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Review Article

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

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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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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

inhibits ribosomal apicoplast, present in the malaria-causing parasite (*Plasmodium falciparum*), which leads to impaired synthesis of fatty acids and the heme biosynthesis pathway in the development cycle of *P. falciparum*.[13,14]

There is evidence of doxycycline's influence on reducing the activity of T and B cells and production decreases of antibody, including Immunoglobulin E (IgE). Antibiotic effects are most pronounced in the process of inhibiting the function of phagocytic cells. Doxycycline decreases the activity of matrix metalloproteinases (MMP), such as elastase, collagenase (an enzyme produced by many cancer cells, especially breast cancer and prostate cancer cells), and gelatinase which are synthesized and secreted by neutrophils.

In addition to inhibiting the activity of MMP, the antibiotic inhibits the expression of MMP both on the ribosomal level and during protein synthesis. Furthermore, doxycycline can induce apoptosis in Jurkat leukemia T lymphocyte cells by the activation of caspase-3. Many studies have proven cytostatic and cytotoxic effects of doxycycline against various tumor cell lines of origin. These additional properties are the subject of clinical trials in patients suffering from cancer. It is because of tetracycline's natural osteotropism, that doxycycline is a highly effective agent in inhibiting MMP production by osteoclasts or tumor cells in bones. A study by Sagar and Sales[15] indicates that doxycycline can be a useful antiproliferative and cytotoxic agent and may be used to improve the effectiveness of cisplatin and oxaliplatin treatment in colorectal cancer patients.

Doxycycline also lowers: the synthesis of nitric oxide (NO), the inflammatory cytokines and the reactive free radicals in granulocytes. The mechanism responsible for the phenomenon of doxycycline on the immune system is: chelating divalent calcium and magnesium ions and also electron trapping and neutralizing super active radicals such as hypochlorous acid (HOCl) and hydrogen peroxide (H_2O_2) from polymorphonuclear leukocytes.

4.3. *Pharmacokinetic properties*

Doxycycline binds to plasma proteins at a rate of approximately 82%–95%, whereas tetracycline is at only 65%. Antibiotic accumulates in the bile, reaching a concentration of 5–10 fold higher than in plasma, and is excreted at 30%–40% in urine as the biologically active form and in feces as inactive chelate.[8] Doxycycline hyclate is the most commonly used form of the drug (easily soluble in water), and doxycycline monohydrate is used less frequently because of its much lower solubility.[5] In renal insufficiency, doxycycline is completely eliminated with feces, so the same dose may be administered without the risk of harm resulting from any possible accumulation of antibiotic. Numerous studies have shown that the half-life of doxycycline (18–22 h) did not change even in patients with renal impairment, as the antibiotic does not accumulate in the kidneys. Antibiotic is not removed from the bloodstream during hemodialysis. Due to the prolonged half-life, the use of the antibiotic once a day is possible. Doxycycline penetrates very easily into many tissues and organs, and the level of the drug at therapeutic concentrations was observed in the kidneys, lungs, lymph fluid and peritoneal, colon, gall bladder, prostate, heart muscle, secretion of the sinuses, tonsils, aqueous humor, and in reproductive tissues and breast milk in lactating women.

More than 90% of the doxycycline dose is removed from the body within 72 h of administration. Reduced plasma protein concentration can impair the doxycycline metabolism and so can cause change in dosage regime.

4.4. *Clinical application*

4.4.1. *Respiratory infections*

The indication for prescribing doxycycline is for the treatment of infections caused by susceptible organisms. The drug concentrates in the lung tissue, and therefore is effective in the treatment of lower respiratory tract infections, chronic bronchitis and pneumonia caused by *M. pneumoniae*, *Rikettsia* spp. and *Chlamydia* spp.

