

The importance of pharmacovigilance in the pediatric population

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Abstract

In order to emphasize the importance of pharmacovigilance in children, a review was carried out with special emphasis on general and conceptual aspects outlined in the Mexican Official Norm and other documents. The different classifications from the Adverse Drug Reactions (ADR) and Adverse Drug Events (ADE) are discussed. Using the database of the WHO Collaborating Centre for International Drug Monitoring, Uppsala Monitoring Centre (Sweden), we analyzed up to the year 2006 the present status of the ADR reports from 82 countries. Mexico ranks in the middle classified by age groups and number of reports in

the database. The impact of ADR stands out in the general population according to morbidity, mortality, sequelae and cost considerations. The impact of ADE and ADR in newborns and pediatric patients reports the experiences of international groups. Several recommendations are mentioned that will allow a system of pharmacovigilance to be established or improved for children in Mexico. The Hospital Infantil of Mexico has initiated an ambitious program.

Key words: pharmacovigilance in children, adverse drug reactions, adverse drug events.

Introduction

The purposes of the present review are to highlight the concepts and operative components of pharmacovigilance, emphasizing the consequences of the use of medications in adults and children based on international experience. Our goal is to increase awareness among Mexican pediatricians, in particular, and health care professionals, in general, about these matters.

General Concepts

Pharmacovigilance is “the science related to compiling, monitoring, researching, qualifying and evaluating the data obtained from health care professionals and patients about the adverse effects of drugs, biological and botanical products as well as those used in traditional medicine. The purpose of pharmacovigilance is to identify data about new adverse reactions and prevent damage to patients.”¹

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The most accepted definition of Adverse Drug Event (ADE) is based on the International Conference on Harmonization Guidelines:² “it is any undesirable medical effect in a patient or in a clinical research where a pharmaceutical product has been administered that does not have an actual relationship with the treatment...” and “... any sign, symptom or unfavorable/non-intentional disease that can be temporarily associated with the use of the medical product at any dose.” This is an ample but comprehensive definition. Physicians, pharmacists, nurses and even consumers exceptionally report an ADR especially if they can link it to the use of a given medication in their daily practice. Frequently, they do not report an ADR because they think it is not related with one or more drugs.

There are five different categories for ADE³

- Adverse Drug Reaction (ADR)
- Medical Errors
- Therapy Failure/Error
- Adverse Drug Event after medication has been suspended
- Overdose

In Mexico⁴, the ADE definition includes vaccine-associated adverse events (VAAEs) and therapeutic error; however, even if the Mexican Official Norm (NOM) does not explicitly include the others, they should also be reported. ADRs are defined as “any harmful and undesired effect that presents when the appropriate dosages are used for prevention, diagnosis, treatment or function modification.”^{4,5} VAAEs are defined as “those clinical manifestations that occur within 30 days after one or more vaccines have been administered and that cannot be associated with a specific disease.”⁴ Therapeutic error is defined as “any case where the therapeutic effect is not achieved when using appropriate dosages as prescribed for humans, either with prophylactic, diagnostic, therapeutic or physiological purposes.”³ Medical errors are defined as “non-deliberate acts, either from commission or omission that result in a potential or actual damage to the patient or as a consequence of administering a medication.”⁶ The latter are considered as commission because of the confusion either during writing the prescription or when the medicine is received by the patient. Omission errors are those where the physician did not consider the possible drug interactions. ADEs, when the medication has been suspended, includes those presented when the drug is suspended abruptly

after the patient has used the medication for a long period. Overdose differs from ADR because the dosage is not usually administered for disease treatment. All these ADEs may present as an independent or combined situation.

ADR and ADE Classification

There are three types of ADRs.⁷ Type A are those generally dependent on the dose. The reaction is predictable according to the pharmacological effects of the drug and have high morbidity rates and low mortality rates. Type B reactions are not predictable from the pharmacological effects of the drug, are not dose-dependent and have a low morbidity rate and high mortality rate. Type C, which was recently described,^{8,9} includes drug reactions associated with a particular disease that are infrequent when the patient has not been exposed to the medication.

