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CHARACTERIZATION OF POLYPHARMACY AND DRUG INTERACTIONS IN PEDIATRIC PATIENTS IN A HOSPITAL IN PACHUCA MEXICO

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ABSTRACT

Objective: To determine the characteristics of polypharmacy in a pediatric secondary-care hospital in Pachuca, México and identify the principal drug interactions. **Material and methods:** This was an observational descriptive cross-sectional study of hospitalized patients with three or more drugs prescribed during the period of September to November 2015 and with an age range of one day to 18 years, of both genders, and in any of the hospital services. Descriptive statistics was performed with SPSS software version 18 and the free access software "Drug Interaction Checker" WebMD LLC was used for the identification of drug interactions. **Results:** A total of 446 drugs were prescribed. Ninety-nine patients were identified with bacterial pneumonia (22%) being the most frequent pathology; 77 patients (77%) were given 3 to 5 drugs with a median of four. The most frequently prescribed drugs were omeprazole (10.09%), paracetamol (6.5%), ketorolac (5.61%), methylprednisolone (4.93%) and amikacin (4.04%) with the latter being the most frequently prescribed antibiotic. A total of 79 drug interactions were identified in 38 (38.4%) patients. Ten interactions occurred in one patient who had 11 drugs prescribed. Phenytoin and omeprazole were the drugs that were most frequently involved in interactions. Of these 49.37% were significant, 48.1% minor, and 2.53% severe. **Conclusions:** The characterization of polypharmacy in pediatric patients provides a guideline for the

development of interventions aimed at the prevention of drug interactions and the promotion of rational drug use with an impact on the quality of life and patient evolution.

KEYWORDS: Polypharmacy, drug interaction, pediatrics, rational drug use.

INTRODUCTION

There is currently a worldwide rapid increase in the pediatric population. In Mexico, it is estimated that children under 15 years of age represent 28% of the total population; in other words, almost one third[1], and in the State of Hidalgo, the State Population Council in 2018 projects approximately a total of 813 thousand children under 15 years of age, representing 30% of the state population.[2]

Drugs are essential instruments in health care services to improve and maintain human health; however, approximately 50% are prescribed or administered inappropriately.[3] Drug prescription in pediatric patients has a series of considerations that need to be addressed when indicating one or another drug. Pediatric patients need to be evaluated from a special perspective and not as adult patients. Physiological changes that are specific in pediatric patients, such as a greater amount of water and therefore a greater distribution volume and immature renal and liver function, alter the pharmacokinetics and pharmacodynamics of drugs with this being particularly important in newborns and breastfed children.[4,6]

Adequate and opportune drug use of in a critically ill patient is a constant challenge for medical personnel since inadequate management contributes to poor results.[7] This reduces the effectiveness of established treatments and increases hospital costs, which makes this a public health problem. Rational drug use is understood not only as the correct choice but also as the correct dose and duration of treatment to avoid negative results.[8,12]

The World Health Organization considers the term polypharmacy as the simultaneous use of three or more drugs with the consequential increase in unwanted side effects, drug interactions (DI), and adverse drug reactions (ADR), which compromises the patient´s quality of life.[13,15]

A DI occurs when one drug alters the pharmacokinetics, mechanism of action or the effect of another drug when it is administered together with another drug or compound. This can result in the appearance a beneficial or toxic effect of greater or lesser intensity or in a reduction of its therapeutic activity. DI can be classified into two types, pharmacokinetic interaction,

which occurs due to altered absorption, distribution, metabolism or excretion of the drug or drugs or pharmacodynamic interaction, which occurs when there is synergism (the effect increases) or antagonism (the effect decreases) of drug action.[16,18]

Pediatric patients are especially vulnerable to DI. The reasons for this are physiological immaturity related to the metabolism, distribution and excretion of drugs that condition changes in pharmacokinetic parameters and thus, in the pharmacological response, and the limited scientific evidence available on the efficacy and safety of drugs in this age group.[8,9]

Despite the advances in pediatric pharmacology in recent years, children are still "therapeutic orphans", an expression coined by Shirkey in the 60s, referring to the lack of therapeutic resources for this population.[10,19] The potential frequency of DI increases with polypharmacy. It is estimated that the incidence of DI in patients treated with a smaller number of drugs is 3% to 5%, but this rate can reach up to 20% in those who receive 10 to 20 drugs; a situation that is expected in hospitalized patients[20], especially in critically ill pediatric patients. Thus the importance of characterizing the most frequently used drugs in a secondary-care pediatric hospital and identifying the potential interactions that can occur as a tool for evaluating if the drug use in the hospital is rational. If use is rational then the trend should be encouraged, if not interventions should be carried out to correct it.

