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Assessment of Iran Medicine List for the Appropriateness of the Six Pharmacological Formulations for Children's Prescription: A Cross Sectional Study

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Abstract

Background: The administration of pediatric medicines in an accurate manner for successful therapy is imperative. This study aimed to investigate the Iran Medicine List for the appropriateness of the six pharmacological formulations for children populations to the success of accurate dose delivery.

Materials and Methods: This is a cross-sectional study to evaluate oral delivery of the pediatric medicines that belong to six pharmacologic categories including anti-infective, anti-asthma**,** non-steroidal anti-inflammatory drugs, corticosteroid, cardiovascular and oral-rehydration-therapy in Iran. WHO pediatric model list has been assigned as the pattern of evaluation. The compatibility of the pediatric liquid formulations for oral route of administration, in Iran Medicine List, has been assessed. To evaluate the efficiency of oral liquid formulations for delivering the appropriate dosage and determining the amount of medication waste, minimum and maximum therapeutic range of each medicine for defined diseases was calculated according to six-year old child's weight. Also, to obtain the minimum amount that could easily deliver the appropriate dose, as well as availability of selected medicines at the pharmacy level, an in-house questionnaire was prepared, validated, and was filled by 40 pediatricians and pharmacists.

Results: The results of comparison between the two lists showed that, among 106 medicines of WHO model list, only 37 medicines had liquid oral formulation and 13 medicines have not been registered in Iran Medicine List. Results obtained from questionnaire indicated that between these 37 oral liquid formulations, just 20 formulations are available in pharmacies.

Conclusion: Based on the results, almost half of the medicines defined in the WHO model list are either not listed in Iran Medicine List or are not in appropriated formulation for pediatric use.

Key Words: Children, Essential Drugs, Medicine List, Pharmaceutical Formulation.

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1- INTRODUCTION

Access to the safe medicine in appropriate dosage forms as the main tool for fighting illness could improve equality of individual lives and in some cases treat life-threatening illnesses. Pediatrics characteristics, growth and development are the major cause of dose adjustment complexity that may lead to the different dosage forms for medication adherent in children (1-5). Children absorb and metabolize a medicine in different ways in comparison to adults (6), while the rapid developmental and biochemical changes especially in early infancy (7) simply emphasize that children must not be considered as "small adults".

Children require formulations that allow administration of accurate therapeutic dose, with attention to different ages and weights of children, while most formulations have not been designed in suitable forms for them (8). In this regard, only one third of pediatrics medicines have safety and efficacy studies, which often leads to off-label and unlicensed use of adult medications (9). This point is usually ignored in developing a new medicine or prescribing it for children.

The factors describing poor results in compliance with prescribed pediatric medicines could be considered in different perspectives including patients, their caregiver and the policymakers. In order to stimulate the further development of better medicines for children, several issues such as capability of swallowing solid forms, taste of formulation, clarity in purpose of prescribed medicine and the efficiency of medicines in pediatric pharmaco-therapy need to be addressed (10). A careful review on the development of liquid dosage forms represents that the oral liquid formulations are more acceptable than solid form and injection for children. American academy of pediatrics has also recommended liquid formulation as one of the best optional formulation for the long-term treatment (11). According to the Pediatric Pharmacy Advocacy Group, for each new chemical compound with unclear safety and efficacy data in children, if oral liquid form of medicine is not available, the manufacturer should produce a formulation with the ability to convert to the oral liquid solution or suspension easily and efficiently (12). A significant number of medicines used for pediatric groups due to unavailability of the liquid formulation are administrated in ways which are totally different from the way that the active substance is formulated into a finished product. These ways such as crushing tablets and dispersing in appropriate liquid or mixing the capsule contents with food may not ensure that accurate dose is delivered, also excipients may be harmful for the children (13). World Health Organization (WHO) reported documents states: the pediatric "holy grail" is an oral liquid preparation (12), which indicates difficulties for children under six years old to swallow whole capsule or tablet.

As an alternative to appropriate formulations, the availability of the preferred formulations and the dose capability (the capability of therapeutic administered doses with available medicine in the market) are other important drivers of pediatric medicines (14). Taken together, these factors help to provide a conception to evaluate the appropriateness of a medicine for children. The Iran National Drug Policy (INDP) is promulgated in accordance with the National Medicine List (NML), which is updated every year. This list is selected by Iran Medicine List Selecting Committee (IMLSC), and contains all required supplies for drugs management including registration and procurement for a medicine that is in the Iran Medicine List (IML). Since an appropriate medicine list has considerable benefits and impacts on health and economic status, it seems

that evaluation of this list could be used as the basis of evaluation for country-adapted policies. In this study, we examined six pharmacologic categories of medicines in IML in order to determine the position of oral liquid formulations among all categories. In addition to this, oral liquid form of drugs has been evaluated if they can deliver accurate therapeutic dose conveniently. These categories among different pharmacologic categories were selected because two of them i.e., anti-infective and non-steroidal anti-inflammatory drugs (NSAIDs) are the most prescribed medicines in children and there is a requirement for suitable formulation in other categories from pediatrician's point of view. Therefore, the main objective of this study was assessment of Iran Medicine List for the appropriateness of the six pharmacological formulations for pediatric prescription.

