Quinidine: potent inhibition of sparteine and debrisoquine oxidation *in vivo*

Genetic deficiencies in the oxidative metabolism of sparteine and debrisoquine in man are well documented (Eichelbaum, 1984; Kalow, 1984). Poor metabolizers of sparteine and debrisoquine having an autosomal recessive trait show a decreased metabolizing capacity of certain drugs leading to elevated plasma concentrations (Lennard, 1985). Susceptible drugs include β-adrenoceptor antagonists and tricyclic antidepressants. An *in vitro* method using human livers has been developed to screen for potentially susceptible drugs and over 100 drugs have been tested (Inaba *et al.*, 1985; Otton *et al.*, 1984). However, it is still necessary to carry out an *in vivo* or 'panel approach' with groups of poor and extensive metabolizers to show the extent of decreased metabolism. The most potent inhibitor of sparteine and debrisoquine oxidation *in vitro* is quinidine (Otton *et al.*, 1984). A similar effect *in vivo* might convert an extensive into a poor metabolizer.

This paper describes preliminary results from studies on the effect of quinidine on sparteine and debrisoquine metabolism. Extensive metabolizers of sparteine (seven healthy volunteers, two female and five male, 23–45 years of age) ingested a tablet of quinidine (Biquin Dureles 250 mg, Astra Pharmaceuticals) at 0 h. One hour later, a capsule containing 50 mg of sparteine sulphate was ingested and urine was collected for the subsequent 12 h. The sparteine test was repeated on the seventh day. Three weeks later, the same volunteers (subjects 1–3) ingested a tablet of quinidine and 1 h later a tablet of 10 mg debrisoquine. Urine was collected for 12 h after debrisoquine. The sparteine and debrisoquine oxidation phenotypes were determined several months before the quinidine study. Sparteine, debrisoquine and their metabolites were measured by previously described GC methods (Inaba *et al.*, 1983). The 'metabolic ratios' were calculated as moles of unchanged drug divided by moles of metabolites recovered in the urine.

Figure 1 shows the dramatic initial increase in the sparteine metabolic ratio after a single dose of quinidine in seven subjects. By the seventh day the metabolic ratio was back to the basal level. Since quinidine was a potent *in vitro* inhibitor of sparteine metabolism, the increase in the metabolic ratio is likely to be due to the

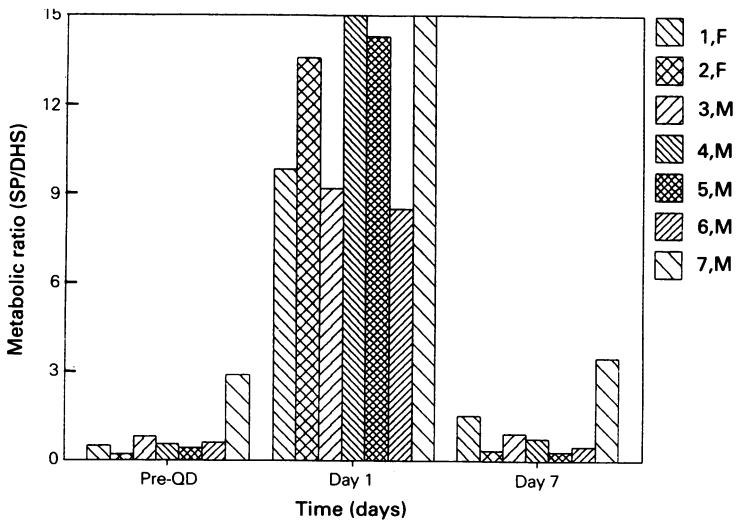

Figure 1 Effect of quinidine (QD, 250 mg p.o.) on the urinary metabolic ratio of sparteine (molar ratio of sparteine/dehydrosparteine = SP/DHS).

inhibitory effect of quinidine at the cytochrome P-450 which metabolizes sparteine (Otton *et al.*, 1984). Although the inhibitory constant of quinidine *in vitro* was extremely low (60 nM), the inhibition seen *in vivo* was reversible and undetectable after 7 days. The metabolic ratio of debrisoquine was also affected by quinidine in the same manner. On day 1 the metabolic ratio increased to 4.8 from the control value of 0.95 in subject 1, to 3.3 from 0.34 in subject 2, and to 8.4 from 0.82 in subject 3. Therefore, during the phenotyping of subjects with sparteine or debrisoquine, concomitant administration of quinidine or other inhibitors must be avoided. The metabolism of other drugs associated with the genetic polymorphism of sparteine/debrisoquine is also likely to be affected by quinidine. Quinidine was indeed shown to inhibit the metoprolol metabolism (Leemann *et al.*, 1986). If quinidine were to be administered repeatedly, as in the treatment of arrhythmia, inhibitory effects could be of considerable clinical significance.

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T. INABA, R. E. TYNDALE &
W. A. MAHON
Department of Pharmacology, Faculty of Medicine, University of Toronto, Toronto M5S 1A8 Canada

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