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(Comparing The Effects And Adherence To Azithromycin Versus Ceftriaxone In Treatment Of Acute Otitis Media In Pediatric Patients In Karbala City)

Hayder Falih Shamikh Al-Saedi *[1]; Samer Ihsan Hadi [2]; Waleed Khalid Younis[3;], Ihsan Hadi Musa[4]

[1*]Ph.D. Pharmacology and therapeutics; College of Pharmacy-University of Al-Ameed. Scopus index :2
[2]M.Sc. Pharmacy Management; College of Pharmacy-University of Al-Ameed.
[3]M.Sc. Physiology; College of Pharmacy-University of Al-Ameed
[4]M.B.CH.B., DLO Otolaryngologist Head and Neck Surgeon; Al-Hussein Medical City- Karbala.

Hayder Falih Shamikh Al-Saedi
Email : pharmhaider@gmail.com
Email : hasedi@alameed.edu.iq
Mobile :009647735244677

Abstract

Objective: the aim of study to evaluate the efficacy ofrelativelyhigh dose of threedays' oralazithromycin(AZ) regimen in comparisonwith doseof threedays'parenteralceftriaxone(CF) for the treatment of patients with acute otitis media.This study was conducted as a prospective, comparative, open randomized controlledtrial between September 2016 to February 2017,and 204patientswere enrolled from few days to 15 yearsold were diagnosed asacute otitis media(AOM) depending on patient'shistory and performing by otoscopic assessment besides the clinical investigations.Patients were divided into two groups: the first one received azithromycin (10mg/kg) a once oral dose daily for three days, the other group received ceftriaxone(50 mg/kg) daily injection for three days. Then, they were examined according to determined schedule of following up after three days; fourteen days; and three weeks of treatment in order to evaluate the successive therapy or recurrent infection after taken specific regimen of antibiotics.The results showed (79) patientsreceived AZ and (29) of them respond to the treatment and (125) patients received CF, (43) patients respond to treatment, so there were non-significant differences between AZ & CF treatment groups by using Fisher test reflecting the benefit and good complain of oral treatment and injectable one.

Conclusion: could be summarized by findings and approving a non-superiority of CFtreatment responsein compare to AZtreatment response toward AOMamong different age groups selected in the study.

Introductions

Acute otitis media is the most common infection in infant & children. Despite 30% had a non-bacterial etiology, AOM is the leading cause for antibiotics prescriptions in children in Iraq and other countries(1, 2).The most common pathogens responsible for AOM are Streptococcus pneumonia, Hemophilusinfluenza, and Moraxella catarrhalis(3). Antibiotic remedy in the AOM is a controversy story amongphysiciansand countries guidelines. However, hearing loss or mastoiditis, CNS complications are considered aserious sequel of persistent or chronic infections, it is an urgent cases to use antibiotics therapy for AOM(4). For suitable choosing of certain antibiotics, its important point of view to consider the pharmacokinetics characteristics which are including their ability to diffuse efficiently to area of the middle earwith sufficient concentration besides their pharmacodynamics activity against certain mentionedpathogens producing minimum inhibitory concentration . The other important factors should be evaluated for prescribing antibiotics are good patients' compliance, availability in Iraqi market , and affordable cost for most patients(5). Amoxicillin, or plus clavulanic acid (amoxiclav)^R, trimethoprim- sulfamethoxazole are the most frequently prescribed oral AB for the treatment of AOM(6). The cause behind the selecting of the AZ and CF in order to avoid major compliance of others common used drugs when they are used orally for seven to ten days course to achieve the therapeutic effect and at same time , it is a problematic event for both patients and their parent for long duration of treatment and cost besides resistances of new strains to these common empiric antibiotics . Its preferable to prescribeantibiotics preparations offered a short; effective therapy course and cheap(7). The alternative line is including short course injectable CFor oral AZ, had been appeared in the field on the treatment of AOM (8).

