Diazepam/ β -adrenoceptor antagonist interactions

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- 1 The effects of diazepam on the pharmacokinetics and pharmacodynamics of two lipophilic β -adrenoceptor antagonists (propranolol and metoprolol) and a hydrophilic β -adrenoceptor antagonist (atenolol) were compared in 12 subjects.
- 2 Administration of propranolol and metoprolol produced small increases in the AUC_{0-8h} for diazepam compared with placebo ($P < 0.05$ for metoprolol). Atenolol had no significant effect on the AUC_{0-8h} for diazepam. The increase in the AUC_{0-8h} was accompanied by increases in the plasma concentrations of *N*-desmethyldiazepam.
- 3 Diazepam had no significant effect on the pharmacokinetics of either propranolol or atenolol.
- 4 The pharmacokinetic interaction could be attributed to inhibition of diazepam metabolism by the lipophilic β -adrenoceptor antagonists.
- 5 The pharmacodynamic studies showed that when compared with placebo or atenolol there was a significant impairment of kinetic visual acuity (KVA) when diazepam was co-administered with metoprolol.
- 6 Although there was a significant correlation ($P < 0.02$) between plasma concentrations of diazepam and impairment of KVA, the pharmacodynamic interactions may not be due solely to the small pharmacokinetic interaction observed.

Keywords atenolol diazepam metoprolol pharmacology propranolol

Introduction

Lipophilic β -adrenoceptor antagonists such as metoprolol and propranolol are metabolised by the cytochrome P-450 oxidative enzyme systems in the liver. There is therefore a potential for interaction with many other drugs which are similarly metabolised by this system. Recently an unsuspected interaction between chlorpromazine and propranolol led to an uncritical acceptance of propranolol as a new agent in the treatment of schizophrenia. It was later shown that the clinical improvement in the patients treated with a combination of these two drugs was due entirely to an increase in chlorpromazine plasma levels (Peet *et al.*, 1981).

Diazepam and other benzodiazepine derivatives are widely used in the treatment of anxiety.

Diazepam is partly metabolised by the P-450 system, although it has a low hepatic extraction ratio (Garattini *et al.*, 1972). β -adrenoceptor antagonists also have a place in the management of anxiety, particularly 'somatic' anxiety (Tyrer, 1976). Combinations of benzodiazepines and β -adrenoceptor antagonists are now being recommended for the treatment of anxiety. Hallstrom *et al.*, (1981) showed that a combination of propranolol with diazepam was apparently more effective than diazepam alone in controlling anxiety; this finding may lead to increased use of benzodiazepine/ β -adrenoceptor antagonist therapy in the future. The sedative effects of benzodiazepines are known to impair car driving (Betts *et al.*, 1972) and diazepam/ β -

adrenoceptor antagonist interactions may therefore be clinically important. The present study was designed to examine the potential interaction between diazepam and two metabolised lipophilic β -adrenoceptor antagonists (propranolol and metoprolol) and one non-metabolised hydrophilic β -adrenoceptor antagonist (atenolol). The hypothesis under test was that pharmacokinetic interactions would occur only between diazepam, metoprolol and propranolol, and not between diazepam and atenolol.

Methods

Volunteers

Twelve males, of mean age 25 years (18–33 years) and mean weight 71.5 kg (66–93 kg), were screened medically and psychologically before being selected for the study. Subjects received no other drugs, and gave informed consent to take part in the study, being free to withdraw at any time. The study was approved by the Ethical Committee of the Queen Elizabeth Hospital, Birmingham.

Protocol

One half of the group received diazepam (5 mg twice daily 09.00 and 21.00 h) orally for the first 5 weeks. After a 2 week washout period these subjects received diazepam placebo for 5 weeks. The other half of the group took the drugs in reverse order. β -adrenoceptor antagonists were administered orally for 5 days: propranolol 40 mg twice daily (09.00 and 21.00 h) for 2 days, increasing to 80 mg twice daily for the next 3 days; metoprolol 50 mg twice daily for 2 days, increasing to 100 mg twice daily for 3 days; and atenolol 25 mg twice daily for 2 days, increasing to 50 mg twice daily for 3 days. β -adrenoceptor antagonists and placebo were made up as matching white tablets. Diazepam and its placebo were identical yellow tablets.

