National Journal of Physiology, Pharmacy and Pharmacology

RESEARCH ARTICLE

Analysis of commonly used pediatric systemic antibacterial liquid formulations for rational drug therapy

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Received: October 05, 2016; **Accepted:** November 21, 2016

ABSTRACT

Background: Antibiotics are frequently prescribed medication. When drugs are dispensed in form of syrups or suspensions, appropriate volume should be dispensed in a bottle otherwise, it may result into wastage of drug, inadequate treatment, and resistance and also increased cost of treatment. **Aims and Objective:** The aim of our study was to analyze systemic antibacterial liquid formulations to ascertain the availability of adequate strength, volume dispensed for adequate treatment. **Materials and Methods:** The commonly available (IDR triple, Issue 2, 2016) oral liquid antibacterial formulations were analyzed. According to the weight of child (for 12 and 18 kg), amount of drug and requirement of number of bottles for 5 days were calculated. **Results:** Majority of manufacturers have dispensed inadequate volume of antibacterial drugs which was not sufficient for one course of therapy. For example, most of the formulations of cephalexin, cefixime, cefpodoxime, and amoxicillin + clavulanic acid were available in dispensing volume of 30 ml. This results into inadequate dose, wastage of drug (residual volume), resistance, and unnecessary social and financial burden to the patient. Hence, more number of bottles shall be required to complete a course of antibiotic. **Conclusion:** The dispensing volume of oral liquid dosage forms of most of the formulations were inadequate and thus, minimum amount dispensed should be 60 ml or as applicable for an antibiotic.

KEY WORDS: Antibiotics; Formulations; Pediatrics; Suspensions; Syrup

INTRODUCTION

Children represents 39% of the total population in our country; hence, the importance of their health status.[1] They are vulnerable to many infections and mortality among this group is usually very high, hence, the need for special attention toward their care. Lower respiratory tract infections are the leading cause of death in children below 5 years of age.[2] Acute respiratory infection, infection of gastrointestinal system, and viral fever are the common childhood illnesses.[3] The antibiotics are one of the important groups of drugs used for treatment of these infections and majority of them are curable. Thus, the use of antibiotic should be rational. It has been found that pediatric oral formulations of antibiotic available in the market are not appropriate with regard to dispensing volume. This may lead to inadequate treatment leading to resistance or increase cost of treatment putting unnecessary financial burden on poor patient.

Access this article online	
Website: www.njppp.com	Quick Response code
DOI: 10.5455/njppp.2017.7.1029421112016	

Pediatricians prescribe antibiotics more frequently than any other pharmacotherapy for their patients.[4,5] When drugs are dispensed in form of syrups or suspensions, appropriate volume should be dispensed such that it is adequate for course of therapy. It should neither excess nor deficient. Rational use of medicines is choosing the right medicines and employed them in the most appropriate manner. Thus, appropriate

use of antibiotic including dispensing volume is important with regard to rational drug therapy. In the present study, we have analyzed systemic antibacterial liquid formulations for pediatric patient.

Aim and Objective

The aim of our study was to analyze systemic antibacterial oral liquid formulations to ascertain the availability of adequate strength, volume dispensed for adequate treatment.

MATERIALS AND METHODS

The commonly used pediatric antibacterial oral liquid formulations were analyzed on the basis of formulation mentioned in IDR triple, Issue 2, 2016.[6]

Analysis includes the following:
1. Strength in which drug is available
2. Volume dispensed in case of syrups
3. Amount of drug required.

Duration of treatment for most of infection for minimum 5 days and may be up to 14 days as in case of atypical pneumonia. According to the weight of child (for 12 and 18 kg), amount of drug (ml), requirement of number of bottles and residual volume (ml) for 5 days were calculated.

Criteria for Analysis

1. Strength and dispensing volume of drug available in the market were analyzed considering following criteria
   a. Standard dose used for mild to moderate infection
   b. Minimum duration of therapy was kept for 5 days
   c. Age 2-5 years (usually syrups are used for this age group)
   d. Weight of child is calculated according to Weech's formula = 2x+8, x is age in year.[7,8]

The observations made were mentioned in tabular form.

