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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Pharmacological Institute, University School of Pharmacy, D-6000 Frankfurt am Main 70, West Germany

H SPAHN, PHD, pharmacologist
E MUTSCHLER, PHD, MD, professor of pharmacology

Medical Department, University School of Medicine, D-4300 Essen 1, West Germany

W KIRCH, MD, clinical physician
E E OHNHAUS, MD, professor of medicine

Gastroenterology Department, Klinikum Charlottenburg, D-6000 Berlin, West Germany

H D JANISCH, MD, clinical physician

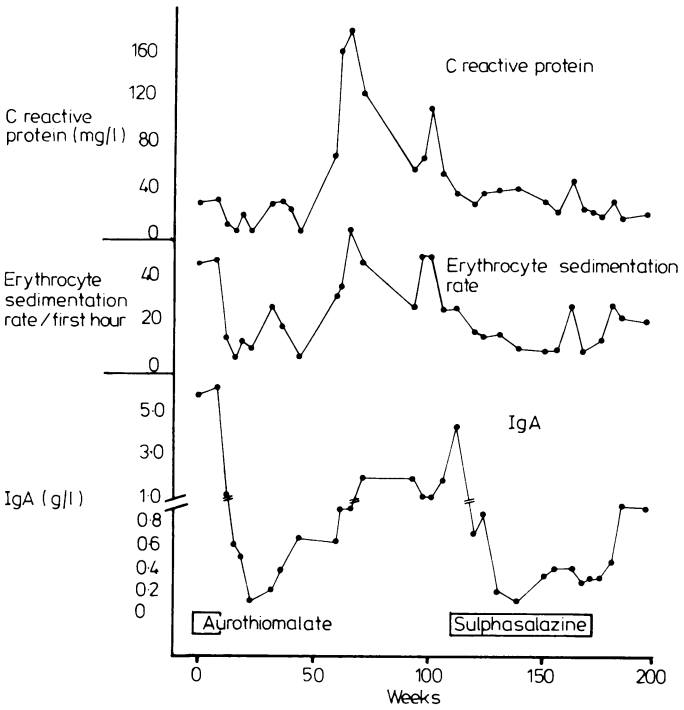
Correspondence and reprint requests to: Dr W Kirch, Medizinische Klinik, Universität Essen, Hufelandstrasse 55, D-4300 Essen 1, West Germany.

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-

tive IgA deficiency, in genetically susceptible individuals, is a phenomenon common to agents possessing properties which modify rheumatoid disease.

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Rheumatology Unit, Queen Elizabeth Hospital, Birmingham B15 2TJ
J P DELAMERE, MB, MRCP, honorary senior registrar
M FARR, MB, clinical research fellow

Department of Medicine, Dudley Road Hospital, Birmingham
K A GRINDULIS, MB, MRCP, registrar

Correspondence to: Dr J P Delamere.

Pressurised aerosol with conical spacer is an effective alternative to nebuliser in chronic stable asthma

Aerosol treatment delivered by a 750 ml conical spacer attached to a pressurised aerosol (Nebuhaler, Astra Pharmaceuticals Ltd) is as effective as a simple nebuliser in acute severe asthma.[1] This may be due to improved deposition of the drug in the lungs because a dense, slowly moving cloud of small drug particles is produced and inhaled in a relatively large volume, over several breaths if necessary, through a one way valve.[2] Intermittent positive pressure breathing is widely used for severe asthma and may be marginally superior to simple nebuliser treatment.[3] The relative value of these techniques has not been established in chronic stable asthma, although nebulisers are often used in preference to pressurised aerosols. We have therefore compared the bronchodilator responses of nine patients with chronic stable asthma to the beta$_2$ stimulant terbutaline administered in cumulative doubling doses by pressurised aerosol fitted with a conical spacer, Acorn nebuliser, and Bennett intermittent positive pressure breathing equipment.

Patients, methods, and results

We studied nine patients aged between 24 and 56 years with atopic asthma. All required regular bronchodilator treatment and none had needed a change in treatment for three months. Each patient gave informed consent and was studied at the same time of day on three separate days within one week. Sodium cromoglycate and bronchodilators were discontinued for at least 12 hours before the tests. On each occasion we asked the patients to inhale cumulative doubling doses of terbutaline (0·5+1·0+2·0+4·0 mg) at 30 minute intervals using each of the three techniques in random order. To determine the magnitude and site of drug action we measured forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), and maximal expiratory flow at 30% FVC ($\dot{V}_{30}$) as an indicator of peripheral airway calibre.[4] We made measurements at 10 minute intervals throughout the studies and used the best of three measurements in analysis. A paired t test was used to compare the mean values obtained at each dose with each technique.

