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Pharmacokinetics and pharmacodynamics of oxazepam and metabolism of paracetamol in severe hypothyroidism

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1 The effect of severe hypothyroidism on the pharmacokinetics and pharmacodynamics of oxazepam 15 mg given orally ($n = 10$) and the metabolism of paracetamol 750 mg given intravenously ($n = 8$) was investigated before and after treatment with levothyroxine.

2 The median total and unbound clearance of oxazepam increased significantly during the study period from 0.78 ml min^{-1} kg^{-1} (0.40–1.25) to 1.22 ml min^{-1} kg^{-1} (0.66–1.94) and from 9.3 ml min^{-1} kg^{-1} (5.2–14.2) to 15.9 ml min^{-1} kg^{-1} (7.8–21.8), respectively ($P < 0.01$).

3 The elimination half-life of oxazepam was prolonged by hypothyroidism to a median (range) value of 9.3 h (5.4–21.9) compared with 7.5 h (4.8–10.5) in the euthyroid state ($P < 0.05$).

4 Hypothyroidism did not affect the protein binding of oxazepam; median values of the free percentage being 8.2% as compared with 7.7% when euthyroid.

5 The median (range) clearance of paracetamol under hypothyroid conditions was 3.12 ml min^{-1} kg^{-1} (1.64–4.40) and 4.70 ml min^{-1} kg^{-1} (3.18–5.70) following replacement therapy ($P < 0.01$). This increase was associated with a comparable increase in the partial clearance to the glucuronide metabolite: 1.86 ml min^{-1} kg^{-1} to 2.70 ml min^{-1} kg^{-1}.

6 Hypothyroidism was associated with decreased performance in a finger tapping test that was exacerbated by oxazepam. When the patients were euthyroid oxazepam did not produce any effect.

Keywords oxazepam paracetamol hypothyroidism pharmacokinetics pharmacodynamics

Introduction

Several studies have evaluated the influence of thyroid disease on the disposition of drugs that are eliminated by phase I oxidative biotransformation (Eichelbaum, 1976; Shenfield, 1981). The results suggest an increased drug clearance in the hyperthyroid state, whereas hypothyroidism may have the opposite effect. However, the existing data are equivocal. Glucuronidation, a major phase II detoxification pathway for both xenobiotic and endogenous compounds, has been less well investigated. A decrease in paracetamol elimination, although not significant, was found in hypothyroidism, but the study was done with only four patients and no attempt was made to estimate partial metabolic clearances (Forfar *et al.*, 1980). Oxazepam tended to

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be eliminated at a slower rate in more severely hypothyroid patients (Scott *et al.*, 1984).

The present study was performed to examine further the glucuronidation pathway in hypothyroidism. We, therefore, investigated the disposition of oxazepam, a benzodiazepine exclusively metabolised by glucuronic acid conjugation, and paracetamol, which is eliminated by conjugation with both glucuronic acid and sulphate, in severely affected hypothyroid patients. At the same time the effect of hypothyroidism on the pharmacodynamics of oxazepam was investigated.

Methods

Study group

Eight female and two male outpatients participated in the study. They ranged in age from 32 to 73 years. Hypothyroidism was diagnosed by laboratory tests and clinical manifestation. None of the patients had diabetes mellitus or known liver disease. They reported adherence to their usual diet until admission. Three were smokers and none had a daily intake of alcohol. One subject was treated with terbutaline and another with frusemide throughout the whole study. All patients were treated with levothyroxine and became clinically euthyroid within 3 to 6 months. Clinical and laboratory characteristics of all patients in the hypo- and euthyroid state are shown in Table 1. Routine biochemical liver tests, albumin, α_1-acid glycoprotein, and creatinine were within normal limits before and after treatment with levothyroxine. Cholesterol was elevated in all patients but normalized during the study. The study protocol was approved by the Ethics Committee of Copenhagen County.

Pharmacokinetic study

Oxazepam After an overnight fast oxazepam kinetics were determined following ingestion of 15 mg of the drug in tablet form (Serepax; Ferrosan). A light meal was allowed 2 h after the dose. Venous blood (10 ml) was collected in heparinized tubes before and at 20, 40, 60, 90 min and 2, 3, 4, 6, 8, 10, 12, 16 and 24 h after the administration of oxazepam. Plasma samples were stored at −20° C until analysis by the h.p.l.c. method of Sonne *et al.* (1988). Plasma protein binding was measured by equilibrium dialysis (Sonne *et al.*, 1988).

