Pharmacokinetics of dextropropoxyphene and nordextropropoxyphene in young and elderly volunteers after single and multiple dextropropoxyphene dosage

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1 The pharmacokinetics of dextropropoxyphene (D) and nordextropropoxyphene (ND) have been studied in 12 healthy young (21–28 years) and 12 healthy elderly (70–79 years) male and female subjects. Each received 65 mg D and plasma D and ND concentrations were measured by h.p.l.c. with electrochemical detection for up to 7 days and again after 65 mg D, 3 times daily for 1 week.

2 There were no significant differences in median D and ND half-life, AUC, $C_{\max}$ and $t_{\max}$ between the male and female subjects in either group. Within the groups the mean D half-life (h) was longer in the young after multiple dosing (mean $\pm$ s.d.: 13.2 ± 5.2 and 23.7 ± 11.3 , $P < 0.05$, paired t -test) but there were no other significant differences.

3 Between the groups, the median single and multiple dose D and ND half-lives were all significantly longer ($P < 0.02$) and the median D AUC for both single and multiple doses was significantly higher ($P < 0.01$ and $P < 0.05$, respectively, Mann-Whitney U-tests) in the elderly.

4 There was no relation between multiple dose $C_{\max}$ and other parameters such as single dose D half-life. However, across the groups D and ND half-lives after both single and multiple dosage correlated significantly with estimated creatinine clearance, the correlation being strongest with ND ($r = -0.76$ and -0.84 , respectively).

Keywords dextropropoxyphene nordextropropoxyphene pharmacokinetics elderly volunteers

Introduction

Dextropropoxyphene (D) is a narcotic analgesic structurally related to methadone and the hydrochloride salt is widely used, often together with paracetamol (acetaminophen) (Co-Proxamol, equivalent to Dolene[®] AP-65), for the relief of mild to moderate pain. D is highly toxic in overdose especially when taken with alcohol and, although the use of blister packaging may have reduced the number of fatal cases, at least in the UK, this must be weighed against any therapeutic benefit (Lawson & Northridge, 1987). Nevertheless, D has little potential for abuse

(Roberts *et al.*, 1986), side-effects are few and patients claim to prefer it to other drugs such as dihydrocodeine, possibly because it does not cause constipation or perhaps because of a mild euphoriant effect (Editorial, 1984).

The pharmacokinetics of D have not been studied in detail in the elderly although preliminary findings suggested that the elimination half-lives of both D and its principal plasma metabolite, nordextropropoxyphene (ND) (ranges 24.0–50.6 and 25.1–76.3 h, respectively) were prolonged in elderly hospital in-patients

after 1 week of D administration (65 mg 3 times daily; Crome *et al.*, 1984). To compare the pharmacokinetics of D and its metabolite in healthy young and elderly male and female subjects, plasma D and ND concentrations were measured for up to 7 days after a single oral dose of D (65 mg) and again after 1 week of D administration (3×65 mg daily).

Methods

Subjects and study design

Twelve healthy adult (six male, six female, aged 21–28 years (median 26 years), weight 62–74 kg (median 66 kg)) and 12 healthy elderly (six male, six female, aged 70–79 years (median 75 years), weight 56–79 kg (median 69 kg)) volunteers were studied. No subject was taking concomitant drug therapy or had received such therapy for at least 1 month prior to the study. The protocol was approved by the Bromley Health Authority ethics committee. Each subject gave informed written consent to the study and was asked to report any side-effects.

Each subject received two tablets of Co-Proxamol (65 mg D hydrochloride) at 09.00 h on day 1 and blood samples (10 ml) were taken into lithium heparin at 0, 1, 2, 3, 5, 7, 9, 12, 24, 36, 48, 72, 96 and 168 h thereafter. Each subject then received 2 tablets of Co-Proxamol 3 times daily for 1 week. Blood samples (10 ml) were obtained at 09.00 h on days 9, 11, 13 and 14 and at 1, 2, 3, 5, 7, 9, 12, 24, 36, 48, 72, 96 and 168 h after the last dose at 09.00 h on day 15. Plasma was separated by centrifugation as soon as possible after sample collection and stored at -20°C until required. Creatinine clearance was estimated from the age, weight and plasma creatinine concentration (Autoanalyser method) on Day 1 (Cockcroft & Gault, 1976).

