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Oxazepam pharmacokinetics in thyroid disease

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1 The pharmacokinetics of oxazepam, a drug mainly eliminated by a single step glucuronidation reaction, were studied in seven hyperthyroid and six hypothyroid patients before and after treatment.

2. Oxazepam elimination half-life was shorter and apparent oral clearance higher in untreated hyperthyroid patients than after treatment. There was no significant change in oxazepam elimination in hypothyroid subjects.

3 Time to peak concentration (t_{max}) was reduced in the hyperthyroid state. Hypothyroidism had no significant effect on t_{max}.

4 Serum bilirubin concentration was lower in the patients while hyperthyroid before treatment than when euthyroid and also lower than in the hypothyroid patients. There was no significant correlation between serum bilirubin concentrations and oxazepam elimination.

5 These results suggest that glucuronyl transferase activity is increased in hyperthyroidism but is not altered in most patients with hypothyroidism. The extent of increase in glucuronyl transferase activity is similar to that produced by enzyme inducing drugs.

Keywords oxazepam pharmacokinetics hyperthyroidism hypothyroidism

Introduction

The effect of thyroid disease on drug metabolism is not predictable. Antipyrine half-life is shortened in hyperthyroidism and prolonged in hypothyroidism (Crooks *et al.*, 1973; Vesell *et al.*, 1975). Similarly tolbutamide half-life is reduced in hyperthyroid patients (Kampmann & Skovsted, 1975). However, elimination of warfarin and phenytoin is not affected by thyroid disease (Hansen *et al.*, 1978; Shenfield, 1981). These studies involve drugs metabolised by the cytochrome P–450 dependent mixed function oxidase system. The effect of thyroid disease on glucuronidation is not known. Paracetamol clearance has been shown to be increased in hyperthyroidism but is not significantly different from the euthyroid state in hypothyroidism (Forfar *et al.*, 1980). However, metabolites were not measured to indicate which metabolic pathway was involved.

We have observed that serum bilirubin concentration is lower in hyperthyroid patients than when euthyroid after treatment. This may indicate that glucuronyl transferase activity is increased in hyperthyroidism.

The aim of this study was to investigate the pharmacokinetics of oxazepam, a drug excreted almost entirely by a single step glucuronidation reaction, in hyperthyroid and hypothyroid patients before and after treatment.

Methods

Patient selection

Hyperthyroid Seven patients (6F; age 31–60 years; mean age 40) were selected for study. The diagnosis of hyperthyroidism was made on the basis of clinical features and elevated serum thyroxine concentration on two separate occasions.

Three patients were smokers (10–20 daily) but there were no regular consumers of alcohol.

Hypothyroid Six female patients (age 36–58 years; mean age 48) were selected for study. The diagnosis of hypothyroidism was made on the basis of clinical features, low serum thyroxine concentration and elevated thyroid stimulating hormone (TSH) concentration. All were non-smokers and rarely drank alcohol.

All subjects were otherwise healthy, taking no drugs other than those used in the treatment of their disease and had normal serum creatinine and aspartate aminotransferase concentrations. Ethical approval was granted by the Area Committee and written informed consent obtained in all subjects.

Procedure

The volunteers attended between 08.30 and 09.00h after an overnight fast. An indwelling cannula was inserted into a forearm vein and kept patent with a slow saline infusion. A basal blood sample was withdrawn for measurement of serum bilirubin, γ–glutamyl transpeptidase (γGT), albumin, α_1- acid glycoprotein (AAG), total protein, thyroxine and TSH concentrations and for preparation of an oxazepam standard curve. Oxazepam (15 mg) was administered orally with 50 ml of water. Further 10 ml blood samples for oxazepam concentration measurement were collected into lithium-heparin tubes after 20 and 40 min and at 1, 2, 3, 4, 6, 8, 12 and 24 h post dosing. The plasma was separated immediately by centrifugation and stored at −20°C. Oxazepam is stable for at least 6 weeks under these conditions.

Patients were studied on the day before commencing treatment for their thyroid disease and at least 3 months later. At the time of the second study, six of the hyperthyroid patients and all those with hypothyroidism had been euthyroid for at least 1 month. One of the hyperthyroid patients had become clinically and biochemically hypothyroid ($T_4 \leq 25$ nmol l^{-1}; TSH 55 μu ml^{-1}).

