reflect reduced renal function,[5] and long-term steroid and immunosuppressive drug administration have no influence on serum PTH.[23] It is therefore likely that the histological and biochemical changes in these patients are due to the slow rate of parathyroid gland involution.

We have shown a positive correlation between serum PTH concentrations, parathyroid gland weights, and skeletal histology in primary hyperparathyroidism,[12] and Ellis and Peart[24] have shown a similar correlation between gland weights and skeletal histology in patients with renal failure. It is difficult to obtain comparable data on parathyroid gland weights after renal transplantation, though we have some necropsy data[25] suggesting that about half the allograft recipients who die with a functioning graft in situ 12 months or more after transplantation have macroscopically enlarged parathyroid glands.

The reason why parathyroid enlargement and hypersecretion persist in some patients but not in others is unknown. The abnormalities in our patients were mild and at the time of writing no allograft recipient had undergone parathyroidectomy.

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Antinuclear Antibodies during Procainamide Treatment and Drug Acetylation

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Summary

Acetylator capacity was determined in two groups of patients who had received procainamide for more than three months. In seven patients antinuclear antibodies (A.N.A.) were detected during treatment, and these changes disappeared (in six patients) or were less pronounced (one patient) after withdrawal of the drug. These patients tended to have faster acetylation rates, and five were phenotypically "rapid" acetylators. Five patients who did not develop A.N.A. during treatment had less rapid ($P < 0.05$) rates of acetylation, and four were "slow" acetylators. We suggest that the immunological changes which may occur during procainamide treatment may be associated with the acetylated metabolite of procainamide rather than the parent compound and that it might be possible to identify patients at risk.

Introduction

Acetylation is the metabolic pathway through which drugs such as hydrallazine,[1] isoniazid,[2] dapsone,[3] phenelzine,[4] and many sulphonamides[5] are inactivated. Acetylation rates are bimodally distributed within populations because of a genetic polymorphism.[6] Adverse effects from hydrallazine,[7] isoniazid,[8] dapsone, and phenelzine[4] are commoner in patients who are phenotypically "slow" acetylators, in whom the slower rates of elimination are presumed to lead to a persistence of the drug in the body. In particular, the development of circulating antinuclear antibodies (A.N.A.) during treatment with hydrallazine is more common in such patients, and clinical evidence of hydrallazine-associated systemic lupus erythematosus (S.L.E.) is apparently confined to those with the "slow" acetylator phenotype.[7]

Procainamide also undergoes extensive acetylation in man,[9] and this may be under polymorphic control.[10] Prolonged treatment with procainamide is associated in some patients[11] with the development of circulating A.N.A. which may be accompanied by a syndrome clinically resembling S.L.E.[11,12] We have tried to establish whether these changes are related to a person's capacity to acetylate drugs.

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Patients and Methods

Twelve patients were investigated (see table). All had received procainamide for over three months, and none were given it during the determination of their acetylator capacity. In the seven patients in group 1 (see table) antinuclear factor (A.N.F.) was detected during procainamide treatment by means of nuclear histofluorescence, and blood from five of them also showed the L.E. cell phenomenon; L.E. cells were not found in case 6 and were not sought in case 2. Procainamide treatment was withdrawn from all seven patients, and six of them showed complete disappearance of A.N.F. and L.E. cells. Case 3, however, remained weakly positive for A.N.F. for two years. The five patients in group 2 (see table) received long-term treatment

Characteristics of the Two Groups of Patients

Case No.	Sex	Age (Years)	Diagnosis	Daily Dose of Procainamide	Duration of Procainamide Treatment (Months)	Clinical Evidence of S.L.E.	Laboratory Evidence of S.L.E.	Drugs Given Concurrently with Procainamide	Isoniazid $t_{\frac{1}{2}}$ (Hours)	Acetylator Phenotype
						Group 1				
1	F.	56	Paroxysmal tachycardia	1·00	9	Arthropathy	A.N.F +, L.E. cells +	None	2·3	Slow
2	F.	50	M.V.D.	2·00	4	None	A.N.F. +	Digoxin	1·8	Rapid
3	M.	48	Myokymia	1·00	81	Arthropathy	A.N.F. +, L.E. cells +	Chlorpromazine, amylobarbitone	1·6	Rapid
4	M.	46	M.V.D.	2·00	10	None	A.N.F. +, L.E. cells +	Digoxin, frusemide, penicillin, phenindione	2·4	Slow
5	F.	50	M.V.D.	2·00	66	None	A.N.F. +, L.E. cells +	Digoxin, phenindione	1·9	Rapid
6	F.	45	M.V.D.	2·00	10	None	A.N.F. +	None	1·7	Rapid
7	F.	25	M.V.D.	1·50	34	None	A.N.F. +, L.E. cells +	Digoxin, chloral phenindione	1·7	Rapid
Mean		46		1·60	31				1·9	
						Group 2				
8	F.	48	M.V.D.	3·00	10	None	A.N.F.,−, L.E. cells −	Phenindione	3·1	Slow
9	F.	35	M.V.D.	1·50	45	None	A.N.F. −	Digoxin, phenindione	1·8	Rapid
10	F.	49	M.V.D.	2·00	4	None	A.N.F. −, L.E. cells −	None	3·4	Slow
11	M.	66	Atrial flutter	2·00	5	None	A.N.F. −, L.E. cells −	Digoxin	3·5	Slow
12	F.	56	M.V.D.	0·75	48	None	A.N.F. −, L.E. cells −	Digoxin, frusemide	3·0	Slow
Mean		51		1·85	22				3·0	