Azithromycinmacrolide antibiotic has prolonged half- life (68hrs.) and achieves sustained tissue concentration in a wide range of body site, including middle ear.The concentration of AZin the tissues over (50) times higher than plasmadue to the high lipid solubility and ion trapping. These pharmacokinetic properties allow for once daily dosing and shorter regimen (9). It Acts by binding to the (50S) ribosomal subunit of susceptible microorganisms, interfering with microbial protein synthesis. Nucleic acid synthesis is not affected(10). Furthermore, high dose AZ enhanced bactericidal activity against Streptococcus pneumonia;H. influenzae, and Streptococcus pyogenesand result in eradication of these pathogen. AZ has similar antimicrobial spectrum as erythromycin, but is more effective against certain gram-negative bacteria, particularly Hemophilusinfluenza.Unlike

erythromycin, AZ is acid-stable, therefore it could be taken orally with no need of protection from gastric acids(11).

Ceftriaxoneis a broad-spectrum, parenterally administered third-generation cephalosporin absorbed rapidly following intramuscular administrationand achieve high mean peak serum level within (2 hrs.), with prolong half-life, make it suitable for single daily dose. It reaches middle-ear fluid concentration of 10% of its serum level, these exceed the MICs of the typical AOM pathogens for approximately (56hrs.) after single intramuscular injection (50mg/kg) (12, 13).

The goal of the present study designed to compare the effectiveness, the safety profiles, and compliance of three days' single daily oral AZ versus CF in the treatment of infant and children with AOM.

Methods

The study was conducted in the ENT outpatient clinic at Al-Hussein Medical City Hospital in KarbalasinceSeptember 2016 to February 2017. There were 204 children enrolled in the present study aging from one day to fifteenyears old were diagnosed as AOM, for the first time, persistent & recurrent AOM**.** These conditions ofAOM course include,but unlimited to, anatomic abnormalities such as cleftpalate, genetic conditions such as Down syndrome, immunodeficiency. The diagnostic criteria depending on the history of otalgia (or pulling of the earin an infant), irritability or toddler, otorrhea, fever, and deafness. However, pneumatic otoscopic examination of the color (red,yellow, blue, bulging) and mobility of the tympanic membrane. They were randomly divided into two treatment groups; the first one received AZ (10mg/kg/ daily /orally) for threedays, another group were received CF(50 mg/kg / daily/i.m.)for three days. The drug-therapy responsewas assisted successively if an improvement or curative occurs based on different signs and symptoms primarilyresolved at third day andremained continuedtill day 14thandday21st. Failure of treatment was evaluated if the signs and symptoms were presented at the baseline withno improvementor had worsened on day 4thor if the patients still had signs and symptoms of AOM on day14th. The data were analyzed by using chi-square test and the level of significance consider (p)value less than 0.05.

Results

The clinical study of(204)patients were randomly recruited for the present study and only (111) patients were completed the treatment and followed up to day 14th.While (93)patients werediscontinued from the follow up of the study.Furthermore, the percent of patients received AZ was (38 %), while thepercent of those treated by CF was (61.3 %). In general, percent of treatment

respond to therapy with completion of follow up was 72/204 (35.3%), while the non-respond represented 39 / 204 (19.1%) besides the discontinued percent was 93/204 (45.6%). Also, (76 %)of patients had recurrent AOM besides (23%) had persistent AOM. According to sex, males'participants' percent represent 115/204(56.4%), while females represent 89/204 (43.6%). From them, this study showed the percent of male treated by AZ was 42/115(36.5%)   in corresponding 73/115 (63.4 %) by CF. In addition, the   percent of   female treated by AZ was 42/89 (26.9%)while 52/89 (58.42%) by CF. The male patients who respond to AZ represent 48/115(41.7%), while whom not respond were 20/115(17.4 %), while it less case who get response to AZ regimen (24/89) (26.9%) while the female get a comparable percent 19/89 (21.3%) the respond compared to male.

