eliminate the need for several back extraction steps. The only interfering peak was a plasma component having a retention time of 20 min. Therefore samples were injected every 15 min using a temperature programme to accelerate the elution of the plasma component.

The reported assay for diphenhydramine is of the required sensitivity and specificity for disposition studies. It should be applicable to other ethanolamines and will be used to investigate the disposition of this group of drugs in man.

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References

- ALBERT, K.S., SAKMAR, E., MORAIS, J. A., HALLMARK, M.R. & WAGNER, J.G. (1974). Pharmacokinetics of diphenhydramine in man. *Res. Comm. Chem. Path. Pharmac.*, 7 95-103.
- BILZER, W. & GUNDERT-REMY, U. (1973). Determination of nanogram quantities of diphenhydramine and orphenadrine in human plasma using gas liquid chromatography. *Eur. J. clin. pharmac.*, 6 268-270.
- GLAZKO, A.J., DILL, W.A., YOUNG, R.M., SMITH, T.C. & OGILVIE, R.I. (1974). Metabolic disposition of diphenhydramine. *Clin. Pharmac. Ther.*, 16, 1067-76.
- JANIK, A. (1975). What is the best measure of the detector signal? The peak area or the peak height? *J. Chromat. Sci.*, 13, 93-96.

BIOAVAILABILITY OF β -ADRENOCEPTOR BLOCKING DRUGS

The effect of various doses and adsorption rates on the area under the plasma concentration curve (AUC) and on the duration of action of oxprenolol was published by West, Kendall, Mitchard & Faragher (1976) in the June issue of the Journal. The article shows *inter alia* a direct proportionality between AUC and the dose of oxprenolol administered (80 and 160 mg) and the authors conclude that oxprenolol is subject to less first-pass elimination than for instance alprenolol, metoprolol and propranolol. This seems to be an irrelevant conclusion as the direct relationship between AUC and the dose only shows that the extent of bioavailability is independent of the dose within the dose range studied. It does not reveal, however, whether the fraction systemically available is small or large.

Preliminary estimates of this fraction can be obtained from the AUC values reported by West *et al.* (1976) by applying the method of Perrier, Gibaldi & Boyes (1973). This gives the single conventional oxprenolol tablet (80 mg) a mean extent of bioavailability of 75%. The method, however, overestimates the extent of bioavailability unless the dose is completely absorbed from the gastrointestinal canal and exclusively cleared by the liver. As regards oxprenolol the urinary recovery of orally administered radioactive doses has varied between 70-95% (Riess, Hürzeler & Raschdorf, 1974a) and < 5% is excreted via the kidneys in unchanged form (Riess, Brechbühler, Brunner, Imhof & Jack, 1974b). The ratio between the AUC from zero to infinite time of the

oral test dosage form and of intravenously administered drug, which is a method frequently used for the assessment of the extent of bioavailability, would therefore give a more accurate estimation of the extent of bioavailability of oxprenolol. This method has also recently been used by Mason & Winer (1976) who found that the systemically available fraction of orally administered oxprenolol varied between 24 and 60% in six healthy subjects. These values are higher than for alprenolol (Ablad, Borg, Johnsson, Regardh & Sölvell, 1974; Perrier *et al.*, 1973) and for propranolol (Shand & Rango, 1972) but in the same range as for metoprolol (Regardh, Borg, Johnsson, Johnsson & Sölvell, 1974; Johnsson, Regardh & Sölvell, 1975). Even for propranolol similar values have been reported by Shand, Nuckolls & Oates (1970) and by Chidsey, Morselli, Bianchetti, Morganti, Leonetti & Zanchetti (1975) whereas the extent of bioavailability of pindolol and practolol approaches 100 per cent (Gugler, Herold & Dengler, 1974; Bodem & Chidsey, 1973).