The pneumonia treatment outside the hospital ward showed a clear advantage of combination therapy over conventional treatment, which consisted of monotherapy. Such combination therapy involves amoxicillin (with clavulanic acid) and intravenous doxycycline. In the group of people with pneumonia treated outside the hospital, the group on amoxicillin alone (with clavulanic acid) often required a second antibiotic, compared with the group treated with combination therapy from the very beginning. The effectiveness may be influenced by the increasing resistance of *Streptococcus pneumoniae* (the most common etiological agent) to the beta-lactams or tetracycline, or involvement of more than one kind of bacteria in these infections. Data obtained from The European Committee on Antimicrobial Susceptibility Testing (EUCAST) allow researchers to evaluate the resistance of *S. pneumoniae* to antibiotics. A study from 2005 shows that the treatment of inflammatory pneumococcal pneumonia using doxycycline alone is embarked with a high-risk of failure.[16,17]

A retrospective study comparing the efficacy and safety of azithromycin and doxycycline in the treatment of pneumonia caused by *Chlamydia* spp. showed no difference in the effectiveness of treatment.[18] So far, there has been just one case reported of fatal hepatitis in a patient with acute *M. pneumoniae* infection, taking doxycycline, levofloxacin, and naproxen together.[16] Strong evidence suggests that when the resistance of pneumococci is quite low, doxycycline treatment of respiratory diseases can be more effective in comparison to fluoroquinolones (moxifloxacin), both in the hospital, or outside the hospital.[19]

4.4.2. *Urinary tract infections*

Doxycycline is alternatively used (when there is an allergy to penicillin) in urogenital tract infections, the female genital organ infections, and in the treatment of gonorrhea, syphilis as well as nonspecific urethritis, cervical and colorectal infections in adults.[2,20] Doxycycline achieves high therapeutic concentrations in the prostate gland; thus it can be used in the treatment of acute uncomplicated inflammation, in combination with ceftriaxone intramuscular injection.[21] For the treatment of pelvic inflammatory disease the appropriate recommended regiment is treatment with doxycycline (given intravenously or orally) with second or third generation cephalosporins.[2] Due to the high rates of resistance, doxycycline is no longer recommended for the treatment of

gonorrhea or venereal ulcers caused by *Haemophilus ducreyi* without the confirmation of susceptibility.

In women undergoing vaginal hysterectomy, a single intravenous dose of doxycycline in preventing bladder infection works as effectively as multiple doses of cefamandole.

4.4.3. *Skin infections*

Doxycycline is an important therapeutic option in the treatment of skin infection. The antibiotic reaches high concentrations in the sebaceous glands, and thus is effective in the treatment of severe acne (*Acne vulgaris*), rosacea (*A. rosacea*) and also in the treatment of Lyme disease. Doxycycline not only inhibits the growth of *Propinibacterium acnes*, but also reduces inflammation through neurophil chemotaxis reduction and inhibition of chemotactic factor production. This has been widely used in the treatment of acne with pus.[22]

4.4.4. *Bartonellosis*

Bartonella spp. can cause many diseases: a five-day fever, endocarditis, fever of unknown origin, cat scratch disease, von Hippel–Lindau syndrome, Oroya fever, Carrion's disease, retinitis and pericardium inflammation. Doxycycline is active against *Bartonella* strains and is recommended as a first-line monotherapy or in combination with other antibiotics such as rifampicin and gentamicin. Treatment generally lasts for a longer period of time.

4.4.5. *Anthrax and other potential bioterrorism threats*

Rod anthrax infection is caused by the bacterium *Bacillus anthracis*. This disease has existed for hundreds of years and can occur in both animals and humans, living in different parts of the world. Anthrax infection can be treated with doxycycline. An existing condition is normally treated for 5 to 7 days, while the treatment and prevention in case of bioterrorism requires the implementation of 60 days of treatment. The treatment of anthrax which has penetrated into the body by inhalation is usually more severe and requires a more complex therapy. Another potential threat of bioterrorism is tularemia. The recommended therapy is streptomycin or gentamicin, although doxycycline is an effective alternative, especially when the patient is seriously ill. Similar guidelines apply to infections caused by *Yersinia pestis*, where a high rate of recovery was obtained after 7–10 days.[23]

4.4.6. *Other infections*

Doxycycline perfectly penetrates the periodontal tissue, and thus is effective in the treatment of ulcerative gingivitis. Other diseases include eye infections caused by *Chlamydia trachomatis*, insertions of the eye and conjunctivitis trachomas, Lyme disease caused by *Borrelia burgdoferi* when there is chronic erythema migrants and other rare infections such as ornithosis (*Chlamydia psittaci*), listeriosis (*Listeria monocytogenes*), rickettsiosis (*Rickettsia acari*), yaws (*Treponema pallidum* ssp. *pertenue*), plague (*Y. pestis*), granuloma inguinale (*Calymmatobacterium granulomatis*). Doxycycline is also used in the eradication of *Helicobacter pylori*.[20,21] The antibiotic was also used in the treatment of gastrointestinal infections e.g.: cholera (*Vibrio cholerae*), infection caused by *Y. pestis*, *Campylobacter fetus* and *Shigella* spp., Whipple's disease, traveler's diarrhea (but only with proven sensitivity to the antibiotic).