Dextropropoxyphene and nordextropropoxyphene assay

Plasma D and ND were measured by h.p.l.c. with electrochemical detection using a modification of the method of Flanagan *et al.* (1984). In summary, sample/standard (400 μl ; 50 μl higher concentrations), internal standard solution (2 mg l^{-1} viloxazine in 2 mol l^{-1} Tris buffer, pH 9.6) (50 μl) and methyl tert-butyl ether (200 μl) were vortex-mixed (30 s) and centrifuged (9950 g, 2 min). A 100 μl portion of the extract was analysed on a 250 $\times$ 5 mm I.D. Spherisorb S5W silica column (Hichrom) using methanolic ammonium perchlorate (10 mmol l^{-1} , apparent

pH 6.7) as eluent (flow-rate 2 ml min^{-1} ; ACS Series 300 pump). Detection was with a glassy carbon working electrode (+1.2 V against Ag/AgCl) and peak heights were measured using a recording integrator (Hewlett-Packard 3392A). Calibration was by analysis of equine serum solutions (Gibco) of both analytes (5, 10, 20, 50, 100 and 200 $\mu\text{g l}^{-1}$; higher concentrations 0.1, 0.2, 0.5, 1.0 and 2.0 mg l^{-1}) stored at -20°C when not in use.

Calculations

Pharmacokinetic analysis was undertaken using the STRIPE interactive curve-fitting procedure (Johnston & Woollard, 1983). Within subject differences after single and multiple dosage were compared using a paired *t*-test and differences between the male and female and between the young and elderly subjects were compared using the Mann-Whitney U-test.

Results

There were no significant differences in median half-lives between the male and female subjects in either group (Figure 1). Within the groups the mean D half-life (h) was longer in the young after multiple dosage (mean $\pm$ s.d.: 13.2 ± 5.2 and 23.7 ± 11.3 , $P < 0.05$; Figure 1) but there were no other significant differences. D was measured for at least two–three times the apparent half-life in most cases and re-calculation of the multiple dose half-lives using only the time points from the single dose plots made little difference to the results. Between the groups, the median single and multiple dose D and ND half-lives (Table 1) were all significantly longer in the elderly ($P < 0.02$). Representative data from individual subjects are shown in Figure 2.

There were no significant differences in the median areas under the curve (AUC), C_{max} and t_{max} between the male and female subjects in either group. Similarly, there was no significant difference in the mean AUC of D within the young and elderly groups despite the increased mean multiple-dose half-life in the young. The median maximum concentrations (C_{max}) for both D and ND were increased after multiple dosing although the time to reach C_{max} (t_{max}) was unchanged. There were no significant relationships between multiple-dose D and ND C_{max} and other parameters such as single-dose D half-life or C_{max} .

Between the groups the median D AUC for both single and multiple doses was significantly higher in the elderly ($P < 0.01$ and $P < 0.05$,

Figure 1 a) Dextropropoxyphene and b) nordextropropoxyphene half-lives in young and elderly male and female subjects ($n = 24$) after single (65 mg dextropropoxyphene) and multiple (65 mg dextropropoxyphene 3 times daily for 1 week) oral dosage.

respectively; (Table 1)). After multiple dosing the median $C_{\max}$ values of both D and ND were higher in the elderly ($P < 0.01$) (Table 1) although there were no significant differences in median $t_{\max}$. When the young and elderly groups were combined there were significant correlations between estimated creatinine clearance and the half-lives ($\log_{10}$ transformation used to normalise the data) after single and multiple dosage (D: $r = -0.48$ and -0.54 , $P < 0.05$; ND: $r = -0.76$ and -0.84 , $P < 0.001$) and also with D AUC ($\log_{10}$) after single dosage ($r = -0.59$, $P < 0.01$).

With ND half-life the gradients of the regression lines after single and multiple dosage were virtually identical (Figure 3).

No adverse reactions were reported in either group.

Discussion

D is rapidly absorbed from the gastro-intestinal tract, the hydrochloride more quickly than the

Figure 2 Dextropropoxyphene (D) and nordextropropoxyphene (ND) plasma concentration-time plots in individual (a) young and (b) elderly male subjects after single and multiple dextropropoxyphene dosage (cf. Figure 1).

napsylate (Nickander *et al.*, 1984). Bioavailability is only about 40% because of hepatic metabolism to ND, a compound with very weak opioid activity but, in animals at least, similar local anaesthetic (membrane stabilising) properties to those of D (Nickander *et al.*, 1984). The single-dose elimination half-life of D was said to be from 2–8 h (Wolen *et al.*, 1971; Wagner *et al.*, 1972; Verebly & Inturrisi, 1974) but studies using more sensitive assays and longer sampling times have given values of 8–24 h (D) and 18–29 h (ND) in healthy adults (Wolen *et al.*, 1975; Gram *et al.*, 1979). It has also been suggested that the half-life of D increases with dose (Perrier & Gibaldi, 1972; Schou *et al.*, 1978). Indeed,

Inturrisi *et al.* (1982) reported increases in D and ND half-lives from 3.3 to 11.8 and from 6.1 to 39.2 h, respectively, after 3 days D, 65 or 130 mg three times daily, but only two subjects were studied and blood samples were only taken up to 10 h post-dose.