Mexican NOM classifies ADRs according to the quality of information and their probability of causing the reaction as follows:⁴

- Certain
- Probable
- Possible
- Doubtful
- Conditional/Unclassifiable
- Non-assessable/Unclassifiable

“Certain” is when a clinical event or laboratory test result occurs shortly after administering the drug and cannot be explained as a natural evolution of the disease, concomitant pathology or as a consequence of administering other drugs. There should be clinical evidence that once the drug is suspended, the adverse reaction begins to subside. The other categories are classified in descending order because of their role as the cause of the reaction. Therefore, the “Doubtful” ADR is described as an event (clinical manifestation or abnormal laboratory test result) that occurs after the last time the drug was administered that brings suspicion about its role as improbable (but not impossible). This may be explained as part of the natural evolution of the disease or because of concomitant pathologies or the combined effect of other drugs.

ADRs and ADEs are classified according to their clinical severity as follows:⁴

- Mild (when there are signs and symptoms easily tolerated that do not require treatment or increase patient's hospital stay and that might require the suspension of the drug)
- Moderate (when they interfere with patient's normal work or school activities without becoming life-threatening, require pharmacological treatment and may require the suspension of the drug)
- Severe (those that are life-threatening or may even cause the patient's death, increase hospital stay, result in persistent or significant disability, or cause alterations or malformations in newborns)
- Lethal (those where the drug contributes directly or indirectly to the patient's death)

ADRs can be preventable or unpreventable. Preventable ADRs are generated by diagnostic errors that lead to an inappropriate prescription, an incorrect prescription that causes overdose, those where the physician failed to warn parents about the potential risk of one or several prescribed drugs, an altered prescription by the child's parents, or an inaccurate evaluation of the drug's interaction with other medicines. Unpreventable ADRs are those not easily predictable because even if the prescription is adequate, the drugs may have an undesirable effect on one particular person, place or time and will only be identified at the time of occurrence.⁴

ADR Notification Reasons

The Mexican Official Norm (NOM) about the installation and operation of pharmacovigilance⁴ states that notification is mandatory in Mexico for institutions and health care professionals, for directors of health record systems and for those who commercialize medicines or herbal remedies, as well as for clinical research units that carry-out drug studies. However, it should be mentioned that spontaneous ADR reports by health care professionals is voluntary as occurs in most countries.

Physicians, nurses, pharmacists and pharmacy technicians are responsible for pharmacovigilance for children admitted to hospitals. They should be ever-vigilant towards ADRs. They should report these reactions even if there is no apparent cause/effect relationship and without considering whether the ADR presented at the beginning, during or after the administration of drugs, substances, biological products and vaccines that meet

one of the following criteria:^{4,10}

- Drugs introduced in our country in the last 2 years
- Lethal reactions
- Life-threatening reactions for the patient
- Reactions that result in hospital admission
- Reactions that increase hospital stay
- Reactions where the patient cannot attend school or work
- Reactions that produce malformations or cancer
- Reactions that cause irreversible effects
- Reactions that produce abnormal laboratory test results
- Reactions present during vaccination campaigns

The report of a suspected ADR should include expected and unexpected reactions either during medical care, clinical research studies, intensive pharmacovigilance studies and vaccination campaigns.⁴ In clinical research studies, suspected ADRs must be reported by the research centers and the sponsoring pharmaceutical company. An unexpected ADR is one that has not been described in its nature or severity in the scientific literature or in the information contained in product labeling, prescription documentation or in the registration data and that is not possible to infer according to the pharmacological activity of the drug.⁴

International ADR Report

There is a large database (WHO Collaborating Centre for International Drug Monitoring [IDM], Uppsala Monitoring Centre, Sweden) that contains information from 82 countries. We obtained the 2006 version of the database from Sten Olsson¹¹ and Prof. J. Leticia Rodriguez Betancourt in order to reorganize the data to be used for this review (see Tables 1-6).

Table 1 shows that the December 2006 database contained >3 million reports, where only 12.69% involved the pediatric population. There is a possible bias in the age proportion because the table shows the accumulated number of ADRs from the 82 countries without considering the date when the country began reporting (e.g., the U.S. began in 1968, whereas Mexico began in 1997). It does not include a rate that should have as a denominator the number of inhabitants/10,000

0/1,000,000 per year that would allow demonstrating¹² that ADRs have a similar frequency among age groups according to the number of drugs administered per group. Unfortunately, the database did not include ADRs/year and number of inhabitants; therefore, we were unable to calculate the proposed rate.