2. Exclusion criteria
   - Drugs having prolonged need of therapy such as tuberculosis, leprosy.

RESULTS

We have analyzed antimicrobial pediatric formulations for mild to moderate infection in 2-5 year age group of children, because in this age group, drugs are given in liquid dosage form by syrup or suspension form. In this study, dose of antibacterial drugs are calculated for 5 days with average dose to avoid bias because minimum 5 days therapy required for any bacterial infection. We have also calculated required amount of drug (in ml), number of bottles required, and residual volume (in ml) for one full course.

The results on analysis of available liquid formulations of antibacterial drugs are as follows. The liquid formulations of fluoroquinolones (FQs) such as norfloxacin and nalidixic acid are manufactured by only two pharmaceutical companies (Table 1).

Ampicillin though available in 30, 40, and 60 ml dispensing volume (125 mg/5 ml) but number of bottles needed are 6, 5, and 3 for 12 kg and 9, 7, and 5 for 18 kg, respectively, for 5 days therapy which is inconvenient. Only amoxicillin pediatric

Table 1: Dispensing volume and amount required of liquid formulation of FQs

Name of drug (standard dose) (mg/kg/day)	Strength of drug (mg/ml)	dispensing volume (ml)	Weight of child (kg)	Amount require for one course for 5 days (ml)	Number of bottles required	Residual volume (ml)	Number of preparations available
Nalidixic acid (50)	300/5	30	12	50	2	10	2
			18	75	3	15	
		60	12	50	1	10	1
			18	75	2	45	
Norfloxacin (10)	100/5	30	12	30	1	-	2
			18	45	2	15	
Ofloxacin (15)	50/5	30	12	90	3	-	30
			18	135	5	15	
		60	12	90	2	30	21
			18	135	3	45	
	100/5	30	12	45	2	15	4
			18	67.5	3	22.5	
		60	12	45	1	15	3
			18	67.5	2	52.5	

FQs: Fluoroquinolones

formulation is rational among all semisynthetic penicillins which covers the whole range. Cloxacillin is available only in single strength (125 mg/5 ml) and one brand with 30 ml dispensing volume and more than 2 bottles are required for majority of patients. Amoxicillin + clavulanic acid pediatric formulation is rational and covers the whole range. For higher strength (400 + 57 mg/5 ml), 5 preparations are available and only 1 bottle has to purchase for full course. In strength (228.5 mg/5 ml) for 30 ml dispensing volume, 2 bottles are required and it is manufactured by 92 companies, but in same strength 60 ml dispensing volume 1 bottle is required and it is manufactured by only 2 companies (Table 2).

Cephalexin though available in 30, 40, and 60 ml dispensing volume (125 mg/5 ml); however, all strength required many bottles 4, 3, and 2 for 12 kg and 6, 5, and 3 for 18 kg, respectively for 5 days therapy which is inconvenient. Cefadroxil at strength of (125 mg/5 ml) 3 and 4 bottles are required for 12 and 18 kg child, respectively and 16 preparations are available. There is no need to manufacture such strength with such dispensing volume. While at higher strength (250 mg/5 ml) with 60 ml dispensing volume, only 1 bottle is required but for it only 1 brand is available. Third generation cephalosporins, cefixime, and cefpodoxime available in 30 ml dispensing volume (50 mg/5 ml) with 91 and 82 no. of preparations in the Indian market (Table 3).

Azithromycin is available in 43 and 54 number of brands for higher strength of 100 mg/5 ml and 200 mg/5 ml, respectively, for 12 kg in comparison to lower strength. Only azithromycin pediatric formulation is rational among all macrolides which covers the whole range (Table 4).

The liquid formulations of miscellaneous drugs such as chloramphenicol 40, 80, and 100 ml dispensing volume (125 mg/5 ml), cotrimoxazole 60 and 100 ml dispensing volume (200 + 40 mg/5 ml), sulfamoxole + trimethoprim (200 + 40 mg/5 ml), and metronidazole 30 ml

Table 2: Dispensing volume and amount required of liquid formulation of semisynthetic penicillin group

