Effect of phenobarbitone on the disposition of lignocaine and warfarin in the dog*

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The invasive measurement of hepatic blood flow in animals has been crucial to understanding the response of the liver to phenobarbitone (Ohnhaus, Thorgeirsson & others, 1971; Branch, Shand & others, 1974; Ohnhaus & Locher, 1975; Nies, Wilkinson & others, 1976). We have used lignocaine, a drug with high, and warfarin, a drug with low hepatic clearance given intravenously and by mouth to examine the effect of phenobarbitone on hepatic blood flow and hepatic enzyme activity, using the approach developed by Nies, Shand & Wilkinson (1976).

Four healthy mongrel dogs were given lignocaine (10 mg kg^{-1}) and warfarin (0·4 mg kg^{-1}) intravenously and by mouth according to a latin square design before and after phenobarbitone given by mouth at 16 mg kg^{-1} day^{-1} for 10–12 days. Two other dogs serving as controls received the same treatment as the *phenobarbitone group* but only gelatin capsules in place of phenobarbitone. Warfarin doses were given seven days apart and lignocaine doses were separated by one day, during either the pre-phenobarbitone or phenobarbitone treatment. Frequent venous blood samples were taken for analysis for 96 h after warfarin, and for 8 h after lignocaine. Lignocaine was measured by the method of Rowland, Thomson & others (1971), and warfarin by a minor modification of the method of Bjornsson, Blaschke & Meffin (1977). This modification, which involved drying the ether phase with a small amount of anhydrous calcium chloride before evaporation, had the effect of removing interfering blood constituents. After the last blood sample, the animals were killed and liver weights determined.

Areas under the blood concentration time curves from zero to infinite time (AUC_0^∞) were obtained using the trapezoidal rule. Systemic clearance (CL_s) was calculated by dividing the dose by the area under the curve AUC_0^∞ after intravenous doses. The intrinsic clearance (CL_{int}) was calculated by dividing the dose by the AUC_0^∞ after oral doses (Nies & others, 1976). Bioavailability (F) was calculated by dividing the AUC_0^∞ after an oral dose by the AUC_0^∞ after an intravenous dose of the same size. Hepatic blood flow (Q) was calculated as the dose divided by the difference between the AUC_0^∞ after intravenous and oral doses.

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Statistical evaluation of the differences observed in the study were performed using a paired *t*-test.

The mean value of CLs, F, CL_{int} and Q during the pre-phenobarbitone (pre-PB) and phenobarbitone (PB) treatment periods for warfarin and lignocaine are presented in Table 1, together with the corresponding data for the controls. As the mean hepatic blood flow in dogs has been reported to be 43 ml min^{-1} kg^{-1} (Greenway & Stark, 1971), the pre-PB systemic clearances in Table 1 indicate that warfarin and lignocaine suitably represent drugs having clearances that are a small fraction (0·06) and a high fraction (0·73) of estimated hepatic blood flow in this species. The mean (with s.d.) hepatic blood flow calculated from the eight sets of control lignocaine data of 64·3 (24) ml min^{-1} kg^{-1} is 50% greater than that reported by Greenway & Stark (1971). The limiting factor in the clearance of warfarin is the capacity of enzyme systems responsible for its metabolism (capacity-limited clearance), whereas lignocaine clearance is limited by hepatic blood flow (flow-limited clearance) (Nies & others, 1976). Agents that increase the amount of hepatic enzyme activity would thus be expected to increase the systemic clearance and intrinsic clearance of warfarin, but differences in bioavailability may be too small to be observed experimentally. On the other hand, the systemic clearance of lignocaine should be insensitive to changes in enzyme activity, but sensitive to changes in hepatic blood flow. However, the intrinsic clearance of lignocaine, being independent of blood flow, should reflect changes in hepatic enzyme activity (Nies & others, 1976).

In spite of the differences in the initial systemic clearance values of warfarin and lignocaine, phenobarbitone has similar effects on the disposition of both compounds (Table 1). The systemic clearance and intrinsic clearance of warfarin are significantly increased after phenobarbitone by a factor of 3·30 and 3·11, respectively, with no significant changes in bioavailability. Lignocaine shows a similar but less pronounced change: systemic clearance increasing by a factor of 1·76 and intrinsic clearance by a factor of 1·81. The change in systemic clearance is significant ($P<0.025$) but the change in intrinsic clearance is indicative only of a trend ($P<0.2$). Since systemic clearance and intrinsic clearance increase in parallel, no net change in bioavailability is observed (Table 1).

An explanation of these findings is provided in the difference in liver weight between phenobarbitone-treated and control animals. The mean liver weight for the phenobarbitone-treated animals was 39·42 g kg^{-1} 1·78 times the mean for the controls of 22·1 g kg^{-1}

Table 1. *Effect of phenobarbitone on drug disposition.*

Phenobarbitone treated (n = 4)	CL_s (ml min^{-1} kg^{-1}) Pre-PB	PB	F Pre-PB	PB	CL_{int} (ml min^{-1} kg^{-1}) Pre-PB	PB	Q (ml min^{-1} kg^{-1}) Pre-PB	PB
Warfarin	0·280 (0·06)++	0·928+ (0·24)	0·858 (0·20)	0·891 (0·25)	0·352 (0·15)	1·096+ (0·41)	†	†
Lignocaine	31·3 (6·6)	55·0+ (14·0)	0·37 (0·11)	0·42 (0·21)	89·2 (27·8)	161·1 (66·1)	51·7 (15·1)	112·5 (55·7)
Control (n = 2)								
Warfarin	0·238 (0·14)	0·256 (0·14)	1·17 (0·49)	1·30 (0·07)	0·247 (0·20)	0·198 (0·04)	†	†
Lignocaine	41·7 (8·2	40·8 (3·7)	0·43 (0·21)	0·44 (0·02)	105·8 (31·8)	92·7 (3·0)	81·0 (43·8)	72·8 (9·6)

+ $P<0·025$ (all other comparisons are not significant, $P>0·05$).
++ Figures in parentheses are standard deviations.
† Calculated for high clearance drug (lignocaine) only.
Abbreviations: CL_s = systemic clearance
F = bioavailability
CL_{int} = intrinsic clearance
PB = phenobarbitone
Q = hepatic blood flow

($P<0·025$), unpaired *t*-test). The difference in liver weight between the two groups almost exactly parallels the increase in lignocaine intrinsic clearance and systemic clearance. This implies that the increase in liver weight is accompanied by a proportional increase in liver blood flow. Liver blood flow has been calculated from the lignocaine data, for which a sufficient difference between AUC_0^∞ after intravenous and oral doses exists to allow this estimate to be made. The liver blood flow increased from a mean of 51·7 ml min^{-1} kg^{-1}, during the pre-phenobarbitone period of the study, to a mean of 112·4 ml min^{-1} kg^{-1} during the phenobarbitone treatment. This difference was not significant (Table 1). There are no significant changes in any of the measured parameters for the control group.

These data are consistent with previous reports of the effect of phenobarbitone on the disposition of drugs and on hepatic blood flow. Phenobarbitone has been reported to increase the blood flow in proportion to increases in liver weight in the rat (Ohnhaus & others, 1971; Ohnhaus & Locher, 1975; Nies & others, 1976). In a detailed study in which hepatic blood flow was measured directly and in which a flow-limited drug (propranolol) and a capacity-limited drug (antipyrine) were administered intravenously to monkeys, conclusions essentially similar to our own were drawn regarding the effect of phenobarbitone on the disposition of these two model drugs (Branch & others, 1974).

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