

BIOAVAILABILITY OF LABETALOL INCREASES WITH AGE

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The antihypertensive drug labetalol was administered orally and intravenously to ten hypertensive patients aged between 28 and 75 years. There was a significant increase with age in both bioavailability and half-life of labetalol. Clearance tended to be lower in the elderly subjects. First pass metabolism results in variable oral bioavailability of labetalol which is greater in the elderly and this should be borne in mind when using the drug in this age group.

Introduction

The antihypertensive drug, labetalol, is subject to presystemic metabolism by the liver (Breckenridge *et al.*, 1977), the 'first-pass' effect. As a result, its oral bioavailability varies widely (McNeill *et al.*, 1979). For drugs such as this, oral bioavailability is inversely related to intrinsic clearance (Nies *et al.*, 1976) which can decrease with age (George, 1979). The present study was designed to determine if ageing affects bioavailability of labetalol.

Methods

Ten drug free, mild to moderate hypertensive patients, aged from 28 to 75 years, took part. Each patient gave informed consent and the study was approved by the local Hospital Ethics Committee. Labetalol was administered to each person on two occasions, once orally and once intravenously. The doses were administered in random order, separated by at least 1 week. The oral dose was 200 mg except in the two oldest and one young subject when 100 mg was given. Three subjects received an intravenous dose of 1 mg/kg and 0.5 mg/kg was given to the remaining seven. Blood samples for estimation of plasma labetalol concentrations were taken over a period of eleven hours following administration of the drugs. The plasma specimens were stored at -20°C prior to assay by a radioreceptor method (Kelly *et al.*, 1981). From the results for each patient were calculated the elimination half-life of labetalol by linear least squares regression analysis of the terminal part of the log concentration-time graph and the area under the plasma concentration-time curve by the trapezoidal rule. Plasma clearance was calculated by dividing the intravenous dose by the area under the plasma concentration time curve extrapolated to infinity ($\text{CL} = \text{Dose}/\text{AUC}_{\infty}$). The apparent volume

of distribution was calculated as $V = \frac{\text{CL} \times t_{1/2}}{0.693}$

Bioavailability was calculated from the ratio of the areas under the oral and intravenous plasma concentration-time curves, extrapolated to infinity and corrected for dose differences.

Results

In Figure 1 the labetalol half life after intravenous administration is plotted against age. Elimination half-life of labetalol varied from 3.5 h to 4.9 h and was significantly correlated with age (half-life = $2.62 + 0.026 \text{ age}$, $r = 0.73$, $P < 0.02$). Labetalol bioavailability varied widely (from 8.9% to 68.4%) but wa

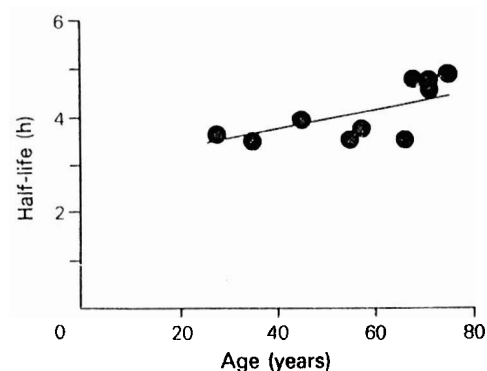


Figure 1 Relationship of labetalol half-life to age.

also significantly correlated with age (see Figure . percent bioavailability = $0.78 + 0.81 \text{ age}$, $r = 0.70$, $P < 0.05$).

lation (Mbanefo *et al.*, 1980) suggesting that the formation of ring-opened carboxylic acids is deficient (Tucker *et al.*, 1977). At least one of the other two pathways of metoprolol metabolism (oxidative deamination and *o*-dealkylation with subsequent rapid oxidation) may, therefore, be impaired. As it normally accounts for 65% of the dose, *o*-dealkylation seems most likely to be defective, a view supported by the fact that the *o*-dealkylation of phenacetin and 4-hydroxylation of debrisoquine are correlated (Sloan *et al.*, 1978).

Metoprolol half-life is said to be 2–4 h (Regardh & Johnsson, 1980). Our data suggest that it may be much

greater in some healthy subjects and this may explain the 17-fold variation in plasma concentrations in patients receiving the same dose (von Bahr *et al.*, 1976). The clinical implications are that poor metabolisers need only once daily dosing for the control of angina but that smaller doses may be required to avoid a relative loss of cardioselectivity and side-effects associated with high plasma concentrations (Formgren, 1976). Further studies are in progress in order to define the metabolic defect.

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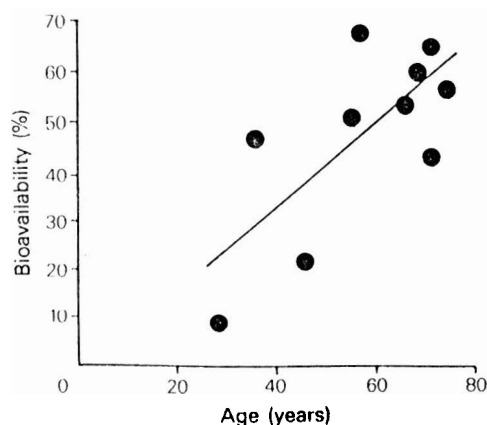


Figure 2 Relationship of labetalol bioavailability to age.

The time to peak concentration after oral administration did not change with age and was observed at 0.5 to 2.5 h after the dose. There was no significant correlation between age and clearance (mean \pm s.e. mean clearance, 22.4 ± 3.5 ml min⁻¹ kg⁻¹) or between age and volume of distribution (mean volume of distribution, 7.7 ± 1.1 l kg⁻¹). Both these

parameters were widely variable (clearance range; 8.8 : 41.8 ml min⁻¹ kg⁻¹; volume of distribution range; 3.2 – 13.7 l kg⁻¹). These ranges and mean values agree well with values found by others (McNeil *et al.*, 1979) in hypertensive patients.

Discussion

Labetalol is a drug which has a high degree of first-pass metabolism and variable oral bioavailability which is greater in the elderly. We also observed a positive correlation between age and half-life. The absence of a significant correlation between age and labetalol clearance is probably due to the large variability in values for clearance. Clearance did tend to be lower in the elderly. Thus the mean clearance in younger subjects (aged less than 60 years, $n = 5$) was 28.3 ± 5.5 ml min⁻¹ kg⁻¹ and in older subjects (aged greater than 60 years, $n = 5$) was 16.4 ± 2.7 ml min⁻¹ kg⁻¹ ($P = 0.08$, Student's *t*-test).

In view of the steep increase in bioavailability of labetalol with age it would appear prudent to use smaller doses of this drug in elderly people.

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