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THE DISPOSITION OF PHENYLBUTAZONE IN THE HORSE

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Phenylbutazone (PBZ) is the most widely used non-steroidal anti-inflammatory drug in equine medicine. Although the 'Rules of Racing' prohibit its use in most countries, it is the only anti-inflammatory drug permitted in horses competing under Federation Equestre Internationale (FEI) rules. Since its introduction into equine medicine some 30 years ago PBZ has been the subject of intensive investigation, further stimulated by the demonstration of gastro-intestinal toxicity in mountain ponies (Snow et al., 1979); however, uncertainty still exists regarding the disposition of phenylbutazone in the horse.

Two gelded horses, (273 and 350Kg) were given PBZ (7.1mg/Kg containing 100μCi of [^{14}C-U-phenyl]PBZ) either orally in dilute $NaHCO_3$ by stomach tube or intravenously on separate occasions. Blood samples were obtained from an indwelling jugular cannula. Urine was collected as previously described (Marsh et al., 1981) and faeces as voided. The elimination of ^{14}C was monitored by scintillation counting, the faecal samples being combusted prior to analysis. Urinary metabolites were separated and characterised by TLC, HPLC and GC/MS by comparison with authentic standards.

An essentially quantitative recovery (95% of dose) of administered ^{14}C was obtained within seven days. Urinary excretion accounted for some 55% of the dose in the 0-72h period. No ^{14}C was detected in the faeces up to 20 hours post dosing, but in the time period 20-150 hours 37% (i.v.) and 40% (p.o.) of the dose was recovered, faecal elimination being complete within this period. The presence of a substantial proportion of the dose in the faeces, strongly suggestive of biliary excretion, explains the large fraction of the dose unaccounted for in previous studies. The similar excretory balance for both routes of administration indicates that PBZ has a high systemic availability.

HPLC analysis of plasma revealed that at all time points PBZ was the major component (>80% of total ^{14}C), accompanied by smaller amounts of p-hydroxyPBZ and γ-hydroxyPBZ. The AUCs for total plasma ^{14}C were very similar for both routes of administration (illustrated for one horse in Figure 1) demonstrating that PBZ is rapidly and well absorbed with negligible first pass metabolism following oral administration.

The major urinary metabolites were unchanged PBZ (4% of dose), p-hydroxyPBZ (20%), and γ-hydroxyPBZ(14%), and two minor metabolites have been characterised, namely p, γ-dihydroxy-PBZ(1.5%) and γ-ketoPBZ(<1%). Overall these five compounds account for some 40% of the dose (73% of urinary ^{14}C). In addition several further metabolites have been separated by reverse phase HPLC, the identities of which have yet to be established. HPLC analysis of individual

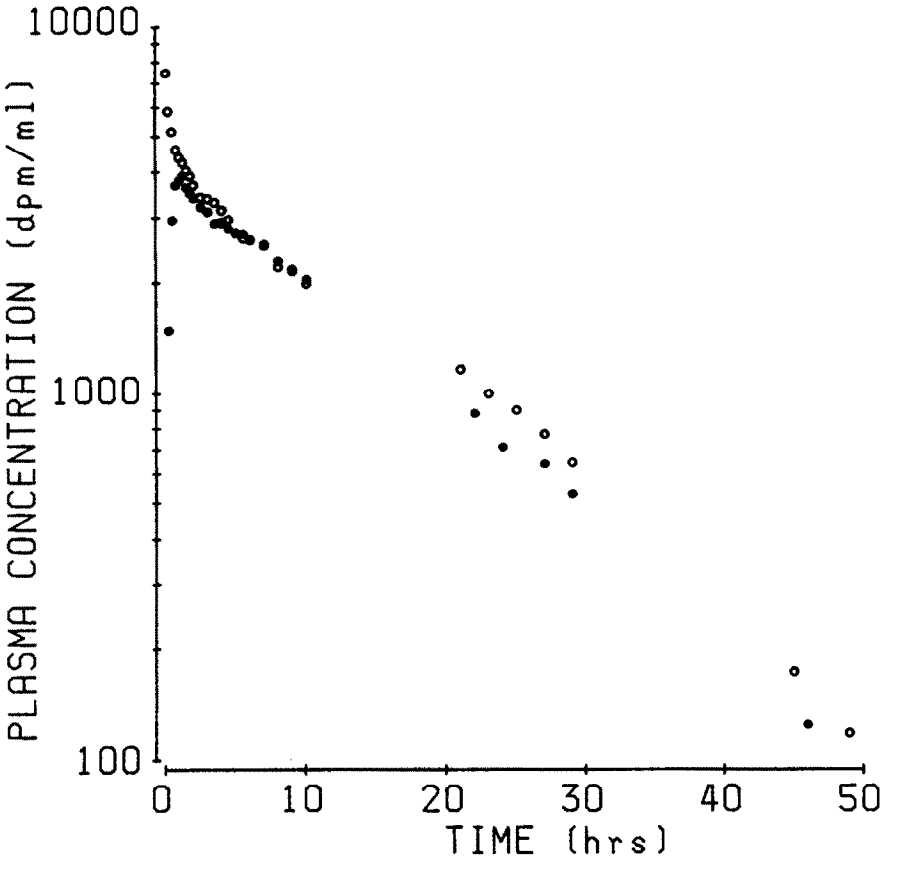

Fig. 1. Plasma concentration-time curves for ^{14}C in a horse given ^{14}C-PBZ orally (•) and intravenously (o) on separate occasions.

urine samples revealed a time dependent change in the urinary profile of the major metabolites. Up to 10 hours after dosing γ-hydroxyPBZ was the major urinary component, but thereafter p-hydroxyPBZ predominated. This alteration in the p-hydroxyPBZ/γ-hydroxyPBZ ratio might enable the time of dosing to be determined from analysis of urinary metabolites.

Taken together, these data show that PBZ is rapidly and extensively absorbed after oral administration, with negligible first pass metabolism. Both urine and faeces are important routes of elimination of ^{14}C, and the administered dose may be completely accounted for in terms of these. PBZ undergoes extensive oxidative metabolism, at both aromatic and aliphatic centres, and the products of these transformations are excreted unconjugated. The relative importance of the principal metabolic routes changes with time after dosing. Studies upon the identification of minor urinary metabolites are continuing.

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References

1. D.H. Snow, J.A. Bogan, T.A. Douglas, and H. Thompson, Vet. Record 105, 26 (1979).
2. M.V. Marsh, J. Caldwell, R.L. Smith, M.W. Horner, E. Houghton, and M.S. Moss, Xenobiotica, 11, 655 (1981).