Table 2 shows only the countries with the largest cumulative number of reports by age group, which

Table 1. Distribution of 3,086,338 ADRs in 82 countries until December 2006 according to the Centre for IDM (WHO)

Age groups	No. of ADR ^a reports	%
0-1 month	11,345	0.36
2 months-4 years	192,179	6.22
5-11 years	105,179	3.42
12-16 years	83,139	2.69
17-69 years	2,108,160	68.30
>70 years	585,855	18.98

ADR, adverse drug reaction; IDM, International Drug Monitoring, Uppsala, Sweden; WHO, World Health Organization.

^aCalculated from the database (Reference 11).

was the U.S. However, if we calculate a rate with the number of reports per 1,000,000 inhabitants per year and country, we observe that first place is attributable to New Zealand, and the U.S. ranks in third place.⁷ The table also shows that the number of cases reported in the U.S. is very large, compared to the cases reported by Mexico by age group. Mexico has a middle position in the table among 81 other countries with 2258 cases reported. However, other Latin American countries that began reporting before Mexico (1997) and with a smaller population show a larger number of cases (e.g., Cuba). Because the information concerning the number of reports per country and age group is not easily accessible, we describe it in detail (Tables 3-6). These tables show that ADRs for pediatric population groups among countries is fairly consistent and that countries with the largest number of cases reported are the U.S., several European countries, Asia and the South Pacific, whereas the number of cases reported by Latin American countries is much lower. As an example, Table 3 shows the distribution of ADRs in newborns in 82 countries. This reveals that developed countries lead the list, which contrasts greatly with the number of reports for Latin American and African countries despite the acquired international commitment. This is probably related to a faulty search of ADRs in the pediatric population.

Table 2. Distribution of ADRs according to age groups for countries with the highest number of reports: the position of Mexico among 82 countries until December 2006 according to the Centre for IDM (WHO)

Age groups	Country	No. of ADR ^a reports	Position	Number of reported ADRs ^a in Mexico
0-1 month	U.S.	5,536	48	2
2 months-4 years	U.S.	65,224	41	113
5-11 years	U.S.	36,902	46	67
12-16 years	U.S.	32,332	43	56
17-69 years	U.S.	853,497	40	1763
>70 years	U.S.	238,426	39	257

^aCalculated from the database (Reference 11).

Table 3. Number of ADR^a reports in newborns (0-30 days) per country according to the Centre for IDM (WHO)

Country	ADRs	Country	ADRs	Country	ADRs	Country	ADRs
USA	5536	Austria	25	Bulgaria	3	Costa Rica	0
France	1841	Serbia, Montenegro	22	Poland	3	Cyprus	0
Germany	757	Brazil	21	Turkey	3	Egypt	0
UK	733	Italy	20	Uruguay	3	Estonia	0
New Zealand	488	Slovakia	17	Argentina	2	Fiji	0
Canada	446	Israel	15	Brunei	2	Ghana	0
Australia	349	Norway	15	Macedonia	2	Guatemala	0
Sweden	236	Morocco	14	Mexico	2	India	0
Thailand	101	Portugal	14	Tanzania	2	Jordan	0
Ireland	81	Iran	13	Tunisia	2	Korea	0
Spain	80	Chile	11	Zimbabwe	2	Kyrgyzstan	0
Czech Republic	76	Croatia	8	Greece	1	Latvia	0
Romania	73	Peru	8	Iceland	1	Lithuania	0
Switzerland	53	Philippines	8	Nigeria	1	Malta	0
Holland	49	Finland	7	Oman	1	Moldova	0
South Africa	48	Hungary	5	Venezuela	1	Mozambique	0
Japan	41	Singapore	5	Vietnam	1	Nepal	0
Malaysia	30	Belgium	4	Armenia	0	Russia	0
Colombia	28	Cuba	4	Belarus	0	Sri Lanka	0
Denmark	27	Indonesia	4	China	0	Surinam	0
Total 11,345							

^aCalculated from the database (Reference 11).

