associated with fenclofenac. Apart from the well known gastrointestinal adverse reactions of the non-steroidal anti-inflammatory drugs it has become increasingly apparent that these agents can cause a number of adverse renal effects, for example, acute renal failure, chronic renal damage, nephrotic syndrome and interstitial nephritis, and also abnormalities of water, sodium, and potassium homeostasis.

We would like to report our experience with a 66-year-old male patient suffering from rheumatoid arthritis for three years who was taking piroxicam for his arthritis and Moduretic for ankle oedema. As his arthritis was deteriorating piroxicam was stopped and instead he was started on diclofenac 50 mg three times a day and also penicillamine 125 mg a day. Before introduction of these drugs the laboratory investigations showed: white cell count 9.5 x 10^9/l, haemoglobin 10.9 g/dl, erythrocyte sedimentation rate 108 mm/h, serum urea 10.3 mmol/l, serum creatinine 96 mmol/l, electrolytes and bicarbonate within normal limits. About 10 days later the patient complained of nausea and malaise and his urinary output fell to 500 ml in 24 hours. Investigations revealed normal urinary microscopy, no proteinuria, serum urea 22.3 mmol/l, serum creatinine 160 mmol/l, and serum potassium 5.2 mmol/l, but the other electrolytes were within normal limits. A straight x-ray of the abdomen showed no abnormality of the renal outlines. Both penicillamine and diclofenac were stopped, after which the serum urea, creatinine, and potassium gradually fell and returned to normal levels in five days.

Our patient developed uraemia after only 10 days' treatment with diclofenac and penicillamine. Adverse reactions on the kidneys due to penicillamine are usually late events and appear initially with proteinuria. We cannot absolutely rule out penicillamine as the offending drug in our patient, but it seems unlikely. A more obvious suspect is diclofenac, as a number of non-steroidal anti-inflammatory drugs have now been reported to cause renal impairment believed due to inhibition of prostaglandins' action in the kidneys. In any patient who develops unexplained uraemia, especially in the presence of previous renal impairment or during the use of diuretics, a full drug history should be taken, and any non-steroidal anti-inflammatory drug should be withdrawn for a period to see if renal impairment improves, before resorting to further renal work up which may be necessary. Due caution should be exercised in prescribing these drugs to patients who may be liable to renal complications, in particular patients with chronic renal insufficiency, hepatic cirrhosis, cardiac failure, and intravascular volume contraction as a result of either nephrotic syndrome or the use of diuretics.

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References

Free thiomalate levels in rheumatoid arthritis

Sir, With reference to the recent article by Rudge et al. we wish to raise the following points:

1. The concluding paragraph states that the methodology devised and employed by us for measuring d-penicillamine is 'unsuitable for human studies'. We have and still are using this method on a routine basis in a large study measuring plasma concentrations of d-penicillamine in patients with rheumatoid arthritis to assess whether any correlations exist between plasma concentration, efficacy, and toxicity. The assay is relatively simple, and on an average day a single person can assay nine samples in duplicate with appropriate standards. To our knowledge this method is the only type that permits such a throughput of samples.

2. We feel it is more appropriate to measure total d-penicillamine or indeed any other drug (thiomalate, captopril) of this type rather than the free, reduced form since (a) it is unclear which is the pharmacologically active form(s) of the drug, and (b) even if the free reduced form of penicillamine is the active moiety, the sulphhydryl oxidation reactions which this type of drug undergoes (plasma protein binding, disulphide formation/exchange) are reversible. Hence all forms of the drug and not just the free reduced form are potentially available for pharmacological activity.

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L J Notarianni

Reference

Sir, In reply to the above letter from Notarianni et al. we entirely agree and have stated previously that studies on the metabolism and pharmacology of thiol-containing drugs should attempt to quantify all individual metabolites. Unlike d-penicillamine where detailed work over two decades by many workers has identified four metabolites, comparable metabolic data for sodium aurothiomalate do not as yet exist. In the paper under discussion we predict that similar metabolites for thiomalate are likely. At present, work is in hand to synthesise these metabolites and develop methods for their chromatographic separation and quantification.
The only published analytical data from the Bath group describe a method which measures either free penicillamine and penicillamine disulphide or total D-penicillamine after treatment with dithiothreitol. It is not clear from their recent report how the method has been modified in order to quantify mixed disulphides accurately. Previous work with direct determination of the mixed disulphides on amino acid analysers has shown that the major plasma metabolite is cysteine penicillamine disulphide, a result inconsistent with data derived from reference 4. We have also been unable to reduce penicillamine disulphide reproducibly using dithiothreitol, which may be due to difficulties either with the reduction or the artefactual chromatography. We have recently reviewed the various approaches to thiol analysis and do not consider that the method so far described by the Bath group provides a true description of the complex metabolism of D-penicillamine in plasma. To our knowledge only one published study approaches that ideal.

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References

Condensed reviews of specific developments in inflammation research which would otherwise be only obtained by a tiresome search of the overpopulated scientific journals.


Between the large reference works on myology and the specialist monographs on investigative techniques and on individual disorders of the muscle and neuromuscular junction there is a lack of a good up to date introductory text for the clinician. This short book by the Director of the EMG Laboratory at the National Naval Medical Centre, Bethesda, aims to meet this need and, in this, it is largely successful.

The first and second chapters are devoted to a description of the symptoms and signs of muscle and neuromuscular disease and diagnostic investigations respectively, and the remaining nine chapters cover the spectrum of muscle disease in a workmanlike and readable fashion. In general the description of investigative techniques is more comprehensive and critical than the sections devoted to natural history and management, and rheumatologists turning the sections on polymyositis and steroid myopathy are unlikely to learn anything new. The main value of this book to them, however, will be to provide a useful reminder that there are many other diseases of muscle some very recently described, which may come their way from time to time. To the rheumatologist in training the book will serve as a reliable guide to the clinical assessment and investigation of muscle disease and an introduction to the literature, containing a good selection of recent (up to 1983) references.

JOHN R SEWELL

Book reviews


This edition maintains the format of previous volumes in presenting reviews of current fields of interest in inflammation. Two chapters that are particularly well written and presented are those by Segal on superoxide generation, cytochrome b555, and chronic granulomatous disease, and the other by Flower outlining the experiments that led to the demonstration that steroids inhibit arachidonic acid oxidation products by inducing the release of a protein (Macrocortin) with antiphospholipase activity; a theme that is later continued by a review of the effects of non-steroidal anti-inflammatory drugs on arachidonic acid metabolism. Of topical interest is the article by Dinarello on the induction of acute phase reactants by interleukin-1, while the chapter dealing with sex steroids and autoimmunity is predominantly concerned with SLE and animal models of this disease.

Two chapters dealing with methylation reactions and lipid alterations in platelet activation and another on neutrophil interactions with oral bacteria as a pathogenic mechanism in periodontal diseases will probably not generate an enthusiastic response from rheumatologists. The failure to define the frequently used term, clathrin, in the chapter on the ultrastructural aspects of phagocytosis is annoying, and the omission of the title of the last chapter on IgE-mediated release of inflammatory mediators from human basophils and mast cells in vitro and in vivo from the main contents’ page may be missed by the casual reader.

Overall, the book serves a useful role in supplying