There was no significant difference in baseline FEV_1, FVC, or $\dot{V}_{30}$ on each study day. The table shows the mean expiratory flow rates for each technique at cumulative doses of terbutaline. For both FEV_1 and FVC there were no statistically significant differences in the responses at any dose. At cumulative doses of 1·5 and 3·5 mg terbutaline the conical spacer produced a mean $\dot{V}_{30}$ which was similar to that from the intermittent positive pressure breathing device and significantly greater than that from the nebuliser ($p < 0.05$).

Comment

In these patients the conical spacer was as effective as the intermittent positive pressure breathing device and nebuliser in delivering an aerosol bronchodilator throughout the therapeutic dose range. In dosages higher than those conventionally used from pressurised aerosols, but often used from nebulisers, the conical spacer was significantly more effective than the nebuliser in improving flow rates at low lung volumes. These results support the theory that the technique enhances peripheral airway drug deposition and bronchodilatation by allowing evaporation of droplets of propellant and production of drug particles of smaller size which are inhaled in a large volume.[2 5] There was no significant difference between the intermittent positive pressure breathing device and nebuliser at any dosage, although there was a trend in $\dot{V}_{30}$ in favour of the former at higher doses. The conical spacer is more than 50 times cheaper than the least expensive nebuliser equipment. The device also removes the risk of failure to coordinate aerosol activation with inspiration, which is a frequent problem in bronchodilator administration.

We conclude that the use of a conical spacer with a pressurised aerosol is a simple, cheap, and effective alternative to a nebuliser or intermittent positive pressure breathing device for bronchodilator treatment in moderately severe chronic stable asthma and is therefore likely to be of great value for domiciliary use.

We thank Astra Pharmaceuticals Limited for supplies of the Nebuhaler conical spacer and terbutaline.

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Department of Respiratory Medicine, City Hospital, Edinburgh EH10 5SD
J F O'REILLY, MA, MRCP, medical registrar
D R BUCHANAN, MB, MRCP, medical registrar
M F SUDLOW, MB, MRCP, consultant physician

Correspondence to: Dr J F O'Reilly, Department of Respiratory Medicine, Bristol Royal Infirmary, Bristol BS2 8HW.

Mean (±SEM) changes in maximum expiratory flow rates after cumulative terbutaline inhalation by three techniques

Cumulative terbutaline dosage (mg)	FEV_1 (l)			FVC (l)			$\dot{V}_{30}$ (l/s)		
	Aerosol and spacer	Nebuliser	IPPB	Aerosol and spacer	Nebuliser	IPPB	Aerosol and spacer	Nebuliser	IPPB
Baseline	2·39 ± 0·37	2·36 ± 0·38	2·25 ± 0·34	3·56 ± 0·41	3·68 ± 0·38	3·53 ± 0·33	1·64 ± 0·29	1·54 ± 0·32	1·71 ± 0·33
0·5	2·67 ± 0·38	2·68 ± 0·37	2·60 ± 0·37	3·86 ± 0·47	4·05 ± 0·41	3·88 ± 0·39	2·15 ± 0·33	2·13 ± 0·34	2·03 ± 0·40
1·5	2·82 ± 0·40	2·74 ± 0·37	2·72 ± 0·38	3·96 ± 0·47	4·22 ± 0·41	4·05 ± 0·37	2·47 ± 0·36	1·93 ± 0·38	2·33 ± 0·50
3·5	2·80 ± 0·42	2·86 ± 0·40	2·82 ± 0·38	4·01 ± 0·45	4·34 ± 0·43	4·25 ± 0·37	2·32 ± 0·41	1·89 ± 0·35	2·42 ± 0·53
7·5	2·85 ± 0·41	2·90 ± 0·40	2·85 ± 0·37	4·21 ± 0·41	4·29 ± 0·46	4·19 ± 0·37	2·39 ± 0·46	2·00 ± 0·31	2·32 ± 0·50

IPPB = Intermittent positive pressure breathing device.