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Erythromycin Versus Azithromycin: Which is the Fittest Substitute for Penicillin in Allergic Patients?

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1. Abstract

1.1. Background: Since the introduction of penicillin in the early 20th century, limitations to its use such as allergy began to demand alternatives, since it can produce death threatening adverse reactions. Plus, the difficulty and cost to establish patient's allergic profile and discrepancy between test results and medical history adds to this problem. In order to find a perfect substitute for penicillin, many articles have reported the successful use of drugs of the macrolide class in treating infections for which penicillin would normally be indicated as first line, but cannot be used due to allergy.

1.2. Material and Methods: Compiling recent publications, we compared erythromycin and azithromycin, the most prominent macrolide agents considering efficacy, microbial spectrum of action and safety to state which is the fittest to substitute penicillin in allergic patients.

1.3. Results: Azithromycin showed overall better profile in all selected criteria. Its most noticeable advantage over erythromycin seems to be its ability to overcome important adverse reactions of the latter. Furthermore, azithromycin is unexpectedly capable of treating other diseases for which it was not meant to treat when created, which is a noticeable feature for such a broad antibiotic.

1.4. Conclusion: We were compelled to conclude that although the drugs are fundamentally similar, azithromycin not only presents better adverse reactions profile, but has proven to be superior in efficacy to erythromycin in many infections where the substitute is needed, and also widens its appliance to atypical infections, which are subject of promising further investigation.

2. Introduction

Penicillin is a ß-lactam antibiotic widely studied and one of the oldest antimicrobial drug known to science, since its introduction by Alexander Fleming in 1928 [1]. Almost a century from its discovery, penicillin have been throughout used worldwide and modified in order to improve its therapeutic results and overcome growing microbial resistance [2] and even though many other antibiotics were introduced to the scientific community, penicillin is still the preferred drug to treat many infections [3].

Although considered a safe drug, many patients report adverse reactions to penicillin, which limit their use, the most important one being allergy. Approximately 10% of US population has reported allergies to ß-lactam agent penicillin, which range in presentation hazard from low-risk cutaneous rashes to anaphylaxis, despite the fact that those reactions are clinically considered uncommon, they configure emergencies that deserve importance [4].

It is reported that hypersensitivity to penicillin - IgE mediated or not - waves over time, and it is stated that 90% of patients labeled as "penicillin allergic" are able to tolerate its use given specific treatments [5]. Cross-reactivity between penicillin and other ß-lactams are also less common than previously speculated, which should undermine the importance of figuring out a substitute for penicillin, but the acute reactions continue to be an important clinical problem [6], mainly considering that in spite of being reasonably viable to identify the risk for a serious response such as anaphylaxis through immunodiagnostic techniques, patients affected

by acute systemic or complicated infections would not be able to undergo penicillin desensitization processes.

Another important consideration, specially in low and average-income countries, is the cost of penicillin allergy evaluation, which seems to be considerably high [7]. Not only should it be costly to assess allergy in such populations, but it would also be challenging to follow-up on the results of diagnostic tools, such as the skin test for sensitivity.

The most well-established alternative treatment for infections for which penicillin would be the first choice is usually using macrolides agents, notably Azithromycin and Erythromycin [3, 8-10]. Thus considering that finding a suitable substitute for penicillin antibiotic therapy is necessary, it is the aim of this review to compare the two alternative drugs in terms of efficacy, spectrum, compared effectiveness and safety profile, in order to find the optimal substitute among them.

3. Methods

The present review focused research on well-oriented clinical trials and reviews concerning comparisons between Erythromycin and Azithromicin, given penicillin allergy as the main reason to figure its optimal substitute.

Article research was conducted on PubMed, Scielo, Science Direct and Medline bases. The following key-words were used: "allergy", "penicillin", “management", “azithromycin”, “erythromycin”, “macrolides”, “management”, “adverse reactions”, “clinical trials”, “antibiotic" as well as its equivalents in Portuguese. Boxes "AND" and "OR" were selected when they were present.

We also recurred to the latest editions of pharmacology textbooks in order to report more fundamental subjects, which would not find place within research articles, all which are referred to accordingly.

Enters and records identified in the electronic data banks were exported to the platform Rayaan, used in selection. Studies were initially filtered by title and abstract independently and those selected on a first filtration were evaluated regarding eligibility and inclusion in this review by full-text analysis.

Articles of opinion and isolated case reports were the only automatic exclusion criteria for article analysis, and no case complications were considered as to differ among infection presentations. Articles were also not excluded based on language, date or place of conduction.

4. Results and Discussion

4.1. Macrolides: An Heterogeneous Class

Erythromycin, azithromycin and clarithromycin are the three classical constituents of the macrolide class of drugs. Erythromicin was the first to be introduced and although Azithromycin and clarithromycin were then presented due to several distinct advantages over the former, they all function in a similar way, by inhibiting protein synthesis in susceptible organisms by binding to the 50S ribosomal subunit [11]. However, it is important to note that Erythromycin does not inhibit the protein binding but a translocation step in which a peptidil-tRNA moves from the acceptor locus over the ribosome to the peptidil donor locus [12].

Despite the same mechanism of action, focusing in the Azithromycin and Erythromycin comparison, the first articles published investigating newer macrolide’s contributions to the class reported great pharmacokinetic results. Those included improved oral bioavailability, longer half-life, higher tissue concentrations and fewer gastrointestinal adverse effects [13].