Importance of ADEs

The information here presented was consolidated from studies carried out in adults. In the U.S.¹³ it has been considered that the combined effect of medical errors and adverse events from iatrogenic damage not associated with identified errors includes:

- 12,000 deaths per year due to unnecessary surgery
- 7,000 deaths per year due to hospital medical errors
- 20,000 deaths per year due to other hospital errors
- 80,000 deaths per year due to hospital-acquired nosocomial infections
- 106,000 deaths per year due to ADEs unrelated to errors

From the aforementioned, it may be inferred that ADEs are an important cause of morbidity and mortality. Therefore, there has been an increase in the number of studies focused on patient safety and pharmacovigilance quality control in the last decade. These events have been recognized as a high-priority project because of their iatrogenic nature and their impact on annual costs. For instance, in the U.S. it has been estimated that these events cost between 76 and 177 billion dollars yearly, which is more than the cost of all diabetes and cardiovascular disease treatments that may reach 150 billion dollars per year.¹⁴⁻¹⁷

Epidemiological studies related to the great diversity of ADEs have found that 3-28% of hospital admissions are related to ADEs; 5-20% of patients experience one ADE

during their admission;¹⁸ patients >65 years old have a risk 2.5 times higher to develop ADE compared to the general population and seek emergency treatment that increase eight times the probability of being admitted.¹⁹ It has been estimated that 75,000 admissions in the U.S. are due to preventable ADEs that would cause 4,839 permanent injuries and 2,577 deaths.^{19,20} Of hospital admissions associated with ADRs,¹⁹ 41.5% are related to drugs that have small therapeutic windows or that require ambulatory care. Two-thirds of these admissions

could be avoided.²⁰

In outpatient consultation, prescription drugs can be associated with ADRs in 4-6% of cases. In hospitalized patients, it accounts for 16.6% of cases in Australia, 10.8% in the UK and 3.7% in the U.S. They also represent the leading cause of death in 13.6% of cases in the U.S., 8% in the UK and 4.9% in Australia.^{21,22} ADRs increase hospital stay by 1.9-2.2 days, with an associated cost of \$1,900-\$5,900 USD per patient/stay.^{17,23}

Table 4. Number of ADRs^a in children from 2 months to 4 years of age per country according to the Centre for IDM (WHO)

Country	ADRs	Country	ADRs	Country	ADRs	Country	ADRs
USA	65224	Chile	513	Mexico	113	Zimbabwe	17
Canada	46360	Malaysia	504	Peru	106	Ukraine	16
UK	20726	Belgium	466	Argentina	102	Guatemala	12
Australia	8876	Slovakia	460	Oman	99	India	10
New Zealand	7652	Serbia, Montenegro	459	Portugal	97	Lithuania	9
Sweden	6318	Romania	430	Latvia	72	Kyrgyzstan	8
France	5729	Bulgaria	402	Turkey	71	Mozambique	7
Thailand	5409	Switzerland	394	Greece	63	Ghana	6
Germany	3574	Norway	360	Hungary	57	Belarus	5
Spain	3484	Israel	357	Poland	54	Iceland	4
Italy	2269	Brazil	249	China	53	Korea	4
Cuba	1507	Singapore	231	Uruguay	46	Nigeria	4
Denmark	1412	South Africa	207	Costa Rica	35	Egypt	3
Ireland	1315	Indonesia	203	Armenia	32	Fiji	3
Czech Republic	1027	Iran	193	Venezuela	31	Brunei	2
Holland	1007	Morocco	172	Macedonia	25	Russia	2
Japan	841	Colombia	160	Sri Lanka	24	Cyprus	1
Austria	803	Philippines	135	Moldova	21	Jordan	1
Croatia	637	Tunisia	134	Tanzania	19	Malta	0
Finland	605	Vietnam	123	Estonia	18	Nepal	0
Total 192,179							

^aCalculated from the database (Reference 11).