In respect to age, the age-group of patients included in this study reflected a percent of susceptibility of AOM among age groups that participated, the highest percent of (0-2) years old represent (43.6 %), whereas (3-5), (6-10) and (11-15) years were represent (30.9 %), (13.7 %), and (11.8 %), respectively.The susceptible age for getting a respond to treatment were (0-2) years 27/72 (37.5%) and (3-5) years 27/ 72 (37.5%) , while the age range (6-10)years7/ 72 (9.72%) and (11-15)yearswas 11/72(15.27%).The age of non- respondwasrepresentingfor (0-2) year was 20/39 (51.2 %);(3-5) years was 11/39(28.2%); (6-10)year was 5/39(12.8%); and (11-15) was 3/39 (7.7 %). The discontinued age groups (0-2)years was 42/93(45%);25/93;(3-5) years was25/93 (26.8 %) ;(6-10) years was16/93 (17.2%); and (11-15) yearswas 10/93(10.7%) (as shown in table 1)

In relation to AZ, the respond of different groups of age showed that the age group (0-2) year was 6 / 29 (20.6 %); (3-5) year was 15/25 (51.7 %); (6-10) year was 3/29(10.3 %); and (11-15) was 5/29 (17.2 %). While the non-respond to AZ reported as following; the age group (0-2) year was 6 / 16(37.5 %); (3-5) years was 4/16 (25 %); (6-10) year was4/16(25 %); and (11-15) was 2 /16(12.5%) (table 2).

The percent of response among patients received CF were 21/ 43 (48.8%);12/ 43(27.9 %); 4/43(9.3 %);and 6/43(13.9%) while the respond patient or CF non-respond resistance according to these sequences 14/23(60%); 7/23 (30.4%);1/23 (4%); and 1/ 23 (4%) (table 3) .

The cure rate was (65%) in the CF group compared with (64.4%) inAZgroup,therefore there was a non-significant difference between the two groups (p ≥ 0.05). Patients treatment preference was assessed on day 14. Among the (111) patients in the study, (78) of them would choose CF again compared to(33) patients choose AZ.Thus, a higher treatment preference rate was observed in CF group.Safety and compliance are included diarrhea and rash. These were most commonly reported drug-related adverse effects. The diarrhea was recorded in three patients of AZ group, whilenone noticed to have these adverse effects inCFgroup. Although, while skin rash was appeared in one patient of CF group

but none inAZgroup.In comparison of respond between AZ & CF of different age groups shared in the present study, the result showed a non-significant differences between them among different age groups p is more than 0.05 (p = 0.09) (as shown in tables 4,5).

Discontinuation of therapy according to age groups of CF treatment was showing as following (0-2) year was 35/59 (59.3%); (3-5) years 13/59 (22 %) ; (6-10) years 7/59 (11.86%) ; and (11-15) years was 4/59 (6.7%). The discontinuation of treatment by patients and avoid the follow-up showed a statistically differences among age group in comparison to specific antibiotics. The most susceptible age was ranging from one month- two years. There were no significant differences between gender in relation to success or failure of treatment for both drugs. Male response to the AZ was (69.5%) besides (70.4%) for CF. Female response was (59.1%)for AZ, (54.5%) for CF.Among (111) patients who continued to complete the study, (39) of them experienced treatment failure that represent a16/45 (35.6%) of patients received AZ, and 23/66 (35%) of patients treated with CF while the rest (72) patients were cured (Table 5).

Discussion:

The systemic and local signs and symptoms of AOM usually resolve in (24) to (72) hours when the patients received an appropriate antimicrobial therapy but the inverse scenario would be seen in children who are untreated. However, persistence of middle ear effusion (MEE) after the resolution of acute symptoms is common.The increment of resistance rate of pneumococciagainst the penicillin and beta- lactamase producing H.influenza and M. catarrhalis, raise additional obstacle to choice an appropriate AB therapy of AOM(14, 15).The efficacy of high dose amoxicillin or amoxiclavwas considered appropriate for the treatment of AOM due to the possibility coverage of some penicillin-resistantPneumococci(16). Amoxicillin, however cannot cover beta-lactamase producing H.influenza and M.catarrhalis(17). Furthermore, a long course oral AB is often inconvenient to family and their patients. So preparations that could be given as a short course,cheep ,and effective against most of resistant bacteria that causing AOM, would provide an advantage to children who might have poor absorption for the oral drugs, who refuse oral drug or who had decreased compliance due to family circumstances especially for the old regimen of long course coasty antibiotic(18-20).

