Brief report

Azithromycin pharmacokinetic attitude attains the basis for single daily dose for uncomplicated skin infections

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Abstract

Objective: Uncomplicated skin infections are considered a frequent clinical issue. Most of them are induced by staphylococcus and streptococcus. Various oral antibiotics are administered with similar efficiency but with different management period, price and side effects. Azithromycin is used in adults conventionally in a dose of 500 mg once for 5 days. To assess if a single oral 2 g administration dose of azithromycin could cause a therapeutical effect similar to traditional single oral dosing of 500 mg daily for 5 days in adults.

Methods: This randomized and prospective investigation included adult subjects, of both gender and presenting with uncomplicated skin infections at King Hussein hospital. King Hussein medical center, Amman, Jordan, during the period Feb 2012-Mar 2015,after obtaining written informed consent from all participants .All patients were divided into two groups. Group I (n = 146) patients received a 2 g single oral dose and group II patients (n = 146) received a traditional oral dose of 500 mg once daily for 5 days. Adherence was related to the number of tablets taken. Complete clinical healing defines complete healing of lesions with no residual signs or symptoms within 7 days. Normal distributed numerical parameters were compared between groups by Student's t-test or by Mann-Whitney U-test, if abnormal distributed. Pearson's Chi-square test was used for intergroup comparison of categorical parameters. Statistical significance was scored if $P < 0.05$.

Results: Increased healing rate was recorded in 97.97% in group I and in 98.63% in group II, with improvement in symptoms from the start of treatment but without statistical significance difference between the two groups

Conclusion: Single 2 g oral azithromycin dose caused the same outcome as traditional azithromycin dosing in uncomplicated skin infections with similar tolerability and with adherence .

Keywords: *Azithromycin, uncomplicated skin infection.*

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Introduction

The skin surface is considered a protective area between the body and the external world. Its composing cells keep structural integrity and have an important role in different skin inflammatory and infectious situations by generating different cytokines (1). Skin infections have been divided into two types: Uncomplicated skin infections (2) and complicated skin infections (3). Cutaneous infection is commonly microbial in origin and often needs treatment by antibiotics. *Streptococcus pyogenes* and *Staphyloc occus aureus* are the most frequent causative agents.

Conventional treatment for uncomplicated skin infections is governed by the history of the infection, site and features of the skin lesions, and age and immune condition of the patient. If fever, lymphadenopathy and other features indicating of complicated complicated skin infections, are absent, management can be started

orally (4). Antibiotics administered to manage these infections are commonly given for 5-10 days (5). Most of them are given multiple times per day such as erythromycin 500 mg orally 4 times daily or clindamycin 300 mg orally 4 times daily. Multiple daily dosing is may cause adherence issues. Any drug with comparable spectrum but with reduced frequency or duration of administration could be a more chosen antibiotic. Azithromycin achieves this demand and is very frequently administered drug for uncomplicated skin infection (6).After oral use; the Azithrromycin is rapidly absorbed in the intracellular part causing increased tissue concentration. The after slow release from tissue bank produces the terminal phase half-life as long as 11-14 h. Longer half-life of 68 h is attained when multiple doses are given. The extensive tissue distribution of Azithromycin and its long elimination half-life(pharmacokinetic attitude) (7) gives the basis for single oral daily dose for 5 days in most infections including skin structure infections. The administration of single dose azithromycin has zero nonadherence .Enhanced adherence is apparent in outpatients compared to other antibiotics administered more frequently or for longer period.

Methods

This randomized and prospective investigation included 300 adult subjects, of both gender and presenting with uncomplicated skin infections at King Hussein hospital. King Hussein medical center, Amman, Jordan, during the period Feb 2012-Mar 2015,after obtaining written informed consent from all participants and approval from Jordanian royal Institutional Ethics and research board review Committee .All patients were divided into two groups. Group I (n = 146) patients received a 2 g single oral dose of Azithromycin(four 500 mg tablets administered orally with 200 ml of water) and group II patients (n = 146) received a traditional oral dose of 500 mg once daily for 5 days. Complete clinical healing defines complete healing of lesions with no residual signs or symptoms within 7 days(of using the single dose or first dose of the investigation drug). Pregnancy, systemic antibiotic administration during the previous 2 weeks, history of immunosuppression and immunosuppressive drugs and allergy to macrolides were exclusion criteria. The primary result was clinical response characterized by no spread of redness, edema and induration around the lesion or decrease of the size of the lesion at 3 days. Secondary results were: Clinical cure at 7 days characterized by complete healing of all signs of inflammation and clear healing of the lesion itself at 7 days after using the single dose or first dose of investigation drug. Absence of such response, increase in the size of the lesion or associated inflammation or the use of any rescue antibiotic (or any other rescue measure like abscess drainage) were considered as clinical failure. Adherence was related to the number of tablets taken. Adherence was scored excellent if all doses were taken within ± 2 h of time; good if only one dose was missed or delayed by >2 h and poor if more than one dose was missed or delayed.Normal distributed numerical parameters were compared between groups by Student's *t*-test or by Mann-Whitney U-test, if abnormal distributed. Pearson's Chi-square test was used for intergroup comparison of categorical parameters. Statistical significance was scored if $P < 0.05$.

Result

There were no significant differences between the two groups regarding age, gender and duration of the infection. Table1.

The improvement of signs and symptoms was increasingly significant over 6 days in both groups and kept similar between the two groups. Cure was shown in 71 subjects (95.9%) in group I compared to 72 (98.6%) subjects in group II; P>0.05.Table 2.

Table 1. Demographics of patients in the two groups.