2- MATERIALS AND METHODS

2-1. Evaluation of oral liquid formulations among other formulations

Medicines evaluated in this study were selected from WHO model list of essential medicines (including formulation date and dosage of medicines) for pediatrics (14) including oral-rehydration anti–asthma, ant-infective, corticosteroids, cardiovascular and NSAIDs (15). Information of Iran medicines was obtained from IML, which includes drug information consisting of dosage and route of administration (16). Medicines were categorized in four classifications of medicines including medicines with and without oral liquid form (oral tablet or capsule form), groups including both illiquid and injectable form, medicines that are available only in the injectable form and lastly medicines that are not registered in the national list. Then, medicines with an oral liquid form were observed to see whether they deliver accurate therapeutic dose in a convenient way. To evaluate the efficiency of oral liquid formulations for delivering the appropriate dosage and determining the amount of medication waste, minimum and maximum therapeutic range of each medicine for defined diseases was calculated according to six-year old child's weight. The calculated range was compared to labeled dose. To this end, the information was obtained from three references, an updated version of the British National Formulary for children, July 2014-2015, offline Up to date, version 21.2, 2013 and Medscape accessed in June 2016 (10, 17, 18).

2-2. Evaluation of oral liquid formulations for accurate delivery of therapeutic doses

Therapeutic dosage has been calculating considering age, weight and type of use in different diseases. Age categories were extracted from British National Formulary for children (10), containing arrangement of therapeutic doses with a minimum and maximum. A comparison between this range and labeled dose of the sample oral liquid form (IML registered), indicated the capability of these forms to deliver an accurate therapeutic dosage through its related tool for serving.

In this study we focused on a reliable way of how the whole process is done to meet the desired goal. To achieve this goal, the dosage of each medicine was calculated with respect to the different types of diseases, ages and corresponding weights. By using results of the previous step, a dosage range was achieved for each oral liquid medicine with a minimum and maximum amount for its dosage. Then the labeled dose of each medicine was compared with its range thresholds. By analyzing the results, it can be concluded whether it is convenient to deliver accurate therapeutic dosage of a medicine through its related tool for serving or not.

From pediatricians and pharmacists' point of view, it is difficult for a caregiver to administrate an amount less than 1ml of oral liquid medicines to a child and most of the time, an adverse error occurs. In addition, if maximum therapeutic dose of a medicine is much more than labeled dose, it is difficult to deliver the amount to a child. In order to evaluate the availability of medicines in liquid form in pharmacies and to estimate the necessity of this formulation in a way to deliver medicines with the least mistake, an in-house questionnaire was planned, validated and distributed to 20 pharmacies and 20 pediatricians. The questionnaire includes respondent's demographic information, information on the availability of medicines in pharmacies, the best dosage form in terms of pediatric administration and the most appropriate measure to minimize caregiver errors.

3- RESULTS

3-1. Determination of oral liquid formulations among pediatric medicines

Among the checked 106 pediatric medicines, 37 medicines (34.9%) are available in oral liquid forms, 14 (14.1%) of them are only available in injectable form. 32 (30.1%) medicines have just the solid form (tablet or capsule), while they do not represent appropriate form for use in children less than six years old. Ten (9.34%) medicines lack the form of oral liquid, but they are available in both oral solids and injectable form, that can be used orally or injected depending on the indications. Thirteen (12.2%) remaining medicines have not been registered in the IML (**Table.1**). In the WHO model list, 10 medicines have oral liquid forms, but they do not have oral liquid formulations in IML and are currently used in solid form or parenteral route (**Table.2**). Results obtained from questionnaire indicated that, some medicines such as Levamisol, Fluconazoland and Chloramphenicol are registered and present in IML in the oral liquid forms, but are not available in pharmacies.

Table-1: Classification of medicines according to their formulations in IML (16).