4.2. Differences in Antimicrobial Spectrum in Common Infections

As we have presented, macrolides were introduced in order to serve as a substitute for penicillin, among other purposes. One good reason to have a safe alternative to penicillin is the cost of its allergy tracking, which is fairly high even with the latest tests, costing around US$540 [14], and is often a great offset to middle-income country patients.

The spectrum of erythromycin was developed in order to ideally cover all penicillin covered microorganisms. As azithromycin was only introduced later, enhancements can be observed concerning their antimicrobial spectrum as we shall see individually compared.

4.2.1. Respiratory tract infections

Famous pharmacology textbook Goodman & Gilman latest edition compiles updated article records concerning their spectrum [15]. Erythromycin is appropriated to treat several respiratory tract infections, the most common etiological agents being S. pneumoniae, H. influenzae and also M. catharralis. In fact, all macrolides are fit to treat those infections, and are usually the most prescribed after penicillin agents, such as amoxicilin. When it comes to atypical respiratory infections, such as pneumonia caused by M. pneumoniae and C. pneumoniae, all macrolides are fit to prescription, together with quinolones and tetracyclines.

The only relevant discrepancy found in efficiency that is also well-documented is in Legionella infections treatment, where azithromycin is usually preferred due to excellent in vitro activity, higher tissue availability, single daily dose and better tolerability [16]. In fact, azithromycin seemed to have taken a great preferability, since most of the recent literature actually compare its efficiency to other drugs, whereas erythromycin is not cited, although also efficient [17].

4.2.2. Cutaneous and soft tissue infections

Macrolides are a suitable alternative to penicillin treating cutaneous and soft tissue infections. In acneic infections, erythromycin is rarely used due to immense bacterial resistance developed since the 80’s, and azithromycin is the preferred drug, although it has also seen minor increase of resistance recently [18].

Common resistance to macrolides is observed in Staphylococcus cutaneous infections, where neither azithromycin nor erythromycin is recommended in penicillin resistant or sensible strains as an immediate alternative [19].

Azithromycin's overall superiority to its counterpart macrolide in these infections have lead researchers to experiment their potential to cure skin infectious conditions even on complicated and atypical cases. It was added to post-cesarean infection antibiotic-prophylaxis treatment and is has been shown to reduce its incidence, although it did not seem to reduce wound complications [20]. Several trials have shown azithromycin is as effective as penicillin in treating early syphilis acute cutaneous manifestations [21] and also have great records in treating cutaneous Leishmaniasis (Leishmania amazonensis) when added to N-methyl glucamine therapy compared to glucamine alone [22]. It's also considered to maintain similar effectiveness and adverse reaction profile in treating cutaneous lyme borreliosis to doxycycline, cefuroxime axetil, ceftriaxone, amoxicillin, penicillin V, and minocycline [23]

4.2.3. Erysipelas and cellulitis

Erysipelas and cellulitis management poses great challenges by itself, even concerning the first-line antibiotic therapies, due to Streptococcus and penicillin-resistant Staphylococcus association [24]. The acute hypodermic infection of erysipelas, usually also concomitant with some form of cellulitis, is mainly caused by a group A beta-hemolytic Streptococcus, which should make macrolides a fit choice [25].

Clinical trials showed that azithromycin and erythromycin present similar effectiveness in treating cellulitis and erysipelas in comparison to beta-lactams and lincosamides, with an overall better cure ratio and better adverse reaction profile - a major parameter considering their use as beta-lactam substitute [26]. However, prophylactic use of erythromycin has shown several adverse reactions in comparison to beta-lactams, which lead to discontinuation of treatment in another study concerning cellulitis and erysipelas [27]. Azithromycin, nevertheless, seemed flawless, and it also very successfully recorded as therapeutic agent on cellulitis even on immunocompromised patients [28].

4.2.4. Chlamydia infections

All macrolides are suitable to treat chlamydia. Authors usually cite that their effectiveness are so similar in chlamydia infections that the choice is mainly among their differences in pharmacokinetics [29, 30].

In this scenario, azithromycin is preferred due to better adverse reaction profile [31], but a shift can be observed in recent literature concerning the very choice for macrolides. High rates of recurrent and persistent chlamydia in women after azithromycin treatment rose the demand for a better drug [32] and this endeavor have found a breakthrough that will probably keep macrolides on the shelfs for the near future: doxycycline. Doxycyclin have aced the treatment for the many presentations of chlamydia infections, highly exceeding azithromycin's success [33, 34].

5. Conclusion

In summary, considering the evidence compiled in recent literature, the authors are compelled to state that macrolides are safe and have great effectiveness in substituting penicillin in allergic patients. Comparing macrolide drugs, as similar as erythromycin and azithromycin might be, the latter overall antimicrobial attributes is highly superior.

Not only azithromycin showed sufficient capability of substituting penicillin in diseases where it was the first line drug, but also surpasses its effectiveness in cases such as respiratory tract infections, and also widens macrolide application potential, as it is being experimented on different diseases previously treated else-wise, like leishmaniasis. Also considering macrolides safety and adverse effects profile, azythromycin has been found to always overcome deficiencies and adverse reactions present on erythromycin treatment, which usually leads to discontinued therapy.

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