YEO, T., THORNER, M.O., JONES, A., LOWRY, P.J. & BESSER, G.M. (1979). The effects of dopamine, bromocriptine, ergotriple and metoclopramide on

prolactin release from continuously perfused columns of isolated rat pituitary cells. *Clin. Endocrinol.*, **10** (in press).

ALTERED ELIMINATION OF DESMETHYLDIAZEPAM IN THE ELDERLY

Desmethyldiazepam (DD), the major metabolite of the widely used tranquilizer diazepam (D), is eliminated by hydroxylation to oxazepam (Schwartz, Koechlin, Postma, Palmer & Krol, 1965). After multiple dosing with D accumulation of DD occurs (Klotz, Antonin & Bieck, 1976). Since this metabolite possesses still considerable biological activity (Randall, Scheckel & Banzinger, 1965), DD will contribute to the clinical effects and untoward side effects of D.

Epidemiological data have indicated that central nervous side effects of D increased significantly with age (Boston Collaborative Surveillance Drug Program, 1973) and pharmacokinetic studies have demonstrated that the distribution of D was influenced by age (Klotz, Avant, Hoyumpa, Schenker & Wilkinson, 1975). In addition to these age-dependent alterations in the pharmacokinetics of D also age-dependent changes in the disposition of the biological active metabolite DD might contribute to the higher toxicity observed in older patients.

Therefore we compared in four young individuals (29–34 years) and in four elderly subjects (65–85 years) the disposition of DD following a single oral dose of 20 mg (Madar Notte, Ravizza, Milano). All subjects were male nonsmokers with normal liver function. Eight venous blood samples were drawn into heparinized tubes over 5 days. Concentrations of DD were assayed in the different plasma samples by a specific and sensitive gaschromatographic procedure (Klotz *et al.*, 1975). For comparison of the pharmacokinetic data the two-tailed Student's *t*-test was used with the minimal level of significance of $P < 0.05$.

In both groups maximal plasma concentrations between 150 and 250 ng/ml were achieved within 10 h following the single oral dose of 20 mg DD. Thereafter a monoexponential decline was observed (Figure 1). The slope of the regression line was much steeper in the younger individuals than in the older subjects. This resulted in a prolonged half-life ($T_{1/2}$) for the elderly. According to Westlake (1970) total plasma clearance (Cl) from the area under the curve and according to Gibaldi, Nagashima & Levy (1969) the apparent volume of distribution ($V_d\beta$) were calculated. All these parameters are compared in Table 1. The age-dependent prolongation in $T_{1/2}$ was

due to a reduced Cl in the elderly, while plasma protein binding (97.6%) and $V_d\beta$ did not differ significantly.

Our results indicate that in man hepatic clearance of DD is influenced by age. Other benzodiazepines, like diazepam (eliminated primarily by demethylation; Klotz *et al.*, 1975), oxazepam (eliminated by glucuronidation; Shull, Wilkinson, Johnson & Schenker, 1976) and lorazepam (eliminated also by glucuronidation; Kraus, Desmond, Marshall, Johnson, Schenker & Wilkinson, 1978) are cleared independent of age. However, chlordiazepoxide which is in part also eliminated by hydroxylation (like DD)

Figure 1 Plasma concentration-time profiles of desmethyldiazepam after a single oral dose of 20 mg in one elderly subject (a, 74 years, $T_{1/2} = 102$ h, $Cl = 6.1$ ml/min), and one young individual (b, 31 years, $T_{1/2} = 56.8$ h, $Cl = 13.7$ ml/min).

Table 1 Pharmacokinetic parameters (mean $\pm$ s.d.; $n=4$) of desmethyldiazepam in young and older male subjects

Parameter	Young (29–34 years)	Elderly (65–85 years)	P value
$T_{\frac{1}{2}}$ (h)	51 $\pm$ 6.2	151 $\pm$ 60	0.008
Cl (ml/min)	11.3 $\pm$ 3.1	4.3 $\pm$ 1.5	0.003
$V_d\beta$ (l/kg)	0.64 $\pm$ 0.17	0.85 $\pm$ 0.14	0.07

has been demonstrated to be cleared age-dependently (Shader, Greenblatt, Harmatz, Franke & Koch-Weser, 1977; Roberts, Wilkinson, Branch & Schenker, 1978). These studies with the benzodiazepines, which possess close chemical and biological activities, clearly demonstrate that there does not appear to be any consistent pattern of changes in the pharmacokinetics of drugs with age. Such inconsistency appears to be reflective of the complex situation of drug disposition and ageing in general and it requires the individual examination of each drug.

