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Lack of drug preparations for use in children in Brazil

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Abstract

Objective: To identify drugs which are not suited for pediatric use in Brazil.

Methods: A descriptive study involving the development of a national list of unlicensed and off-label medications for pediatric use (problem drugs in pediatrics, PDP) through a literature review, a comparison among sources of the Brazilian pharmaceutical industry, and a survey with pediatricians. Drugs coded at the Anatomic Therapeutic Chemical (ATC) classification system were analyzed regarding licensing status in Brazil and recommendations/indications in pediatrics, based on the following reference sources: the list of licensed drugs of the Brazilian National Health Surveillance Agency (2005), the Brazilian Dictionary of Pharmaceutical Specialties (2005-2007) and the website www.bulas.med.br.

Results: Our literature search returned 126 PDP, but 24 drugs were excluded due to absence of national reference. To compose the final list, 24 other drugs referred by pediatricians were added. Of the 126 PDP, 23 drugs were not licensed in the country for use in children; and of the 103 licensed drugs, 24 presented age-related restrictions for pediatric use. The pharmaceutical list included 42 therapeutic groups and 68 subgroups. The groups containing larger numbers of PDP were: antibiotics for systemic use (15), antiepileptics (8), antiasthmatics (7), and analgesics (7). The most frequent problems were: inappropriate dosage (35), unlicensed for pediatric use (28), age-related restrictions (23).

Conclusions: The lack of pediatric drug formulations in Brazil shows a profile similar to that observed in other countries, which involves a wide range of clinically important products. This study brings a contribution to the evaluation of the needs and priorities that support the development of suitable medicines for the pediatric patient.

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Introduction

Prescription of unlicensed or off-label medications in children is a reality associated with factors such as absence of licensed products for pediatric patients, lack of suitable pharmacological formulations, and high prevalence of marketed drugs with absence of specific pediatric labeling information.[1-4] Due to these difficulties, the use of medications in children is likely to be less safe and results to be less predictable and reliable than in adults. This is a reality in the world today.[5-7]

Only recently, however, has attention been devoted to unlicensed or off-label drug use in children by regulatory authorities, even in developed countries. Thus, in the USA, regulatory actions proposed by the Food and Drug Administration have attempted, since the 1990s, with

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partial and questionable success, to financially motivate the pharmaceutical industry to provide required and adequate drugs for use in children.[5]

In turn, the European Medicines Agency (EMEA) established, in the beginning of 2007, a set of actions including specific regulation in the licensing of medical products for pediatric use, incentive to clinical research and development of pediatric drugs.[8] Within the United Kingdom, regulatory authorities have also adopted a similar specific policy involving regulatory actions, a network for pediatric drug investigation and development of a specialized therapeutic formulary (the British National Formulary for Children, BNFC).[7]

In global terms, the World Health Organization (WHO) introduced, in 2007, the first list of essential drugs for children together with a survey on research priorities in this area and a campaign with the slogan *Make Medicine Child Size*, drawing the world's attention to this issue.[7]

With respect to Brazil, a specific regulation for labeling and use of pediatric drugs is yet to be established, as well as a policy to stimulate clinical research in pediatrics. A few studies carried out in the country have demonstrated that, similar to other settings, unlicensed or off-label drugs used in inappropriate age groups, as well as inadequate drug use in general, is frequent particularly in hospitalized children.[9-13] Therefore, the lack of products with characteristics suited for use in children may be an important risk factor for adverse drug reactions and poisoning, a situation that has been observed in the country, as well as in other realities.[14]

The objective of the present study was to identify drugs that show problems for their pediatric use in Brazil because they are not available in an adequate pharmaceutical formulation or do not have a specific pediatric indication, pointing to the need for research and development in this area.

Methods

A literature review was conducted to identify drugs whose pharmaceutical dose form or formulation represents a problem for pediatric use, resulting in a group of medications that we called problem drugs in pediatrics (PDP). In order to do that, we conducted literature searches of the following databases: Medical Literature Analysis and Retrieval System Online (MEDLINE), from January 1993 to May 2005; *Literatura Latinoamericana y Del Caribe en Ciências de la Salud* (LILACS), from January 1982 to May 2005; and Scientific Electronic Library Online (SCIELO), from July 1999 to May 2005; using the following descriptors: drug utilization children, drug children, paediatric prescribing, off label children, drug preparation, non-prescription drugs, methods of drug preparation; and, as limits, the following words: humans, newborn; humans, child; humans, preschool; and humans, infant.

