A STUDY OF THE ACETYLATOR PHENOTYPE IN NORMAL SUBJECTS

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SYNOPSIS

A number of basic drugs are metabolised by N-Acetylation. Because of genetic differences, individuals vary in their ability to acetylate these drugs and can be phenotyped into being either fast or slow acetylators.

The Acetylator phenotypes of 74 medical students were determined using the ratios of acetylated metabolite to free Sulphadimidine in blood and urine samples taken 6 hours after an oral 10 mg/kg dose of Sulphadimidine. The results are presented. The clinical relevance of the acetylator phenotype is discussed with reference to, (a) drug induced and spontaneous SLE, (b) therapy with hydrallazine, isoniazid, salicylazosulfapyridine and phenelzine, (c) carcinogenesis of bladder and liver tumours.

INTRODUCTION

A number of commonly used basic drugs are inactivated by an acetylation process. N-Acetyltransferase, the enzyme responsible, can be found in various tissues but its main activity is concentrated in the liver and gut mocosae (1). It is primarily in these regions, that the enzyme has been found to exhibit genetically determined variations in activity. Phenotyping individuals according to their acetylator status therefore represents one step in the understanding of the activity and side effects of some therapeutic agents inactivated by this pathway.

Acetylator phenotyping has been carried out using mainly Sulphadimidine, Isoniazid, Procainamide or Dapsone as test drugs (2, 3). Because of the possibility that different isoenzymes may be responsible for acetylating different drugs (4), the test drug should be the drug that is to be used in the treatment of the patient. However, for routine screening, the use of Sulphadimidine is still unsurpassed in terms of convenience and cost.

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METHOD

Seventy-four medical students without any history of drug allergies were recruited to participate in the study. Sulphadimidine (SM) 10 mg/kg (5) was given as a single oral dose and blood samples were collected at the end of the sixth hour. The subjects were required to void the urine at the fifth hour and the urine produced during the sixth hour was collected.

SM and its acetylated metabolite (AcSM) were measured colorimetrically by the Bratton-Marshall method (6). Ratios of the acetylated metabolite to free Sulphadimidine in blood and urine were plotted in a histogram display on a logarithmic scale. In addition, a scatter diagram of the percentages of acetylated metabolites in the blood against that in the urine was plotted.

RESULTS

Of the seventy-four subjects, six were non Chinese. The distribution of the ratios of acetylated metabolite to free Sulphadimidine (AcSM/SM) is shown in Fig. 1. The bimodal distribution is characteristic. A ratio of 0.5 for blood and 2.0 for urine samples were found to be effective in separating the slow from the fast acetylators. There was 100% correlation between the use of blood and urine samples.

However, when the percentages of acetylated metabolite (AcSM X 100/AcSM + SM) in the blood were plotted against that in the urine, two subjects were found to be unclassifiable. (Fig. 2).

This study therefore confirms the reliability of urine or blood AcSM/SM in separating the two phenotypes. Of the two methods, blood estimations are preferred for its convenience and lack of variation during physiological changes (7).

When only Chinese subjects were considered, the percentage of slow acetylators in the study was 32%.

DISCUSSION

The percentage of fast acetylators vary according to the ethnic origins of that population, being highest in Mongoloid and lowest in Caucasoid races (2). Our own figures of 68% fast acetylators in sample of 68 Chinese subjects is consistent with previous observations (2, 8).

The genetic determinant for N-acetyltransferase activity is inherited in a simple Mendelian fashion; the gene for 'fast' acetylation being dominant, while that for 'slow' acetylation recessive. Current screening methods for separating the two phenotypes are unable to distinguish the heterozygous from the homozygous fast acetylators (9).

a) Drug induced and spontaneous SLE.

Since 1945, the list of drugs giving rise to antinuclear antibodies and the clinical SLE syndrome has been steadily increasing (10). Of these drugs, perhaps the better studied one include hydrallazine and procainamide, both of which are broken down by N-acetylation. Slow acetylators have been found to be more likely to develope hydrallazine- or procainamide-induced SLE than fast acetylators (2, 3). The periods of their usage prior to the development of SLE are also much shorter in slow acetylators (2, 3). Studies in Caucasoid races have shown the same predominance of slow acetylators in spontaneous SLE (11-13). This has led to postulates that the aetiological processes in drug induced and spontaneous SLE may be similar (3). However, local experience suggests that relationship of acetylator status to spontaneous SLE may not be so straightforward. It has been known for some time that the prevalence of spontaneous SLE is higher in Chinese than in white populations (14). If the slow acetylator phenotype plays any significant role in the "lupus diathesis" one would expect that with the relatively small population of slow acetylators amongst Chinese, the prevalence of SLE would be lower rather than higher as is the case. Current studies are underway to establish the pattern locally.

b) Therapeutic response and drug toxicity

Knowledge of the acetylator phenotype would also assist in the rationalisation of dosages for various drugs. It has been shown that for equivalent dosages of hydrallazine, the therapeutic response is less in fast than in slow acetylators and that this difference is most obvious in the presence of adequate β-blockade (3, 15).