Evaluation of oxazepam kinetics was repeated in all patients after a mean interval of 12 months (10–17:range), at which time the euthyroid state was confirmed by the establishment of normal TSH levels in all patients.

Paracetamol Simultaneously with the administration of oxazepam the patients were given paracetamol 750 mg, diluted in 75 ml distilled water, intravenously over a 5 min period. From an indwelling cannula in the contralateral arm 10 ml venous blood samples were collected in heparinized tubes before and at 20, 40, 60, 90 min and 2, 4 and 6 h after the dose. Plasma was separated and stored at −20° C until analysis. Urine was collected for 24 h after paracetamol administration for measurement of parent drug and metabolites. Plasma paracetamol and paracetamol and metabolites in urine were

Table 1 Clinical and biochemical characteristics of 10 hypothyroid patients before (1) and after (2) treatment with levothyroxine

	1	*2*
Age (years)	53 (32–73)	
Weight (kg)	76 (52–93)	72 (48–89)
S-thyroxine (nmol l^{-1}) (56–129)*	28 (24–45)	109 (86–120)
S-triiodothyronine (nmol l^{-1}) (1.6–2.8)*	0.8 (< 0.6–1.3)	1.9 (1.2–2.3)
Resin-T_3-uptake (arbitrary units) (0.80–1.25)*	0.77 (0.66–0.81)	1.05 (0.84–1.28)
TSH (mu l^{-1}) (0.4–3.7)*	165 (38–200)	1.5 (0.2–4.4)

Values are median and range
* Normal range

measured by h.p.l.c. (Poulsen *et al.*, 1985). Two patients did not complete the paracetamol study. The metabolism of paracetamol was reinvestigated simultaneously with the repeated oxazepam study when the patients had become clinically and biochemically euthyroid.

Pharmacodynamic study

To investigate the degree of impaired psychomotor performance due to the hypothyroid condition and a possible further deterioration following the administration of oxazepam a finger tapping test was employed. Before the oxazepam dose the patients were asked to press a button repeatedly as fast as possible during a period of 30 s. A mean of five test results was calculated and used as a baseline value. The test was repeated 3 h after the oxazepam dose. The degree of sedation expressed as sleeping time was also registered. The time at which the performance test was done was chosen according to the predicted time of peak plasma drug concentration (Sonne *et al.*, 1988). The pharmacodynamic study was repeated together with the kinetic study when the patients had become euthyroid. Since all patients were outpatients it was not possible to conduct the performance test in a more controlled manner.

Pharmacokinetic calculations

The ESTRIP programme was used to analyse the plasma oxazepam and paracetamol concentration data (Brown *et al.*, 1978). The area under the plasma concentration *vs* time curve (AUC) of oxazepam and paracetamol was calculated according to the linear trapezoidal rule with extrapolation to infinity. Total clearance (CL) of oxazepam and paracetamol was calculated as the ratio of the dose and the AUC. The absorption of oral oxazepam was considered complete (Sonne *et al.*, 1988) and the elimination half-life and the apparent volume of distribution (V) were calculated from the slope of the terminal log drug concentration *vs* time curve and the CL. Unbound clearance of oxazepam (CL_u) was calculated by dividing CL by the unbound fraction of oxazepam.

The V_{ss} of paracetamol was calculated on the basis of a two compartment model (Gibaldi & Perrier, 1975). The metabolic clearance to the glucuronide (CL_{GLU}), sulphate (CL_{SUL}) and the renal clearance (CL_R) of paracetamol were calculated by multiplying total clearance by the fractional urinary recovery of each conjugate or parent drug. Partial clearance down the glutathione conjugation pathway (CL_{GSH}) was estimated from the urinary recovery of the sulphur containing paracetamol metabolites (cysteine-P + mercapturate-P) multiplied by the total drug clearance.

Statistics

The Wilcoxon signed rank sum test for paired data was used for statistical analysis (Wulff & Schlichting, 1988). P values less than 0.05 were considered significant.

Results

The laboratory investigations in all patients revealed a relatively severe hypothyroid condition. All but one of the subjects lost weight during the treatment with levothyroxine (4 kg, 0–13; median and range; $P < 0.05$). Apart from marked sedation following oxazepam, when the subjects were hypothyroid, no adverse drug effects were observed during the study.