The hyperthyroid patients were treated with radioactive iodine ($n = 5$) or carbimazole ($n = 2$). Two patients were also treated with β-adrenoceptor blocking drugs (1 propranolol, 1 atenolol) but these were withdrawn at least 2 weeks before the second study day. The hypothyroid patients were treated with increasing doses of thyroxine until they were clinically and biochemically euthyroid (final dose 150 μg in four patients, 100 μg in two patients).

Analytical methods

Samples for oxazepam were analysed in duplicate by a modification of the method of Patwardhan *et al.* (1980) as described previously (Scott *et al.*, 1983). The serum biochemical parameters were measured by the Department of Chemical Pathology except for AAG (radial immunodiffusion) and TSH (radioimmunoassay).

Oxazepam elimination half-life was calculated using linear regression analysis. The area under the plasma concentration-time curve up to the final detectable plasma concentration was obtained by the trapezoidal rule. To this was added the residual area, calculated as the final plasma concentration divided by the elimination rate constant (λ_z), to give the total AUC. Statistical analysis was by Student's *t*-test for paired samples.

Results

The oxazepam kinetic parameters in the hyperthyroid and hypothyroid patients before and after treatment are shown in Table 1. The elimination half-life ($t_{½,z}$) was three times greater and apparent oral clearance (CL_o) 65% lower after treatment in

Table 1 Oxazepam pharmacokinetic parameters (mean ± s.e.mean) in hyperthyroid and hypothyroid patients before and after treatment. *P* values refer to the effect of treatment.

	C_{max} ($ng\ ml^{-1}$)	t_{max} (h)	$t_{½,z}$ (h)	AUC ($ng\ ml^{-1}h$)	CL_o ($ml\ min^{-1}$)
Hyperthyroid					
Before	227 ± 34	1.20 ± 0.25	2.97 ± 0.65	1136 ± 130	248 ± 38
After	255 ± 21	3.08 ± 0.50	9.85 ± 1.04	3092 ± 310	86 ± 8
P	NS	≤0.05	≤0.01	≤0.01	≤0.01
Hypothyroid					
Before	258 ± 47	1.62 ± 0.30	7.94 ± 1.17	1718 ± 549	146 ± 47
After	216 ± 25	2.60 ± 0.50	8.41 ± 2.53	1582 ± 375	158 ± 37
P	NS	NS	NS	NS	NS

the hyperthyroid patients when compared with values before treatment. There was no significant change in either of these parameters in the hypothyroid group. The individual oxazepam half-life values are further illustrated in Figures 1 and 2. It is clear that half-life increased after

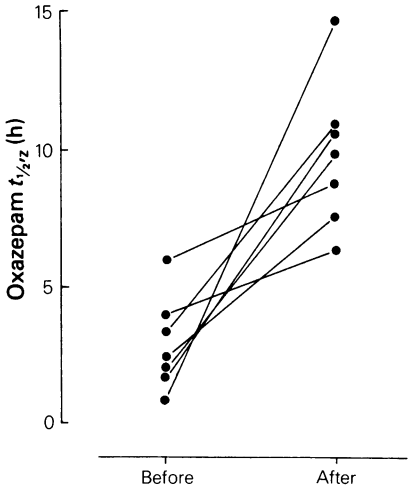

Figure 1 Individual values for oxazepam half-life in hyperthyroid patients before and after treatment.

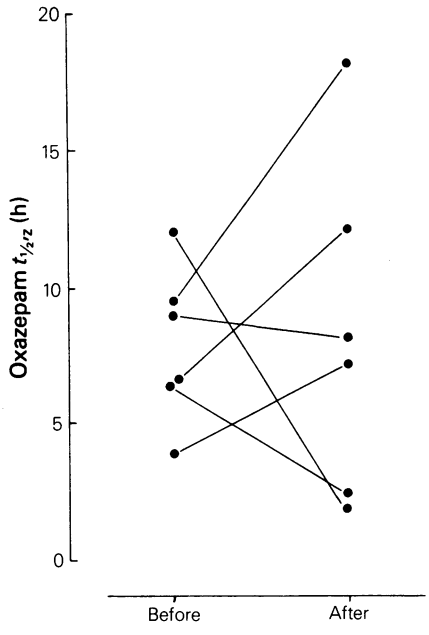

Figure 2 Individual values for oxazepam half-life in hypothyroid patients before and after treatment.

treatment in all the hyperthyroid patients but there was no consistent pattern in the hypothyroid group. Time to reach peak concentration (t_{max}) was significantly shorter before treatment in the hyperthyroid group. Treatment had no significant effect on t_{max} in hypothyroidism. Peak concentration (C_{max}) was similar in both groups and not significantly altered by treatment.

