The relationships between liver volume and the disposition of antipyrine and indocyanine green before and after phenobarbitone treatment

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A relationship has previously been reported in normal subjects and in patients with chronic liver disease between the clearances of antipyrine and indocyanine green (Branch, James & Read, 1975). Antipyrine is a drug which is slowly metabolized by the hepatic microsomes and its clearance is independent of liver blood flow. Indocyanine green is actively and rapidly excreted into bile and its clearance is therefore limited by liver blood flow. It has been suggested that the common rate-limiting factor is the total functional hepatic mass. Phenobarbitone increases the concentration of mixed function oxidase enzymes in man (Lecamwasam, Franklin & Turner, 1975) and increases liver weight and blood flow in the rat (Ohnhaus, Thorgiersson, Davies & Breckenridge, 1971) and in the rhesus monkey (Branch, Shand, Wilkinson & Nies, 1974).

The effect of oral administration of 180 mg/day of phenobarbitone for three weeks on liver volume and clearances of antipyrine and indocyanine green has been investigated in ten normal subjects. Liver volumes were determined by an ultrasonic scanning technique similar to that of Rasmussen (1972). Antipyrine was assayed by the method of Brodie, Axelrod, Soberman & Levy (1949) and indocyanine green by the method of Caesar, Shaldon, Chiandussi, Guevara & Sherlock (1961). Dosages and sampling procedures were as described previously (Branch, *et al.*, 1975).

The technique used for liver volume estimation was reproducible. One subject had a very high initial antipyrine clearance and this did not change after phenobarbitone administration indicating that this subject was maximally induced at the start of the study. The antipyrine clearance of the other nine subjects correlated with liver volume ($r + 0.69$, $P < 0.05$). The initial clearances of indocyanine green of seven subjects approximated to the expected liver blood flow and related to liver volume. The indocyanine green clearance in the other three subjects was lower than predicted by this relationship.

After phenobarbitone there was no increase in liver volume. The clearance of antipyrine increased by $90 \pm 14.1\%$ ($P < 0.001$) (mean ± s.e. mean). There was still a correlation between antipyrine clearance and liver volume ($r + 0.86$, $P < 0.01$). There was no significant increase in indocyanine green clearance. The relationship between the indocyanine green clearance and liver volume was maintained in the same seven subjects who had demonstrated such a relationship prior to phenobarbitone. The clearances in the other three subjects remained low.

In conclusion, the effect of phenobarbitone on the interrelationships examined suggests that, in the absence of enzyme induction, variation in drug elimination is related to the total functional hepatic mass, and that phenobarbitone is able to increase the drug metabolizing capacity per unit of mass, without causing an increase in total liver size.

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