It should be emphasized that the crucial role of doxycycline in the treatment of intracellular infections was achieved by effective therapeutic concentration levels inside the cells.[24] Doxycycline administered for six weeks plus streptomycin administered for two to three weeks is the main therapeutic regimen for the eradication of bovine brucellosis (*Brucella* spp.), although it is difficult to talk about the full eradication of the pathogene. In *Chlamydia*, *Rickettsia* infections and treatment of Lyme disease, doxycycline is usually a first-line treatment.[2,25,26] However, in case of infections caused by atypical bacteria (*Mycoplasma*, *Legionella*) this antibiotic is a second line treatment after macrolide.

When penicillinis contraindicated (because of allergic patients), doxycycline is an alternative to this type of treatment.

Doxycycline is not recommended for the treatment of common urinary tract infections and the central nervous system (CNS), because it respectively achieves low concentration in the urine and the kidney parenchyma and does not penetrate into the CNS.

4.4.7. *Other treatments where doxycycline is used*

In addition to the wide range of activity against bacteria, doxycycline also has anti-inflammatory and immunomodulatory properties. Therefore, there are additional indications for the use of the drug, e.g. in the treatment of toxic shock induced by a bacterial super antigen such as staphylococcal or streptococcal superantigen exotoxin.

The protective effect of doxycycline on the polymorphonuclear neutrophil apoptosis in the presence of an infectious agent and neuronal protection when treated earlier with ionizing radiation has also been indicated. There has been confirmed activity in inhibiting metalloproteinase. There is an application in the treatment of diseases caused by the pathological activation of the enzyme, for example in the treatment of the inflammation of apical teeth. The effect on tumor cells is due to a combination of various functions of doxycycline, e.g. MMP inhibition, and the negative effects on osteoclast differentiation and survival. The cytostatic effect on prostate and kidney cancer cells has been proven, and the long-lasting therapy reported cytotoxic activity on the above-mentioned cells. Other studies carried out on in vitro cell cultures confirmed the cytotoxic activity of doxycycline on prostate cancer cells, breast cancer cells, osteosarcoma and malignant mesothelioma cells.

4.5. *Interaction*

So far, there have been clinically relevant interactions reported with other medications taken concomitantly.

Doxycycline, though only slightly in comparison with other tetracyclines, forms chelates with bi- and trivalent cations; therefore, in the case of oral forms the absorption of the antibiotic from the gastrointestinal tract is impaired. Doxycycline should not be given together with dietary supplements containing calcium, magnesium or iron nor with antacids, such as aluminum, magnesium, and calcium products.[27] The antacids alter the pH of the gastrointestinal tract. Modified released forms of doxycycline may then find their justification because they will eliminate the issues of absorption and the formation of chelates in the gastrointestinal tract.[7]

Patients who are on coumarin anticoagulant therapy should be vigilant as doxycycline may reduce prothrombin activity in plasma.

Many drugs such as rifampicin, barbiturates, phenytoin, carbamazepine, primidone, acetazolamide, sodium bicarbonate and alcohol (consumed chronically) are liver enzyme inducers, so they reduce the biological half-life of doxycycline.[8] Doxycycline also enhances the effects of alcohol on motor functions.[28]

After concomitant treatment with doxycycline and methoxyflurane, several cases of fatal kidney damage were reported. Also, taking doxycycline with oral contraceptives can reduce the effectiveness of contraception and additional security barriers such as condoms are required.

Doxycycline may also displace methotrexate from its binding site, which leads to increased levels of methotrexate and toxicity.[29]

Experimentally synergistic or additive effects of doxycycline with beta-lactams against bacteria of the genus *Stenotrophomonas maltophilia* and *Chlamydophila trachomatis* were demonstrated.