Oxazepam study

The kinetic characteristics of oxazepam before and after replacement therapy are summarised in Table 2. Peak plasma oxazepam concentrations tended to be higher and time to peak longer before treatment, although the difference did not reach statistical significance. Elimination proceeded at a slower rate when hypothyroid with a median $t_{½}$ value of 9.3 h compared with 7.5 h during therapy (median difference = 2.35 h (−0.05–8.5; 95% confidence limits)). The volume of distribution (V) was constant during the study. Total clearance increased significantly during treatment from 0.78 ml min^{-1} kg^{-1} to 1.22 ml min^{-1} kg^{-1} (median difference = 0.29 ml min^{-1} kg^{-1}, (0.17–0.69)). The free fraction of oxazepam in plasma was lower on the second study day, but not significantly so. The unbound clearance of oxazepam increased from 9.3 ml min^{-1} kg^{-1} to 15.9 ml min^{-1} kg^{-1} after treatment (median difference = 3.35 ml min^{-1} kg^{-1} (2.5–10.6)).

Paracetamol study

The clearance of paracetamol increased significantly following restoration of the euthyroid state (Table 3) from a median value of 3.12 ml min^{-1} kg^{-1} to 4.70 ml min^{-1} kg^{-1} on the second study day (median difference = 1.05 ml min^{-1} kg^{-1} (0.31–2.52; 95% confidence limits.) A similar increase in the partial clearance to the glucuronide (CL_{GLU}) metabolite was found,

Table 2 Oxazepam kinetics in 10 hypothyroid patients before (1) and after (2) treatment with levothyroxine

	1	*2*	*Median difference (95% CI)*
Peak plasma drug concentration (ng ml^{-1})	313 (162–570)	262 (142–554)	NS
Time to peak (h)	3.0 (1.0–6.0)	2.8 (1.0–4.1)	NS
Terminal elimination half-life (h)	9.3	7.5	2.35* (−0.5–8.5)
Clearance (ml min^{-1} kg^{-1})	0.77 (0.41–1.25)	1.22 (0.66–1.94)	0.29** (0.17–0.69)
Unbound drug (%)	8.2 (6.6–9.9)	7.7 (6.0–11.4)	NS
Unbound clearance (ml min^{-1} kg^{-1})	9.3 (5.2–14.2)	13.7 (7.8–19.7)	3.35** (2.5–10.6)
V (l kg^{-1})	0.62 (0.46–1.03)	0.64 (0.48–1.13)	NS

Values are median and range
* $P < 0.05$ ** $P < 0.01$, NS: not significant

Table 3 Paracetamol kinetics in 10 hypothyroid patients before (1) and after (2) levothyroxine

	1	*2*	*Median difference (95% CI)*
Terminal elimination half-life (h)	3.3 (2.4–4.7)	2.9 (1.5–3.0)	0.6* (−0.3–2.0)
V_{ss} (l kg^{-1})	0.82 (0.09–1.09)	0.79 (0.23–0.92)	NS
Clearance (ml min^{-1} kg^{-1})	3.12 (1.64–4.40)	4.70 (3.25–5.70)	1.05** (0.31–2.52)
CL_{GLU} (ml min^{-1} kg^{-1})	1.68 (0.98–2.93)	2.70 (1.25–3.19)	0.68* (0.0–1.50)
CL_{SUL} (ml min^{-1} kg^{-1})	1.10 (0.39–1.53)	1.25 (0.73–2.20)	NS
CL_{GSH} (ml min^{-1} kg^{-1})	0.29 (0.08–0.37)	0.31 (0.15–0.57)	NS
CL_R (ml min^{-1} kg^{-1})	0.34 (0.05–0.44)	0.45 (0.11–0.54)	0.11* (0.0–0.31)

Values are median and range
* $P < 0.05$, ** $P < 0.01$, NS: not significant

from 1.86 ml min^{-1} kg^{-1} to 2.70 ml min^{-1} kg^{-1} (median difference = 0.68 ml min^{-1} kg^{-1} (0.00–1.50)). These changes were accompanied by a significant decrease in elimination half-life from 3.3 h to 2.9 ($P < 0.05$). The renal clearance of paracetamol (CL_R) increased slightly but significantly from 0.34 ml min^{-1} kg^{-1} to 0.45 ml min^{-1} kg^{-1}. No significant differences could be demonstrated in the volume of distribution (V_{ss}) or the clearances to the sulphate or GSH-metabolites between the two study days (Table 3).