In the present study D was measured for much longer after multiple than after single dosage in the young subjects (Figure 2) and this provides a possible explanation for the difference in mean D half-life observed. However, this explanation seems unlikely since D was measured for two–three times the half-life in most cases and recalculation of the multiple dose half-lives using the time points as used in the single dose half-life

Table 1 Dextropropoxyphene and nordextropropoxyphene half-lives, maximum concentration ($C_{\max}$), time to reach $C_{\max}$ ($t_{\max}$) and dextropropoxyphene AUC (zero to infinity, single dose; zero to 8 h, multiple dose) after single and multiple dextropropoxyphene dosage (median, range)

	<i>Dextropropoxyphene</i>		<i>Nordextropropoxyphene</i>	
	<i>Single dose</i>	<i>Multiple dose</i>	<i>Single dose</i>	<i>Multiple dose</i>
<i>Half-life (h)</i>				
Young	13.0 (6.4–26.4)	22.0 (9.8–49.3)	22.2 (16.3–28.0)	22.1 (15.6–34.0)
Elderly	35.4 (1.9–86.8)	36.8 (17.4–110)	40.9 (28.4–106)	41.8 (32.9–62.8)
<i>C_{max} (µg l⁻¹)</i>				
Young	59 (26–90)	116 (51–214)	195 (151–229)	673 (477–839)
Elderly	156 (39–366)	239 (151–509)	193 (112–283)	1100 (775–1500)
<i>t_{max} (h)</i>				
Young	2.0 (2.0–3.0)	2.0 (2.0–5.0)	2.0 (2.0–5.0)	2.0 (2.0–12)
Elderly	1.5 (1.0–5.0)	2.0 (1.0–3.0)	2.0 (2.0–9.0)	2.8 (2.0–7.0)
<i>AUC (µg l⁻¹ h)</i>				
Young	509 (217–1309)	731 (163–1420)		
Elderly	1402 (177–3976)	1155 (467–2664)

Figure 3 Nordextropropoxyphene half-lives in young and elderly subjects after single and multiple dextropropoxyphene dosage in relation to estimated creatinine clearance.

calculation had little effect. It is possible that continued diffusion into tissues may have contributed to the decrease in plasma concentration observed after single D dosage in the young subjects.

The elimination half-lives of many drugs such as phenazone (antipyrine), clobazam, diazepam and flurazepam which have relatively low hepatic extraction ratios and undergo oxidative metabolism are prolonged in the elderly, often more so in males than in females (Greenblatt *et al.*, 1986). Some data suggest that *N*-demethylation is impaired to a greater extent than aromatic hydroxylation in the elderly (Antal *et al.*, 1982; Dawling, 1982; Abernethy *et al.*, 1985). Lowered clearance of some high extraction ratio drugs such as lignocaine (Abernethy & Greenblatt, 1983), imipramine and desipramine (Abernethy *et al.*, 1985), triazolam (Greenblatt *et al.*, 1983) and midazolam (Greenblatt *et al.*, 1984) has also been described.

It is well known that renal function decreases with increasing age and that the clearance of renally-excreted drugs (lithium, digoxin) is also

reduced in the elderly (Greenblatt *et al.*, 1986). ND is largely excreted by the kidney (Gram *et al.*, 1979) and the results show that the clearance of this compound is also reduced in the elderly. The strong correlation between estimated creatinine clearance and ND half-life suggests an association with renal function although this result is complicated by the underlying effect of age (Figure 3).

Thus, as with many other compounds which undergo hepatic oxidation and renal elimination, respectively, D and ND often have prolonged half-lives in the elderly. We gave Co-Proxamol (paracetamol 325 mg and D hydrochloride 32.5 mg) since this mixture was easily available and is the form in which dextropropoxyphene is prescribed most frequently, at least in the UK. The results clearly demonstrate accumulation of ND and, to a lesser extent, of D itself in both young and elderly subjects. However, the implications of this finding for therapy remain unclear since no side effects were reported in this study.

