Safety Comparative Study on Azithromycin Oral and IV Dosage Form in Pediatric Respiratory Infection Therapy

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Citation

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Abstract

Azithromycin is widely used for treatment in various of pediatric respiratory infections and there is no any strict requirement for selection of oral or intravenous (IV) dosage form. There is few comparative data in respective of safety between these two dosage forms. The purpose of this study was to review safety data between oral and IV for the treatment under 16-year-old children and intend to give pediatricians reference in the two dosage forms of azithromycin. This paper has reviewed adverse events (AEs) data which include 3960 cases of children in 79 published paper for treatment in respiratory infection. There are 1628 cases in oral group,2302 cases in IV group and 30 AE individuals case reports (IV). The study result shows that the AE incidence is 14.12% in IV group and 9.28% in the oral group. It is significant different between the two groups (u=4.699, P<0.0005). In conclusion, Azithromycin oral dosage form resulted in better tolerance in children than that of IV, suggest pediatricians to prescribe oral dosage form as first line therapy.

MATERIAL AND METHODS

All data came from the Wanfang Data-base and Weipu Data-base. The publishing date of literature used is from Jan.1 1997 to Dec. 1 2007. Meanwhile, we traced every reference literature. The index keyword included children, azithromycin, intravenous and oral administration.

INCLUSION AND EXCLUSION CRITERIA

INCLUSION CRITERIA

It is concomitantly demanded to meet next conditions:

1. Patients under16 years old;
2. Children are confirmed respiratory infection;
3. IV group children are treated only by azithromycin IV administration and oral group children are treated only by azithromycin oral dosage form;
4. Classified recording of AE in details.

EXCLUSION CRITERIA

1. If the case has any following AE before administration of azthiromycin should be excluded:
2. Combination therapy with any other drug will be excluded.

MATERIALS SCREENING

There are 79 paper have been collected in this review which include 22 paper[1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22] for oral administration ,42 paper[2,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63] for IV administration and 16 individual case report[64,65,66,67,68,69,70,71,72,73,74,75,76,77,78,79] for IV. Detailed see table 1.

Figure 1

Table 1: Materials screening

Type of reports	No of paper	No of children	No of AEs	Incidence of AE (%)
IV	42	2302	325	14.12
Oral	22	1628	151	9.28
Case report(IV)	18	30	30	100%
Total	82	3960	506	

Refer to azithromycin oral and IV administration paper, the total number of children who have been used azithromycin oral and IV administration, the total number of children who have AE experience and total number for each kind of AE respectively were extracted from the qualified screening paper.

DATA ANALYSIS

Calculate the incidence of AE. The difference between oral group and IV group in AE incidence is tested through U test. All data will be processed using SAS 8.2 statistics software.

RESULTS

The total number of AE reported and incidence in azithromycin oral and IV group see table 2: the incidence of AE is 9.28% (151/1628) in oral group. The most common AE are gastrointestinal (GI) (122 cases), rash (20 cases), liver enzyme (ALT) increasing (5 cases) and headache (3 cases). The rate of AE is 14.12% (325/2302) in IV group which include rash (22 cases), wheal (3 cases), Injected site pain (16 cases), Phlebitis (4 cases), ALT elevated (13 cases). The incidence of AE between oral and IV groups were examined through u test (u=4.699, P<0.0005), it can be determined that it is different between the two groups in AE incidence, and AE incidence of IV group is higher than that of oral group.

Figure 2

Table 2: The total AE number and incidence of azithromycin oral and IV group

Adverse Events	Oral		IV	
	No of AE	Rate of AE (%)	No of AE	Rate of AE (%)
GI	122	7.49	263	11.42
Rash	20	1.23	22	0.96
Wheal	0	0	3	0.13
Site pain	0	0	16	0.7
Phlebitis	0	0	4	0.17
ALT elevated	5	0.30	13	0.56
Two leg pain	0	0	1	0.04
BP decreasing slightly	1	0.06	0	0
Urine frequency	0	0	1	0.04
Dizzy	0	0	1	0.04
Headache	3	0.18	0	0
Tinnitus	0	0	1	0.04
Total	**151**	**9.28**	**325**	**14.12**

Note: BP: blood pressure; GI : gastrointestinal; ALT: alanine transaminase;

Figure 3

Table 3: Individual case AE reports of azithromycin IV in children

Adverse event name	Case number	Time after IV	Prognosis
Anaphylaxis			
Died of anaphylaxis	1	70min	death
Allergic shock	3	10-40min	recovery
Allergic reaction	1	6min	recovery
Drug eruption	2		recovery
Multiform Erythema	1	20min	recovery
Reversible supraventricular tachycardia	1	6d	recovery
Superficial phlebitis	2	5d	recovery
Extra-pyramid reaction	1	30min	recovery
Liver enzyme(ALT)elevated	16	4-12d	recovery
Night sweat on the head and neck	1	1d	recovery
Ankles joint pain	1	2d	recovery

DISCUSSION

Azithromycin is the most widely used macrolide antibiotics for treatment of pediatric respiratory infections caused by common pathogens such as Staph.aureus Streptococcus pneumoniae, Moraxella catarrhalis, Haemophilus influenzae, Mycoplasma pneumoniae and Chlamydophila pneumoniae. Because once daily administration pharmacokinetic feature of azithromycin, both oral and IV are prescribed widely by Chinese doctors. At present, the prescribing dosage forms of oral or IV and the treatment duration will depend on the habit of the doctors individually. The duration can be 3 to 4 weeks[65] by intermission administration for treatment of Mycoplasma and Chlamydophila infection. Now, there is no evidence based clinical study to compare these two dosage forms in safety and efficacy for treatment of children. However, two open comparative small sample China studies[4,77] indicated that the two dosage forms are equal in safety and efficacy for treatment of pediatric infections. From the theoretical point of view, oral administration should be safer than IV administration. It may be the sample is too small to show the difference between oral and IV administration in the previous local two studies. However, this 3930 cases review analysis shows that oral dosage form is safer than that of IV.

From the detailed individual AE reports of IV administration, we found that there are 1 dead case[70] of anaphylaxis and 3 allergic shock cases[71,72,73] happened. The results suggest that it should pay attention to allergic shock at the beginning of azithromycin IV administration. All 16 liver enzyme (ALT) elevated cases[64,65] have a long therapy experience from 4 to 12 continue days. The result suggest that it should be paid attention to the liver functions damage risk after 3 days duration therapy because azithromycin is eliminated through liver and an elimination half-life is 65.2 hours in 0.5 to 16 years old children[80] and children's liver functions are premature in necessary enzymes synthesis[81]. Contrast to IV dosage form, oral dosage form has not been found the report of dead of anaphylaxis or allergic shock yet. It is only found ALT minor reversible increasing, lower AE rate and safer than IV dosage form. So, we suggest pediatrician to prescribe azithromycin oral dosage form as priority choice in under-16-years-old children respiratory infection treatment.

Because we only reviewed the clinical observation data, it is possible that there are some shortages in this paper. First, the AE diagnosis criteria are different. Secondly, collected literatures sample can not represent the whole situation of China children. Last, lack of detailed information of every AE case and AE happened history and so on has hindered us to accurately analyze these data.

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