The values for serum bilirubin, γGT, proteins and cholesterol are shown in Table 2. Serum bilirubin concentration was lower in the hyperthyroid patients before treatment than when euthyroid. There was no significant effect of treatment in the hypothyroid patients but both values were lower than in the hyperthyroid group. Serum γGT was not significantly affected by treatment in either group.

The serum proteins (albumin, AAG and total protein) were significantly lower before treatment of hyperthyroidism than after treatment. There was no significant effect of treatment in the hypothyroid group but the trend was towards lower values after treatment.

There was a significant rise in serum cholesterol concentration after treatment of hyperthyroidism but the fall on treatment of hypothyroidism was not statistically significant at the 5% level.

In the hyperthyroid group serum thyroxine concentration (mean ± s.e. mean) was 216 ± 16 nmol l^{-1} (normal range 70–150 nmol l^{-1}) before treatment and 70 ± 21 nmol l^{-1} after treatment. There was a rise in mean weight from 58 to 63 kg ($P \leq 0.05$) after treatment. In the hypothyroid group pre-treatment serum thyroxine concen-

Table 2 Serum bilirubin, γGT, protein and cholesterol concentrations (mean ± s.e.mean) in hyperthyroid and hypothyroid patients before and after treatment.

	Bilirubin ($\mu mol\ l^{-1}$)	*γ GT* ($u\ l^{-1}$)	*Albumin* ($g\ l^{-1}$)	*AAG* ($mg\ l^{-1}$)	*Total protein* ($g\ l^{-1}$)	*Cholesterol* ($mmol\ l^{-1}$)
Hyperthyroid						
Before	9.3 ± 1.7	31 ± 9	40 ± 1	573 ± 25	64 ± 2	4.2 ± 0.3
After	12.6 ± 1.9	16 ± 3	43 ± 1	676 ± 32	70 ± 2	7.4 ± 1.0
P	≤0.05	NS	≤0.01	≤0.002	≤0.05	≤0.01
Hypothyroid						
Before	8.3 ± 1.4	18 ± 4	42 ± 1	690 ± 58	70 ± 3	6.9 ± 0.5
After	8.2 ± 1.4	12 ± 4	41 ± 1	606 ± 32	66 ± 2	5.5 ± 0.2
P	NS	NS	NS	NS	NS	NS

tration was 42 ± 9 nmol l^{-1} and TSH 34 ± 10 μu ml^{-1} (normal range ≤ 4μu ml^{-1}). After treatment these values were 121 ± 14 nmol l^{-1} and 1.3 ± 0.2μu ml^{-1} respectively. There was a fall in mean weight from 74 to 72kg (*P* NS) after treatment.

Discussion

This study shows that in hyperthyroid patients there is a reduction in half-life and increase in apparent oral clearance of oxazepam. All subjects showed these changes as illustrated in Figure 1. The degree of change in oxazepam elimination did not depend on the extent of change in thyroid function. Oxazepam has a low extraction ratio and its elimination (by glucuronidation) depends on intrinsic enzyme activity (Wilkinson & Shand, 1975). This suggests that oxazepam glucuronyl transferase activity is increased in hyperthyroidism. In the hypothyroid group there was no overall change in oxazepam elimination. However, the two most severely affected patients (TSH ≥ 50μu ml^{-1}) did show a reduction in oxazepam half-life after treatment. Patients with milder degrees of hypothyroidism do not appear to have impaired oxazepam glucuronidation. This suggests that there is a considerable reserve of glucuronyl transferase activity. Glucuronyl transferase is membrane bound and may be markedly activated by 'a wide variety of membrane perturbants' (Bock, 1977). If membrane lipids are altered in thyroid disease it is possible that this could affect glucuronyl transferase activity. Further study of drug glucuronidation is necessary in patients with severe and long standing hypothyroidism.

