

METABOLIC INTERACTION OF CINCHONA ALKALOIDS WITH METHOXYPHENAMINE AND
CHLORPROMAZINE : PHARMACOGENETIC STUDIES IN MAN AND RAT

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for her patience and support

MY WIFE

and to

for their love and encouragement

MY PARENTS AND SISTER

Dedicated to

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ABSTRACT

Genetic polymorphism in metabolism is exhibited by several drugs including debrisoquine and methoxyphenamine which are metabolized by debrisoquine 4-hydroxylase (designated in human as cytochrome P450IID6). In the case of methoxyphenamine, the poor metabolizer phenotype differs from the extensive metabolizer in that after an oral dose there is impairment in the formation of only those primary oxidative metabolites of methoxyphenamine that are catalyzed by cytochrome P450IID6, namely O-desmethoxymethoxyphenamine and 5-hydroxymethoxyphenamine. However, such an impairment is not seen in the formation of N-desmethoxymethoxyphenamine, the other known primary metabolite of methoxyphenamine. A similar situation occurs on administration of methoxyphenamine to Lewis and Dark Agouti strains of rats, the purported extensive and poor metabolizer models, respectively, of human debrisoquine polymorphism.

Various studies were conducted in humans and rats (Lewis and Dark Agouti strains) wherein the various phases methoxyphenamine was administered with and without prior treatment with quinidine (the most potent inhibitor known of the metabolic pathways of drugs that are catalyzed by cytochrome P450IID6) or its diastereomer, quinine. Consistent to observations made using human liver preparations for drugs metabolized by cytochrome P450IID6, it was seen in vivo that quinidine was a potent inhibitor of the O-demethylation and 5-hydroxylation of methoxyphenamine in human, whereas quinine failed to inhibit these metabolic pathways. In rats, however, quinine was a far more potent inhibitor of these metabolic pathways than quinidine. Thus for the

first time indication was obtained from in vivo studies that the isozymes catalyzing the metabolism of those drugs which co-segregate with debrisoquine polymorphism are different in human and rat. These studies provided further support for the use of methoxyphenamine as a phenotyping agent for drugs exhibiting 'debrisoquine type' metabolic polymorphism.

Administration of the prototype phenothiazine antipsychotic agent chlorpromazine with and without prior quinidine treatment to humans helped to identify the involvement in part of cytochrome P450IID6 in its 7-hydroxylation. This was confirmed by using methoxyphenamine as a phenotyping agent. Thus, a metabolic pathway of this class of drugs which exhibits polymorphism was identified for the first time.

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