases the effects of enoxaparin by pharmacodynamic synergism. Avoid or use alternative drugs.
Fentanyl	Atracurio	7/143	4.89%	One drug increases the effects of the other by pharmacodynamic synergism. Avoid or use alternative drugs. It can cause respiratory depression, hypotension, deep sedation, coma and/or death.
Carbamazepine	Midazolam	5/143	3.50%	Carbamazepine will decrease the level or effect of midazolam by affecting the metabolism of the liver/intestinal enzyme CYP3A4. Avoid or use alternative drugs.

Table 4. Potential most frequent significant drug interactions.

Medicine 1	Medicine 2	n/N	Percentage (N=110)	Potencial DAR
Phenytoin	Diazepam	15/143	10.50%	Phenytoin will decrease the level or effect of diazepam by affecting the metabolism of the liver/intestinal enzyme CYP3A4. Use caution/monitor
Phenytoin	Amikacine	12/143	8.39%	Phenytoin will decrease the level or effect of amikacin by the P-glycoprotein exit transporter (MDR1). Use caution/monitor.
Phenytoin	Heparin	12/143	8.39%	Heparin increases phenytoin levels by an unknown mechanism. Use caution/monitor.
Phenytoin	Ciprofloxacine	11/143	7.69%	Ciprofloxacin decreases the effects of phenytoin by an unknown mechanism. Use caution/monitor. Serum concentrations of phenytoin should be monitored in patients.

Phenytoin	Omeprazole	11/143	7.69%	El Omeprazole aumentará el nivel o efecto de la phenytoin al afectar el metabolismo de la enzDIa hepática CYP2C9/10. Use precaución/monitorear.
Ciprofloxacina	Ibuprofen	11/143	7.69%	Omeprazolee increases the level or effect of phenytoin by affecting the metabolism of the liver enzyme CYP2C9/10. Use caution/monitor.
Phenytoin	Ketorolac	11/143	7.69	Modify therapy/monitor closely. Mechanism: unknown. Increased risk of central nervous system stimulation and seizures with high doses of fluoroquinolones.

Table 5. Most frequent minor drug interactions.

Medicine 1	Medicine 2	n/N	Percentage (N=110)	Potencial DAR
Phenytoin	Ranitidine	17/143	11.89%	Ranitidine increases phenytoin levels by decreasing metabolism.
Phenytoin	Ibuprofen	7/143	4.89%	Phenytoin increases the level or effect of ibuprofen.
Phenytoin	Atracurio	5/143	3.50%	Phenytoin decreases the effects of atracurium by pharmacodynamic antagonism.
Phenytoin	Paracetamol	5/143	3.50%	Phenytoin decreases paracetamol levels by increasing metabolism. Increased levels of metabolites of hepatotoxic metabolites
Omeprazole	Diazepam	6/143	4.20%	Omeprazolee will increase the level or effect of diazepam by affecting liver enzyme metabolism CYP2C19.
Atracurio	Clonazepam	6/143	4.20%	Clonazepam decreases the effects of atracurium by pharmacodynamic antagonism

48.57% of the patients in the study had drug-nutrient type interactions **(Table 6)**, corresponding to 3.50% of the total drug interactions. The most frequent potential interaction was that of Phenytoin with Calcium (8.39%).

Table 6. Drug-nutrition interactions.

Medicine	Nutrient	n/N	Percentage	Potencial DAR
Phenytoin	Calcio	12/110	10.91%	Pueden aumentar las necesidades de Calcio
Omeprazole	Calcio	8/110	7.27%	Se produce déficit de Calcio
Paracetamol	Calcio	4/110	3.63%	Se produce déficit de Calcio
Furosemida	Calcio	2/110	1.81%	Se produce déficit de Calcio
Phenytoin	Ácido fólico	1/110	0.91%	Puede reducir la concentración plasmática de phenytoin

DISCUSSION

The prevalence of interactions observed in the present study was directly proportional to the increase in the age of the patients, suggesting that older patients are more vulnerable due of their greater number of prescribed drugs, the complexity in treatment and a reduction in renal function [2,4].

Pharmacological interactions themselves are a cause of hospital admission, but in practice this is relatively unusual. In daily practice only some of them have relevant clinical consequences that warrant hospitalization. Although it is very difficult to know the real frequency and clinical relevance of the interactions, it is currently known that many of them do not pose a risk to the patient and those that are clinically significant only occur in a small proportion of patients.

In this study 143 interactions in 937 patients were detected, which are significantly smaller than the data provided from other published studies. Several authors found 329 theoretical interactions in 412 patients, although it should be noted that these data cannot be directly compared with our study, due to the methodological differences, population and design, which contributes considerably for the variation of the observed frequencies [4].

The interactions found in our work were classified into 3 levels: serious, significant and minor; the "significant" ones were the most prevalent (51.04%), a fact that matches with other observations made by various authors [2].

Co-morbidities and the amount of drugs co-administered can increase the incidence of drug-related adverse effects and therefore, increase the risk of injury. For example, drowsiness is a common side effect of antiepileptic drugs and could be enhanced due to their association with hypnotic drugs or with psychiatric problems [5].

Regarding the number of medicines administered and their indication, it was observed that there was a higher frequency of medicines with action on the nervous system, being phenytoin (anti-epileptic) the most administered drug (54.34%) and therefore the medicine most involved in possible interactions. In addition, carbamazepine and clonazepam, also used to control epileptic seizures, were found within the group.

Some of the anti-epileptics bind extensively to plasma proteins. Only the unbound (free) fraction of the drug is able to pass through membranes and have pharmacological activity, hence many drug-drug interactions may occur as a result of competition for protein binding sites as observed in the case of phenytoin-ibuprofen or phenytoin-diazepam in our results.

From these data it is inferred that it might be appropriate to monitor the levels of the free fraction of drugs only in those cases where drug interactions are important and have sufficient risk to the health of patients [6].

Although monitoring would not be useful in all cases, it should be performed for drugs with the greatest potential to produce interactions: those with a narrow therapeutic index, which require precise control of plasma concentrations, those with dose-response curves with a broad slope, saturable metabolism or in case there is an indication of chronic treatment [7].

In the second place in the ranking of the interactions, we identified drugs from therapeutic group called "anti-infective for systemic use" (Group J), in 34.78% interaction of the cases, being ciprofloxacin the most prevalent in the group.

Microbial use was associated with age, co-

morbidities and toxic habits such as smoking and alcoholism of patients [8].

It was detected that 48.57% of the patients under study presented an interaction of the drug-nutrient type. The most frequent case of this type was that phenytoin with calcium (8.39%), an essential component of nutritional supplements. This fact is clinically relevant, since anticonvulsants have a higher risk of producing bone demineralization and fracture on pathological bone, events that are facilitated by risk factors such as vitamin D deficiency and hypocalcaemia [9].

To assess the safety of concomitant use of drugs, the different characteristics of the interaction must be studied.

In this context, the presence of the clinical pharmacist in each of the hospital units is essential to be able to monitor the pharmacotherapeutic treatment and taking into account other variables inherent to the patient, which go unnoticed by other disciplines and professions; in order to minimize the incidence of preventable drug interactions [2].

CONCLUSION

The present study 48.57% of hospitalized patients with epilepsy, a drug-nutrient or drug interactions were detected. The drugs involved belong predominantly to the group acting on the nervous system, being phenytoin the medicine that presented the greatest interaction risk.

The presence of a clinical pharmacist could help to prevent and reduce the incidence of drug interactions, optimizing health care practice.

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