Name of drug (standard dose) (mg/kg/day)	Strength of drug	Dispensing volume (ml)	Weight of child (kg)	Amount require for one course for 5 days (ml)	Number of bottles required	Residual volume (ml)	Number of preparations available
Ampicillin (75)	125 mg/5 ml	30	12	180	6	-	5
			18	270	9	-	
		40	12	180	5	20	3
			18	270	7	10	
		60	12	180	3	-	1
			18	270	5	30	
	250 mg/5 ml	30	12	90	3	-	3
			18	135	5	15	
Amoxicillin (40)	50 mg/ml	30	12	240	8	-	1
			18	360	12	-	
	125 mg/5 ml	30	12	96	4	24	17
			18	144	5	6	
		60	12	96	2	24	23
			18	144	3	36	
	250 mg/5 ml	30	12	48	2	12	1
			18	72	3	18	
		60	12	48	1	12	2
			18	72	2	48	
Cloxacillin (75)	125 mg/5 ml	30	12	180	6	-	1
			18	270	9	-	
Amoxicillin+clavulanic acid (30)	125+31.25 mg/5 ml	30	12	58	2	2	6
			18	86	3	4	
	228.5 mg/5 ml	30	12	40	2	20	92
			18	60	2	-	
		60	12	40	1	20	2
			18	60	1	--	
	400+57 mg/5 ml	30	12	20	1	10	5
			18	30	1	--	

Table 3: Dispensing volume and amount required of liquid formulation of cephalosporins

Name of drug (standard dose) (mg/kg/day)	Strength of drug (mg/ml)	Dispensing volume (ml)	Weight of child (kg)	Amount require for one course for 5 days (ml)	Number of bottles required	Residual Volume (ml)	Number of preparations available
Cephalexin (50)	125/5	30	12	120	4	--	14
			18	180	6	--	
		40	12	120	3	--	1
			18	180	5	20	
		60	12	120	2	--	2
			18	180	3	--	
	250/5	30	12	60	2	--	6
			18	90	3	--	
		50	12	60	2	40	1
			18	90	2	10	
Cefadroxil (30)	125/5	30	12	72	3	18	16
			18	108	4	12	
	250/5	30	12	36	2	24	12
			18	54	2	6	
		60	12	36	1	24	1
			18	54	1	6	
Cefaclor (30)	125/5	30	12	72	3	18	5
			18	108	4	12	
	187/5	30	12	48	2	12	1
			18	72	3	18	
Cefuroxime (8)	50/5	30	12	48	2	12	1
			18	72	3	18	
	125/5	30	12	20	1	10	9
			18	28	1	2	
Cefixime (8)	50/5	30	12	48	2	12	91
			18	72	3	18	
	100/5	30	12	24	1	6	10
			18	36	2	24	
	200/5	30	12	12	1	18	1
			18	18	1	12	
Cefpodoxime (8)	50/5	30	12	48	2	12	82
			18	72	3	18	
	100/5	30	12	24	1	6	17
			18	36	2	24	
		60	12	24	1	36	1
			18	36	1	24	
Cefdinir (50)	125/5	30	12	120	4	--	11
			18	180	6	--	

dispensing volume (200 mg/5 ml) are manufactured by only one pharmaceutical company (Table 5).

Only three formulations are manufactured in adequate amount by pharmaceuticals while others are manufactured in inadequate amount.

DISCUSSION

Ofloxacin number of brands available due to its extensive use than other FQs such as nalidixic acid and norfloxacin. FQs brands are less in number because of adverse effects in pediatric patients, in comparison to other antibacterial

Table 4: Dispensing volume and amount required of liquid formulation of macrolides

Name of drug (standard dose) (mg/kg/day)	Strength of drug	Dispensing Volume (ml)	Weight of child (kg)	Amount require for one course for 5 days (ml)	Number of bottles required	Residual volume (ml)	Number of preparations available
Azithromycin (10)	20 mg/ml	15	12	30	2	--	1
			18	45	3	--	
	40 mg/ml	15	12	15	1	--	1
			18	22.5	2	7.5	
	50 mg/5 ml	15	12	60	4	--	1
			18	90	6	--	
	100 mg/5 ml	15	12	30	2	--	43
			18	45	3	--	
		30	12	30	1	--	2
			18	45	2	15	
	200 mg/5 ml	15	12	15	1	-	54
			18	22.5	2	7.5	
		30	12	15	1	--	2
			18	22.5	1	7.5	
Clarithromycin (15)	125 mg/5 ml	30	12	36	2	24	5
			18	54	2	6	
Erythromycin (40)	100 mg/5 ml	60	12	120	2	--	3
			18	180	3	--	
	125 mg/5 ml	60	12	96	2	24	6
			18	144	3	36	
Roxithromycin (5)	50 mg/5 ml	30	12	30	1	--	6
			18	45	2	15	
		60	12	30	1	30	1
			18	45	1	15	

drug therapy (e.g., damage in growth of plate cartilage). Tendinitis, arthropathy, arthralgia, joint swelling, and tendon rupture also reported due to FQs use.[9-11] Thus, overall, FQs have less manufacturing brands compare to other antibiotics.

