Phenobarbitone and feeding in dogs

Thurman and co-workers (JSAVA 59: 86-89) reported an apparent effect of food on the systemic availability of phenobarbitone administered by mouth in dogs. Their data showed that feeding dogs immediately after dosing resulted in an $AUC_{0-24}$ (area under the serum drug concentration - time curve from 0 to 24 h after dosing) which was 10% less than that obtained after dosage on an empty stomach. The peak mean serum drug concentration also appeared to be reduced by feeding while times to peak concentrations were unaffected.

The authors suggested that these findings indicated that ingesta reduced phenobarbitone absorption. However, comparison of $AUC_{0-24}$ values might be inadequate for assessing changes in the extent of absorption, given the long half-time of elimination of the drug (mean 29.3 h). The flatter slope of the terminal portion of the curve shown for fed dogs suggests absorption might have been delayed, even though peak times were unchanged. In rats, food intake delayed phenobarbitone absorption by slowing gastric emptying, thus increasing the time for the drug to reach its main absorption site in the small intestine. By contrast, no consistent effect of food was evident in a clinical study involving human infants.

As the authors noted, even a 10% reduction in phenobarbitone absorption might have no effect on control of epilepsy. However, if higher doses are given with food in compensation, and if absorption is delayed rather than reduced, phenobarbitone might accumulate to toxic concentrations. If such adjustments are made, it would be advisable to monitor serum or plasma drug concentrations to ensure they remain in the safe and effective range.

There appears to be an error on page 88, as the factor 0.232 should convert $\mu$mol to mg, not mmol to mg as shown (i.e. 1 $\mu$mol = 0.232 mg phenobarbital).


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At steady state $AUC_{0-\infty}$ is adequate to describe the extent of absorption. AUC over a dose interval at steady state is usually equivalent to AUC after a single dose extrapolated to infinity. The only reason it is not so in this case is that enzyme induction occurs with phenobarbitone.

Although the mean curves in our paper (JSAVA 59: 86-89) appear to indicate a flatter terminal slope after feeding, elimination rate constants were not significantly different on Days 22 and 24 (paired t-test $p=0.56$, median $K_e$ for Day 22 was 0.025 h$^{-1}$ and for Day 24 was 0.024 h$^{-1}$).

It is most unlikely that absorption could be slowed to such an extent that it would affect 8-24 h samples. The mean, standard deviation, and range of gastric emptying time, small intestinal transit time, and small intestinal emptying time of normal dogs is 76 ± 16.7 (30-120), 73 ± 16.4 (30-120), and 214 ± 25.1 (180-300) min respectively.

Since phenobarbitone in the therapeutic range obeys linear elimination kinetics, a 10% dose compensation and thus 10% accumulation would be expected to increase serum concentrations by 4 to 11 $\mu$mol $h^{-1}$ (therapeutic range 40-110 $\mu$mol $h^{-1}$). This is most unlikely to lead to toxicity of clinical significance.

We acknowledge the typographical error on page 88 and thank Dr. Watson for bringing this to our attention.


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