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Review Article

A current opinion on the safety and efficacy of doxycycline including parenteral administration – A review

Michał Majewski *

Department of Pharmacology and Toxicology, Faculty of Medical Sciences, University of Warmia and Mazury in Olsztyn, Poland

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ABSTRACT

Introduction: Doxycycline was introduced into medical practice over 40 years ago but because of increasing bacterial resistance its value has decreased. It remains, however, the treatment of choice for infections caused by atypical organisms such as chlamydia, rickettsia, brucella and the spirochete. Recent studies indicate other possible benefits.
Aim: The aim of this study was to present the pharmacological characteristic of doxycycline antibiotic focusing on parenteral administration.
Material and methods: The attempt was made to characterize thoroughly doxycycline antibiotic and its effect on human health. Using keywords ''doxycycline,'' ''vibramycin,'' ''parenteral injection,'' ''atypical bacteria'' we performed a review of relevant mainly English articles based on a Medline search before May 2013, focusing on last five years.
Discussion: Doxycycline is primarily used in the treatment of infections of the upper and lower respiratory tract, as well as with gastrointestinal and sexually transmitted diseases. Furthermore, anti-inflammatory and immunomodulatory properties of doxycycline were found, which enable this medication to be used in the treatment of serious diseases, often with an immunological background or prophylactically, as a protective agent against the development of excessive inflammation in the human body. Moreover an anticancer effect of doxycycline has been described.
Conclusions: Currently, doxycycline is rarely used, mainly because of the presence of a high percentage of drug-resistant strains of bacteria. However, there is a group of infections, in which the antibiotic has not lost its therapeutic value and is still the first choice. The additional advantage is the beneficial effect on the human immune system. Further studies are indicated, to confirm the effectiveness of doxycycline in the treatment of various cancers.

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* *Correspondence to*: Department of Pharmacology and Toxicology, Faculty of Medical Sciences, University of Warmia and Mazury in Olsztyn, Żołnierska 14 C, 10-561 Olsztyn, Poland. Tel.: +48 89 524 61 88; fax: +48 89 524 61 88.
E-mail address: michal.majewski@uwm.edu.pl

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1. Introduction

Doxycycline belongs to the tetracycline group, which was introduced into medical practice in 1948 and which can be used to treat many infections in children as well as adults. Doxycycline is a broad spectrum bacteriostatic agent against many Gram-positive and Gram-negative bacteria, spirochetes and atypical organisms, as well as some protozoa such as malaria. Like other tetracyclines, doxycycline may cause tissue irritation after injection. In contrast to oxytetracycline, chlortetracycline and tetracycline, doxycycline is different in that it is 5–10 times more lipophilic. Compared with oxytetracycline and chlortetracycline doxycycline has a higher affinity for plasma proteins, a greater ability to penetrate into tissues, a greater volume of distribution, better antimicrobial properties and a longer half-life. Moreover doxycycline is relatively inexpensive, having a broad antibacterial spectrum.[1] Up to now it has been rarely used mainly because of the high rate of occurrence of drug-resistant strains of bacteria. However, there is a group of infections caused by *Mycoplasma pneumoniae* and *Chlamydia pneumoniae*, in which antibiotic treatment has not lost its therapeutic efficacy.[2]

The mechanism inhibits the protein synthesis of ribosomes in susceptible microorganisms, resulting in a stoppage of the growth of bacterial cells. Doxycycline may be administered by slow intravenous injection, bearing in mind that the solution for injection should not be administered intramuscularly or subcutaneously. The side effects after intravenous administration are known as thrombophlebitis. The medication is contraindicated in pregnancy, breastfeeding and in children under 12 years of age, as it can cause damage to the tooth buds and the growth plate.

2. Aim

The aim of this study was to present the pharmacological characteristic of doxycycline antibiotic focusing on parenteral administration.

3. Material and methods

The attempt was made to characterize thoroughly doxycycline antibiotic and its effect on human health. Using keywords ''doxycycline,'' ''vibramycin,'' ''parenteral injection,'' ''atypical bacteria'' we performed a review of relevant mainly English articles based on a Medline search before May 2013, focusing on last five years.

4. Discussion

4.1. *Chemical structure, salts, nomenclature, forms, routes of administration, toxicology*

INNs name: doxycycline.[3] INNMs name: doxycycline hyclate.[4]

Doxycycline is a semi-synthetic derivative of second generation oxytetracycline of potent antibacterial properties. National pharmacopoeias present different doxycycline salts according to the pharmaceutical preparations which include: doxycycline monohydrate (free base), doxycycline hyclate (in some pharmacopoeias as ''hydrochloride'') and a calcium salt.[5–7] In both the Polish IX Pharmacopoeia and the European Pharmacopoeia occur only monographs of doxycycline monohydrate and doxycycline hyclate.[5,6] Doxycycline hyclate in the Japanese Pharmacopoeia (JP XVI) is called doxycycline hydrochloride hydrate, while Martindale (UK) uses the term doxycycline hydrochloride.[7,8]

On the market, doxycycline is available in a variety of forms, such as doxycycline monohydrate, doxycycline calcium salt (vibramycin syrup), a powder for the preparation of oral solution, doxycycline hyclate – hard capsules, tablets, and lyophilisate for parenteral administration. For the prolonged injectable preparation, poloxamer was used as a template in the production.[9]

The dosage is dependent on the medical condition and response to the treatment. When prescribing to children over 8 years of age (some sources say not to use doxycycline for children under 12 years of age), the dose of the drug depends on the weight of the patient. For children weighing less than 45 kg, the starting daily dose is 4 mg/kg and the following daily dosage – 2 mg/kg, but only if the benefits outweigh the risk of the adverse effects on the development of teeth and bones.[8,10]

Parenteral formulations are not widely available in most parts of the world. The most common forms of solutions for injection are prepared at a concentration of 0.1–1.0 mg/mL. Solutions with concentrations lower than 0.1 mg/mL or higher than 1.0 mg/mL are not recommended. Doxycycline can be administered by intravenous injection, usually once or twice a day. It should be injected very slowly, for at least 1 h (usually the range is from 1 h to 4 h). According to the list of drugs, a dose of 100 mg (as hydrochloride) can be used as an antimicrobial agent.[11] Intravenous solutions should be injected with caution to avoid accidental injection into the adjacent soft tissues. The antibiotic may be absorbed through the skin, gastrointestinal tract, or (as an aerosol) by inhalation. The lower dose (e.g. 20 mg twice a day) is used to treat acne vulgaris and rosacea. Under normal circumstances, doxycycline possesses a small health risk, but there are some contraindications to the usage of this antibiotic.

According to the Food and Drug Administration definition, doxycycline is considered as having a robust therapeutic index, and in general it is not necessary to monitor the level of the drug in the blood.[12]

4.2. *Mechanism of action*

The bacteriostatic effect of doxycycline is based upon blocking protein synthesis at the bacterial ribosome level. The antibiotic connects permanently to the small ribosome subunit – 30S, resulting in a blocking of the binding of aminoacyl-tRNA (acceptor site) on the mRNA–ribosome complex. This connection terminates the growth of bacterial cells. Further inhibition of protein synthesis occurs in the mitochondria, by binding to the 70S ribosomal subunit. Doxycycline enters the cell through pores in the outer part of the hydrophilic membrane and also with a pH-dependent active transport, which is located in the inner part of the cytoplasmic membrane. The antibiotic also

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