Medicines	Name	Number (% of total 106 items)
Medicines in oral liquid forms.	Ibuprofen, Acetaminophen, Dexamethason, Salbutamol, Digoxin, Albendazol, Levamisole, Pyrantel, Amoxicillin, Co-Amoxiclave, Ampicillin, Cefalexin, Penicillin V, Azithromycin, Chloramphenicol, Ciprofloxacin, Erythromycin, Metronidazole, Nitrofurantoin, Cotrimoxazole, Clindamycin, Vancomycin, Rifampin, Linezolid, Fluconazol, Nystatin, Abacavir, Lamivudine, Stavudine, Zidovudine, Efavirenz, Nevirapine, Lopinavir/Ritonavir, Oseltamivir, Valganciclovir, Chloroquine, Paromomycin.	37 (34.9%)
Medicines which just have parenteral forms.	Epinephrine, Dopamine, Benzylpenicillin, Cefazolin, Ceftriaxone, Cefotaxime, Ceftazidime, Imipenem, Gentamycin, Amikacin, Capreomycin, Streptomycin, Artesunate, Pentamidine.	14 (13.2%)
Medicines that just have solid forms.	Prednisolone, Enalapril, Mebendazol, Niclosamide, Praziquentel, Diethylcarbamazine, Triclabendazole, Trimethoprim, Clofazimine, Dapsone, Ethambutol, Pyrazinamide, Cycloserine, Ethionamide, Flucytosine, Griseofulvin, Potassium Iodide, Diloxanide, Pramiquine, Sulfadoxine/Pyrimethamine, Proguanil, Pyrimethamine, Sulfadiazine, Eflornithine, Ivermectin, Atazanavir, Darunavir, Ritonavir, Lamivudine/Zidovudine, Mitelfosine, Artemether/Lumefantrine, Mefloquine.	32 (30.1%)

Medicines which are in both parenteral and solid forms.	Hydrocortisone, Cloxacillin, Furesomide, Doxycycline, Levofloxacin, Isoniazide, Acyclovir, Ribavirin, Artemether, Quinine	10 (9.4%)
Medicines that have not been registered in IML.	Oxamniquine,Kanamycin,Abacavir/Lamivudine,Lamivudine/Nevirapine/Stavudine,Lamivudne/Nevirapine/Zidovudine,Entecavir, Amodiaquine, Artesunate/Amodiaquine, Artesunate/Mefloquine, Suramin Sodium, Nifurtimox, Melarsoprol, Benznidazol	13 (12.2%)

IML: Iran Medicine List.

Table-2: Some of the medicines which do not have oral liquid formulation in IML (16) but there are oral liquid forms in WHO model list (15) for them.

Medicines	Formulation in IML	Oral liquid form in WHO model list
Furesomide	Injection solution 10 mg/ml, tablet 40 mg	Oral solution 20 mg/5ml
Cloxacillin	Tablet and capsule 250,500 mg, powder for injection 250, 500 mg	Powder for oral liquid 125 mg/5ml
Doxycycline	Tablet and capsule 50 mg,100 mg, injection 100 mg/vial	Oral liquid 25 mg/5ml, 50mg/5ml
Acyclovir	Ophthalmic ointment 5%, topical cream 3%, tablet 200, 400, 800 mg, injection powder 250, 500 mg	Oral liquid 200 mg/5ml
Prednisolone	Tablet5,20,50 mg, ophthalmic drop1%	Oral liquid 5 mg/5ml
Trimethprime	Tablet 100 mg	Oral liquid 50 mg/5ml
Ethambutol	Tablet 400 mg	Oral liquid 25 mg/ml
Pyrazinamide	Tablet 500 mg	Oral liquid 30 mg/ml
Griseofulvin	Tablet 125,500 mg	Oral liquid 125 mg/5ml

IML: Iran Medicine List; WHO: World Health Organization; mg: milligram; ml: milliliter.

3-2. Relationship between medicines formulations and accurate delivery of therapeutic doses

According to the results of the questionnaire, 90% of the pediatricians completing the form believed that the most appropriate formulation for children's pharmacotherapy is the form of oral liquid (suspension, syrup, drops, etc.). From pharmacists and pediatricians' point of view and considering data gathered from questionnaire, administration of oral liquid medicines less than 1 ml would not be convenient for a caregiver and there is a high probability of making an error in administration. To this end, the amount of medicine present in each ml of selected medicines was calculated then compared to minimum therapeutic dose of defined indications (**Table.3**). **Table.3** also represents the medicines which may not deliver accurate therapeutic dose for infants and small children in a convenient way, and the feasibility of accurate dose delivery is uncertain for them. Although all of the medicines which come in oral liquid part, are included in IML, some of them have not been registered yet to be accessible in Iran and are not available in pharmacies.