The objective of this work was to determine the characteristics of polypharmacy in patients from a secondary-care pediatric hospital in Pachuca, Mexico, and identify the principal DI in this age group with the aim of generating interventions directed at increasing the knowledge and participation of the attending physician, especially identifying potential DI and encouraging rational drug use.

MATERIAL AND METHODS

This was an observational, descriptive cross-sectional study carried out in the secondary-care Children's Hospital DIF Hidalgo in Pachuca, Mexico. A non-probabilistic convenience sample was obtained by including 99 consecutive cases, using as inclusion criteria, hospitalized patients with three or more prescribed drugs during the period of September-November 2015, with an age range of 1 day to 18 years, of both genders and in any of the hospitalization services (Infants, Internal Medicine, Neonatal Intensive Care Unit [NICU]). The variables collected were age, sex, hospitalization service, drug prescribed (generic name), route of administration and its formulation. Data were captured for analysis in a

database in SPSS statistical software version 18. Descriptive statistics were used. In the case of quantitative variables, central tendency measures were applied and for qualitative variables proportions and ratios were obtained. For the identification of DI the free access software "Drug Interaction Checker" of WebMD LLC, which consists of a matrix where the generic name of the drug is entered, was used. To classify the theoretical relevance of the DI, the criteria of Hansten and Horn[21], which categorize interactions as severe (avoid association), significant (monitor closely) and minor (theoretical interaction), were used. The Ethics and Research Committees of the Children´s Hospital DIF Hidalgo approved the protocol.

RESULTS AND DISCUSSION

A total of 99 hospitalized patients were identified during the period of September – November 2015, of which 50 (50.5%) were girls. The distribution by age groups (Table 1) was of schoolchildren 46.46%, followed by preschoolers with 16.16%, adolescents and infants, both with 15.15%, and newborns with 7.08%. The service with the greatest number of cases was internal medicine with 77%, followed by infants with 15% and the NICU with 8%. A total of 100 illnesses were recording with bacterial pneumonia being the most frequent (22%), followed by bone fractures in different parts of the body (8%) and appendicitis (7%) (Table 2).

Table 1: Patient distribution by age group.

Age group	Frequency	Percentage
Adolescents 12-18 years	15	15.15
School children 5-12 years	**46**	**46.46**
Preschool children 2-5 years	16	16.16
Infants 1 month – 2 years	15	15.15
Newborn 1-30 days	7	7.08
Total	**99**	**100**

Table 2: Main pathologies.

CIE10 code	Pathology	Frequency (%)
J13-J16	Bacterial pneumonia	22 (22)
T02.0 - T02.9	Fractures in different parts of the body	8 (8)
K35	Acute appendicitis	7 (7)
J20	Acute bronchitis	5 (5)
G40	Epilepsy	5 (5)
L02	Abscess	3 (3)
T80-T83	Catheter complication	3 (3)
T20-T32	Second-degree burns	3 (3)
P36	Neonatal sepsis	3 (3)
P22	Newborn respiratory distress syndrome	3 (3)
	Other	38 (38)
	TOTAL	**100 (100)**

The total number of drugs consumed was 446. In 77 (77%) patients three to five drugs were administered with a median of four. There were 17 patients who had 6 to 8 drugs and five who had 9 to 11 drugs. The main formulation used was an injectable solution in 85.43%; therefore, the most frequent route of administration was intravenous, followed by the oral route in 11.66%.