Table 5. Number of ADRs^a in children 5-11 years old per country according to the Centre for IDM (WHO)

Country	ADRs	Country	ADRs	Country	ADRs	Country	ADRs
USA	36902	Serbia, Montenegro	439	Argentina	104	Korea	6
Canada	13528	Switzerland	390	Oman	90	Ghana	5
UK	13146	Bulgaria	371	Philippines	83	Nigeria	5
France	5281	Belgium	350	China	69	Ukraine	5
Sweden	5096	Slovakia	338	Peru	69	Armenia	4
Australia	4686	Croatia	309	Mexico	67	Estonia	4
Thailand	3819	Austria	304	Poland	55	Iceland	4
Germany	3354	Chile	298	Greece	52	Fiji	3
Spain	2525	Romania	239	Turkey	43	Kyrgyzstan	3
New Zealand	2402	Iran	226	Uruguay	43	Moldova	3
Ireland	1643	Colombia	207	Costa Rica	40	Egypt	2
Italy	1418	Indonesia	202	India	29	Nepal	2
Holland	1117	Israel	200	Hungary	24	Belarus	1
Denmark	1005	South Africa	182	Sri Lanka	23	Cyprus	1
Japan	866	Singapore	178	Venezuela	17	Lithuania	1
Czech Republic	588	Brazil	175	Brunei	16	Mozambique	1
Finland	517	Morocco	159	Latvia	15	Russia	1
Cuba	494	Tunisia	158	Tanzania	13	Guatemala	0
Malaysia	455	Portugal	138	Macedonia	12	Jordan	0
Norway	449	Vietnam	108	Zimbabwe	8	Malta	0
Total 105,179							

^aCalculated from the database in Reference 11

ADR in Children

In addition to the WHO IDM reports¹¹ for the pediatric population, it is worth mentioning that further information is required to better understand their relevance. Because there are few pharmacovigilance reports for the pediatric population, we describe here next to each relevant article the figures and percentages as a reference of the importance of ADRs on children during their hospital stay or in outpatient consultation and their impact on morbidity, morbidity and consequences.

Of 65,864 admissions in the Children's Hospital of Columbus (Ohio, U.S.)¹⁷ there were 565 ADRs (0.85%). Voluntary reports by health care personnel were distributed as follows: 69.1% by the clinical pharmacist and 5.3% by physicians with the remainder distributed among nurses, pharmacy students, pediatric residents and others. These were all verified in clinical

files. Treatment was required to reduce ADR signs or symptoms in 72% of cases, using IV medications in 55.7% of cases. Of children, 72.9% required at least two medications to treat the ADR. ADRs were classified as unexpected in 65% of cases, 18.2% as overdose, 15.6% as overreaction and 1.9% as drug interaction. Of ADRs, 20.7% were regarded as preventable. Consequences for children aged 6 months or younger were 4.3% and required increased monitoring without harmful effects; 8.7% required surgery or presented temporary damage; 6.1% required hospital admission without permanent damage; and 19% developed a severe clinical profile. There were no actual deaths. It was estimated recently in the U.S.²⁴ that between 2004 and 2005, 158,250 children <18 years of age arrived at an emergency service as a consequence of an ADE. Of these cases, 44.9% were regarded as unintentional overdose 35% 9

as allergic reactions and 12.6% as ADR. The leading causes for ADRs were antibiotics in 25.2%, analgesics in 13.7% and respiratory medications in 10.6%; 1/10 patients required hospital admission or increased length of their hospital stay.

In Switzerland²⁵ during a 15-year study period, there were 5,771 ADR reports in children <16 years old among a pediatric population ~1.7 million. There were an average of 385 reports per year. The most frequent reactions were topical (24%), fever (12%) and exanthem (6.7%). The largest number of cases was reported as 63.8% for vaccination and 10.1% for systemic antibiotics. Of children, 13% suffered a severe ADR and 0.14% of deaths were related to medications. Of these cases, 9% had not recovered at the time of this study and 1% recovered with sequelae.

In a pediatric hospital in California,²⁶ there were a total of 1,087 ADRs reported during a period of 10 years, representing 1.6% of cases. Their clinical severity was classified as mild to moderate in 89% of cases and patients were admitted to the general pediatric unit and neonatal ICU. Moderate ADRs were associated with the use of penicillin, cephalosporin and vancomycin. Of ADRs, 11% were regarded as severe or lethal, being the cause of hospital admission or occurred during surgery with the use of certain anticonvulsive and antineoplastic drugs. Although 93% of ADRs were reported by health care personnel, only 29% were actually documented in the clinical file.