In the first week of both 5 week periods, the subjects took nothing but diazepam or placebo. During weeks 2–5 the subjects took additionally one of the β -adrenoceptor antagonists or placebo in a balanced order design over the first 5 days. Day 5 of weeks 2–5 was the test day. On that day subjects had a light breakfast (toast and orange juice but no coffee or tea) before attending the clinical test centre at intervals between 08.00 and 09.00 h. Using an intravenous cannula 10 ml of blood was taken, centrifuged, and the plasma was stored in a plain tube at -20°C . The subjects then took the morning dose of diazepam/placebo and β -adrenoceptor antagonist/placebo tablets. Blood samples (10 ml) were

taken at intervals up to 8 h post-dosing and were centrifuged and stored at -20°C . Samples were analysed for β -adrenoceptor antagonist, diazepam and *N*-desmethyldiazepam concentrations as described below.

The subjects' kinetic visual acuity (KVA) and choice reaction time (CRT) (see below) were measured at 2 h and 8 h post-dosing, and subjects completed a visual analogue rating scale (VAS) of subjective feelings. Another subjective VAS was completed at 4 h. Subjects were given practice on the various tests before the study started. Subjects were asked not to drive whilst taking the drugs and to avoid alcohol and smoking. A medical member of the team was on call at all times to deal with any problems.

Assay of drug plasma concentrations

($\pm$)-propranolol HCl was obtained from Sigma Limited, and metoprolol tartrate and atenolol HCl were gifts from Geigy Pharmaceuticals and ICI Pharmaceuticals plc, respectively. Diazepam and *N*-desmethyldiazepam were gifts from Roche, and 3-OH diazepam (temazepam) and oxazepam were gifts from Wyeth Laboratories.

Propranolol and atenolol plasma concentrations were measured using GLC methods described by Di Salle *et al.* (1973) and Scales & Copsey (1975) respectively. Diazepam and *N*-desmethyldiazepam were extracted from plasma using a modification of the method described by Klotz *et al.* (1975). The parent drug was separated from metabolites by h.p.l.c. using a 25 cm Spherisorb 5 ODS column with a mobile phase of methanol:water (65:35, v/v) at a flow rate of 1.3 ml min^{-1} and detected at 229 nm using an Altex 160 detector.

Pharmacokinetic and statistical analyses

The area under the plasma concentration time curve up to 8 hours ($\text{AUC}_{0-8\text{h}}$) was calculated using the trapezoidal rule. C_{max} (peak plasma concentration), t_{max} (time to reach peak concentrations) and $\text{AUC}_{0-8\text{h}}$ for diazepam and desmethyldiazepam alone or in the presence of a β -adrenoceptor antagonist were compared by analysis of variance (Dunnett, 1964). Student's paired *t*-test was used for comparing propranolol and atenolol plasma concentrations in the presence or absence of diazepam. The clinical data were compared by non-parametric analysis of variance (Friedman Test) and Wilcoxon's Matched Pairs Signed Ranks Test.

Microsomal metabolism of diazepam in vitro

Hepatic microsomal fractions from male Sprague-Dawley rats (230–280 g) (Ericksson *et*

al., 1978; Ichikawa & Yamano, 1967) were incubated with cofactors at 37°C (pH 7.4) with or without propranolol, metoprolol or atenolol for 2 min before adding diazepam (10 μ M). Incubation was continued for 10 min before the reaction was terminated by the addition of diethyl ether. Diazepam, desmethyldiazepam, 3-OH diazepam (temazepam) and oxazepam were assayed as described above. Microsomal protein was determined by the method of Lowry *et al.* (1951).

