

**Second Meeting of the Subcommittee of the Expert Committee on the
Selection and Use of Essential Medicines**

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Tetracycline group in children

WHO Model List of Essential Medicines for Children lists doxycycline 100 mg capsule or tablet for the treatment of cholera. A review was requested to compare safety and efficacy of different tetracyclines to decide whether a square box listing is appropriate.

Summary

Several oral tetracyclines are currently available in the market. All of them are bacteriostatic drugs with similar spectrum of activity. Bacteria resistant to one drug are usually resistant to others. However, there are significant differences in pharmacokinetics – better absorption, longer half life, better penetration and bioavailability - which favour doxycycline and minocycline. Adverse events are similar but severity of some events is more with demeclocycline and minocycline, making them less suitable for oral use in children.

Currently, one of the important indications for the use of tetracyclines is fevers caused by *Rickettsiae* and *O tsutsugamushi*. Doxycycline is the drug of choice for this indication. Tetracycline can also be used. For severe cases of cholera, either tetracycline or doxycycline is recommended, except in young children. However, because of varying prevalence of resistance, current recommendations do not specify tetracycline, but advice to choose antimicrobial based on local susceptibility data. Tetracycline group is one of the choices. There are other indications also for using tetracyclines.

Tetracyclines are not recommended for treatment in children younger than 8 years of age. BNF C 2006 lists tetracycline, demeclocycline, doxycycline, lymecycline, minocycline and oxytetracycline for use in children above 12 yrs. However, these drugs have been used successfully in younger children. Limited data show that doxycycline use is associated with only a low incidence of teeth discoloration in

young children. This group is better used in younger children only when other drugs are likely to be ineffective and when benefits clearly outweigh risks.

Dosage schedules and strength of formulations differ. Tetracycline is available as 250/500 mg per tab/cap and doxycycline as 50/100 mg tab/cap.

Recommendations

Square box listing is not appropriate

Retain doxycycline, but review the statement on cholera to take into account its use in other life-threatening infections like typhus fevers and malaria prophylaxis.

Discuss whether age restriction needs to be put in for certain indications

Review

Tetracycline group of drugs include chlortetracycline, oxytetracycline, demeclocycline, methacycline, tetracycline, doxycycline, and minocycline [1]. Of these, oxytetracycline, demeclocycline, tetracycline, doxycycline, and minocycline are currently available in the United States for oral use (drugs@FDA). Only doxycycline and tetracycline are listed in the International Drug Price Indicator Guide

Activity

The spectrum of activity of these bacteriostatic drugs is similar and includes a wide range of gram-positive and gram-negative bacteria. In addition, they are highly effective against rickettsiae causing spotted fevers, rickettsial pox and typhus fevers and *C. burnetii*. They act on spirochetes, including *Borrelia recurrentis*, *Borrelia burgdorferi* (Lyme disease), *Leptospira* spp and *Treponema pallidum* and also on *Mycoplasma pneumoniae*, *Chlamydia* spp., *Legionella* spp., *Ureaplasma* and some atypical mycobacteria. By weight, doxycycline and minocycline are more active followed by tetracycline.

Resistance

Prevalence of resistance among Gram positive cocci and Gram negative bacilli to this group are already very high in most parts of the world. Therefore, as a group they are

not recommended for these infections without susceptibility testing [1-3]. Strains of *Neisseria gonorrhoeae* no longer are predictably susceptible to tetracyclines. With very few exceptions, resistance to any one member of the class [1-3] result in cross-resistance to other tetracyclines.

Pharmacokinetics [1]

There are differences between different drugs in absorption, half life and bioavailability[1]. Absorption is greater in the fasting state and the percentage of an oral dose absorbed on an empty stomach is low for chlortetracyclines (30%); intermediate for oxytetracycline, demeclocycline, tetracycline (60% to 80%); and high for doxycycline (95%) and minocycline (100%). High lipid solubility of doxycycline and minocycline contribute to this. Food, including dairy products, does not significantly interfere with the absorption of the latter two drugs, but affect absorption of others.