Of the articles retrieved, those which included the name of medications identified as problem drugs, as well as the nature of the problem, were selected, and data on unlicensed and off-label drug use in different age groups and clinical practices were collected.

In the present study, we included under the unlicensed category those drugs not approved or contraindicated for use in children, prepared or modified in the pharmacy department of a hospital, or without a specific drug dosage for children. Under the off-label category, we included drugs prescribed outside the product license regarding age group, frequency, formulation, route of administration, and pediatric indication.[2,4,15]

From this preliminary list, we excluded those drugs commercially unavailable in Brazil, which returned from our search of the following sources: the Brazilian Dictionary of Pharmaceutical Specialties (Dicionário de Especialidades Farmacêuticas, DEF) (2005-2007); the website www.bulas.med.br; the therapeutic formulary of the Department of Health of State of Ceará, northeastern Brazil; and the list of licensed drugs of the Brazilian National Health Surveillance Agency (*Agência Nacional de Vigilância Sanitária*, ANVISA).[16-20] To compose our final list, we added those PDP identified through a survey with pediatricians from a public reference hospital in the city of Fortaleza, State of Ceará, Brazil.[21]

The identified drugs were coded at the Anatomic Therapeutic Chemical (ATC) classification system and their frequency analyzed regarding therapeutic group and subgroup and type of problem identified.[22] Drug labels of all pharmaceutical specialties were analyzed regarding pediatric indication, pharmaceutical formulation and exclusion of use in subgroups defined by age or weight, based on the following reference sources: DEF, ANVISA list of licensed drugs, and the website www.bulas.med.br.[16-20] A survey on the pharmaceutical formulations needed in the country was carried out by comparing with a list containing data from the following sources: BNFC (2007), Pediatric Dosage Handbook (2005) and List of Essential Drugs for Use in Children, published by WHO.[14,23,24]

Results

The search strategy retrieved 44 articles, 26 of which were excluded because the names of the drugs involved were not mentioned. The 18 studies included in the analysis were carried out in 20 different countries, as follows: European countries (14), Brazil (2), USA (1), New Zealand (1), and Israel (2). Of all papers, 13 investigations were conducted in hospitals, two in primary health care centers and three in other settings.[1-4,9,10,25-36]

In the selected articles, 126 PDP were identified, but 24 of these were excluded due to absence of reference in the sources searched in the Brazilian market. As shown in Table 1, the list of excluded drugs contains several natural products (extract of *Echinacea purpurea* and *Lichen islandicus*, herbal extract and mucolytic formulation, and formulation with camphor and *Crataegus*) and single drugs that, in Brazil, are available only in drug associations (caffeine, dihydroergotamine, framycetine, pyridoxine and tyrothricin).

To the remaining list (n = 102), we added 24 drugs suggested by pediatricians in a survey conducted at the same hospital, thus composing the final list of 126 PDP.[21] This final list included 42 therapeutic groups and 68 subgroups, allocated according to the ATC classification. The therapeutic groups containing larger numbers of PDP were: antibiotics for systemic use (15), antiepileptics (8), antiasthmatics (7), and analgesics (7). The most frequent therapeutic subgroups (drug classes) were: antiepileptics (7); penicillins, β-lactam antibiotics (6); decongestants and other nasal preparations for topical use (5).

Of the 126 drugs in the national list, 23 were not licensed for use in children in Brazil; and of the 103 licensed drugs, 24 showed age-related restrictions for pediatric use. Table 2 shows unlicensed drugs, as well as drug use restricted by age group and weight. The first group comprises antibacterials, antihypertensives, diuretics, analgesics, anti-inflammatories, among other drugs. The licensing status concerns pharmaceutical dose form or formulation specified in the national PDP list.

Restrictions regarding age group were divided into groups, as follows: neonates and up to 2 years of age (11 PDP), 3 to 6 years of age (8 PDP), and over 10 years of age (5 PDP).

Table 3 shows pharmaceutical formulations for oral administration considered as necessary according to the pediatricians' responses to the survey, or by comparing with the reference sources searched,[14,20-22] but that are currently lacking in the country. It is worth mentioning that "lack" could be related not only to dose form/formulation, but also to drug dosage. Of 86 pharmaceutical formulations considered as necessary for oral administration, 54 concerned solid dose forms, 38 being tablets, seven chewable tablets, six capsules, and three powder for oral suspension. In addition, 32 medications were considered necessary as liquid, 21 being in the form of oral solution, seven in the form of syrup, and four in suspension. Table 4 shows a list of drugs with the pharmaceutical formulation and dosage needed. PDP lacking injection and nasal, ophthalmic, and rectal formulations are also listed in Table 4.