Results

Drug plasma concentrations

The area under the plasma concentration time curve (AUC_{0-8h}) for diazepam was significantly increased when the drug was co-administered with metoprolol, but not with atenolol or propranolol (Table 1). Mean peak plasma concentrations of diazepam were also significantly increased in the presence of metoprolol, but none of the β -adrenoceptor antagonists markedly affected the time taken to reach peak diazepam concentrations. Over eight hours mean concentrations of *N*-desmethyldiazepam, the major plasma metabolite, were also significantly increased in the presence of propranolol and metoprolol. Diazepam plasma concentrations were significantly correlated with *N*-desmethyldiazepam concentrations when diazepam was administered with placebo or metoprolol (Table 2). In only two individuals did the lipophilic β -adrenoceptor antagonists produce more than two-fold increases in the plasma concentrations of diazepam and *N*-desmethyldiazepam.

Co-administration of diazepam had no significant effect on any of the pharmacokinetic parameters measured for the two β -adrenoceptor antagonists, propranolol and atenolol (Table 3).

Clinical results

Each subject acted as his own control and was exposed to eight treatments in a balanced order

Table 2 Mean plasma concentrations of *N*-desmethyldiazepam in the presence of placebo or β -adrenoceptor antagonist. Values represent means $\pm$ s.e. mean.

	Mean concentration <i>N</i> -desmethyldiazepam (ng ml ⁻¹)	Correlation with diazepam AUC_{8h}
Placebo	243 $\pm$ 20	0.67 <0.05
Atenolol	244 $\pm$ 18	0.44 NS
Metoprolol	286 $\pm$ 19*	0.66 <0.05
Propranolol	286 $\pm$ 24*	0.49 NS

* $P < 0.05$ compared with placebo (Dunnett, 1964)

design: placebo alone, diazepam alone, atenolol alone, propranolol alone, metoprolol alone, and diazepam plus atenolol, diazepam plus propranolol, and diazepam plus metoprolol. With the necessarily complex nature of the design, learning and order effects will be confounding variables and will not be completely allowed for by the balancing of the experimental design.

Kinetic visual acuity was measured at 2 and 8 h and the mean score of twenty presentations was calculated. Kinetic visual acuity is the ability to recognise a moving object travelling at constant speed in a horizontal plane towards the eye. The farther the point of recognition is away from the eye, the better the subject's performance. Poor performance is associated with fatigue and accident proneness and performance on this test is impaired by psychotropic medication.

Comparison was made between mean scores for each subject for each of the eight drug groups at 2 h and at 8 h. Table 4 shows that there was an overall significant difference between scores at 2 h. There was no overall significant difference at 8 h. Between-groups comparison shows that when compared with placebo or atenolol there was a significant impairment of kinetic visual acuity when subjects took the combination of diazepam and metoprolol. When mean kinetic visual acuity scores for each subject were compared in order of presentation, no significant learning effect appeared on this test. Using Spearman's test there was a significant correlation ($P < 0.02$) between increase in diazepam concentrations and a decrease in KVA score at both 2 and 8 h.

Table 1 Diazepam pharmacokinetics in the presence of placebo or β -adrenoceptor antagonist. Values represent means $\pm$ s.e. mean.

	Peak concentration (ng ml, l)	Time to peak (h)	AUC_{8h} (ng ml ⁻¹ h)
Placebo	363 $\pm$ 26	1.3 $\pm$ 0.3	1823 $\pm$ 174
Atenolol	392 $\pm$ 31	1.6 $\pm$ 0.3	1928 $\pm$ 174
Metoprolol	439 $\pm$ 39*	1.5 $\pm$ 0.3	2274 $\pm$ 213*
Propranolol	422 $\pm$ 41	1.7 $\pm$ 0.4	2169 $\pm$ 200

* $P < 0.05$ compared with placebo (Dunnett, 1964).

Table 3 Propranolol and atenolol pharmacokinetics in the presence of diazepam or diazepam placebo. Values represent means $\pm$ s.e. mean.

