Plasma prazosin was measured in five patients. In the four with normal renal function there was close agreement between plasma prazosin concentrations at corresponding times; also, the mean values were consistently higher on day 4 than on day 1 at each observation from 0730 to 1700 (P < 0.05). Peak plasma prazosin levels averaged 14.9 ± 3.5 ng/ml on day 1 and 26.8 ± 18 ng/ml on day 4. These levels coincided with the maximal antihypertensive response on day 1 but preceded the maximal response on day 4. Plasma levels in the fifth patient who had renal impairment were much higher (peak level 31.6 ng/ml on day 1; 80.5 ng/ml on day 4).

Comment

After the introduction of prazosin 2 mg all patients developed a still unpronounced diastolic response associated with severe postural hypotension and significant tachycardia. These effects had almost disappeared after the second 2 mg tablet on day 2, although adverse effects persisted until the second day of continuous prazosin therapy (day 3) in two patients. By day 4 all patients were asymptomatic even after the exercise test, while the antihypertensive effect was only marginally greater than the placebo response. Furthermore, the lying heart rate remained stable compared with the placebo response, while standing heart rate rose only transiently.

Adverse effects may have been exaggerated in this study because (a) all patients were in balance on a diet that probably contained less sodium than the average diet of our hypertensive population, and (b) three of the patients, who were also receiving a beta-blocking agent and a diuretic, had a stronger and more persistent response. Nevertheless, our findings suggest that all patients, if sufficiently stressed, may show symptomatic postural hypotension after the introduction of prazosin at the 2 mg dose level.

The uniformity of the response in our patients and a report of similar but more profound and sustained postural hypotension after a 5-mg dose of prazosin to normotensive subjects suggests that this effect may be dose-related rather than idiosyncratic. Further studies are being undertaken to investigate the responses after smaller doses of prazosin. Our preliminary findings indicate that appreciable first-dose effects, less severe and shorter than those reported above, still occurred after 0.5 mg.

As prazosin is extensively metabolised in the liver in rats and dogs (Pfizer, unpublished observations), plasma levels were measured to investigate the possibility that the first-dose phenomenon results from initial high concentrations of prazosin which subside with continued treatment, owing perhaps to enhanced drug metabolism, such as that resulting from induction of hepatic enzymes. Our results clearly indicate that the reaction cannot be explained on this basis, for in all cases the response had subsided by day 4 despite the presence of much higher plasma drug levels.

The finding of exceptionally high plasma levels of prazosin in a single patient with renal impairment but without clinical or biochemical evidence of hepatic disease agrees with the observation of Collins et al. Unlike their patient, however, ours was not receiving a beta-blocking drug.

We conclude that the first-dose phenomenon is due to severe symptomatic postural hypotension which rapidly subsides with protracted treatment and may be dose-related. It is therefore advisable to start treatment with a dose of 0.5 mg or less, particularly in patients who are already receiving beta-blocking drugs or who may be relatively sodium-depleted as a result of previous diuretic treatment.

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Requests for reprints should be addressed to Dr G S Stokes, Cardiological Unit, Medical Research Department, Kanematsu Memorial Institute, Sydney Hospital, Sydney, NSW 2000, Australia.

Local gold toxicity

With the growing use of gold salts in the treatment of rheumatoid disease there will no doubt be increasing reports of the rarer side effects related to its administration. The more readily avoidable toxic reactions should, however, not be forgotten.

Case report

A 51-year-old Glaswegian housewife had had progressive, seropositive, nodular rheumatoid disease for one year when she was referred for chrysotherapy, having undergone routine screening investigations. These showed a normal platelet count and normal urine analysis. She said that she had had no generalised rash. She weighed 55 kg.

Treatment — She was given a test dose of 10 mg intramuscular sodium aurothiomalate (Myocrisin), as an outpatient and told to continue with ibuprofen 400 mg three times a day and paracetamol as required. This was her total medication.

Adverse effects — About eight hours after starting gold treatment the patient experienced mild irritation of the left ring finger, neck and earlobe, and gold, and, on review 24 hours after the initial injection, there was obvious swelling and pustulation of the affected regions. Further questioning showed that a gold wedding ring worn continuously for 27 years and gold earrings worn intermittently for 10 years had had to be discarded at the onset of the rheumatoid disease because of contact dermatitis. Interestingly, the patient denied wearing a gold necklace. There was no personal or family history of adverse drug reaction, and limited investigations showed a normal platelet count, normal white blood cell and differential counts, and normal urine analysis. The signs and symptoms settled in a fortnight after the topical application of betamethasone.

Comment

Specific questions about local gold toxicity were omitted before the test dose of gold was given. The patient had not considered the relevance of local gold toxicity to gold injections and did not mention her previous experience. Clinicians should not forget to ask the basic question about local gold toxicity. It is also our experience that patients on established chrysotherapy are unwilling to report minor skin reactions spontaneously for fear of treatment being withdrawn. Patients are therefore specifically asked about such reactions at each attendance.


Centre for Rheumatic Diseases, Baird Street, Glasgow G4 2RH

J A N RENNIE, MD, MB, senior registrar.