Discussion

In the present study, we used an indirect method of identifying medications whose pharmaceutical formulation represents a problem in pediatric practice. Such method was based on the identification of unlicensed and off-label drugs in studies published in the international literature, on the subsequent identification of such products in the Brazilian pharmaceutical market, and on the enhancement

Table 1 - List of problem drugs commercially unavailable in Brazil

Isolated drugs (n = 20)	Associated drugs (n = 4)
Caffeine	Codeine and buclizine
Cyclizine	Doxylamine and paracetamol
Cetylpyridinium chloride	Formulation with camphor and *Crataegus*
Dihydrocodeine	Herbal mucolytic formulation
Dihydroergotamine	
Echinacea purpurea extract	
Herbal extract	
Lichen islandicus extract	
Framycetine	
Chloral hydrate	
Levetiracetam	
Malathion	
Nicardipine	
Noscapine	
Pyridoxine	
Pipenzolate	
Succimer	
Sulthiame	
Tyrothricin	
Urokinase	

Table 2 - Unlicensed or off-label problem drugs for pediatric use in Brazil

Unlicensed drug	Drug	Number of drugs
Pediatric use	Acetazolamide, ursodeoxycholic acid, allopurinol, amiloride, atropine (tablet), azithromycin (injection), bethanechol, candesartan, ciprofloxacin, diclofenac (topical gel), etoposide (capsule), filgrastim, fludrocortisone, gabapentin, lorazepam, nifedipine, nimodipine, ofloxacin, sucralfate, protamine sulfate, warfarin, multivitamins and minerals, codeine, buclizine	23
0-2 years old		11
Neonates and over	Cyclopentolate	
Age 6 months and over	Clobazam	
Age 1 month and over	Dipyrone	
Age 1 year and over	Flumazenil, diclofenac suspension, omeprazole	
Age 2 years and over	Transdermal fentanyl, griseofulvin, loratadine, ketoconazole, salbutamol syrup	
3-6 years old		08
Age 3 years and over	Vigabatrin, codeine	
Age 4 years and over	Ondansetron, fluticasone dipropionate	
Age 5 years and over	Ivermectin	
Age 6 years and over	Beclomethasone dipropionate, formoterol, xylometazoline	
> 10 years old		05
Age 10 years and over	Digoxin	
Age 12 years and over	Lamotrigine, amphotericin B (capsule), magaldrate	
Age 14 years and over	Diclofenac tablet	
Total		47

of the resulting list with responses to the survey carried out with pediatricians in the city of Fortaleza, State of Ceará, Brazil. The studies included in our review were conducted in several countries, in different settings (hospitals, outpatient clinics and community health care facilities), and involved a representative sample, indicating a comprehensive resulting list that might be useful as a reference source in determining national needs in terms of pediatric drugs. It is possible that additional PDP have escaped identification through the indirect method herein employed; however, the most representative drugs were surely apprehended.

The search strategy revealed that most of PDP (79.37%) found in the international literature were marketed in Brazil, indicating that similar problems might occur among different countries and, therefore, solutions to resolve these problems should be shared. Our national PDP list included therapeutic groups highly used in children, such as antimicrobials, anticonvulsants and antiasthmatics. On the other hand, medications excluded from the list due to lack of reference in the Brazilian market show low or none therapeutic relevance, such as plant extracts, cisapride (withdrawn from the Brazilian market and from other countries as a matter of safety) and medications with questionable clinical benefits.[37] Of the 26 unlicensed drugs for use in children in Brazil, which were included in our national PDP list, six are cited in the BNFC (2007) and are licensed in the United Kingdom, including amphotericin B, ciprofloxacin, diclofenac sodium, gabapentin, lorazepam, and mesalazine, which means that safety, efficacy and clinical relevance of these products have been recently assessed by specialists in the area, and risks have been considered acceptable. Therefore, a regulatory action by ANVISA is needed to provide incentive for the pharmaceutical industry regarding development and request for new product licenses, according to their clinical usefulness in Brazil. Some medications in the PDP list are not licensed for use in children in other countries, but are licensed for pediatric use in Brazil, namely: flumazenil, transdermal fentanyl, vigabatrin, formoterol, xylometazoline, and loratadine. A critical evaluation of the alternative therapeutics used in such countries would be necessary to verify whether these drugs are, actually, the best choices for use in children. By analyzing licensed pediatric drugs with age-related restrictions in Brazil, we concluded that treatment of under-2-year-old children is