It seems, that the conjugation of drugs might be less effected by the ageing process than hydroxylation. With respect to the lowered Cl of DD in the elderly, this fact will lead in those patients to a more pronounced accumulation of DD following multiple dosing with D or DD, which could account, at least partially, for the increased incidence of side effects observed in aged individuals treated with diazepam.

This study was supported by the Robert Bosch Foundation, Stuttgart, W. Germany.

U. KLOTZ & P. MÜLLER-SEYDLITZ

Dr. Margarete Fischer-Bosch-Institut für Klinische Pharmakologie, Auerbachstr. 112, D-7000 Stuttgart 50, Germany

Received October 4, 1978

References

- BOSTON COLLABORATIVE SURVEILLANCE DRUG PROGRAM (1973). Clinical depression of the central nervous system due to diazepam and chlordiazepoxide in relation to cigarette smoking and age. *N. Engl. J. Med.*, **288**, 277–280.
- GIBALDI, M., NAGASHIMA, R. & LEVY, G. (1969). Relationship between drug concentration in plasma or serum and amount of drug in the body. *J. pharm. Sci.*, **58**, 193–197.
- KLOTZ, U., AVANT, G.R., HOYUMPA, A., SCHENKER, S. & WILKINSON, G.R. (1975). Effects of age and liver disease on the disposition and elimination of diazepam in adult man. *J. clin. Invest.*, **55**, 347–359.
- KLOTZ, U., ANTONIN, K.H. & BIECK, P.R. (1976). Comparison of the pharmacokinetics of diazepam after single and subchronic doses. *Eur. J. clin. Pharmac.*, **10**, 121–126.
- KRAUS, J.W., DESMOND, P.V., MARSHALL, J.P., JOHNSON, R.F., SCHENKER, S. & WILKINSON, G.R. (1978). The effects of aging and liver disease on the disposition of lorazepam in man. *Clin. Pharmac. Ther.*, **24**, 411–419.
- RANDALL, L.O., SCHECKEL, C.L. & BANZINGER, R.F. (1965). Pharmacology of the metabolites of chlordiazepoxide and diazepam. *Curr. Ther. Res.*, **7**, 590–606.
- ROBERTS, R.K., WILKINSON, G.R., BRANCH, R.A. & SCHENKER, S. (1978). The effect of age and parenchymal liver disease on the disposition and elimination of chlordiazepoxide. *Gastroenterology*, **75**, 479–485.
- SCHWARTZ, M.A., KOEHLIN, B.A., POSTMA, E., PALMER, S. & KROL, G. (1965). Metabolism of diazepam in rat, dog, and man. *J. Pharmac. exp. Ther.*, **149**, 423–435.
- SHADER, R.I., GREENBLATT, D.J., HARMATZ, J.S., FRANKE, K. & KOCH-WESER, J. (1977). Absorption and disposition of chlordiazepoxide in young and elderly male volunteers. *J. clin. Pharmac.*, **17**, 709–718.
- SHULL, H.J., WILKINSON, G.R., JOHNSON, R.F. & SCHENKER, S. (1976). Normal elimination of oxazepam in acute viral hepatitis and cirrhosis. *Ann. intern. Med.*, **84**, 420–425.
- WESTLAKE, W.J. (1970). Time integral of drug concentration in the central (plasma) compartment. *J. pharm. Sci.*, **59**, 722–723.

THE BIOTRANSFORMATION OF CICLAZINDOL IN MAN

Ciclazindol, Wy 23409 (Figure 1) is currently under investigation in the clinic as a potential antidepressant. The compound is derived from a novel tetrahydropyrimidoindole nucleus and the metabolism of such structures has not previously been reported. This communication describes studies on the biotransformation of ciclazindol in human volunteers.

The volunteers had received [$2-^{14}\text{C}$] ciclazindol as part of a clinical pharmacokinetic study, the results of which have already been published (Swaisland, Franklin, Southgate & Coleman, 1977).

Metabolites were extracted from the first-day urines using Amberlite XAD-2 resin. Chromatography was carried out using silica gel thin layers (Kontes