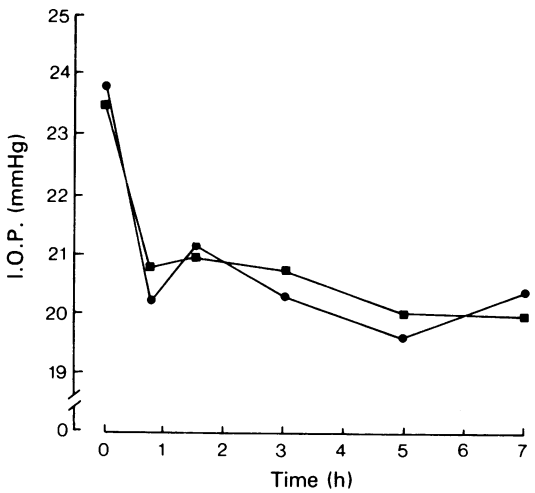

Figure 2 Unadjusted mean I.O.P. levels for adrenaline 1% (■) and combined adrenaline-thymoxamine treatment regimes (●) over a 7 h post-administration period.

aqueous humour, sufficient to inhibit α-mediated mydriasis, could also be reasonably expected to antagonize α-mediated effects in the aqueous veins, although this argument may not be applicable to the afferent intrascleral vessels. The alternative interpretation of the data assumes adequate antagonist concentrations at the relevant sites and therefore it can be argued that the ocular hypotensive response to a single drop of 1% adrenaline is not mediated via α-adrenoceptor mechanisms.

Data from a concentration response study of topical adrenaline support this latter interpretation. Langham, Kitazawa & Hart (1971) reported that concentrations of 2% or less lowered I.O.P. without producing either pupillary dilatation, an established α-effect, or increasing the facility of outflow, a putative α-effect.

Further interaction studies are required to differentiate between the possible interpretations. Such studies should involve higher topical concentrations and/or oral administration of thymoxamine. I.O.P. recording could be usefully supplemented by pupil size measurement to provide direct evidence of intraocular α-adrenoceptor blockade under the experimental conditions employed.

I gratefully acknowledge the assistance provided by the Clinical Pharmacology Unit nursing staff (Mrs J Young, Miss S. Gambles and Miss A.G. Shields) and I am indebted to Mr N.P. Barker for the statistical analysis and to the Pharmacy Department, Moorfields Eye Hospital, for formulation of the thymoxamine eye drops.

A. RUSHTON

Clinical Pharmacology Unit, Clinical Research Department, ICI Pharmaceuticals Division, Alderley Park, Nr Macclesfield, Cheshire

Received November 8, 1979

References

LANGHAM, M.E., KITAZAWA, Y. & HART, W. (1971). Adrenergic responses in the human eye. *J. Pharmac. exp. Ther.*, **179**, 47–55.

LANGHAM, M.E. & PALEWICZ, K. (1977). The pupillary, the intraocular pressure and the vasomotor responses to noradrenaline in rabbits. *J. Physiol.*, **267**, 339–355.

LANGHAM, M.E., SIMJEE, A. & JOSEPHS, S. (1973). The alpha and beta adrenergic responses to epinephrine in the rabbit eye. *Exp. Eye Res.*, **15**, 75–84.

MAPSTONE, R. (1970). Safe mydriasis. *Br. J. Opthal.*, **54**, 590–692.

PATERSON, G.D. & PATERSON, G. (1972). Drug therapy of glaucoma. *Br. J. Opthal.*, **56**, 288–294.

RUSHTON, A. (1979). Interaction of adrenaline and atenolol with respect to intraocular pressure. *Br. J. clin. Pharmac.*, **7**, 575–578.

TURNER, P. & SNEDDON, J.M. (1968). Alpha receptor blockade by thymoxamine in the human eye. *Clin. Pharmac. Ther.*, **9**, 45–49.

EFFECT OF FOOD ON THE BIOAVAILABILITY OF LABETALOL

In the literature there are reports in which food reduces, delays, increases, or has no effect at all on the bioavailability of drugs (Melander, 1978). Food has been found to increase the bioavailability of propranolol and metoprolol (Melander, Danielson, Schersten & Wahlin, 1977). In this study we have examined the influence of food on the bioavailability of the α- and β-adrenoceptor antagonist labetalol in healthy volunteers.

The subjects were four male and four female healthy volunteers aged between 21 and 45 (mean 28) years and weighing between 50 and 77 (mean 69) kg.

