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

β-adrenoceptor-blocking agent pindolol (Visken, LB 46) is excreted up to 80% in the urine, of which about 40% is unchanged. As it is used in the treatment of hypertension, we were interested in testing the 'intact nephron hypothesis' in the case of unchanged pindolol, in order to find the appropriate individual dose schedule for patients with renal impairment.

Twenty-five patients with different degrees of renal impairment, endogenous creatinine clearance ranged from 0–125 ml/min, were given 3 mg pindolol I.V. The concentrations of pindolol in the plasma and urine were measured by a fluorimetric method (Pacha, 1969). From these measurements, the 'overall' (k_e), the renal (k_r) and the extrarenal (k_m) elimination rate constants for each individual patient were calculated on the basis of a first order one compartment open model. At the same time, endogenous creatinine clearance ($\dot{V}_{cr}$) was estimated.

No linear correlation according to the equation $k_e = k_m + a \cdot \dot{V}_{cr}$ could be calculated between the elimination constant and the endogenous creatinine clearance. Using the method of 'the least squares of errors', the following equation was calculated: $k_e = 0{\cdot}185 - 0{\cdot}00023 \cdot \dot{V}_{cr}$; $r = 0{\cdot}17$; $s_{y/x} = \pm 0{\cdot}056$; $P > 0{\cdot}05$. This means that the calculated line is parallel to the abscissa and that no change in the elimination rate constant or the half-life, respectively, of unchanged pindolol takes place in patients with renal impairment. According to the equation $k_e = k_m + a \cdot \dot{V}_{cr}$, k_r gets lower with decreasing endogenous creatinine clearance and accordingly k_m increases. From this fact it must be concluded that in patients with renal impairment a much increased metabolism of the substance occurs. Explanations for this increased metabolism are not known.

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Isoprenaline antagonism and duration of action in exercise induced tachycardia of three β-adrenoceptor blocking drugs: pindolol, LF 17-895 and propranolol

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Orally administered pindolol (Visken, LB 46, 1-(indol-4-yloxy)-3-(isopropylamino)-2-propanol) has been shown to be between 20 and 40 times as potent as propranolol in antagonizing tachycardia due to isoprenaline inhalation (Hill & Turner, 1969). In this study the 2-methyl derivative of pindolol (LF 17-895, 1-(isopropylamino)-3-(2-methylindol-4-yloxy)-2-propanol) has been compared with pindolol and propranolol in healthy volunteers for their antagonism to isoprenaline induced tachycardia. In addition the duration of action of all three drugs has been investigated using the model of exercise induced tachycardia.

Subjects rested supine and isoprenaline hydrochloride was infused into a left antecubital vein. Starting with 2 μg/min, the dose was doubled every 5 min until a heart rate of above 130 beats/min was reached. The infusions were repeated 2 h after pindolol (1 mg, 2·5 mg, 5 mg), LF 17-895 (0·5 mg, 1·25 mg, 2·5 mg), propranolol (40 mg, 80 mg) and placebo administered to all three volunteers orally in random sequence. From isoprenaline dose response curves the dose of isoprenaline required to increase heart rate to 120 beats/min was extrapolated for each dose of the three drugs and placebo (Table 1). These results indicate that orally administered LF 17-895 was 2·5 times more potent in this test than pindolol, which showed, in accordance with Hill & Turner (1969), about 40 times the activity of propranolol.