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References

- Abernethy, D. R. & Greenblatt, D. J. (1983). Impairment of lidocaine clearance in elderly male subjects. *J. cardiovasc. Pharmac.*, **5**, 1093–1096.
- Abernethy, D. R., Greenblatt, D. J. & Shader, R. I. (1985). Imipramine and desipramine disposition in the elderly. *J. Pharmac. exp. Ther.*, **232**, 183–188.
- Antal, E. J., Kramer, P. A., Merick, S. A., Chapron, D. J. & Lawson, I. R. (1981). Theophylline pharmacokinetics in advanced age. *Br. J. clin. Pharmac.*, **12**, 637–645.
- Cockcroft, D. & Gault, M. K. (1976). Prediction of creatinine clearance from serum creatinine. *Nephron*, **16**, 31–41.
- Crome, P., Gain, R., Ghurye, R. & Flanagan, R. J. (1984). Pharmacokinetics of dextropropoxyphene and nordextropropoxyphene in elderly hospital patients after single and multiple doses of Distalgesic. Preliminary analysis of results. *Human Tox.*, **3**, 41S–48S.
- Dawling, S. (1982). Monitoring of tricyclic antidepressant therapy. *Clin. Biochem.*, **15**, 56–61.
- Editorial (1984). Distalgesic: safe and effective? *Lancet*, **ii**, 616.
- Flanagan, R. J., Jane, I. & Ramsey, J. D. (1984). Measurement of dextropropoxyphene and nordextropropoxyphene in biological fluids. *Human Tox.*, **3**, 103S–114S.
- Gram, L. F., Schou, J., Way, W. L., Helberg, J. & Bodin, N. O. (1979). d-Propoxyphene kinetics after single oral and intravenous doses in man. *Clin. Pharmac. Ther.*, **26**, 473–482.
- Greenblatt, D. J., Abernethy, D. R., Locniskar, A., Harmatz, J. S., Limjuco, R. A. & Shader, R. I. (1984). Effect of age, gender and obesity on midazolam kinetics. *Anesthesiology*, **61**, 27–35.
- Greenblatt, D. J., Abernethy, D. R. & Shader, R. I. (1986). Pharmacokinetic aspects of drug therapy in the elderly. *Ther. Drug Monit.*, **8**, 249–255.
- Greenblatt, D. J., Divoll, M., Abernethy, D. R., Moschitto, L. J., Smith, R. B. & Shader, R. I. (1983). Reduced clearance of triazolam in old age: relation to antipyrine oxidizing capacity. *Br. J. clin. Pharmac.*, **15**, 303–309.
- Inturrisi, C. E., Colburn, W. A., Verebey, K., Dayton, H. E., Woody, G. E. & O'Brien, C. P. (1982). Propoxyphene and norpropoxyphene kinetics after single and repeated doses of propoxyphene. *Clin. Pharmac. Ther.*, **31**, 157–167.
- Johnston, A. & Woollard, R. C. (1983). An interactive computer program for the analysis of drug pharmacokinetics. *J. pharmac. Methods*, **9**, 193–199.
- Lawson, A. A. H. & Northridge, D. B. (1987). Dextropropoxyphene overdose. Epidemiology, clinical presentation and management. *Med. Tox.*, **2**, 430–444.
- Nickander, R. C., Emmerson, J. L., Hynes, M. D., Steinberg, M. I. & Sullivan, H. R. (1984). Pharmacologic and toxic effects in animals of dextropropoxyphene and its major metabolite, norpropoxyphene: a review. *Human Tox.*, **3**, 13S–36S.
- Perrier, D. & Gibaldi, M. (1972). Influence of first-pass effect on the systemic availability of propoxyphene. *J. clin. Pharmac.*, **12**, 449–452.
- Roberts, I., Flanagan, R. J., Strang, J. & Prescott, L. F. (1986). Toxicological studies in a Distalgesic addict. *Human Tox.*, **5**, 207–210.

- Schou, J., Angelo, H., Dam, W., Jensen, K. & Christensen, J. M. (1978). Pharmacokinetics of dextropropoxyphene in acute poisoning. *Arch. Tox.*, **1** (suppl.), 343–346.
- Verebely, K. & Inturrisi, C. E. (1974). Disposition of propoxyphene and norpropoxyphene in man after single oral dose. *Clin. Pharmac. Ther.*, **15**, 302–309.
- Wagner, J. G., Welling, P. G. & Sedman, A. J. (1972). Plasma concentration of propoxyphene in man – pharmacokinetics. *Int. J. clin. Pharmac.*, **5**, 381–388.
- Wolen, R. L., Gruber, C. M., Kiplinger, G. F. & Scholz, N. E. (1971). Concentration of propoxyphene in human plasma following oral, intramuscular and intravenous administration. *Tox. appl. Pharmac.*, **19**, 480–492.
- Wolen, R. L., Ziege, E. A. & Gruber, C. M. (1975). Determination of propoxyphene and norpropoxyphene by chemical ionization mass fragmentography. *Clin. Pharmac. Ther.*, **17**, 15–20.

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