PINDOLOL, A β-ADRENOCEPTOR BLOCKING AGENT WITH A NEGLIGIBLE FIRST-PASS EFFECT

Several β-adrenoceptor-blocking drugs are known to be subject to a marked first-pass effect, e.g. alprenolol (von Bahr, Alvan, Lind, Mellström & Sjöqvist, 1974; Regardh, 1975), metoprolol (Regardh, 1975; Johnsson, Regardh & Sölvell, 1975) propranolol (Shand & Rangno, 1972; Coltart, 1975; Paterson, Conolly, Dollery, Hayes & Cooper, 1970). For oxprenolol (Riess, Brechbuehler, Brunner, Imhof & Jack, 1975) the first-pass effect, which is independent of the dose, yields a value of 50–60% when calculated according to the method proposed by Gibaldi, Boyes & Feldman (1971). This formula can be applied when intravenous data are not available and when the drug is eliminated mainly by metabolism as in the case of oxprenolol (Riess *et al.*, 1975). Since pindolol (LB 46, Visken®), a β-adrenoceptor blocking agent (Aellig, 1976a), is metabolized in man to only a moderate extent and is mainly excreted unchanged in the urine (Gugler, Herold & Dengler, 1974), it was of interest to review published and unpublished pharmacokinetic data on this compound in order to ascertain whether or not it is subject to an appreciable first-pass effect.

Data from the eight pharmacokinetic studies in a total of 57 volunteers listed in Table 1 were used to investigate the first-pass effect of pindolol in man. In all the studies the drug was determined in plasma and urine by a fluorimetric method (Pacha, 1969). This method proved to be sensitive and specific for the unchanged drug, because the polar metabolites (Kiechel, Niklaus, Schreier & Wagner, 1975) were eliminated by the extraction procedure. The volunteers participating in the studies A to E were all different, except for the six in studies A1 and A2 who received the drug orally and intravenously. Bioavailability was estimated according to Wagner (1971) by multiplying the area under the plasma level curve (AUC) by the elmination constant k_{el} separately for each subject. The AUC was calculated by the trapezoidal rule. To compare the plasma concentrations for studies in which different dosages were used, the $AUC \times k_{el}$ values were standardized for 1 mg of drug. The urinary excretion of unchanged drug as a percentage of the dose may be compared directly. The overall means after intravenous and oral administration were calculated by weighting the single means of each study with the corresponding reciprocal square of the standard error.

Table 1 shows bioavailability data from the eight studies and the calculated overall means. The studies with ^{14}C-labelled pindolol suggest that the compound

Table 1 Summary of results (mean ± s.e. the mean)

i.v. studies	*dose (mg)*	*AUC × k_{el} (ng/ml)*	*AUC × k_{el}/dose (ng ml^{-1} mg^{-1})*	*Urinary excretion unchanged drug (% of dose)*	*Urinary excretion ^{14}C-activity (% of dose)*	n	*References*
A1	0.4	—	—	—	82.0 ± 3.9	6	Schwarz (1970)*
B1	4.65	41.2 ± 9.6	8.9 ± 2.1	39.2 ± 0.9	—	5	Gugler *et al.* (1976)
C	3	29.8 ± 1.6	9.9 ± 0.5	37.2 ± 3.1	—	9	Ohnhaus *et al.* (1974)
Overall mean		—	9.8 ± 0.5	39.0 ± 0.9	82.0 ± 3.9	20	
Oral studies							
A2	5	—	—	32.4 ± 2.0	81.2 ± 3.1	6	Schwarz (1970)*
A3	10	—	—	35.9 ± 2.4	77.9 ± 5.6	6	Schwarz (1970)*
B2	5	46.8 ± 7.5	9.4 ± 1.5	36.1 ± 4.4	—	12	Gugler *et al.* (1974)
D	10	75.7 ± 8.6	7.6 ± 0.9	—	—	5	Aellig (1975)†
E	20	202.6 ± 28.0	10.1 ± 1.4	32.2 ± 4.9	—	8	Aellig (1975)†
Overall mean		—	8.5 ± 0.7	33.9 ± 1.4	80.4 ± 2.7	37	

* Schwarz (1970). Unpublished data, Sandoz Ltd.
† Aellig (1975). Unpublished data, Sandoz Ltd.

is absorbed completely (98 ± 8%), since 80.4% of the amount of ^{14}C-activity (drug plus metabolites) is excreted in the urine after oral administration and 82.0% after intravenous injection. Gugler *et al.* (1974), reported an absolute bioavailability of 92% for pindolol by the oral route. The systemic availability of orally administered pindolol based on the weighted overall means in Table 1, amounts to 87%. This percentage is obtained both by comparison of the standardized areas under the plasma levels (8.5/9.8) and by comparison of the urinary excretion of unchanged drug (33.9/39.0). In view of this high systemic availability of at least 87% after oral administration, it may be concluded that in man the first-pass effect with pindolol is so low as to be negligible, viz. less than 13%. The low first-pass effect of pindolol in man is attributable to the relatively modest extent to which it is metabolized (30–40% of the administered drug is excreted in the urine, Table 1).

In the investigations which form the basis of this study of the first-pass effect of pindolol, the drug was given in single doses of 0.4 to 20 mg (Table 1, studies A1 to E). It was of interest to examine whether a linear or nonlinear relationship exists between dose and response (plasma and/or urinary excretion) in this dose range. For the oral studies the bioavailability was assumed to be 90%, and the AUC and the urinary excretion values were corrected accordingly. If the $AUC \times k_{el}$/dose values or the urinary excretion (percentage of unchanged pindolol) were then plotted versus the administered doses, the slopes of the calculated regression lines did not differ statistically from zero in both cases. It may therefore be concluded that the systemic availability of pindolol in man does not depend in a nonlinear fashion on the dose (absorption and low first-pass effect) in the dose range studied.

In conclusion it may be stated that pindolol, which is metabolized to a small extent in man (Riess *et al.*, 1975), is absorbed completely and, owing to the low first-pass effect, possesses a high systemic availability. Similarlily good oral bioavailabilities are reported for practolol (100%) and sotalol (⩾60%) (Johnsson & Regardh, 1976).

In the dose range studied from 0.4 to 20 mg the high systemic availability of pindolol is uniform and is not dose-dependent. Since 2 h after oral administration the β-adrenoceptor blocking activity of pindolol was found to be comparable to that seen 75 min after intravenous administration of the same dose (Aellig, 1976b), the pharmacodynamic effect agrees well with this pharmacokinetic study.

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