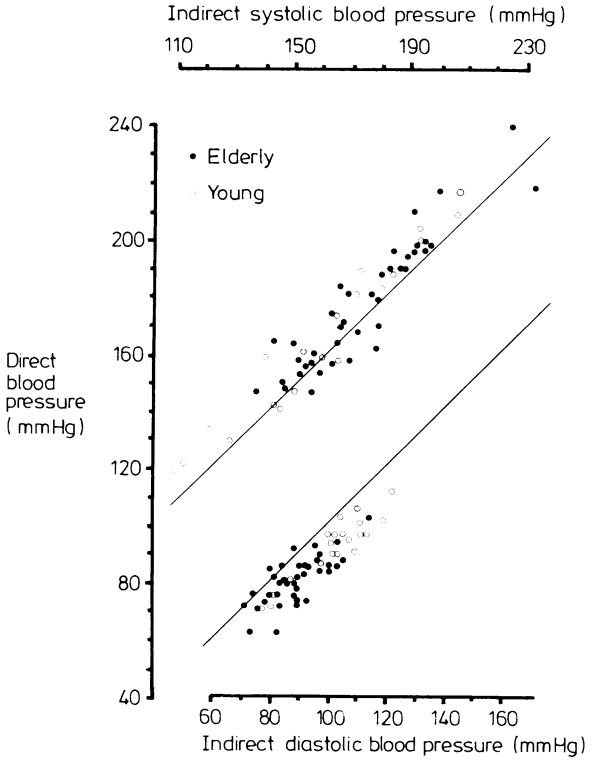
and strip recorder. Great care was taken with calibration, and the frequency response of the entire system was flat to 15 Hz. Direct intra-arterial recordings were compared with simultaneous indirect recordings made on the opposite arm, an event marker indicating on the strip recorder the first and last Korotkoff sounds. Indirect recordings were corrected for the difference between arms. Student's *t* test was used for comparison within groups (paired) and between groups (unpaired). The relation between direct and indirect pressures was compared between the two groups by covariance analysis.

The figure shows the relation between direct and indirect pressures in both age groups. Indirect pressure underestimated direct systolic pressure by 4·4± 1·3 mm Hg in the elderly ($p<0·005$) and 7·0±1·6 mm Hg in the young ($p<0·001$) and overestimated direct diastolic pressure by 9·2±1·0 mm Hg ($p<0·001$) and 10·4±1·1 mm Hg ($p<0·001$) respectively. These differences between techniques were not significantly different in the two age groups.



Relation between direct and indirect measurements of blood pressure in elderly and young patients. Unbroken lines are lines of identity.

The correlation between direct and indirect systolic blood pressure was significant in both groups (elderly: $r=0·92$, $p<0·001$; young: $r=0·97$, $p<0·001$). There was a similar positive correlation for diastolic pressure (elderly: $r=0·76$, $p<0·001$; young: $r=0·93$, $p<0·001$). Covariance analysis showed no difference between age groups in the agreement between direct and indirect pressures or in the slopes of the regression lines, which did not differ from unity.

Comment

The criteria for therapeutic intervention are ill defined in elderly patients with hypertension.[3] The report[1] of inaccuracies in the standard method of measuring blood pressure in the elderly added to this problem. There were, however, potential sources of error in this study: the patients were suspected of having large differences between direct and indirect pressures, the frequency response characteristics of the recording system were not stated, blood pressure recordings were not simultaneous, and, finally, the dimensions of the inflatable bladder used to measure indirect pressure (10 × 14 cm) might give a falsely high pressure.[4] Indeed, when a larger cuff was used the differences between direct and indirect measurements in the elderly were greatly reduced. These sources of error were excluded from our study, and we could not find any significant difference in the relations between indirect and direct pressures in the young and old. There were, however, discrepancies between direct and indirect measurements in both age groups, which cannot be explained by the level of blood pressure or arm circumference. Three of the young patients and seven of the elderly patients had differences in systolic pressure of 14 mm Hg or more, and similar differences were observed for diastolic pressures in five of the young and 11 of the elderly patients.

This study shows that the standard technique of measuring blood pressure with a mercury sphygmomanometer is as accurate in the elderly as it is in young patients, and the indications for direct intra-arterial measurement are no different in the elderly than in other age groups.

