Dear Sir/Madam,

The following memorandum has been prepared by Dr. D. Macintosh, Department of Pharmacology, Otago University Medical School, Dunedin.

TETRACYCLINES

Introduction

Although the therapeutic value of the tetracycline group of drugs has declined since their introduction over 25 years ago, they are still useful in a number of Gram-positive and Gram-negative infections. Individual variations in antibacterial activity amongst members of the tetracyclines appear to be of a minor nature, although with minocycline there may be a greater frequency of sensitivity of staphylococcus aureus than with other tetracyclines. Tetracyclines are employed in prophylaxis against recurrent infection in chronic bronchitis and there is evidence that minocycline penetrates sputum more readily than oxytetracycline or doxycycline. Minocycline is considered to be of major importance in the treatment of the meningococcal carrier state and for prophylaxis among contacts. Parenteral preparations include rolitetracycline for intramuscular and intravenous administration (Tetrex-PMT, IM, and IV) and doxycycline (Vibramycin) for intravenous administration only.

Tetracyclines may be useful alternatives to penicillin in treponemal and gonococcal infection where hypersensitivity to penicillin exists, although in gonococcal disease they have to compete with co-trimoxazole. More specific indications are brucellosis used with or without streptomycin, rickettsial diseases, and infections due to mycoplasma and chlamydia. In cholera they reduce fluid requirement, and recently tetracyclines have been shown to possess antimalarial activity and may contribute to the management of infestation by chloroquine-resistant Pl. falciparum. There are, however, differences in pharmacokinetic properties, particularly in the presence of
impaired renal function which are highly significant. Thus, the newer compounds doxycycline and minocycline are more completely absorbed from the alimentary tract than the older tetracyclines. The half life in serum of tetracycline is 8.5 hours with normal renal function but 57–108 hours in severe renal failure. Doxycycline has a serum half life of between 10 hours and 15 hours and is not prolonged in renal insufficiency. Minocycline has a serum half life of between 13.3 and 15.9 hours which like that of doxycycline may be little altered with impaired renal function. Since minocycline has some potentially serious side-effects (vide infra), then where tetracycline therapy is called for in a patient with inadequate renal function, doxycycline would appear to be the compound of choice. Apart from the emergence of resistant organisms, Gram-positive and Gram-negative (in the latter group Proteus and Pseudomonas spp. are particularly insensitive), the disadvantages of the tetracycline group may be considered under the following headings, interactions with other chemical compounds and adverse reactions.

**Interactions**

Sodium bicarbonate may interfere with tetracycline absorption by altering the pH of the small bowel. Calcium aluminium and magnesium preparations form non-absorbable complexes with tetracyclines and milk and dairy products have the same effect. Antacid preparations may be prescribed to control symptoms of gastrointestinal irritation. Non-absorbable complexes are also formed with salts of iron from which neither tetracycline nor iron are absorbed.

**Adverse Reactions**

Gastrointestinal symptoms (anorexia, nausea, vomiting, and diarrhoea) are common and may be sufficiently severe to necessitate a change of antibiotic. Allergic reactions occur and tetracyclines have been implicated in the Stevens-Johnson syndrome. Fatty infiltration of the liver (steatosis) may be a sequel of tetracycline administration and fatal hepatic damage has followed the intravenous use of large doses (in excess of 2g/day) in pregnancy. Administration of conventional doses in pregnancy leads to deposition of tetracycline in teeth with discoloration and deformity of teeth. Deposition also occurs in bone with reversible inhibition of bone growth. Most paediatricians now prefer to avoid tetracycline therapy in children under 8 years of age. Renal function may be seriously compromised by tetracyclines. Azotaemia may develop in patients with normal renal function and patients with stable chronic renal failure may be precipitated into terminal renal failure without associated oliguria. Concomitant diuretic therapy with salt and water loss aggravates the azotaemia. The rise in blood urea may be partly due to an antianabolic effect of tetracycline and also partly to its ability to induce a
sodium diuresis\textsuperscript{16}. In addition to the rise in blood urea, however, there is also elevation of serum creatinine and depression of creatinine clearance\textsuperscript{19}.

Minocycline is also capable of exacerbating uraemia with poor correlation between this effect and levels of minocycline in serum\textsuperscript{20}. Although in one series of patients with chronic renal failure doxycycline did not elevate blood urea levels\textsuperscript{21}, other investigators have shown a modest rise in blood urea\textsuperscript{22} unaccompanied, however, by any increase in serum levels of doxycycline\textsuperscript{23}. This is due to the fact that doxycycline is largely excreted by non-renal pathways\textsuperscript{9}.

Less common adverse reactions are photosensitivity in which demethylchlorotetracycline has been particularly implicated and the rare syndrome of benign intracranial hypertension reported in children\textsuperscript{23} and in adults\textsuperscript{24}.

A particular problem has arisen with minocycline. It commonly causes severe vertigo and nausea no matter for what reason it is prescribed. Although commonly described as "vestibular", this is by no means established and the mechanism of effect is not clear. There is no evidence that minocycline is toxic to the eighth cranial nerve and the symptoms are transient and reversible on discontinuation of the drug\textsuperscript{3}.

Yours faithfully,

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References:


