Pharmacokinetics of M&B 17,803A in animals and man

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M&B 17,803A [±-1-(2-acetyl-4-*n*-butyramidophenoxy)-2-hydroxy-3-isopropylaminopropane hydrochloride] is a β-adrenoceptor blocking agent which shows cardioselectivity in experimental animals (Basil, Jordan, Loveless & Maxwell, 1971).

Plasma levels of M&B 17,803A were determined colorimetrically following the oral and intraduodenal administration of the compound to anaesthetized dogs in which the degree of cardiac β-receptor blockade was determined by isoprenaline antagonism. There was a linear regression between the isoprenaline dose ratio (DR) and the logarithm of the plasma concentration of M&B 17,803A, a DR of 7 being obtained at a plasma concentration of 0·23 μg/ml.

Three healthy volunteers received single oral doses of either M&B 17,803A (300 mg), practolol (400 mg) or propranolol (40 mg) on separate occasions separated by weekly intervals. The degree of antagonism of isoprenaline tachycardia (Cuthbert & Owusu-Ankomah, 1971) and plasma levels of the β-blockers were determined at intervals after drug administration. M&B 17,803A and practolol were determined colorimetrically using a modification of the method of Fitzgerald & Scales (1968); propranolol was determined spectrofluorimetrically (Shand, Nuckolls & Oates, 1970). Although the oral dose of M&B 17,803A was similar to that of practolol and the degrees of β-blockade obtained with these two drugs were comparable, the plasma levels of practolol were considerably higher than those of M&B 17,803A, the respective plasma levels of M&B 17,803A and practolol for a DR of 7 on tachycardia being 0·2 and 1·2 μg/ml.

Up to 6 h after the oral dose of 5 to 10 mg/kg of acetyl-1-^{14}C-labelled M&B 17,803A to the rat or the dog, 51–53% of the plasma ^{14}C was unchanged M&B 17,803A, whilst 6% appeared to be the diacetyl analogue [±-1-(2-acetyl-4-acetamidophenoxy)-2-hydroxy-3-isopropylaminopropane]. It is unlikely that any of the metabolites thus far detected are important in the pharmacological actions of orally administered M&B 17,803A in experimental animals.

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The pharmacokinetics of unchanged pindolol in patients with impaired renal function

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Based on the so-called 'intact nephron hypothesis' (Bricker, Morrin & Kime, 1960), a linear relationship between the endogenous creatinine clearance (V_{cr}) and the overall elimination rate constant (k_e) of many drugs can be demonstrated: $k_e = k_m + a \cdot V_{cr}$. The