4.6. *Adverse reactions, contraindications and precautions*

Doxycycline prescription in the absence of confirmed bacterial infection and its prophylactic use do not provide any benefit to the patient and increases the risk of developing resistant strains. Although of the entire tetracycline group, doxycycline has the least side effects, the use of this drug during the development of teeth buds, during pregnancy, infancy and in children under 12 years of age may cause permanent damage or discoloration of teeth (yellow-gray-brown).[8,10] This adverse reaction is more common during long-term use of other tetracyclines, but similar cases have also been reported after repeated administration of doxycycline. In some cases, enamel hypoplasia has been described, so doxycycline should not be used in children under 12 years of age.

Animal studies have shown that doxycycline crosses the placenta into the developing fetus tissues and exerts its toxic effect, often causing retardation in the development of the skeleton. Evidence of embryo toxicity has also been noted in animals treated with the drug in early pregnancy. If the antibiotic is used during pregnancy or if the patient becomes pregnant while taking doxycycline, then the patient should be informed as soon as possible of the existing hazard to the developing fetus.

Pregnancy: teratogenic effect – Category D which means that the medication's side effects carry the human fetal risk but potential benefits may warrant use of the drug in pregnant women despite potential risks.

Doxycycline forms stable complexes with calcium ions in bones forming tissues. There has been a decrease in the fibula growth in preterm infants treated with this antibiotic (dose given: 25 mg/kg given every 6 h). This reaction proved to be reversible when the treatment was withdrawn. It should be noted, however, that doxycycline may be used in these groups of patients only if the benefit to the patient outweighs the risk (life rescue or lack of other treatment options, it applies especially to *Rickettsia* eradication and the treatment of anthrax).

During doxycycline treatment, several cases of diarrhea were reported, which may enhance, and even lead to fatal colitis. This is due to the change of the physiological bacterial flora of the intestine and to the proliferation of *Clostridium difficile*. Doxycycline therapy should be stopped and appropriate treatment is necessary: high fluid intake, electrolytes and amino acid supplementation, or even the use of an appropriate antibiotic active against *C. difficile*. Doxycycline is also contraindicated in people who have previously exhibited hypersensitivity to any of the tetracyclines or in patients with porphyria.[8]

In patients suffering from pneumonia treated with doxycycline and procaine penicillin there was no difference in the effectiveness of therapy, or the percentage of side effects.

The anti-metabolite action of tetracyclines may cause an increase in the concentration of urea (blood urea nitrogen – BUN). Studies indicate that a significant increase in BUN does not occur in patients with impaired renal function; therefore, doxycycline can be safely used as the antibiotic for this disease.

The use of doxycycline causes skin disorders. A few rare cases of Stevens-Johnson syndrome were described.[30] Doxycycline accumulates in the skin, so sensitivity was observed in some patients exposed to UV radiation, consisting of an excessive reaction to the sun, as well as the occurrence of photo toxicity.[10] Patients who may be exposed to direct sunlight or UV light should be advised of the possibility of an allergic reaction and doxycycline therapy should be discontinued after the first signs of erythema on the skin.

When the antibiotics kill bacteria (which most often relates to spirochetes) toxin is secreted which leads to Jarisch–Herxheimer reaction.

Doxycycline can also cause side effects in the hematopoietic system. Some cases of hemolytic anemia, neutropenia, thrombocytopenia, anaphylaxis, and eosinophilia were observed.

During the prolonged administration of antibiotics, the formation of a brown-black microscopic discoloration of thyroid was observed, but there were no abnormalities in the function of this gland.

4.6.1. *Laboratory examinations*

In case of long-term therapy, laboratory tests should be periodically performed, including tests on blood-forming organs, kidneys and liver.

4.6.2. *Overdose*

Sporadic reported overdose of doxycycline lead to liver and kidney damage as well as inflammation of the pancreas.[31] In case of overdose, doxycycline therapy should be stopped and treated symptomatically. Dialysis has no effect on the half-life of the drug, and thus the application of this treatment is not effective.

5. Conclusions

Doxycycline at a 100–200 mg dose per day is typically used in clinical practice for the treatment of various infectious diseases for over 40 years and the safety profile of this antibiotic is well known. Currently, the drug 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, as doxycycline can stimulate immunocompetent cells, strengthen the function of phagocytes, and reduce the production of inflammatory mediators. Further studies are indicated, especially in order to confirm the effectiveness of doxycycline in the treatment of various cancers.

Conflict of interest

None declared.

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