In discussing the lack of dose-dependent bioavailability of oxprenolol further confirmed by studies of Brunner, Imhof & Jack (1975) and by Mason & Winer (1976), West *et al.* (1976) mention alprenolol, metoprolol and propranolol as examples of β -adrenoceptor blocking drugs for which the AUC increases disproportionately with the dose administered due to a saturable 'first-pass' effect of the liver. Particularly a study on metoprolol by Johnsson *et al.* (1975) is referred to. This study, however, clearly demonstrated that the

saturable 'first-pass' mechanism had virtually no effect on the extent of bioavailability of therapeutic doses, i.e. > 50 mg. As this is not mentioned by West *et al.* (1976), the uninitiated reader of their article might get the impression that the dose-dependent first-pass effect of metoprolol might be a disadvantage of the drug and this is clearly not the case according to our findings (Johnsson *et al.*, 1975).

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References

- ABLAD, B., BORG, K.O., JOHNSSON, G., REGARDH, C.-G. & SOLVELL, L. (1974). Combined pharmacokinetic and pharmacodynamic studies on alprenolol and 4-hydroxy-alprenolol in man. *Life Sci.*, **14**, 693-704.
- BODEM, G. & CHIDSEY, C.A. (1973). Pharmacokinetic studies of practolol, a beta adrenergic antagonist in man. *Clin. Pharmac. Ther.*, **14**, 26-29.
- BRUNNER, L., IMHOF, P. & JACK, D. (1975). Relation between plasma concentrations and cardiovascular effects of oral oxprenolol in man. *Eur. J. clin. Pharmac.*, **8**, 3-9.
- CHIDSEY, C.A., MORSELLI, P., BIANCHETTI, G., MORGANTI, A., LEONETTI, G. & ZANCHETTI, A. (1975). Studies on the absorption and removal of propranolol in hypertensive patients during therapy. *Circulation*, **52**, 313-318.
- GUGLER, R., HEROLD, W. & DENGLER, H.J. (1974). Pharmacokinetics of pindolol in man. *Eur. J. clin. Pharmac.*, **7**, 17-24.
- JOHNSSON, G., REGARDH, C.-G. & SOLVELL, L. (1975). Combined pharmacokinetic and pharmacodynamic studies in man of the adrenergic β_1 -receptor antagonist metoprolol. *Acta Pharmac. Tox.*, **36**, Suppl. V, 31-44.
- MASON, W.D. & WINER, N. (1976). Pharmacokinetics of oxprenolol in normal subjects. *Clin. Pharmac. Ther.*, **19**, 111-112.
- PERRIER, D., GIBALDI, M. & BOYES, R.N. (1973). Prediction of systemic availability from plasma-level data after oral drug administration. *J. Pharm. Pharmac.*, **25**, 256-257.
- REGARDH, C.-G., BORG, K.O., JOHANSSON, R., JOHNSSON, G. & SOLVELL, L. (1974). Pharmacokinetic studies on the selective β_1 -receptor antagonist metoprolol in man. *J. Pharmacokin. Biopharm.*, **2**, 347-364.
- RIESS, W., HURZELER, H. & RASCHDORF, F. (1974a). The metabolites of oxprenolol (Trasicor) in man. *Xenobiotica*, **4**, 365-373.
- RIESS, W., BRECHBUHLER, S., BRUNNER, L., IMHOF, P.R. & JACK, D.B. (1974b). The metabolism of beta-blockers in relation to their pharmacokinetic and pharmacodynamic behaviour. In *Beta-blockers-present status and future prospects*. Ed. Schweizer, W. pp. 276-294. Berne: Hans Huber Publishers.
- SHAND, D.G., NUCKOLLS, E.M. & OATES, J.A. (1970). Plasma levels in adults with observations in four children. *Clin. Pharmac. Ther.*, **11**, 112-120.
- SHAND, D.G. & RANGNO, R.E. (1972). The disposition of propranolol. I. Elimination during oral absorption in man. *Pharmacology*, **7**, 159-168.
- WEST, M.J., KENDALL, M.J., MITCHARD, M. & FARAGHER, E.B. (1976). A comparison of slow release with conventional oxprenolol: Plasma concentrations and clinical effects. *Br. J. clin. Pharmac.*, **3**, 439-443.