Isoniazid is another drug affected by acetylation polymorphism and despite two decades of research, its exact biotransformation pattern has still not been fully elaborated. What is known, however, is that slow acetylation allows accumulation of isoniazid during long term therapy and although it produces a higher cure rate in once or twice weekly regimes (2, 3, 8), predisposes to the development of isoniazid peripheral neuropathy (2, 3). Slow acetylators are also more prone to run into problems with isoniazid-phenytoin drug interactions (2). Isonazid inhibits the metabolism of phenytoin and when the two are given together, slow acetylators have a higher tendency to develope phenytoin toxicity unless the dosage of phenytoin is reduced.

On the other hand, isoniazid hepatitis occurs to a greater extent in fast acetylators (3). This is thought to be due to the accumulation of the acetylated metabolite, acetylhydrazine, which is hepatotoxic.

Slow acetylators are more prone to develope side effect with the use of phenelzine (2, 3) and salicylazosulfapyridine (2, 3, 16). There is also a predominance of slow acetylators in patients with cutaneous drug reactions (17).

c) Carcinogenesis

That N-acetylation can modify the activity of carcinogenic arylamines have been shown mainly in animal experiments. In dogs, the acetylated metabolite of 4-aminobiphenyl can induce not only bladder but liver tumours as well while

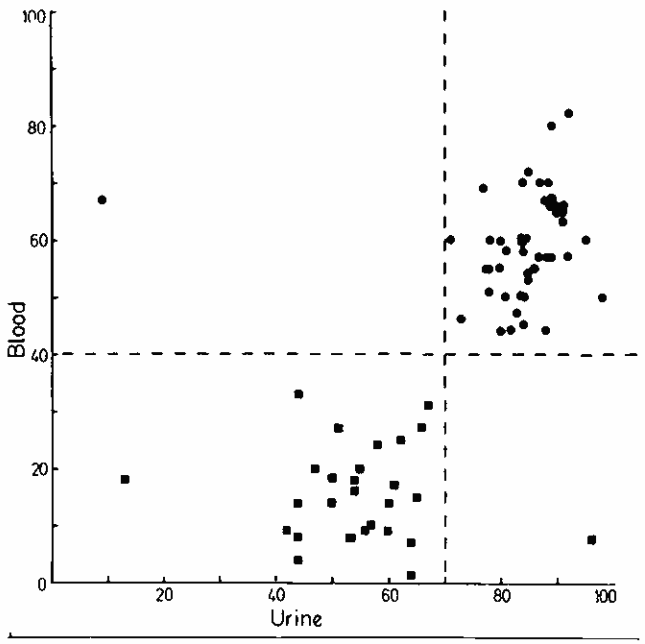

Figure 1 Scatter diagram showing the distribution of seventy-four normal subjects according to the percentages of Acetylated Sulphadimidine (AcSM) in the blood and urine.
(Slow ■ and fast ● acetylators according to blood AcSM/SM).

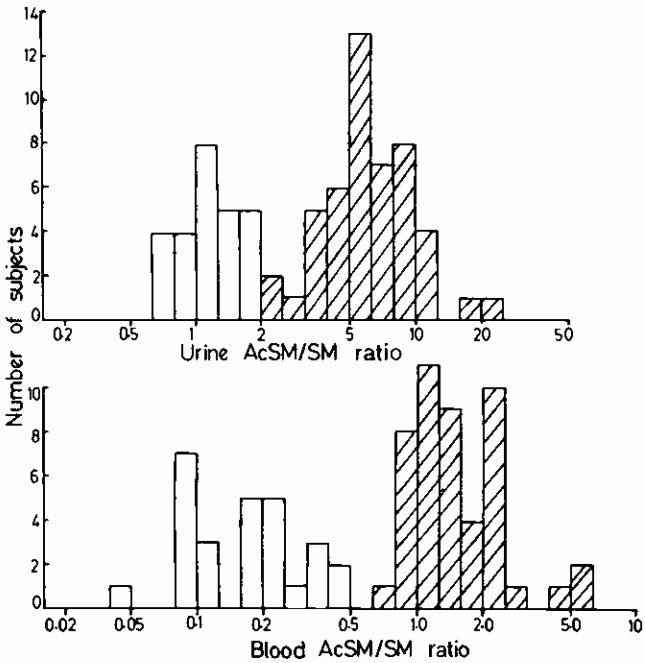

Figure 2 Histograms showing the distribution of seventy-four normal subjects according to the ratios of Acetylated Sulphadimidine (AcSM) to Free Sulphadimidine (SM) in the (a) urine and (b) blood.

4-aminobiphenyl itself can only induce bladder tumours. On the other hand, the acetylated metabolite of 2 naphthylamine cannot produce bladder tumours while the parent compound is a potent bladder carcinogen (18). Studies have suggested that a higher percentage of slow acetylators occur in patients with bladder tumours (19). It might be that the reverse may be true for hepatomas.

CONCLUSION

There is a simple screening method to separate the two acetylator phenotypes. While acetylation polymorphism is not altogether a new concept, studies have mostly been carried out in the west where the phenotype is predominantly that of the slow variety. We are therefore relatively ignorant about the role of acetylation polymorphism as disease determinants in our Asian populations. It is hoped that this preliminary study would encourage more detailed observations as to the relevance of acetylation polymorphism to therapeutics and occurrence of disease locally.

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