Most of the studies published, compare amoxicillin oramoxicillin withclavulanic acid to AZ or CF in the treatment of AOM, while this study this study compared oral AZ toparenteralceftriaxone(20, 21). Antonio Arrieta showed success rate (87%) for AZ in the treatment of AOM. Chung-Yi Wang study showed success rate (75.6%) for CF. In this study (64.4%) for AZ and (65%) for CF.So, there is no

significant deference in the success rate between the two drugs (0.6%)(20, 22).For the side effect three patients used AZ had diarrhea and vomiting, compared to one pt. had skin rash used CF, this result was expectable with any broad-spectrum oral antibiotic, and add another cause for the high preference rate we had get for the CF.From economic point of view, three tablets course of AZ is cheaper than CF course, but Iraqi patients social attitude convinced on the using parental medication better than to use the oral one(23), this fact is culturally bounded despite its allergic possibility Preparations that could be given parenterally would provide an advantage to children who might had poor absorption for the oral drugs, who refuse oral drug or who had decreased compliance due to family circumstances especially for the old regimen of long course antibiotic, that is why we get high preference to CFin this study (71%)(24) . The study had the following limitation; no middle ear fluid had been aspirated for culture and sensitivity. Placebo had not use, and follow up to one month had not been done. In addition to the high false result we had got from the culture and sensitivity, ethically it was unnecessary to do tympanocenthisis for most of the patents in the study who already had uncomplicated AOM where scientifically tympanocenthisis done only for complicated AOM.Furthermore, follow up for one month had been done to some patients, the other rolled out due to study violencecost of the drug, the consultation and traveling, and the danger of transportation between Iraqi countries and village. In our country specially in the poor family, most of the patients were still complaining of AOM,until their parent arrange a time to visit the physician, so the watching period suggested by some doctors & the use of placebo, had been passed away by these period, and the only patients who were still complaining,were enrolled in this study.In summary**,** this study from clinical efficiency and economic viewpoints, use of CF and AZ single daily dose for three days can be justified in the management of AOM under special circumstances Both drugs had the same cure rate but the treatment preferences of the patients and parents' convenience, was higher for CF particularly in cases when the patients' ability to tolerate and absorb drugs is compromised.

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Table1: The age -response status for antibiotics treatment of otitis patients of present study

Age	Response status			Total
	Responed	No-response	Discontinued	
0-2	27	20	42	89
3-5	27	11	25	63
6-10	7	5	16	28
11-15	11	3	10	24
Total	72	39	93	204

Table2 : The Azithromycin -response status for antibiotics treatment of otitis patients of present study

Treatment			Age				Total
			0-2	3-5	6-10	11-15	
Azithromycin	Response statuse	Responed	6	15	3	5	29
		No-response	6	4	4	2	16
		Discontinued	7	12	9	6	34
	Total		19	31	16	13	79

Table 3 : the ceftriaxone -response status for antibiotics treatment **of otitis patients of present study**

Treatment	Age				Total
	0-2	3-5	6-10	11-15	

Ceftriaxone	Response statuse	Responed	21	12	4	6	43
		No-response	14	7	1	1	23
		Discontinued	35	13	7	4	59
	Total		70	32	12	11	125

Table 4 : The respond of different age groups to Azithromycin or Ceftriaxone

Response statuse			Treatment		Total	P-value
			Azithromycin	Ceftriaxone		
Responed	Age	0-2	6	21	27	
		3-5	15	12	27	
		6-10	3	4	7	
		11-15	5	6	11	
	Total		29	43	72	0.09

Table 5: the antibiotics – unresponsive relation to different age groups

Response statuse			Treatment		Total	P-value
			Azithromycin	Ceftriaxone		
No-response	Age	0-2	6	14	20	
		3-5	4	7	11	
		6-10	4	1	5	
		11-15	2	1	3	0.1

| | Total | | 16 | 23 | 39 | |

Table 6: the antibiotics – discontinuation relation in different age groups

Response statuse			Treatment		Total	P-value
			Azithromycin	Ceftriaxone		
Discontinued	Age	0-2	7	35	42	
		3-5	12	13	25	
		6-10	9	7	16	
		11-15	6	4	10	0.003
	Total		34	59	93	