Table 3 - Drugs currently marketed in Brazil and the need for new formulations for oral administration

Pharmaceutical formulation	Formulation needed	Number of drugs
Solid dose form		
Tablet	Folic acid (0.1 mg, 0.4 mg, 0.8 mg and 1 mg), folinic acid (5 and 10 mg), amitriptyline (10 mg), captopril (2 mg), carbamazepine (10 mg), calcium carbonate (250 mg), cephalexin (125 mg), dantrolene (25 mg, 50 mg and 100 mg), diazepam (2 mg), digoxin (62.5 mcg and 125 mcg), phenytoin (30 mg, 50 mg), phenobarbitone (15 mg, 16 mg, 30 mg, 32 mg, 60 mg and 65 mg), furosemide (20 mg), griseofulvin (250 mg), griseofulvin microsize (165 mg, 330 mg, 125 mg and 250 mg), isoniazid (150 mg), metoclopramide (5 mg), prednisone (1 mg, 2.5 mg), promethazine (5 mg), tocopherol (100 IU, 200 IU)	38
Chewable tablet	Carbamazepine (100 mg), calcium carbonate (320 mg and 420 mg), phenytoin (50 mg), ibuprofen (50 mg, 100 mg), betamethasone (500 mcg)	07
Capsule for oral use	Griseofulvin (125 mg, 250 mg), hydrochlorothiazide (12.5 mg), theophylline (50 mg, 65 mg, 75 mg)	06
Powder for oral suspension	Amoxicillin and clavulanic acid (125 mg + 125 mg), vancomycin (250 mg/5 mL, 500 mg/6 mL)	03
Liquid form		
Oral solution	Aminophylline (105 mg/ 5mL), baclofen (5 mg/5 mL), captopril (5 mg/mL), calcium carbonate (200 mg/mL), cimetidine (100 mg/10ml), caffeine citrate (20 mg/mL), diazepam (5 mg/5 mL, 2 mg/5 mL), spironolactone (5 mg/5 mL, 10 mg/5 mL, 25 mg/5 mL, 50 mg/5 mL, 100 mg/5 mL), phenobarbitone (15 mg/ 5 mL, 20 mg/5 mL), hydrochlorothiazide (50 mg/5 mL), morphine (10 mg/5 mL), ondansetron (4 mg/5 mL), prednisone (5 mg/mL), propranolol (4 mg/mL or 8 mg/mL)	21
Syrup	Chloroquine (80 mg/5 mL, 50 mg/5 mL), isoniazid (50 mg/5 mL), lithium citrate (300 mg/5 mL), midazolam (2 mg/mL), promethazine (6.25/5 mL), theophylline (80 mg/15 mL)	07
Oral suspension	Azithromycin (100 mg/5 mL), ketoconazole (100 mg/5 mL), hydrocortisone cypionate (10 mg/5 mL), griseofulvin (125 mg/5 mL)	04

Table 4 - PDP currently marketed in Brazil and the need for new formulations for injection and other administrations

Pharmaceutical formulation	Formulation needed
Injection	
Solution	Adrenaline chloride (0.01 mg/mL, 0.1 mg/mL, 0.5 mg/mL) human albumin (5%), amitriptyline (10 mg/mL,), atropine sulfate (0.1 mg/mL, 0.4 mg/mL and 0.8 mg/mL), baclofen (50 mcg/mL), caffeine (20 mg/mL), clonazepam (100 mcg/mL), chloroquine (40 mg/mL), digoxin (100 mcg/mL), dopamine (40 mg/mL), erythromycin lactobionate (500 mg), heparin (1000 units per mL), hydroxyzine (10 mg/5 mL), mercaptopurine (500 mg), paracetamol (injection 150 mg/mL), tobramycin (10 mg/mL)
Powder	Azathioprine (100 mg), rifamycin (600 mg), procaine penicillin G (500,000 units/mL, 600,000 units/mL)
Intravenous infusion	Dopamine (0.8/mL, 1.6/mL, 3.2 mg/mL)
Nasal use	
Capsule for inhalation	Beclomethasone (100 mcg), salbutamol (0.02 mg)
Spray	Salbutamol (90 mcg/dose)
Solution for inhalation	Tobramycin (60 mg/mL), ipratropium (nasal spray 0.03%, oral inhalation 18 mcg/dose, nebulizer 0.02%)
Ophthalmic use	
Ointment	Dexamethasone (0.05%), gentamicin (0.1%)
Ophthalmic solution	Diclofenac (0.1%)
Rectal use	
Suppository	Domperidone (30 mg), morphine (5 mg, 10 mg)
Rectal suppository	Hydrocortisone base (100 mg/60 mL)