In countries such as Germany or Sweden, ADR occurs in children at a rate of 15-17%. Of these, 1-5% are due to the administration of unlicensed drugs to be used in

Table 6. Number of ADRs^a in children 12-16 years old per country, according to the Centre for IDM (WHO)

Country	ADRs	Country	ADRs	Country	ADRs	Country	ADRs
USA	32332	Belgium	323	Oman	65	Estonia	5
UK	13223	Cuba	318	Philippines	57	Nigeria	5
Canada	6234	Malaysia	306	Mexico	56	Zimbabwe	5
France	4520	Austria	264	Argentina	53	Korea	4
Australia	4074	Bulgaria	264	Poland	50	Lithuania	3
Thailand	3130	Slovakia	264	Portugal	46	Moldova	3
Germany	2778	Serbia, Montenegro	239	Greece	37	Armenia	2
Sweden	2454	Chile	231	Peru	36	Russia	2
Spain	2271	Singapore	186	Turkey	33	Brunei	1
New Zealand	1517	Israel	179	Venezuela	25	Cyprus	1
Ireland	1237	Romania	167	Costa Rica	22	Jordan	1
Holland	864	Indonesia	153	Uruguay	21	Kyrgyzstan	1
Denmark	856	Iran	126	India	18	Mozambique	1
Italy	776	South Africa	104	Ukraine	16	Belarus	0
Japan	555	Tunisia	101	Hungary	14	Egypt	0
Czech Republic	465	Morocco	98	Ghana	13	Fiji	0
Norway	433	Brazil	91	Macedonia	13	Guatemala	0
Croatia	400	Colombia	84	Latvia	10	Iceland	0
	381	Vietnam	74	Tanzania	9	Malta	0
Finland	366	China	66	Sri Lanka	7	Nepal	0
Total 83,139							

^aCalculated from the database in Reference 11

the pediatric population. As for authorized medications, at least 25% of prescriptions do not meet the minimum age required on the license (off-label) with a high prevalence used on newborns.²⁷⁻³²

In 2001, during a period of 5 months in a Brazilian pediatric hospital, there were 420 ADR reports, representing a cumulative incidence of 12.5%. The skin was the most affected organ with 49% of cases, and antibiotics were associated with 53.2% of reactions. Of ADRs, 97% were classified as mild to moderate with a probable cause of 57.5%.³³

During a 1-week observation period, a regional French pediatric hospital reported that 4/260 children were admitted as a consequence of ADR and that an additional six children developed this condition during their hospital admission.³⁴

According to the findings in 63 U.S. emergency services³⁵ between 2004 and 2006, ADEs were detected in children <12 years old who were prescribed drugs against the common cold and sore throat. It was estimated that a total of 7,091 children would be treated annually because of ADEs related to such drugs, representing 5.7% of the total emergency visits when compared to other medications. The largest number of visits to emergency units was for children 2-5 years old (64%). Of these visits, 66% were due to the administration of non-supervised drugs, whereas 47% were associated with medications against the common cold and sore throat.

Of 1,689 children who attended ambulatory services in a Boston hospital³⁶ and received 2,155 prescriptions, 243 presented an ADR (14%). Of these, 23% were preventable, having a higher frequency of cases when parents had a poor understanding of English or low socioeconomic level.

The first article published in Mexico³⁷ concerning medical errors during the use of prescription drugs found, in the first review, that 53% of clinical files showed one or more errors and after corrective measures this percentage was reduced to 17.6%. It is worth mentioning that medical errors include³⁸ prescription, supply, administration, patient monitoring and drug management. Each may present different errors such as writing errors, dosage failure, administration failure, infusion time, misinterpretation by the personnel

responsible for dosage/preparation, dilution failure, labeling, drug interactions, and failure to monitor laboratory test results. Miller et al.³⁸ conducted an extensive study regarding medical errors and, after a detailed literature review, found 358 articles but included only 31 articles in their study. However, it was not possible to carry out a systematic review of all of these because most focused only on the prescription process and only a few included other information related to errors. The most important results were overall medical errors at a range between 5 and 27%. Even though not all 31 articles evaluated all aspects of errors, they found that errors occurred as follows: 4-30% were prescription errors, 5-58% were supply errors, 42-50% were administrative errors, and 1-20% were administrative record errors.