M.V.D. = Mitral valve disease.

with procainamide but throughout the course of treatment were repeatedly negative for A.N.F. and L.E. cells. Case 9 was investigated only for the presence of A.N.F.

Acetylator capacity was estimated from the elimination half life ($t_{\frac{1}{2}}$) of isoniazid. Venous blood was taken for baseline measurements, and then isoniazid 10 mg/kg body weight (to the nearest 50 mg) was given by mouth after an overnight fast. Further blood samples were taken at $1\frac{1}{2}$, 3, $4\frac{1}{2}$, and 6 hours. The patients remained seated throughout the $t_{\frac{1}{2}}$ estimations. Plasma was stored at −20°C until analysed in duplicate for isoniazid by a spectrophotometric method.[13] The $t_{\frac{1}{2}}$ of isoniazid was calculated from least-squares regression analysis of the curve of plasma isoniazid concentration against time. Patients were taking various drugs at the time of the $t_{\frac{1}{2}}$ measurements but none are known to interfere with acetylation; they included digoxin, frusemide, warfarin, penicillin, phenindione, quinalbarbitone, guanethidine, and practolol.

Results and Discussion

In patients who developed A.N.A. no drug other than procainamide could be implicated. Moreover, in six of these patients withdrawal of the procainamide was followed by the disappearance of A.N.A. and in the seventh by a pronounced reduction in A.N.F. This suggests that no patient in group 1 had the spontaneous form of S.L.E.

The individual isoniazid $t_{\frac{1}{2}}$ values are shown in the table. Epidemiological studies under conditions identical with ours established that the antimode for isoniazid $t_{\frac{1}{2}}$ is 2·0-2·1 hours.[14] On this basis five of the seven patients who developed A.N.A. during procainamide treatment were phenotypically "rapid" acetylators, while four of the five patients who did not develop A.N.A. were "slow" acetylators. The mean isoniazid $t_{\frac{1}{2}}$ in group 1 was 1·9 hours and in group 2 3·0 hours ($P < 0.05$; Wilcoxon's sign test). In respect of age, sex, diagnosis, and daily procainamide dosage, the two groups were reasonably comparable. The mean duration of treatment, however, was longer in group 1, which probably reflects the fact that therapeutic failure was responsible for the withdrawal of treatment in group 2. Patients in group 2 were also receiving fewer drugs concurrently with procainamide (see table) but none of these in either group induces A.N.A.[15]

Many factors, including dosage, duration of treatment, and genetic influences, are likely to be implicated in the development of A.N.A. in patients on prolonged procainamide therapy.[15] Though ours was a small series, our results suggest that a person's capacity to acetylate drugs may be an additional factor. The present study, however, indicates that with procainamide, unlike hydrallazine, more-rapid rates of acetylation are associated with the development of A.N.A.

If our findings are confirmed they carry important implications. Firstly, they suggest that it might be possible to identify patients at risk of developing A.N.A. before they start treatment with procainamide. Secondly, they suggest that the immunological changes which may occur during long-term procainamide treatment may be caused not by the drug itself but by its acetylated metabolite *N*-acetylprocainamide. This metabolite is present in plasma from patients on procainamide at concentrations similar to those of the parent drug, and the amount excreted in the urine after procainamide administration is much greater in "rapid" acetylators.[16] Finally, *N*-acetylprocainamide shows certain structural similarities to practolol (see fig.), which is also capable of inducing immunological changes, including A.N.A.[17] Possibly the structural similarities between these drugs represent hazardous chemical features, either per se or by further metabolic transformation.

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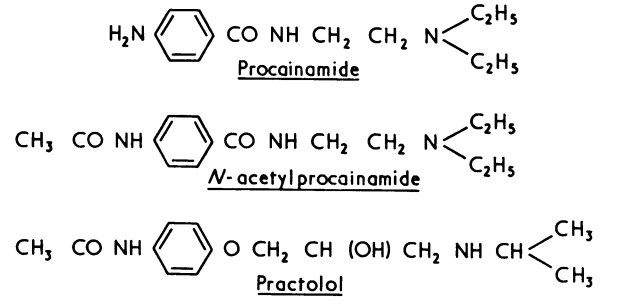

Chemical structures of procainamide, *N*-acetylprocainamide, and practolol.