Pharmacodynamic study

The hypothyroid patients slept 0.5 to 3 h following the oxazepam dose. Only one subject did not fall asleep. When euthyroid only three patients

Table 4 Results of a finger tapping test in eight patients under hypothyroid and euthyroid conditions before (1) and after (2) the administration of oxazepam 15 mg and sleeping time after oxazepam

	Hypothyroid state		*Median difference*
	1	*2*	*(95% CI)*
Finger tapping (counts in 30 s)	120 (90–171)	103 (82–151)	18* (−5–36)
Sleeping time after oxazepam (h)		1.5 (0–3)	
	Euthyroid state		
Finger tapping (counts in 30 s)	151 (108–190)	151 (101–189)	NS
Sleeping time after oxazepam (h)		0 (0–1.5)	

Values are median and range
* $P < 0.05$, NS: not significant

slept 1 to 2 h ($P < 0.05$). The results of the finger tapping test are shown in Table 4. Under hypothyroid conditions the median number of tappings was reduced significantly ($P < 0.05$) 3 h after oxazepam. In the euthyroid state oxazepam did not affect finger tapping performance (Table 4). The basal finger tapping performance was significantly lower in the hypothyroid compared with the euthyroid state ($P < 0.01$).

Discussion

The results indicate impaired glucuronidation of oxazepam in hypothyroidism expressed by an increase in elimination half-life and a lowering of clearance. Thus, the suggestion of Scott *et al.* (1984) that the elimination of oxazepam may proceed at a slower rate in more severe degrees of hypothyroidism is confirmed. Our patients were characterized by routine thyroid laboratory tests as suffering from longstanding and advanced hypothyroidism.

We have previously found that oxazepam is absorbed completely in normal individuals (Sonne *et al.*, 1988). In general, few studies have considered the drug absorption process in thyroid disease (Shenfield, 1981). However, an increase in intestinal transit time, which is a pathophysiological consequence of hypothyroidism, might be expected to accelerate the rate of absorption. Although peak plasma concentrations of oxazepam in our subjects tended to be higher during the hypothyroid state they did not change significantly after replacement therapy.

The increase in paracetamol clearance following replacement therapy with levothyroxine was substantial, and could be related almost entirely to the increase in partial clearance of the glucuronide. Paracetamol and oxazepam were given simultaneously and the question of a possible interaction must be raised. However, drug administration was identical on both study days and we have shown previously that oxazepam does not affect the clearance or metabolism of paracetamol (Sonne *et al.*, 1986). A possible effect of paracetamol on oxazepam clearance has not been investigated.

In prior studies on drug metabolism in hypothyroidism the clearance of several drugs which undergo oxidative metabolism, e.g. antipyrine (Eichelbaum *et al.*, 1974) has been shown to be decreased. The present observations with oxazepam and paracetamol suggest that decreases in the clearance of other drugs undergoing phase II conjugation might be anticipated. However, such extrapolation may not be warranted since the metabolism of some drugs, to other drugs should not made, e.g. phenytoin appears to be unaffected by hypothyroidism (Hansen *et al.*, 1978).

Little information is available concerning drug binding to plasma proteins in hypothyroidism. A negative correlation between serum thyroxine and the degree of plasma protein binding was found for both propranolol (a basic drug) and warfarin (an acidic drug) in hyperthyroidism (Feely *et al.*, 1981). In hypothyroidism, however, only the binding of propranolol was increased, whereas the binding of warfarin was unchanged. In the present study no change in the binding of oxazepam, an amphoteric drug, was found in the hypothyroid patients. This is consistent with the results of laboratory tests

that did not reveal any deviations from the normal range for the concentrations of plasma proteins. Therefore, although the clearance of oxazepam is sensitive to changes in protein binding, this would not have contributed to the observed change in its elimination rate. On the other hand the degree of protein binding found in the present study is slightly lower than has been found in normal volunteers (Greenblatt *et al.*, 1980; Sonne *et al.*, 1988).

The finger tapping test, disclosed a decreased performance in the hypothyroid patients compared with the euthyroid state, which is compatible with the frequent clinical finding of central disturbances in hypothyroidism. The administration of oxazepam resulted in a further decrement in the result of the test. The fact, that no significant difference was found in peak plasma drug concentration following the two administrations of oxazepam or in plasma protein binding, suggests an increased sensitivity to the action of oxazepam. This was also suggested by Scott *et al.* (1984). When subjects were euthyroid the same effect could not be produced by a 15 mg dose of oxazepam. However, conclusions from the performance test, especially the post-oxazepam results, must be made with caution since the test was not performed under controlled and blinded conditions.

In conclusion, we have shown that the clearance of oxazepam and the metabolism of paracetamol by glucuronidation are decreased in severe hypothyroidism. An increased central action of oxazepam in hypothyroidism was also suggested.

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