Serum bilirubin concentration increased by a small but statistically significant amount after treatment of hyperthyroidism. This may indicate increased bilirubin glucuronyl transferase activity. However, there was no significant correlation between serum bilirubin concentration and oxazepam elimination as in our previous study of the effects of enzyme induction on oxazepam kinetics (Scott *et al.*, 1983). This could be due either to the occurrence of different glucuronyl transferases or non-metabolic factors affecting bilirubin production. Studies in animals suggest that bilirubin is metabolised by a different glucuronyl transferase from that acting on drug substrates (Watkins *et al.*, 1982). Serum total bilirubin concentration depends on rate of red blood cell destruction as well as bilirubin glucuronyl transferase activity. There is evidence that red blood cell survival time is shortened in hyperthyroidism (Das *et al.*, 1975). This would tend to increase the serum bilirubin concentration in the hyperthyroid state and partly mask the effects of increased bilirubin glucuronyl transferase activity in this condition.

The oxazepam t_{max} was significantly shorter in the patients while hyperthyroid than after treatment. This may reflect the increased gastrointestinal motility in hyperthyroidism (Thomas *et al.*, 1973) and/or the effect of increased elimination. No significant effect of treatment was observed in the hypothyroid group.

The lower serum protein concentrations in hyperthyroidism with a tendency to higher concentrations in hypothyroidism have been reported previously (Kimberg, 1971) though this finding is not widely appreciated. The small changes in albumin concentration would seem to be unlikely to cause an important change in protein binding of acidic drugs. However, the lower AAG concentration in hyperthyroidism could result in reduced binding of basic drugs. Reduced binding of both warfarin (acidic) and propranolol (basic) has been reported in hyperthyroid patients (Feely *et al.*, 1981). Whether this is due to the low protein concentration or the presence of endogenous binding inhibitors is uncertain. Methodological problems with measurement of oxazepam binding (Scott *et al.*, 1983) prevented us from determining the effect of these protein changes on oxazepam protein binding.

The dose of oxazepam (15 mg) used in this study was selected to avoid any sedative effect. Despite this, five of the six hypothyroid patients complained of drowsiness and slept for most of the first study. These patients did not complain of drowsiness on the repeat study when they were euthyroid. While hypothyroid patients often complain of tiredness and increased tendency to sleep, the patients in this study appeared to be more severely affected than other hypothyroid patients observed in our unit. No significant change in drug concentration was noted between the two study days. The possibility of increased receptor sensitivity to benzodiazepines in hypothyroidism requires further investigation.

Oxazepam elimination is increased in hyperthyroid patients to an extent similar to that seen in patients on long-term treatment with phenytoin alone or in combination with phenobarbitone as shown in Figure 3. After treatment, oxazepam $t_{½,z}$ values were similar to normal controls. Oxazepam $t_{½,z}$ values in the hypothyroid group were similar to control values both before and after treatment.

The pharmacokinetic data suggest that oxazepam glucuronyl transferase activity is increased in hyperthyroidism. This may be due to hepatic enzyme induction by thyroxine or some unknown factor present in hyperthyroid patients. These results suggest that an increase in oxazepam dose or frequency of dosing is necessary in

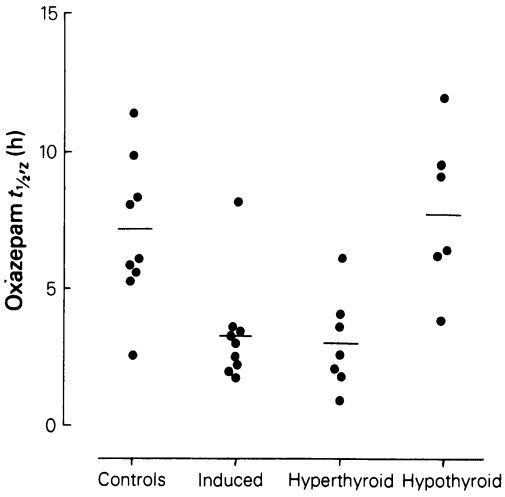

Figure 3 Individual values for oxazepam half-life in healthy controls, patients on enzyme inducing drugs, hyperthyroid and hypothyroid patients. Mean values are shown as horizontal lines.

hyperthyroid patients. Although no significant difference was observed in the pharmacokinetics of oxazepam in hypothyroid patients, the increased sedative effect observed in such patients suggests that the dose could be reduced in hypothyroidism. Particular care is necessary in patients with severe disease.

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