Table-3: Minimum and maximum of therapeutic dosages for children less than six years-old, registration of oral liquid forms for use in Iran (10, 17, 18).

Medicine	Oral liquid form in IML	Whether medicine has been registered?	Minimum and maximum of therapeutic doses for children less than six
Ibuprofen	Suspension 100 mg/5ml	Yes	30-1025 mg
Acetaminophen	Suspension100 mg/5ml, 120 mg/5ml, solution 100 mg/5ml, 120 mg/5ml	Yes	45-300 mg
Dexamethasone	Elixir 0.5 mg/5ml	No	0.2-42 mg
Salbutamol	Syrup 2 mg/5ml	Yes	1.5-4 mg
Digoxin	Elixir 0.05 mg/ml	Yes	0.05-2 mg
Albendazol	Suspension 200 mg/5ml	No	32-512.5 mg
Levamisol	Syrup 40 mg/5ml	Yes	10-60 mg
Pyrantel	Suspension 250 mg/5ml	No	150-225 mg
Amoxicillin	Suspension 125 mg/5ml, 200 mg/5ml, 250 mg/5ml, 400 mg/5ml	Yes	110-500 mg
Co-amoxiclave	Suspension 156 mg/5ml, 312.5 mg/5ml 228 mg/5ml, 457 mg/5ml, 643 mg/5ml	Yes	1-5 ml of suspension 156 mg/5ml
Ampicillin	Suspension 125 mg/5ml, 250 mg/5ml	Yes	110-500 mg
Cefalexin	Suspension 125 mg/5ml, 250 mg/5ml	Yes	50-500 mg
Penicillin V	Suspension 125 mg/5ml, 250 mg/5ml	Yes	62.5-250 mg
Azithromycin	Powder for suspension 1gr/sachet, 100 mg/5ml, 200 mg/5ml, powder for solution 2gr	Yes	80-205 mg
Chloramphenicol	Suspension 150 mg/5ml	Yes	50-250 mg
Ciprofloxacin	Suspension 250 mg/5ml	No	35-410 mg
Erythromycin	Powder for suspension 200 mg/5ml	Yes	43-250 mg
Metronidazol	Suspension 125 mg/5ml	Yes	30-800 mg
Nitrofurantoin	Suspension 25 mg/5ml	Yes	4.5-15.4 mg
Cotrimoxazol	Suspension 200/40 mg/5ml	Yes	120-1230 mg
Clindamycin	Suspension 75 mg/5ml	No	10.5-250 mg
Vancomycin	Powder for suspension 500 mg/6ml	No	20-62.5 mg
Rifampicin	Suspension 20 mg/ml, oral drop 153 mg/ml	No	35-200 mg
Linezolid	Powder for suspension 100 mg/5ml	No	43-205 mg
Nystatin	Powder for suspension 100000 U/ml	Yes	100000-600000 U
Fluconazol	Suspension 200 mg/5ml	Yes	10.5-250 mg
Lamivudine	Solution 10 mg/ml	No	17-150 mg
Stavudine	Powder for suspension 5 mg/5ml	No	4.5-20 mg
Abacavir	Oral solution 20 mg/ml	No	48-150 mg
Zidovudine	Syrup 50 mg/5ml	No	50-200 mg
Efavirenz	Solution 150 mg/ml	Yes	200-450 mg
Nevirapine	Suspension 50 mg/ml	No	40-160 mg
Lopinavir/ritonavir	Solution 400/100 mg/5ml	No	50-200 mg
Oseltamivir	Powder for solution and suspension 60 mg/5ml	No	7-45 mg
Valgancyclovir	Powder for solution 250 mg/5ml	No	25-900 mg
Paromomycin	Syrup 125 mg/5ml	No	35-920 mg
Chloroquine	Syrup 25 mg/5ml, 50 mg/5ml	No	25-150 mg

IML: Iran Medicine List; WHO: World Health Organization; mg: milligram; ml: milliliter.

4- DISCUSSION

The main purpose of this study is to review and assess the Iranian Medicine List in six frequently used pharmacological groups in terms of appropriateness for pediatric prescription. According to the WHO model list for children (14), and the results obtained from the IML (15), among 106 drugs, just 17 (16.03%) medicines have oral liquid dosage form registered for use in Iran and available in pharmacies, delivering accurate therapeutic dose conveniently. Thirteen medicines have not been registered in the IML, mainly due to this fact that these medicines are used for African or American trypanosomiasis which is not prevalent in Iran. This study could be roughly defined as a sample for most of medicines in other pharmacologic categories. However, the trends reveal that there is a requirement for changes in order to help pediatric patients to be treated with suitable formulations and doses more effectively. When a suitable oral liquid formulation is not available, it is inevitable that a pediatrician prescribes a solid form for oral route of administration.