PDP = problem drugs in pediatrics.

extremely hindered by the lack of evidence for safe and effective drug use in this population. Other countries share this common condition, such as the USA, where the majority of drugs granted pediatric license do not provide labeling information for the use in under-2-year-old children.[25]

Age-related restrictions vary greatly among countries, indicating low-consistency information and the need for a consensus between specialists regarding this issue. For example, griseofulvin is licensed for pediatric use, with no age-related restrictions, in several countries, whereas in Brazil its use is allowed only in children aged 2 years or over, according to the labeling information of Sporostatin®.[20] Cyclopentolate is indicated for children aged 3 months or over in the BNFC (2007), whereas in Brazil it is licensed for use in children over 1 month of age. Codeine is considered an important drug in the treatment of pain in the United Kingdom, intramuscular route being used to children over 1 year of age, whereas in Brazil it is indicated only for use in children over 12 years of age, according to labeling information.[14,25]

Solid dose forms represent the majority of drugs with inadequate dosage indication for children, therefore the need to crush tablets to make them suitable for children. In a previous article, we revealed procedure failures in a Brazilian children's hospital regarding fractioning and crushing tablets to prepare suspensions.[21] These stages present risk of dose inaccuracy and even loss of effectiveness of the medication. By analyzing the drugs available in Brazil in tablet form, and required in lower doses for children (Table 2), we identified drugs that are essential to the treatment of epilepsy and convulsion (diazepam, phenytoin, phenobarbitone, and carbamazepine), as well as corticosteroids (prednisone and betamethasone), diuretics, and antihypertensives (hydrochlorothiazide, furosemide and captopril). Some of these dosages are already commercially available in countries other than Brazil, where these drugs should be marketed as well.

Some of the PDP not available in liquid form in Brazil are widely used in hospitals and prepared in the pharmacy department of the hospital, commonly hydrochlorothiazide, spironolactone, captopril, griseofulvin, ketoconazole, prednisone, isoniazid, and baclofen.[29] The use of solid oral dosage forms to prepare new formulations is a well-known risk factor, since little information exists to support the bioavailability and the physical, chemical and microbial stability of the final product.[14]

We also verified a need for lower doses of powder for oral suspension of some anti-infectives, such as cephalexin, amoxicillin, and amoxicillin associated with clavulanic acid – which are already marketed in countries other than Brazil –, the latter being available only as injection in Brazil.

Other drugs needed in lower doses to facilitate their administration to younger children include: phenobarbitone, cimetidine, aminophylline, azithromycin, promethazine, and ondansetron; all of them already available in other markets. With respect to injections in lower doses, it is worth mentioning that dilution of the currently available products represents a significantly high risk and might cause severe damages due to under- or overdosage. We should also take into account the subsequent economic losses associated with storage problems and short duration of product action.

A medication that is currently lacking in the arsenal of drugs for pediatric use in Brazil is the caffeine citrate, well-known as a useful tool in the treatment of apnea in preterm infants, which is not marketed in Brazil as a single drug, but only in association with analgesics.

In the identification of oral formulations lacking in the country (Table 2), some drug associations were suggested by the interviewees, such as vitamins and minerals, codeine and buclizine; however, according to our reference sources, these associations are not considered adequate due to a high risk for inappropriate use and variation in dosage management.[21]

The lack of adequate drugs for pediatric use is a problem worldwide, with some aspects peculiar to Brazil. The existence of technical, scientific and industrial capacity in the country in the pharmaceutical field allows us to conceive of an effective policy by the Brazilian Ministry of Health and ANVISA to foster research on medications for use in pediatric patients, as observed in many countries around the world. In order to do that, clinical research in pediatrics should be fostered as well, through specific announcements and programs funding the development of qualified researchers in this area. In addition, it must be emphasized that there will always be a need for drug manipulation by the hospital pharmacy, hence the need for appropriate laboratory infrastructure and qualified professionals, situation which has yet to be improved in the country.[38] At last, it sounds important to include basic knowledge on pharmacotechnique and pharmaceutical calculations as part of the education and information delivered to all prescribers in order to help them on the delicate task of adapting formulations and accommodating dosages for pediatric patients.

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