ADR in Newborns

Information available about ADRs in newborns is scarce. Newborns have several immature organs and systems that impact on their physiology, biochemistry and immunology, and this is even more noticeable in premature newborns. All these factors affect pharmacodynamics, pharmacokinetics and the metabolic mechanisms of drugs that are less efficient, rendering newborns more vulnerable to drug effects. We should also add that neonatal ICUs (NICUs) usually administer concomitant medications that are not recommended for children (unlicensed) or, when they are authorized for use in children, have not been approved for their use in newborns (off-label).^{39,40}

During a 4-month period, the NICU of a Glasgow hospital observed 105 medical errors: four were severe, 45 were potentially severe and 50 were mild. The four severe errors were caused by the administration of a dose 20 times greater than recommended. Of errors, 75% were attributable to a poor prescription process. Once specific actions were taken after the first evaluation month, the number of errors was reduced from 24.1 to 5.1/1000 of neonatal activity during a 3-month period.⁴¹

A total of 176 prescriptions involving 61 different medications were found during a 2-month evaluation period in an Italian NICU. Of these, 12% were not approved for children (unlicensed). Of the 88% approved for children (licensed), 22.7% were not recommended for use in newborns (off-label).⁴²

A systematic review of 11 studies reporting medical errors at NICUs⁴³ reveals that the largest number of errors associated with medications was 5.5/100 prescriptions in one study and the others showed ample variations explained by the different *error* definitions or by the rigor applied. The authors comment that in most of those studies there was no evaluation of the error consequences in children. These reviews identified that the most common strategies used to evaluate errors were computer-assisted methods to produce medical orders, prescription review and the presence of a pharmacist during visits; however, authors note there was scarce information contained in the review articles about the result of such strategies. A study performed during a 9-month period in a NICU at a hospital in Marseille, France focused on the frequency of iatrogenic errors in 388 admitted and studied patients during 10,436 days/patient. That study found 267 iatrogenic events in 116 patients. The incidence was 25.6/1000 days/patient of which 92 (34%) were preventable and 78 (29%) were severe. Of the events, 1% resulted in death. Iatrogenic events were related with nosocomial infections in 79% of cases, with respiratory problems representing 35% and with medications during their administration in 76% of the cases. The most important risk factors were low birth weight, gestational age, duration of hospital stay, central catheters and mechanical ventilation.⁴⁴

Another study conducted by the National University of Colombia during a 4-month period reported 20 newborns with ADRs related to the use of antibiotics and were classified as mild (65% of cases), moderate (35% of cases) and no cases as severe. According to laboratory test results, 38.1% of cases presented nephrotoxicity, 24.7% hemotoxicity, 21.6% electrolytic abnormalities and 15.5% hepatotoxicity. ADR distribution by antibiotic type was 20.6% gentamicin, 17.5% vancomycin, 16.5% amikacin, 15.5% ceftriaxone and 13.4% piperacillin with tazobactam.⁴⁵

Given the importance of studies on drug administration in newborns, it is worth mentioning the study carried out by 220 NICUs⁴⁶ in 32 states of the U.S. including Puerto Rico (1997-2004). The total number of analyzed discharges was 253,651, of which 45,192 were discarded (18%) because there was no certainty regarding administered medications. As for premature newborns with an average of 32 gestation weeks, drugs administered frequently were caffeine, citrate, surfactant, vancomycin, furosemide, metoclopramide, dopamine,

nystatin and aminophylline. In contrast, full-term newborns received ampicillin, gentamicin, cefotaxime, phenobarbital, morphine and vitamin K. After that first analysis, they evaluated which medications were the most frequently used in newborns with a mortality >20% and they found that in premature newborns the most frequently used were amphotericin B, lysosomal amphotericin and bumetanide, whereas in full-term newborns the most common drugs were clonazepam, milrinone, nitric oxide and phenytoin. Authors suggest that these findings should be further investigated in order to find possible relationships between death and the use of one or several medications.