According to the Anatomical Therapeutic Chemical (ATC) Classification System (Table 3), of the 446 prescribed medications, the most frequently used group was systemic antibiotics in 36.10%, followed by of anti-inflammatories such as ketorolac with 13.45%, and anti-peptic ulcer and gastroesophageal reflux agents such as omeprazole and ranitidine with 11.66%. It is important to point out that among the antibiotics, amikacin and clindamycin were more frequently prescribed, both in 11.18%, followed by ampicillin, cefotaxime, and ceftriaxone, each with 9.32%.

Table 3: Main drug groups prescribed.

	Drug group according to the ATC classification	**Frequency (%)**
J01	Systemic antibacterials	161 (36.10)
M01	Anti-inflammatory and anti-rheumatic drugs	60 (13.45)
A02B	Anti-peptic ulcer and gastroesophageal reflux	52 (11.66)
N02A	Opioids	31 (6.95)
H02	Systemic corticosteroids	30 (6.73)
N03	Antiepileptics	26 (5.83)
C03	Diuretics	14 (3.14)
A03	Agents against functional diseases of the stomach and intestine	12 (2.69)
A11	Vitamins	7 (1.57)
R01	Nasal preparations	6 (1.35)
C09	Agents that act on the renin-angiotensin system.	5 (1.12)
B05	Plasma substitutes and solutions for perfusion	4 (0.90)
C01CA	Adrenergic and dopaminergic agents	4 (0.90)
R03	Agents against obstructive diseases of the respiratory tract	4 (0.90)
A16	Other products for the alimentary tract and metabolism	3 (0.67)
D06	Antibiotics and chemotherapy for dermatological use	3 (0.67)
M03	Muscle relaxants	3 (0.67)
N05C	Hypnotics and sedatives	3 (0.67)
R06	Systemic Antihistamines	3 (0.67)
	Others	15 (3.36)
	Total	**446**

ATC: Anatomical Therapeutic Chemical Classification System.

The five most commonly used drugs were omeprazole (A02B), followed by paracetamol (M01) and ketorolac (M01) with 10.09%, 6.50% and 5.61%, respectively,

methylprednisolone (H02) with 4.93% and amikacin (J01) with 4.04% Although antibiotics as a group were the most frequently prescribed, omeprazole was the most frequently prescribed drug, and amikacin, the most frequently prescribed antibiotic, occupied fifth place.

A total of 79 DI were identified in 38 patients (38.4%) with a median of two per patient. Twenty-four patients (63.2%) presented one DI. Four presented two DI (10.5%) and three, three DI (7.9%), and three other patients, four DI (7.9%). Two patients (5.3%) were identified with five DI and in one patient (2.6 %), six DI were identified. Finally, a maximum of 10 DI occurred in one patient (2.6%) (Table 4). The number of DI was greater than that reported by Yuriko et al.[22]

Table 4: Number of interactions present in pediatric patients.

Number of interactions	Number of persons with interaction	Percentage
1	24	63.2
2	4	10.5
3	3	7.9
4	3	7.9
5	2	5.3
6	1	2.6
10	1	2.6
Total	**79**	**100**

The relationship between polypharmacy and the number of potential DI that can occur is shown in Table 5. The patient with 10 prescribed drugs had six interactions and the maximum number of interactions identified (10) corresponded to a patient who had 11 drugs prescribed. Thus, if a greater number of drugs are prescribed, there is a greater probability of a greater number of DI; a fact similar to that reported in the literature.[23,25]

Table 5: Relationship between drugs prescribed and drug interactions identified in pediatric patients.

Number of drugs prescribed	Interactions identified	Number of patients
3	1	8
	2	2
4	1	5
	3	1
5	1	4
	2	1
	3	1
6	1	3
7	1	3
	2	1
	3	1
	5	2
8	1	1
	4	1
9	4	2
10	6	1
11	10	1
Total		**38**

The main interactions identified are shown in Table 6; of these, the most frequent, according to their clinical significance, were significant in 49.37%, minor in 48.1%, and severe in 2.53%.

Table 6: Main interactions identified.