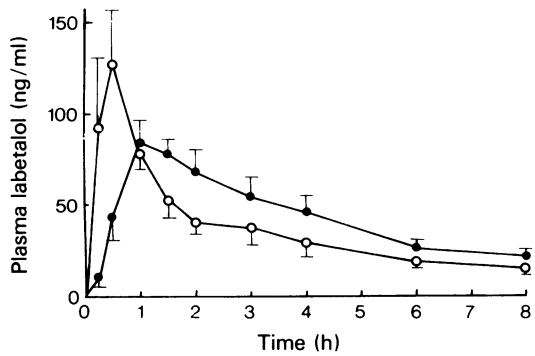

Figure 1 The mean ± s.e. mean plasma labetalol concentrations (ng/ml) in eight healthy volunteers after fasting (○) and food (●) intake.

They received 200 mg labetalol as a single coated tablet (Albetol®, Leiras) in a randomized cross-over study. On one occasion the tablet was taken after an overnight fast which was continued for 4 h after the ingestion of the tablet, and on another occasion separated by 7 days the tablet was taken together with a standardized meal of 2100 KJ (20% carbohydrate, 8% fat, 8% protein).

Venous blood samples (12 ml) were taken from a forearm vein at 0 h and then at 0.25, 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0 and 8.0 h after administration. Urine was collected for 32 h. The plasma and urine were frozen at −20°C until analysis.

The spectrophotofluorometric method of Martin, Hopkins & Bland (1976) was used to determine the concentrations of labetalol in the plasma. To measure the concentrations of conjugated labetalol in the urine the pH of an aliquot (100 µl) of the urine was adjusted to 5.2 with an acetate buffer. Urine was incubated with 25 µl of glusulase (Endo Laboratories) at 37°C for 17 h. Glusulase contains a mixture of enzymes including β-glucuronidase (3600 units/25 µl) and sulphatase (1200 units/25 µl). Free and conjugated concentrations of labetalol in the urine were measured by the same method as used in the plasma. Although other conjugates may be present, the amount of labetalol measured after glusulase incubation is designated here as 'total'.

The statistical significances of the differences were evaluated by paired *t*-test and by Wilcoxon rank test. The variation is given as the s.e. mean.

The concentrations of labetalol in plasma after the two dosage regimens are presented in Figure 1. The differences of the plasma levels after fasting and food intake did not reach a level of statistical difference at any time. The mean peak plasma concentrations were 134 ng/ml and 105 ng/ml after fasting and food intake, respectively ($0.05 < P < 0.1$). The mean times of peak plasma levels were 0.5 h and 1.3 h ($P < 0.05$), respectively. The elimination half-lives (3.73 and 3.95 h) did not differ. The respective AUCs up to 8 h were 291 and 348 ng ml^{-1} h ($P < 0.05$) (Table 1).

The 32 h excretions of unchanged labetalol amounted to 2.0 ± 0.3 mg and 2.7 ± 0.5 mg after fasting and food intake, respectively ($P < 0.05$). After glusulase-hydrolysis the respective amounts were 47.5 and 34.4 mg ($P < 0.01$). Thus, the unchanged fraction over the total in the urine was increased from 4.2 ± 0.7% after fasting to 7.9 ± 1.7% after food intake ($P < 0.01$) (Table 1).

The effect of labetalol on the blood pressure was slightly delayed after food intake. The maximal blood pressure responses were not changed but occurred at 1.5 h in fasting and at 2 h in nonfasting state. The heart rates were not significantly changed after the meal in comparison with the fasted condition.

In the present study the absorption of labetalol was delayed when taken with food. This kind of effect of food on the absorption of several drugs has been reported earlier (Melander, 1978; Welling, 1977). Food may decrease the intestinal absorption rate by slowing the gastric emptying. Similarly, anticholinergic drugs may slow down the absorption of drugs and metoclopramide, which increase the gastric emptying rate, may hasten absorption (e.g. nitrofurantoin, Männistö, 1978).

A certain degree of gastrointestinal motility is required for the absorption of substances. However,

Table 1 Pharmacokinetic parameters of labetalol in eight healthy volunteers, after an overnight's fast or with a breakfast (mean ± s.e. mean)

	Fasting	*Nonfasting*	*P*
Peak level (ng/ml)	134 ± 29	105 ± 8	NS
Time of peak (h)	0.53 ± 0.11	1.31 ± 0.19	0.05
Elimination half-life (h)	3.73 ± 0.46	3.95 ± 0.60	NS
AUC 0–8 h (ng ml^{-1} h)	291.3 ± 48.7	347.5 ± 35.2	0.05
32 h urinary excretion			
unconjugated (mg)	2.0 ± 0.3	2.7 ± 0.5	0.05
total (mg)	47.5 ± 4.4	34.4 ± 5.7	0.01

the bioavailability of poorly water soluble drugs may be reduced by increased motility (e.g. digoxin after metoclopramide, Manninen, Apajalahti, Melin & Karesoja, 1973) and *vice versa* (e.g. digoxin after propantheline, Manninen *et al.*, 1973). In the present study the bioavailability of labetalol was increased after food intake, as indicated by enhanced AUC. This might be due to changes in the gastric and intestinal motility, but as labetalol is readily water soluble, this would not be a satisfactory explanation for the increased bioavailability.