The presence of ADRs related to drugs received by children through breastfeeding (without including abused drugs) identified that in 100 children <2 years old, 47% of ADRs were regarded as probable and 53% as possible. Of these, 63% occurred in newborns and 37% in children <2 months old.⁴⁷

Between 1997 and 2000, the FDA received 500,000 ADR reports of which 7,111 were for children <2 years old. This represented 243 deaths per year. Of these, 41% occurred during the first month of life. Exposure to the medication occurred during pregnancy, birth, or breastfeeding. Of 1902 different medications, biological products or other substances administered, only 17 were considered as the suspected cause in 54% of severe or fatal ADRs. The incidence of ADR in the newborn was ~10%.⁴⁸

Some of the most important elements for pharmacovigilance analysis are medication usage patterns in NICUs with evaluations on antibiotic tolerance and recording of ADRs as mentioned in one study⁴⁹ carried out over a 7-year period where a progressive increase of antibiotics (vancomycin and cefepime) and a significant decrease in the use of morphine was observed. Antibiotics were used to treat infectious diseases of the central nervous system, as well as endocrine, cardiovascular and gastrointestinal systems.

Regarding the use of non-approved medications in children (unlicensed) and those used outside the appropriate time range (off-label), it is worth mentioning the systematic review carried out in the pediatric population⁵⁰ where 52 studies conducted between 1999 and 2006 allow the identification of the

fact that unlicensed and off-label drugs were used with a higher frequency in the neonatal areas, followed by ICU and oncology services. The most frequent ADRs were for unlicensed and off-label drugs. Finally, in a recent publication,⁵¹ a study carried out during 2 years in a Chicago NICU revealed that with 2,304 admissions there were 61 medications used where 45% prescribed were off-label, with a higher incidence of analgesics, vasopressors and hematological drugs.

Surveillance Strategies

Because ADRs and ADEs in children represent an important health care problem and have gone beyond organizations and the public in general, it is necessary to propose different strategies in Mexico that allow a decrease in the number of ADRs for the pediatric population:

1. Specific communication of all matters related to pharmacovigilance in public and private institutions
2. Prepare well-qualified personnel to assist children during the prescription process, preparation, supply and administration of medications
3. Create a system that verifies the quality as well as correct usage of medications
4. Create an educational program using web technology including examinations
5. Create a manual (printed or digital) with specific dosages for each pediatric age, as well as dosages according to body weight and surface area where administration times are clearly specified, as well as other relevant information
6. Make a list of medications approved by Mexican Health Authorities that clearly identifies those medications not approved for use in children and the age limit for their prescription
7. Implement policies that allow identifying incomplete or incorrect prescriptions where the physician receives feedback on those errors and presents the results during relevant meetings⁵²⁻⁵⁴
8. Standardize medication dosages in children based on relevant evidence or pharmacokinetics and pharmacodynamics
9. Specify, in greater detail, adverse drug

events, adverse drug reactions, medical errors, overdose, etc.

10. Include as a medical error the processes for prescription, supply, administration, drug interaction in patient, and management
11. Use bar codes to fully identify medications
12. Establish a medications committee that defines those considered as “Basic Formulary Medications” and also specifies those that are considered as pharmacovigilant activities
13. Employ qualified pharmacy personnel
14. Establish policies to avoid, as much as possible, verbal prescriptions
15. Implement during the midterm (next decade) control systems to reduce errors such as computerized monitoring based on laboratory test results that have demonstrated high sensitivity but low specificity^{55,56} (use of other automated systems has yet to be assessed regarding their cost-benefit ratio and results published in literature are inconclusive)⁵⁷

In conclusion, as we have elucidated in each section of the current study, actions that should be carried out to comply with international norms and the Mexican Official Norm (NOM) require continued education where healthcare professionals should become involved both in the public and private sector. As we mentioned, Mexico ranks behind other countries in the control and reporting of ADRs when compared to the international community. We consider that the articles selected here are high-quality research examples and demonstrate consequences of ADEs and ADRs in the general population, including the pediatric population.

Therefore, a series of actions is suggested nationally and the Hospital Infantil de Mexico implemented one of these at the end of the year 2007 with a pharmacovigilance computerized system that allows each area to report ADRs, print them in the specific format for the NOM and send to the National Pharmacovigilance Center. The information may also be used reliably with research and educational purposes. The path is long, but we must begin the walk.

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