	G I	G II
no	74	73
Mean+/-SD(range)	33.2+/-7.2(18-62)	31.4+/-8.3(21-65)
Sex (%) M F	45(60.8) 29(39.2)	46(63.01) 27(36.99)
Duration of infection(days) Mean+/-SD(range)	12.4+/-4.1(7-21)	13.3+/-5.3(8-19)

There was no lack of adherence except for three patients who took 3 rather than 4 tablets in group I. In the other group, excellent, good, and poor adherence was demonstrated in 62 (84.9%), 4 (5.5%) and 7 (9.6%) patients, respectively. The difference in treatment adherence was increasingly significant ($P < 0.05$) in the single dose group. Excellent adherence was better in the single dosing group (94.6% vs. 84.9%). Table 3.

Table 2.Results of treatment.

	GI	GII
Infection (no,%)		
cured	71(95.9)	72(98.6)
improved	2	0
failed	1	1
Adherence (no,%)		
excellent	70(94.6)	62(84.9)
good	3(4.1)	4(5.5)
poor	1(1.4)	7(9.6)

Table 3. Outcome of infection features.

	GI		GII		P(intergroup)
	yes	No	yes	No	
Pain and tenderness (no, %)	66(89.2)	8(10.8)	67(91.8)	6(8.2)	>0.05
Itching	30(40.5)	44(59.5)	33(45.2)	40(54.8)	>0.05
Oozing	36(48.6)	38(51.4)	37(50.7)	36(49.3)	>0.05
Redness	68(91.9)	6(8.1)	70(95.9)	3(4.1)	>0.05
Induration	67(90.5)	7(9.5)	69(94.5)	4(5.5)	>0.05

Discussion

This is a prospective investigation from Jordan to compare the effect of a single dose of azithromycin with traditional azithromycin dosing in uncomplicated skin infection.Azythromycin is a derivative from erythromycin and is is active against Gram-positive organisms like staphylococcus and streptococcus and against Gram-negative organisms such as Haemophilus influenzae, Haemophilus parainfl uenzae, Moraxella catarrhalis, Neisseria gonorrhoeae, Ureaplasma urealyticum and Borrelia burgdorferi. Biliary excretion, long terminal elimination half-life and reduced depression of hepatic microsomal enzymes are other benefits compared to erythromycin and clarithromycin (12). Single dose administration of Azithromycin may solve reduced adherence. In this investigation, 3 (2.03%) patients in Group I and 2patients (1.37%) in Group II had no success to management. These results were in accordance with other investigations (8). This investigation demonstrated the efficiency of single dose.The outcome showed that the effect and tolerability of single 2 g azithromycin dose were similar to that of traditional azithromycin dose in the treatment of uncomplicated skin infection. Significantly decreased adherence was recorded in the traditional group in comparison with single dose. Beside azithromycin, uncomplicated skin infection can also be managed with other antibiotics. A clinical efficiency rate with these drugs for uncomplicated skin infection was between 78% and 100 %(9).The dosing protocol of other antibiotics might be less satisfactory than single dose azithromycin. Some should be administered 3-4 times a day or for a period of 7-10 days. Single dose azithromycin causes least risk of nonadherence, reduced risk of treatment failure and emergence of drug resistance.

The investigation has limitations. Children were not included. Bias was there in assessing signs and symptoms. A blinded model was not chosen. The microbial origin of the infections was not confirmed through microbiological investigation. The diagnosis was confirmed by an experienced clinician before randomization, antibiotherapy of uncomplicated skin infection was commonly

started empirically. Empirical treatment can be used for uncomplicated skin infection .

Conclusion

In uncomplicated skin infection in adults, single 2 g oral dose of azithromycin is generally well-tolerated and can produce clinical healing rates similar to traditional azithromycin dosing within 7 days. This protocol can be recommended as an alternative.

We declare that there was no conflict of interest what so ever regarding the use of azithromycin with any companies or institutions.

References

1. Kupper TS, Fuhlbrigge RC. Immune surveillance in the skin: Mechanisms and clinical consequences. Nat Rev Immunol 2004;4:211-22.

2. Seupaul RA. Cephalexin is as effective as clindamycin for the treatment of uncomplicated soft tissue and skin infections in children. J Pediatr 2011;158:861-2.

3. Dryden MS. Complicated skin and soft tissue infection. J Antimicrob Chemother 2010;65 Suppl 3:iii35-44.

4. Jorup-Rönström C, Britton S, Gavlevik A, Gunnarsson K, Redman AC. The course, costs and complications of oral versus intravenous penicillin therapy of erysipelas. Infection 1984;12:390-4.

5. Hepburn MJ, Dooley DP, Skidmore PJ, Ellis MW, Starnes WF, Hasewinkle WC. Comparison of short-course (5 days) and standard (10 days) treatment for uncomplicated cellulitis. Arch Intern Med 2004;164:1669-74.

6. Peters DH, Friedel HA, McTavish D. Azithromycin. A review of its antimicrobial activity, pharmacokinetic properties and clinical efficacy. Drugs 1992;44:750-99.

7. Anonymous. ZITHROMAX ® package insert. New York: Pfizer Inc.; 2013.

8. Wilson SE. The management of skin and skin structure infections in children, adolescents and adults: A review of empiric antimicrobial therapy. Int J Clin Pract 1998;52:414-7.

9. Schatz BS, Karavokiros KT, Taeubel MA, Itokazu GS. Comparison of cefprozil, cefpodoxime proxetil, loracarbef, cefixime, and ceftibuten. Ann Pharmacother 1996;30:258-68.