Oxytetracycline and tetracycline have half-lives in the range of 6 to 12 hours and are administered two to four times daily. Demeclocycline has a half-life of 16 hours. Since doxycycline and minocycline are well absorbed and have half-lives of 16 to 18 hours, less frequent and lower doses are possible.

The oral dose of tetracycline in children is 25 to 50 mg/kg daily in two to four divided doses and ranges from 1 to 2 g per day in adults. The dose of doxycycline for children is only 4 to 5 mg/kg per day in two divided doses and for adults it is 100 mg twice daily. The dose of minocycline is similar to that of doxycycline. Tetracycline is available as 250/500 mg per tab/cap and doxycycline as 50/100 mg tab/cap.

Tetracyclines distribute widely throughout the body and into tissues and secretions.

High lipid solubility of doxycycline and minocycline allow better penetration.

Primary route of elimination for most tetracyclines, except doxycycline, is the kidney.

They are also concentrated in the liver and excreted in bile. However, rate of clearance can vary and renal clearance of demeclocycline is less than half that of tetracycline. There is no significant difference in the serum half life of doxycycline between normal individuals and patients with severe renal impairment [3]. For minocycline, serum half life in normal individuals range from 11 to 22 hrs and 18 to 69 hrs in those with renal impairment [2].

Adverse events [1]

The group has similar adverse events, but the severity may be more with some members. Demeclocycline use has significant risk of photosensitivity reactions and nephrogenic diabetes insipidus. Systematic reviews confirm that long term minocycline use (as in treatment of acne) can induce lupus[4] and severe autoimmune liver damage [5]. Long-term use can also cause brownish discoloration of skin [1]. Vestibular toxicity, manifested by dizziness, ataxia, nausea, and vomiting, which disappear within 24 to 48 hours after stopping the drug, is another effect of minocycline [1].

Animal studies show that the goitrogenic effect is more with minocycline. Oncogenic activity was seen in rats with oxytetracycline (adrenal and pituitary tumours) and minocycline (thyroid tumour) [2, 3]

Australian Medicines Handbook states that minocycline use is associated with higher incidence of vestibular and CNS adverse effects, lupus like syndrome, serum sickness like disease and hepatitis especially on prolonged use, but less likely to cause photosensitivity.

Children can develop permanent brown discoloration of the teeth due to drug deposition, probably due to its chelating property and the formation of a tetracycline–calcium orthophosphate complex. Therefore, the risk is when the teeth are being calcified [1]. The period of greatest danger is from mid pregnancy to about 4 to 6 months of the postnatal period for the deciduous anterior teeth, and from a few months to 5 years of age for the permanent anterior teeth [1]. However, children up to 8 years old may be susceptible to this complication of tetracycline therapy. Enamel defects and hypoplasia can also occur.

There are no good studies to fully understand incidence of this adverse event or its relationship to dosage and duration of therapy. Although all doses and duration can bring about this event, larger drug doses relative to body weight appear to cause more intense enamel discoloration [1]. Staining was more frequent in those receiving total tetracycline dose of >3gms and when duration of therapy was >10 days [19]. There is probably a linear relationship with number of doses and darkness of teeth [19].

Duration of therapy may be less important than the total quantity administered [1]. Binding of doxycyclines to calcium appears to be less than other tetracyclines and reports from a small number of children show that staining is infrequent with

doxycycline [19]. In a study involving 25 premature babies and 282 children, aged 1m to 12 yrs, only 6 children developed discoloration [19]. Four of these were below 2 yrs. In another study evaluating 10 children (mean age 5 yrs) who received doxycycline for 2- 8 days, there were no significant differences in teeth coloration from the control group. Vibramycin (doxycycline) and Minocin labels state that this adverse event is more common with long term use or repeated short courses.

Tetracyclines are deposited in the skeleton during gestation and throughout childhood and may depress bone growth in premature infants. Decrease in fibula growth rate has been observed in premature babies [19]. This is reversible if the period of exposure to the drug is short.