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SHORT REPORTS

Haemolytic Anaemia due to Penicillin

A case of penicillin-induced haemolytic anaemia is described. Unusual features were that the penicillin was given in the usual therapeutic dose and only IgM antibodies were shown.

Case Report

A 22-year-old woman was admitted after a car accident in which she sustained a compound fracture of her frontal bone. She was given prophylactic antibiotics: an immediate dose of 600 mg of benzyl penicillin intramuscularly followed by 300 mg of benzyl penicillin q.d.s. for 24 hours, then 500 mg of phenoxy-methyl penicillin four times a day. Eight days after admission her haemoglobin had fallen from 13·7 g/dl on admission to 10·7 g/dl, her reticulocyte count was 4·4% and a direct Coombs test was positive. The serum haptoglobins were 0·13 g/l. The result of the Schumm's test was negative. Three days after this her haemoglobin had fallen to 7·8 g/dl with a reticulocyte count of 12·5%. The next day haemoglobin was 6·8 g/dl. At this time her serum contained an antibody which reacted against her red cells when they had been sensitized with penicillin, and against penicillin-sensitized pooled red cells. There was no reaction with unsensitized red cells. The conclusion was that haemolytic anaemia was being caused by penicillin. The penicillin was stopped and eight days later her haemoglobin had risen to 11·3 g/dl, the reticulocyte count was 15%, and the Coombs test was only weakly positive.

The temperature at which maximum activity occurred was between 25°C and 30°C. The antibody was tested for activity against red cells sensitized by the different penicillins and by cephaloridine: benzyl penicillin *B.P.* gave a titre of 1/128, phenoxy-methyl penicillin gave 1/256, and cephaloridine *B.P.* gave no titre. Assay of the immunoglobulin fractions showed that the IgG and IgA levels were normal but that the IgM level was increased. The serum was exposed to 2-mercaptoethanol for two hours and then dialysed overnight. The treated serum did not react with penicillin-sensitized red cells in saline at 20°C or by the indirect Coombs technique at 37°C. The inhibition of activity by 2-mercaptoethanol is peculiar to IgM.

Discussion

Since haemolytic anaemia due to penicillin allergy was first described by Ley *et al.*[1] fewer than 20 cases have been reported. Nearly all of these were in patients with subacute bacterial endocarditis who had been treated with high doses of intravenous penicillin. There is some discussion about the roles of the IgG and IgM fractions of the immunoglobulins in the pathogenesis of this condition. Levine and Redmond[2] found that only patients with a high IgG titre were positive on Coombs test. White *et al.*[3] thought that a strongly positive Coomb test result due to IgG was an important diagnostic feature. Bird *et al.*[4] have recently described a case similar to ours; their patient was a 3-year-old boy who was treated with 125 mg of phenoxy-methyl penicillin four times a day for 48 hours for an upper respiratory tract infection. He developed a haemolytic anaemia which regressed rapidly when the penicillin was stopped. They showed that the antibody was in the IgM class. It has been thought that the hapten responsible is a part of the molecule common to penicillins and cephaloridine, but as shown above the antibody in this case did not react against cephaloridine. This case confirms that penicillin can cause a haemolytic anaemia in adults at doses customarily used for minor infections. It is interesting to speculate how many patients who develop an anaemia while on penicillin are suffering from this type of haemolytic anaemia.

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Rhesus Sensitization Associated with I.U.D. in Pregnancy

Finn first put forward the idea that it might be possible to prevent immunization of Rh-negative mothers by giving them antibody to destroy Rh-positive fetal cells.[1] Others subsequently suggested the use of anti D-globulin as such an antibody; and, by its use, Clarke showed that fetal red cells were removed from the maternal circulation and their antigenicity reduced.[2]

It is well known that a diseased or disturbed placenta increases the risk of maternal/fetal transfusion and of sensitization. Numerous reports have been published of fetal erythrocytes appearing in the maternal circulation after surgical intervention in pregnancies at or near term, as a result of termination of early pregnancy, or following intranatal procedures such as external cephalic version. Toxaemia of pregnancy, with its resultant placental infarcts of uncertain age, is recognized as an obstetric determinant of Rhesus sensitization. The immunizing effects of spontaneous or induced abortions in cases of fetal/maternal blood group incompatibility was recognized by Levine.[3] And Weiner discussed the sufficiency of a microtransfusion of 0·05 ml of fetal cells in sensitizing the mother.[4] The following case illustrates the sensitizing effect of microtransfusion.

Case Report

In 1965 a 20-year-old married woman had a normal spontaneous delivery in hospital, at 33 weeks' gestation, of a healthy infant weighing 1930 g. Her blood group is O Rhesus D negative, genotype cde/cde.

In 1967 she had an uneventful domiciliary delivery at 39 weeks of a healthy 3630 g infant. In 1971 she spontaneously aborted and underwent an evacuation of uterus at 10 weeks by dates. Rhesus antibodies were not noted on regular routine screening in any of her pregnancies.