	Peak concentration (ng ml ⁻¹)	Time to peak (h)	AUC _{8h} (ng ml ⁻¹ h)
<i>Propranolol</i>			
Diazepam	130 $\pm$ 21	2.0 $\pm$ 0.3	1182 $\pm$ 228
Placebo	137 $\pm$ 22	2.0 $\pm$ 0.3	1304 $\pm$ 242
<i>Atenolol</i>			
Diazepam	499 $\pm$ 50	2.7 $\pm$ 0.3	5758 $\pm$ 646
Placebo	571 $\pm$ 37	2.4 $\pm$ 0.3	6290 $\pm$ 430

Table 4 Mean scores for kinetic visual acuity at 2 h post-dosing. Values represent means $\pm$ s.d.

Placebo	Atenolol	Metoprolol	Propranolol
0.59 $\pm$ 0.23	0.60 $\pm$ 0.24	0.56 $\pm$ 0.24	0.59 $\pm$ 0.23
Diazepam	Diazepam	Diazepam	Diazepam
	+ atenolol	+ metoprolol	+ propranolol
0.54 $\pm$ 0.23	0.55 $\pm$ 0.22	0.49 $\pm$ 0.18*	0.53 $\pm$ 0.20

Overall difference $P < 0.02$ (Friedman's test)

*Diazepam + metoprolol significantly less than atenolol or placebo ($P = 0.005$ Wilcoxon Test).

Table 5 Choice reaction time (μ s) at 2 h/8 h. Values represent means $\pm$ s.d.

Placebo	Atenolol	Metoprolol	Propranolol
320	323	318	319
± 37	± 37	± 38	± 39
Diazepam	Diazepam	Diazepam	Diazepam
	+ atenolol	+ metoprolol	+ propranolol
328	336	335	335
± 34	± 46	± 44	± 43

Choice reaction time was measured using an electronic device which presented the subject with a row of three lights, which would light up in a random sequence one at a time. The subject had to cancel the light as quickly as possible by pressing a button. The time taken to do this was presented in microseconds on a digital display on the machine (which meant that subjects were aware of their own performance). Repeated presentations were made until the subject had successfully completed forty trials. Mean scores of the forty trials were compared under the eight drug conditions. When account was taken of order of presentation, there was a significant learning effect: raw scores were therefore

adjusted to allow for learning. Table 5 shows the corrected scores (trials at 2 and 8 h combined). Choice reaction time did not differ significantly overall at 2 or 8 h. There was no apparent correlation between plasma concentrations of diazepam and scores on reaction time. However, scores obtained under diazepam conditions ($334 \pm 41 \mu$ s) were significantly greater than scores under non-diazepam conditions ($320 \pm 37 \mu$ s) ($P = 0.009$ Mann Whitney).

The 18 item VAS is sensitive to the effect of psychotropic drugs in normal subjects (Betts & Blake, 1977). The 18 items of the scale represent three factors: arousal (or subjective CNS impairment), mood and tension (Betts & Harvey,

unpublished observations). Scores were obtained for each subject under each condition 2, 4 and 8 h after drug ingestion. Analysis of the individual 18 items over the eight conditions showed overall significant differences on several scales, mostly concerned with impairment of arousal and mostly at 2 h. This was clearly an effect of diazepam, and no significant differences emerge between diazepam on its own and diazepam in combination.

However, on three items not only were there significant overall differences, but between-groups comparison showed that diazepam in combination with the lipophilic β -adrenoceptor

antagonists impaired measures of subjective arousal, relaxation and mood (Tables 6, 7 and 8).

There were other significant differences in VAS between propranolol and metoprolol on their own, and the combination of these drugs with diazepam, particularly on measures of impaired subjective arousal. No significant differences emerged between atenolol and the atenolol/diazepam combination.

On each test day subjects were asked to recall any adverse side effects encountered during the preceding 4 days. These were recorded and the total number of adverse side effects for each drug combination is presented in Table 9. The three

Table 6 Subjective VAS 'quick-witted—mentally slow' (arousal) at 2 h/4 h. Values represent means $\pm$ s.d.