Use of this group may cause increased intracranial pressure in young infants, even when given in the usual therapeutic doses. The pressure returns to normal when drug is discontinued.

All tetracyclines can produce a variety of gastrointestinal manifestations.

Oesophagitis, esophageal ulcers, and pancreatitis are also reported. Cheilosis, atrophic or hypertrophic glossitis and pruritus ani which can persist for weeks or months after cessation of therapy is reported.

Vaginal, oral, and even systemic superinfections caused by bacteria or fungi resistant to these agents are observed. Severe pseudomembranous colitis can also occur.

Demiclocycline, doxycycline, and other tetracyclines to a lesser extent produce mild-to-severe photosensitivity reactions. Onycholysis and pigmentation of the nails can develop.

Hepatic toxicity usually follows large dose parenteral therapy, but can also occur following oral administration. Oxytetracycline and tetracycline are least hepatotoxic. This group may aggravate azotemia in patients with renal disease. Doxycycline and minocycline are safer than the others in this group (BNF C 2006).

Fanconi syndrome has been observed in patients ingesting outdated and degraded tetracycline.

Thrombophlebitis frequently follows intravenous administration. Long-term therapy may produce leukocytosis, atypical lymphocytes, toxic granulation of granulocytes, and thrombocytopenic purpura. Fever and asthma are also reported.

Hypersensitivity skin reactions, angioedema and anaphylaxis can occur. Cross-sensitization among the various tetracyclines is common.

Uses in children above 8 years

1. Infections due to *Rickettsia* spp and *Orientia tsutsugamushi*: Tetracyclines are effective and life-saving in different types of spotted fevers and typhus fevers [6-8]. A Cochrane review on therapy for scrub typhus identified 4 trials involving 451 adults. There was no difference between tetracycline and chloramphenicol (1 study, RR 1.00; 95% CI 0.07 to 15.26) or between doxycycline and tetracycline (2 trials, RR 0.46; 95% CI 0.12 to 1.75) [9]. A recent randomised control trial in patients with scrub typhus shows that doxycycline is effective and comparable to other newer drugs [10]. It is the drug of choice for scrub typhus and rickettsial illnesses [6-8].

Recent reports show that the incidence of these infections is on the rise in several developing countries and the actual magnitude is unknown [7]. Because of the high mortality associated with this infection empirical use based on clinical findings is recommended [7]. Children are also affected. In younger children the benefit of treating this potentially fatal infection can outweigh the risk of staining of teeth [7]. Currently, this is a very important indication for doxycycline use in many affected areas. However, resistance has appeared especially in Thailand [7]. A recent multicentre randomised controlled trial in an area where leptospirosis and typhus fevers are endemic, doxycycline was shown to be an effective and affordable mode of therapy for acute febrile illnesses without obvious focus of infection[11]. This situation occurs in many areas in the Asia Pacific region.

2. Cholera: Primary mode of management is fluid and electrolyte replacement. Doxycycline is effective in reducing the duration of diarrhoea, stool volume and duration of *V cholerae* excretion in stool. WHO in 2004, recommended either tetracycline as four doses for three days or doxycycline as single dose in patients with severe dehydration [12]. For young children, azithromycin was the recommendation. However, resistance to tetracyclines has appeared among *V. cholerae* and prevalence can vary from place to place and year to year [13]. There is insufficient data to assess

impact of in vitro resistance on clinical failure. However, epidemiological data from outbreak situations suggest that resistance to primary drugs can result in increased mortality and prolonged disease [13]. Hence other publications from WHO advocate appropriate antibiotics based on current local susceptibility data [14]. Tetracycline group is one of the choices.