A crushed tablet or content of a capsule would be mixed with suitable food or drink and caregivers must prepare this mixture for each dose, resulting in an inaccurate dose delivery or making errors in dose preparation (8). Safety of excipients in these preparations are the other issue that may require a better collaborative action with manufacturer. In addition to appropriate formulation, optimal doses for oral liquid medicines and tools for serving accurate medicines to a child are the other points, which must be considered to have efficacious treatment. In this regard, where the desirable therapeutic dose is very low or there is a need to dilute an amount of medicine, children will be exposed to the risk of reduction in medication efficacy and safety. This suggests that the special considerations must be given to the medicines with narrow margin between effective therapeutic and toxic dosage. According to British National Formulary for children (10), an oral syringe is required to take accurate dose of oral liquid medicines. The syringe is marked in 0.5 ml divisions from 1 ml to 5 ml. However, the only measurement tool in Iranian medicines packages is a spoon, which is marked in the amounts of 2.5 ml, 5 ml and occasionally 10 ml, which makes it difficult for a caregiver to administrate accurate therapeutic doses to a child. This might validate the point that most of the therapeutic doses of the medicines in different diseases and ages should not be administered by spoon, and suggesting that this useless expenditure can be replaced by a suitable substitute. Moreover, the results obtained from the questionnaire in this study, showed that the administration of oral liquid medicines less than 1 ml would not be convenient for a caregiver and there is a high probability of making a mistake in administering it.

Researches in pediatric medicines formulations usually emphasize on the lack of appropriate formulation, off-label use of drugs and ignoring children in the process of developing a medicine. Most of them with the same direction signify the necessity of providing suitable treatment process in pediatrics. For example, in a study published in 1999 by the American academy of pediatrics different formulations and their stability to receive desired medicine doses more efficiently in children were discussed, while the current study presented the similar issues indicating that the concerns remain unsolved after many years (13). In this study, oral liquid formulation was preferred and the accessibility of this formulation and the feasibility of accurate dose delivery in pediatrics were the main segments to be considered. A similar study (19) has evaluated lack of appropriate oral solutions in relation to

status of licensing of medicine. The authors concluded that many of the children were treated by inappropriate oral liquid formulations. Concerning medicine formulations for children, it has been indicated that pediatric formulations must administrate accurate therapeutic dosage for different age and weight of children. In this regard, it should be considered that the oral liquid medicines are usually prescribed for children for long-term treatment, masking the bitter taste of these medicines and their stability are notable issues (9). Van Riet-Nales et al. have done a research reviewing the availability and age appropriateness of medicines in the Netherlands, based on dose, route of administration and harmful excipient examinations.

The results of this study showed the availability is limited for pediatric medicines, besides, the appropriateness of therapeutic dose of medicines and dosage form increased with age (14). Therefore, according to the issues discussed in this study, it seems that in order to improve pharmacotherapy of pediatric dosage, some modifications are necessary to be conducted in the medicine list in association with availability and accessibility of the essential medicines for children.

The main modifications include: addition of prevalent disease medicines which are not in IML, addition of oral liquid formulations which are not in IML, but the oral liquid forms are in WHO model list of essential medicines for children, take the required action for oral liquid formulations which are not registered, being made available in pharmacies, and replacing measuring spoon which can serve few doses of medicines accurately with a suitable substitute such as oral syringe or a drop preserving different doses accurately.

4-1. Limitations of the study

It was not possible to check all categories of medicines for children. There were no local guidelines available to calculate the precise amount of medication waste in terms of pediatric use.

5- CONCLUSION

The results of this study showed that almost half of the medicines defined in the WHO list model are either not listed in IML or are not in suitable formulation for pediatric use. Thus, the availability and accessibility of the essential medicines for children might be strongly improved by suggesting some modifications to the IML. Healthcare system, government and manufacturer must cooperate to improve medicines and formulations. The results of this research and some of the information that has been gathered can be a base for further studies. In addition, these data may be used as baseline information for policy makers to have a perspective of what changes in which backgrounds are necessary to provide appropriate formulations and doses with the most effective responses.

6- ABBREVIATIONS

NSAIDs: Non-Steroidal Anti-Inflammatory Drugs

WHO: World Health Organization

IML: Iran Medicine List

NML: National Medicine List

IMLSC: Iran Medicine List Selecting Committee.

7- CONFLICT OF INTEREST: None.

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