Interaction	Effect	Frequency (%)
Severe		**2 (2.53)**
Ceftriaxone + calcium gluconate	Potentially fatal precipitation of particles in the lungs and kidneys	1
Phenobarbital + cisapride	Phenobarbital reduces cisapride levels or its effect by affecting the metabolism of the CYP3A4 live enzyme.	1
Significant		**39 (49.37)**
Omeprazole + Phenytoin	Omeprazole increases the level or effect of phenytoin by affecting the metabolism of the liver enzyme CYP2C9/10	8
Clarithromycin + methylprednisolone	Clarithromycin increases the level or effect of methylprednisolone by affecting the metabolism of the liver enzyme CYP3A	6
Phenytoin + dexamethasone	Phenytoin reduces the level or effect of dexamethasone by affecting the metabolism of the liver enzyme CYP3A4.	3

Phenytoin + midaozlam	Phenytoin reduces the level or effect of midazolam by affecting the metabolism of the liver enzyme CYP3A4.	2
Phenytoin + amikacin	Phenytoin increases the level or effect of amikacin by affecting the P-glycoprotein transporter (MDR1)	1
Phenytoin + diazepam	Phenytoin reduces the level or effect of diazepam by affecting the metabolism of the liver enzyme CYP3A4.	1
Phenobarbital + hydrocortisone	Phenobarbital reduces the level or effect of hydrocortisone by affecting the metabolism of the liver enzyme CYP3A4	1
Methylprednisolone + metronidazole	Metronidazole increases the level or effect of methylprednisolone by affecting the metabolism of the liver enzyme CYP3A4.	1
Methylprednisolone + midazolam	Methylprednisolone reduces the level or effect of midazolam by affecting the metabolism of the liver enzyme CYP3A4.	1
Dexamethasone + fentanyl	Dexamethasone reduces the level or effect of fentanyl by affecting the metabolism of the liver enzyme CYP3A4.	1
Other		14
Minor		**38 (48.10)**
Amikacin + ketorolac	Ketorolac increases the levels of amikacin by reducing renal clearance	6
Dexamethasone + omeprazole	Dexamethasone reduces the level or effect of omeprazole by affecting the metabolism of the liver enzyme CYP3A4.	4
Buprenorphine + Nalbuphine	Sedative effect is increased	3
Valproic acid + phenytoin	Valproic acid increases the level or effect of phenytoin by affecting the metabolism of the liver enzyme CYP2C9/10	2
Cefepime + furosemide	Increases the risk of nephrotoxicity	2
Ketorolac + vancomycin	Ketorolac increases the levels of vancomycin by reducing renal clearance	2
Omeprazole + midazolam	Omeprazole increases the levels of midazolam by reducing its metabolism	2
Omeprazole+ clonazepam	Omeprazole increases the levels of clonazepam by reducing its metabolism	1
Ceftriaxone + furosemide	Increases the risk of nephrotoxicity	1
Metronidazole + paracetamol	Metronidazole increases the level or effect of paracetamol by affecting the metabolism of the liver enzyme CYP2E1.	1
Other		14

After identifying severe and significant DI, close communication was maintained with the attending physician to monitor them and avoid more adverse events. Alternatives were also suggested regarding separately administrating the medications. Among the drugs that were more frequently involved in the 79 DI, phenytoin was present in 30%, omeprazole in 20%, dexamethasone and methylprednisolone in 15% each, and amikacin in 10%. It is important to mention that these drugs are among the 20 most frequently prescribed.

CONCLUSION

The characterization of polypharmacy in hospitalized pediatric patients provides a guideline for the development of interventions aimed at preventing DI with the consequential appearance of frequent adverse drug reactions since hospitalized pediatric patients commonly present more than one pathology, which increases the number of prescribed drugs. Avoiding DI is important to avoid patients losing functionality, to reduce costs both for the patients and the health services, and above all, to increase quality of life and disease evolution, situations that could help produce a faster recovery. This characterization helps promote rational drug use, since it becomes necessary to carefully assess the pharmacotherapy and posology in the pediatric patient. Furthermore, it contributes in making health care personnel prevent and identify adverse events.

Drugs are essential instruments in health care services because they improve and help maintain human health. Drug prescription in pediatric patients has a series of considerations that need to be addressed when indicating one or another drug so they can be used effectively. Pediatric patients need to be evaluated from a special perspective and not as adult patients.

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Conflicts of Interest

Thea research team declares that they have no conflict of interest.

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