According to recent reports, the incidence of cholera is on the increase. Cases reported to WHO during 2006 rose dramatically - 236 896 cases from 52 countries - an overall increase of 79% compared to 2005. Reported cases probably represent only about 10% of the actual. 80% of cases are of mild to moderate severity.[15]

3. Trachoma: Doxycycline or tetracycline is effective for this infection. However in children, azithromycin, effective as a single dose, is preferred. Current WHO recommendation is oral azithromycin. If this is not available, tetracycline ophthalmic ointment is to be used [16]

4. Anthrax: Doxycycline is recommended as an alternative for post exposure prophylaxis of anthrax [17] .

5. Brucellosis: Tetracyclines, usually doxycycline, in combination with rifampicin or streptomycin are effective for acute and chronic brucellosis.

6. *Mycoplasma pneumoniae* respiratory infections

7. Leptospirosis [11], relapsing fever and Lyme disease, bartonellosis, tularaemia, plague

8. Doxycycline is used for *P falciparum* malaria prophylaxis during travel to antimalarial drug resistant areas [18].

Most available evidence on safety and efficacy is on doxycycline. Compared to other oral tetracyclines, it has the best pharmacokinetic and safety profile. Doxycycline, and in some instances tetracycline, is specifically recommended for infections of public health relevance. Tetracycline is available as 250/500 mg per tab/cap and doxycycline as 50/100 mg tab/cap.

References

1. *Goodman & Gilman's The Pharmacological Basis of Therapeutics, 11th Edition*, ed. L.L. Brunton, et al. 2006.
2. *Minocin, Label, Triax pharmaceuticals,LLC.*
3. *Vibramycin, Label. Pfizer labs, 2007.*

4. Schlienger, R.G., A.J. Bircher, and C.R. Meier, *Minocycline-induced lupus. A systematic review*. *Dermatology*, 2000. **200**(3): p. 223-31.
5. Lawrenson, R.A., et al., *Liver damage associated with minocycline use in acne: a systematic review of the published literature and pharmacovigilance data*. *Drug Saf*, 2000. **23**(4): p. 333-49.
6. Botelho-Nevers, E. and D. Raoult, *Fever of unknown origin due to rickettsioses*. *Infect Dis Clin North Am*, 2007. **21**(4): p. 997-1011, ix.
7. Parola, P. and D. Raoult, *Tropical rickettsioses*. *Clin Dermatol*, 2006. **24**(3): p. 191-200.
8. Walker, D.H., et al., *Diseases Caused by Rickettsia, Mycoplasma, and Chlamydia - Rickettsial Diseases*. *Harrison's Internal Medicine (Online)*. 2005.
9. Panpanich, R. and P. Garner, *Antibiotics for treating scrub typhus*. *Cochrane Database Syst Rev*, 2002(3): p. CD002150.
10. Kim, D.M., et al., *Controlled trial of a 5-day course of telithromycin versus doxycycline for treatment of mild to moderate scrub typhus*. *Antimicrob Agents Chemother*, 2007. **51**(6): p. 2011-5.
11. Phimda, K., et al., *Doxycycline versus azithromycin for treatment of leptospirosis and scrub typhus*. *Antimicrob Agents Chemother*, 2007. **51**(9): p. 3259-63.
12. WHO, *First steps for managing an outbreak of acute diarrhoea*. 2004, Global task force on cholera control.
13. Sack, D.A., et al., *Antimicrobial resistance in shigellosis, cholera and campylobacteriosis, in Background document for the WHO global strategy for containment of antimicrobial resistance*. 2001.
14. WHO, *Cholera outbreak assessing the outbreak response and improving preparedness*. 2004.
15. WHO, *Fact sheet, 107, Cholera*. 2007.
16. WHO, *Trachoma control A guide for programme managers*. 2006.
17. Meehan, P.J., et al., *Responding to detection of aerosolized Bacillus anthracis by autonomous detection systems in the workplace*. *MMWR Recomm Rep*, 2004. **53**(RR-7): p. 1-12.
18. WHO, *International travel and health, chapter 7 Malaria*. 2007.
19. Benavides, S. and M.C. Nahata, *Anthrax: safe treatment for children*. *Ann Pharmacother*, 2002. **36**(2): p. 334-7