Tetracycline and Blood Urea

Drugs of the tetracycline group cause a rise of blood urea.[1 2] Patients with stable chronic renal failure may be precipitated into terminal renal failure when they are treated with these antibiotics.

Drugs of the tetracycline group can produce a rise in the blood urea of people with normal kidneys. M. E. Shils[3] gave tetracycline hydrochloride 1-2g/day by mouth to eight patients with normal renal function. The blood urea nitrogen rose in seven of the eight. Because the plasma creatinine did not change he concluded that the rise of blood urea nitrogen was due to the known antianabolic effect of tetracycline on amino-acid incorporation into protein. H. Roth and colleagues[4] reported that two out of six healthy male volunteers showed impairment of urine-concentrating ability when given demethyl-chlortetracycline by mouth. In these two volunteers there was concomitant polyuria and in one a rise of blood urea.

With normal renal function the biological half-life of tetracycline is 8·5 hours.[5] In patients with severe renal failure it is between 57 and 108 hours, and tetracycline blood levels are high.[3 5] In one patient described by Shils[3] therapeutic levels were still present eight days after stopping the drug. It is not surprising, therefore, that toxic effects of tetracycline are common in chronic renal failure. In 1952 J. C. Bateman and her colleagues,[2] looking for possible antimitotic effects of antibiotics on neoplastic lesions, found that in eight of 10 patients given intravenous oxytetracycline there was a rapid rise of serum non-protein nitrogen followed by thirst, dehydration, hypotension, and death from renal failure. Shils[3] gave tetracycline hydrochloride by mouth to 11 patients, seven with chronic renal failure and four with "borderline" renal function. In all 11 there was a rise of blood urea nitrogen, and the more advanced the renal failure the greater the rise of blood urea nitrogen. The patients also experienced a pronounced diuresis and loss of weight. Shils concluded that when tetracycline is given to patients with chronic renal failure the rise in blood urea is due partly to its antianabolic action and partly to its ability to produce a sodium diuresis. Since that time there have been sporadic reports of the deleterious effects of both tetracycline and oxytetracycline in chronic renal failure.[6-9] C. R. P. George and R. A. Evans[10] showed that in addition to the rise in blood urea there was also a rise in plasma creatinine and a fall in creatinine clearance.

There is no doubt that the rise in blood urea is often accompanied by deterioration of renal function. It is important that this potentially lethal effect of tetracycline should not be clouded by a comforting impression that tetracycline produces only a harmless and transient rise in blood urea. The deterioration in renal function is often accentuated by the loss of salt and water produced by the nausea, vomiting, and diarrhoea which may accompany the high blood levels of tetracycline in chronic renal failure. It has also been shown recently that loss of salt and water owing to administration of diuretics accentuates the rise of blood urea produced by tetracycline.[11]

These deleterious effects of tetracycline are distinct from the rare Fanconi-like syndrome which results from the administration of outdated or improperly stored tetracycline. In this syndrome it has been shown that the effects are due to anhydro-4-epi-tetracycline, which is one of the degradation products of the antibiotic.[12]

In 1970 P. J. Little and R. R. Bailey[13] showed that doxycycline, in contrast to tetracycline, oxytetracycline, lymecycline, and demethylchlortetracycline, did not cause a rise in blood urea even in patients with chronic renal failure. Eleven patients with a blood urea of from 50 to 200mg/100 ml were given the drug and none showed a rise of blood urea. This lack of toxicity is presumably because the serum half-life of doxycycline in patients with advanced chronic renal failure is the same as that in patients with normal renal function.[14 15] As doxycycline is a safe alternative there seems to be no justification for giving other members of the tetracycline group to patients with renal disease.

1 Womack, C. R., *et al.*, *Archives of Internal Medicine*, 1952, **89**, 240.
2 Bateman, J. C., Barberio, J. R., Grice, P., Klopp, C. T., and Pierpont, H., *Archives of Internal Medicine*, 1952, **90**, 763.
3 Shils, M. E., *Annals of Internal Medicine*, 1963, **58**, 389.
4 Roth, H., Becker, K. L., Shalhoub, R. J., and Katz, S., *Archives of Internal Medicine*, 1967, **120**, 433.
5 Kunin, C. M., in *Proceedings of the Third International Congress of Nephrology*, ed. G. J. Schreiner, vol. 3, p. 193. Basel, Karger, 1967.
6 Wray, S. H., Kocen, R. S., and Wright, K. J., *Postgraduate Medical Journal*, 1965, **41**, 18.
7 Hanson, G. C., *Postgraduate Medical Journal*, 1968, **44**, 870.
8 Perkash, I., Kataria, P. N., and Khanna, O. P., *Journal of Urology*, 1969, **102**, 102.
9 Edwards, O. M., Huskisson, E. C., and Taylor, R. T., *British Medical Journal*, 1970, **1**, 26.
10 George, C. R. P., and Evans, R. A., *Medical Journal of Australia*, 1971, **1**, 1271.
11 Boston Collaborative Drug Surveillance Program, *Journal of the American Medical Association*, 1972, **220**, 377.
12 Benitz, K. F., and Diermeier, H. F., *Proceedings of the Society for Experimental Biology and Medicine*, 1964, **115**, 930.
13 Little, P. J., and Bailey, R. R., *New Zealand Medical Journal*, 1970, **72**, 183.
14 Mérier, G., Laurencet, F. L., Rudhardt, M., Chuit, A., and Fabre, J., *Helvetica Medica Acta*, 1969-70, **35**, 124.
15 Mahon, W. A., Wittenberg, J. V. P., and Tuffnel, P. G. *Canadian Medical Association Journal*, 1970, **103**, 1031.