The fixed dose combinations (FDCs) of ampicillin + cloxacillin and amoxicillin + cloxacillin are immensely used by practitioners due to wrong prescribing pattern as these FDCs are irrational. As a result pharmaceuticals do not favor production of cloxacillin alone. Amoxicillin + clavulanic acid is widely prescribed for pediatric patients and safe.[12,13] Thus, its sufficient brands are available.

Third- and fourth-generation cephalosporins are safer alternative for Gram-negative infection and thus sufficient number of brands is available.[14]

Azithromycin has more manufacturing brands compare to other macrolides owing to fact that it has distinctive pharmacokinetic properties, safety and has a relative long half-life by 40-68 h lead to increasing patient compliance.[15,16]

Due to serious adverse effects by chloramphenicol[17,18] and better options available for cotrimoxazole and metronidazole, use and manufacturing of these drugs are declining now a day.

For mild infection, 2 bottles are sufficient for 5 days therapy. If more than 2 bottles are required, it shows financial and social burden to society. If number of bottles are increased for therapy then patient will purchase 1-2 bottles only and discontinue the rest of therapy; hence, incomplete treatment leading to resistance.

Formulations which are manufactured in adequate amount by pharmaceuticals are amoxicillin + clavulanic acid, ofloxacin and azithromycin.

On the other hand, formulations which are manufactured in inadequate amount are nalidixic acid (300 mg/5 ml), norfloxacin (100 mg/5 ml), ampicillin (125 mg/5 ml, 60 ml), cloxacillin (125 mg/5 ml), cephalexin (125 mg/5 ml, 60 ml), cefadroxil (250 mg/5 ml, 60 ml), cefaclor (187 mg/5 ml, 60 ml), cefixime (200 mg/5 ml, 60 ml), roxithromycin (50 mg/5 ml, 60 ml), cotrimoxazole (200 + 40 mg/5 ml, 60 ml, 100 ml), and metronidazole (200 mg/5 ml, 60 ml).

Table 5: Dispensing volume and amount required of liquid formulation of miscellaneous drugs

Name of drug (standard dose) (mg/kg/day)	Strength of drug	Dispensing volume (ml)	Weight of child (kg)	Amount require for one course for 5 days (ml)	Number of bottles required	Residual volume (ml)	Number of preparationsavailable
Chloramphenicol (50)	125 mg/5 ml	40	12	120	3	--	1
			18	180	5	20	
		60	12	120	2	--	3
			18	180	3	--	
		80	12	120	2	40	1
			18	180	3	60	
		100	12	120	2	80	1
			18	180	2	20	
Cotrimoxazole sulphamethoxazoe+trimethoprim (8)	200+40 mg/5 ml	50	12	60	2	40	7
			18	90	2	10	
		60	12	60	1	--	1
			18	90	2	30	
		100	12	60	1	40	1
			18	90	1	10	
Sulfamoxole+trimethoprim (8)	200+40 mg/5 ml	60	12	60	1	--	1
			18	90	2	30	
Metronidazole (50)	200 mg/5 ml	30	12	75	3	15	1
			18	112.5	4	7.5	
		60	12	75	2	45	2
			18	112.5	2	7.5	

CONCLUSION

This study demonstrated irrationality in manufacturing in various pediatric liquid dosage forms in relation to age group. The dispensing volumes of oral liquid dosage forms of most of the formulations were inadequate. When number of bottles is increased for therapy, lead to financial and social burden. It also increases antibiotic resistance and number of social visits. Clinicians should aware about this rationality of formulations and modify prescribing pattern accordingly. This study gives guidance to companies to manufacture proper pediatric liquid preparations and thus, minimum amount dispensed should be 60 ml or as applicable for an antibiotic.

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How to cite this article: Naik PP, Mehta CD, Srivastava SK. Analysis of commonly used pediatric systemic antibacterial liquid formulations for rational drug therapy. Natl J Physiol Pharm Pharmacol 2017;7(4):348-354.

Source of Support: Nil, **Conflict of Interest:** None declared.