First-pass effect of the beta-adrenoceptor blocking agent pindolol in the dog

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Pindolol ((±)-4-(2-hydroxy-2-isopropylaminopropoxy)-indole; Visken), a potent and specific beta-adrenoceptor blocking agent (Aellig, 1976a), is chemically related to all other beta-adrenoceptor blocking substances. The pharmacokinetic behaviour of the compound in man, however, has been found to be different from other beta-adrenoceptor antagonists in clinical use in that it is only partially metabolized in man and has a high systemic availability after oral administration (Johnsson & Regårdh, 1976; Meier & Nüesch, unpublished observations). Metabolism by the liver during its first passage is referred to as the first-pass effect. The major cause of the low bioavailability of most beta-adrenoceptor blocking agents is due to a high first-pass effect. Since the dog metabolizes pindolol in a similar way, but to a greater extent than man, experiments were performed to investigate the first-pass effect of the drug in the dog.

Two beagle dogs, each weighing 13 kg, were given an intravenous injection of [^{14}C]-pindolol labelled in the 3-position of the indole ring; the dose (25 mg) given contained 250 μCi ^{14}C activity. After a wash-out period of 3 weeks, the same dose was administered orally. Following both doses, blood samples were taken at intervals during 48 h and urine and faeces collected for 96 h following administration. [^{14}C] activities (pindolol plus metabolites) were determined in blood, plasma, urine and faeces by liquid scintillation counting. Unchanged pindolol was determined in plasma and urine samples fluorimetrically (Pacha, 1969).

Absorption of pindolol from the gastrointestinal tract was found to be rapid and complete. After both oral and intravenous administration, approximately 74% of the administered [^{14}C] activity was excreted in the urine and 23% in the faeces during the 96 h collection period. Only 4 to 7% of the dose was excreted in the urine as unchanged pindolol. This strong metabolism of pindolol in the dog was confirmed by comparing the area under the plasma concentration versus time curve (AUC) of [^{14}C] activity and that of unchanged substance. These results are in contrast to those previously obtained in man in which unchanged pindolol amounted to 40% of the total dose administered. Based on the urinary excretion and the AUC's of unchanged pindolol after oral and intravenous administration the bioavailability of pindolol in the two dogs was calculated to be 54.2% and 55.2% respectively. The first-pass effect of pindolol in the dog was therefore 45%, compared to 13% in man (Meier & Nüesch, unpublished observations). These values correlate well with the degree of beta-adrenoceptor blocking activity estimated in the dog (Saameli, 1972) and man (Aellig, 1976b) following oral administration compared with that following intravenous administration.

It is concluded that, as with other beta-adrenoceptor blocking agent, the first-pass effect of pindolol is directly related to the degree of metabolism of the drug by the liver.

We thank Dr R. Voges for the synthesis of the [^{14}C]-labelled pindolol.

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