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Influence of ranitidine on plasma metoprolol and atenolol concentrations

A previous report indicated that ranitidine failed to alter the pharmacokinetics of propranolol,[1] although cimetidine exerts a considerable influence.[2] Although both of these H_2-receptor antagonists reduce liver blood flow, ranitidine differs from cimetidine in not appearing to affect the hepatic metabolism of certain drugs. We studied the effect of ranitidine on metoprolol, another β-receptor antagonist that is predominantly metabolised in the liver and whose metabolism is also altered by coadministration of cimetidine.[2] We used the predominantly renally excreted β-receptor antagonist atenolol as a control.

Methods and results

The pharmacokinetics of metoprolol and atenolol were studied in six healthy volunteers after seven days of oral treatment with each drug alone (metoprolol 100 mg twice daily, atenolol 100 mg daily). The pharmacokinetic profile of the drugs was then re-examined after a further seven days of combined oral treatment with ranitidine (150 mg twice daily)—that is, intra-subject comparison was performed. Blood was collected throughout the study (before the morning dose and three hours later) and at appropriate intervals up to 24 hours after the last morning dose on the seventh day (during wash out). Plasma concentrations of atenolol and metoprolol were determined by measuring the fluorescence on thin layer chromatography plates.[3,4]

The table shows the results of the pharmacokinetic analysis. Carry over effects between the four treatments were excluded. The kinetics of atenolol were not significantly altered by concurrent administration of ranitidine, whereas the area under the plasma concentration time curve for metoprolol from 0 to 24 hours on day 7 increased by about 50% ($p<0·05$) with ranitidine

Mean ± SEM kinetic variables on day 7 ($n=6$)

Treatment	Peak concentration (ng/ml)	Area under curve (ng/ml h)	Half life (h)
Metoprolol alone	198·8 ± 23·3	1333·8 ± 115·6	3·9 ± 0·2
Metoprolol + ranitidine	266·0 ± 40·4	2069·9 ± 435·4	6·0 ± 0·4
Atenolol alone	660·1 ± 117·1	5786·8 ± 979·9	7·0 ± 0·7
Atenolol + ranitidine	621·3 ± 103·8	6635·3 ± 931·1	8·5 ± 0·9

and the mean observed peak plasma metoprolol concentration by about 33%. Furthermore, the elimination half life of metoprolol was prolonged from 3·9 hours during monotreatment to 6·0 hours when ranitidine was given in combination ($p < 0.05$). There was no evidence that any of the volunteers were poor metabolisers of metoprolol.

Beta-blockade was assessed on the sixth treatment day by examining the inhibition of exercise induced tachycardia three and 12 hours after the morning dose. No significant difference between monotreatment with metoprolol or atenolol and each of the two drugs combined with ranitidine could be shown. This might be because the concentration response curve of the β-receptor antagonist becomes very shallow at the upper range of plasma concentrations.

Comment

Our results agree with the observations of Hoensch and Hetzel, who found that, like cimetidine, ranitidine is bound to microsomal enzymes.[5] Kinetic interaction may occur between ranitidine and a β-receptor antagonist such as metoprolol that is predominantly metabolised. Physicians should be aware of this. We have carried out similar studies with nifedipine (to be published) which is also extensively metabolised by the liver, which have shown that the area under the plasma concentration time curve is increased by about 30% when ranitidine is administered concomitantly and by 70% after ingestion of cimetidine; this appears to confirm our results with metoprolol.

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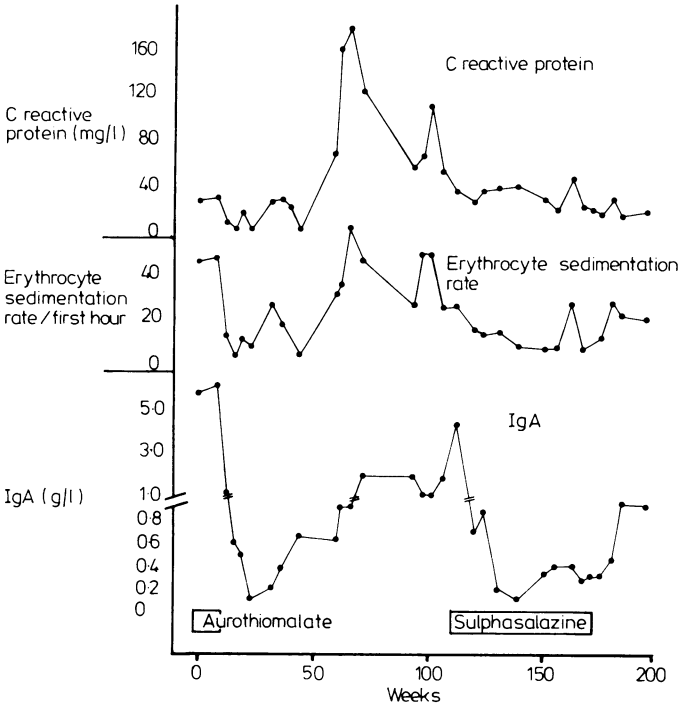
Sulphasalazine induced selective IgA deficiency in rheumatoid arthritis