Food intake increases the splanchnic blood flow (Brandt, Castelman, Ruskin, Greenwald, Kelly & Jones, 1955). Increase in the liver blood flow increases the systemic availability of drugs with high hepatic extraction ratio (Gibaldi, Boyes & Feldman, 1971). By means of computer simulations McLean, McNamara, du Souich & Gibaldi, (1978) have demonstrated that the increase in the splanchnic blood flow has significant effects on the availability of drugs subjected to high first-pass metabolism. Such drugs are propranolol and metoprolol for which Melander *et al.* (1977) found increased bioavailability when taken with food. Changes in the first-pass metabolism or hepatic blood flow were possible mechanisms. Labetalol undergoes also an extensive first-pass metabolism (Martin *et al.*, 1976). In chronic liver disease the bioavailability of oral labetalol is markedly increased, presumably because of reduced first-pass metabolism, leading to an exaggerated blood pressure response (Homeida, Jackson & Roberts, 1978). The greater bioavailability of labetalol after food intake, as indicated in our study by increased AUC and an increased excretion of unconjugated labetalol into the urine, may be due to a reduction in the first-pass metabolism caused by a food-induced increase in the splanchnic blood flow.

The mean 32 h urinary excretion of unconjugated labetalol in the fasting subjects was 2.0 mg or 1% of the dose. This finding is comparable to that of Martin *et al.* (1976), who found 0 to 5% of the oral dose in the 24 h urine. After glusulase-hydrolysis the mean fluorometrically measurable amount of labetalol in the 32 h urine was 47.5 mg or about 24% of the dose. Glusulase hydrolyses glucuronide and sulphate conjugates. Thus, the 'total' excretion of labetalol in this study consists of unchanged labetalol and its glucuronide and sulphate conjugates. Martin *et al.* (1976) found the main metabolite to be an unidentified conjugate, which was not hydrolysable with β-glucuronidase or arylsulphatase. *O*-phenyl-glucuronide conjugate was excreted to a much lesser extent. In the present study the ratio of unchanged over total amount in the urine was increased from 4.2% to 7.9% when the drug was ingested with a meal. This suggests a decreased metabolism of labetalol due to food, and agrees with the suggested mechanism of the increased bioavailability, as discussed above.

R. MÄNTYLÄ, H. ALLONEN, J. KANTO, T. KLEIMOLA & R. SELLMAN

Leiras Research Laboratories, Box 415, SF-20101 Turku 10, Finland

Received August 14, 1979

References

BRANDT, J.L., CASTELMAN, L. RUSKIN, H.D. GREENWALD, J., KELLY, J.J. & JONES, A. (1955). The effect of oral protein and glucose feeding on splanchnic blood flow and oxygen utilization in normal and chirrotic subjects *J. clin. Invest.*, **34**, 1017–1025.

GIBALDI, M., BOYES, R.N. & FELDMAN, S. (1971). Influence of first-pass effect on availability of drugs on oral administration. *J. pharm. Sci.*, **60**, 1338–1340.

HOMEIDA, M., JACKSON, L. & ROBERTS, C.J.C. (1978). Decreased first-pass metabolism of labetalol in chronic liver disease. *Br. med. J.*, **2**, 1048–1050.

MANNINEN, V., APAJALAHTI, A., MELIN J. & KARESOJA, M. (1973). Altered absorption of digoxin in patients given propantheline and metoclopramide. *Lancet*, **i**, 398–399.

MÄNNISTÖ, P. (1978). The effect of crystal size, gastric content, and emptying rate on the absorption of nitrofurantoin in healthy human volunteers. *Int. J. clin. Pharmac.*, **16**, 223–228.

MARTIN, L.E., HOPKINS, R. & BLAND, R. (1976). Metabolism of labetalol by animals and man. *Br. J. clin. Pharmac.*, **3**, Suppl. 3, 695–710.

McLEAN, A.J., McNAMARA, P.J., DU SOUICH, P. GIBALDI, M. (1978). Food, splanchnic blood flow, and bioavailability of drugs subject to first-pass metabolism. *Clin. Pharmac. Ther.*, **24**, 5–10.

MELANDER, A. (1978). Influence of food on the bioavailability of drugs. *Clin. Pharmacokin.*, **3**, 337–351.

MELANDER, A., DANIELSON, K., SCHERSTEN B. & WAHLIN, E. (1977). Enhancement of the bioavailability of propranolol and metoprolol by food. *Clin. Pharmac. Ther.*, **22**, 108–112.

WELLING, P.G. (1977). Influence of food and diet on gastrointestinal drug absorption: A review. *J. Pharmacokin. Biopharm.*, **5**, 291–333.