Selective IgA deficiency (serum IgA concentration less than 0·4 g/l in the presence of normal or raised concentrations of IgG and IgM) can develop when sodium aurothiomalate or D-penicillamine are used in the treatment of rheumatoid arthritis.[1 2] While recognised to be of major therapeutic importance in inflammatory bowel disease, sulphasalazine has recently been reported to have a disease modifying action in rheumatoid arthritis.[3] We report three cases of rheumatoid arthritis in which sulphasalazine was associated with the onset of selective IgA deficiency.

Case reports

Case 1—A man aged 33 years had had seropositive rheumatoid arthritis for four years before starting parenteral gold treatment (sodium aurothiomalate 50 mg/week). Treatment with this agent was maintained for 11 weeks, at which time mouth ulcers, a rash, proteinuria, and a concurrent selective fall in serum IgA necessitated its withdrawal. Two years later a similar decrease in circulating IgA followed treatment with sulphasalazine (1·5 g/day). On this occasion the immunodeficiency persisted for two years and resolved only when the sulphasalazine was discontinued after a localised rash had developed. The figure shows the serum IgA concentrations in relation to both of these agents. The rheumatoid activity, as assessed by the usual clinical and laboratory indices, reflected the changes in IgA and is indicated in the figure by the erythrocyte sedimentation rate and C reactive protein. His HLA type was A_1A_3; B_8B_{40}.



Changes in immunoglobulin A concentration, erythrocyte sedimentation rate, and C reactive protein in the patient in case 1 during treatment with aurothiomalate and sulphasalazine. Break in IgA scale indicates a fivefold increase in the value of IgA above 1 g/l compared with below 1 g/l.

Case 2—A 40 year old woman, the sister of the patient in case 1, was found to have developed selective IgA deficiency five months after starting treatment with sulphasalazine 1·5 g/day (IgA; 1·2 g/l initially, 0·3 g/l at five months) for long standing seropositive rheumatoid arthritis. During the past two years, while she continued to take sulphasalazine at the same dosage, there was minimal evidence of rheumatoid activity and her serum IgA concentration (estimated at three monthly intervals) remained below 0·2 g/l with normal or raised concentrations of IgG and IgM. Her HLA type was A_3, A_9, B_{40}.

Case 3—A woman, aged 58, with seronegative rheumatoid arthritis for 31 years had a good clinical response to sulphasalazine (1·5 g/day) with concomitant falls in her erythrocyte sedimentation rate and C reactive protein. Her serum IgA concentration was 0·8 g/l before treatment but fell progressively thereafter (0·34 g/l at three months, 0·21 g/l at six months, and 0·15 g/l at one year). During the last 16 months of sulphasalazine treatment her rheumatoid arthritis remained quiescent and the serum IgA concentration persisted at 0·1 g/l or less with normal concentrations of IgG and IgM. Her HLA type was A_9, B_{12}.

Various different non-steroidal anti-inflammatory agents were prescribed for the three patients before and during the period of IgA deficiency.

Comment

Drug induced selective IgA deficiency has been reported in association with aurothiomalate,[1 2] D-penicillamine,[1 2 4] and phenytoin.[5] It has not, however, previously been associated with sulphasalazine in the treatment of either inflammatory bowel disease or rheumatoid arthritis. Although the mechanisms underlying this drug induced immune deficiency in rheumatoid patients remain obscure, a genetic predisposition is suggested by both the sibship of the patients in cases 1 and 2 and the association between its development and the possession of the HLA antigens B_{12} or B_{40}. This HLA association, previously reported when the IgA deficiency was related to treatment with aurothiomalate or D-penicillamine,[2] is further highlighted in this report.

More work is required to determine whether the induction of selec-