Placebo	Atenolol	Metoprolol	Propranolol
49.0	49.5	56.1	49.9
± 8.3	± 17.4	± 13.7	± 17.1
Diazepam	Diazepam + atenolol	Diazepam + metoprolol	Diazepam + propranolol
52.1	56.4	61.4	63.5
± 14.7	± 13.5	± 17.8	± 13.9

Overall difference $P < 0.05$ (Friedman's Test)

Propranolol + diazepam significantly more mentally slow than diazepam alone $P < 0.025$ (Wilcoxon Test)

Table 7 Subjective VAS 'troubled-tranquil' (tension) at 2 h/4 h. Values represent means $\pm$ s.d.

Placebo	Atenolol	Metoprolol	Propranolol
47.9	42.2	43.9	41.4
± 7.9	± 11.8	± 11.4	± 10.9
Placebo	Diazepam + atenolol	Diazepam + metoprolol	Diazepam + propranolol
43.7	50.1	56.0	54.8
± 12.5	± 12.7	± 20.1	± 17.1

Overall difference $P < 0.02$ (Friedman's Test)

Diazepam + metoprolol more troubled than diazepam alone $P < 0.025$ (Wilcoxon)

Table 8 Subjective VAS 'self-centred—outward going' (mood) at 2 h. Values represent means $\pm$ s.d.

Placebo	Atenolol	Metoprolol	Propranolol
44.2	43.6	45.5	45.2
± 11.6	± 17.3	± 13.4	± 11.9
Diazepam	Diazepam + atenolol	Diazepam + metoprolol	Diazepam + propranolol
43.6	45.5	51.7	53.9
± 14.1	± 13.4	± 17.5	± 16.7

Overall difference $P < 0.05$ (Friedman's Test)

Diazepam significantly more outward going than diazepam + propranolol $P < 0.025$ (Wilcoxon)

Table 9 Total number spontaneously reported adverse side effects.

Placebo	Atenolol	Metoprolol	Propranolol
5	7	15	11
Diazepam	Diazepam + atenolol	Diazepam + metoprolol	Diazepam + propranolol
15	7	17	14

$P < 0.05$ Chi-squared one sample test (Siegel, 1956)

most common side effects were nocturnal sleep disturbance, daytime drowsiness and dizziness/faintness. Placebo, atenolol and the atenolol diazepam combination had the least number of spontaneously reported side effects. The chi-squared test shows a significant ($P = 0.05$) overall difference between the number of side effects.

For all of the tests the effects of the β -adrenoceptor antagonists were indistinguishable from placebo. The subtle effects (often of improvement) that can sometimes be detected when β -adrenoceptor antagonists are compared with placebo were likely to be obscured by the repetitive and complex nature of the experimental design.

Inhibition of diazepam metabolism in vitro

The effect of the three β -adrenoceptor antagonists, over a twenty-fold concentration range, was tested on the metabolism of $10 \mu\text{M}$ diazepam. The mean control rate of diazepam metabolism was $0.24 \text{ nmol mg}^{-1} \text{ protein, min}^{-1}$, the major metabolite formed being oxazepam. The percentage inhibition of the rate of formation of oxazepam was calculated for each β -adrenoceptor antagonist. In the presence of $200 \mu\text{M}$ propranolol or metoprolol there were decreases in the formation of oxazepam of 65% and 35% respectively. At equimolar concentrations of diazepam and the β -adrenoceptor antagonists, the effect was less marked (Table 10). Atenolol had no detectable effect on diazepam metabolism over the range of concentrations studied.

Discussion

The area under the plasma concentration-time curve calculated to 8 h for orally administered diazepam, was significantly increased when the drug was co-administered with metoprolol, but not with atenolol or propranolol. Since the half-life for diazepam elimination in young male subjects is approximately 36 h (Greenblatt *et al.*, 1980) and drug plasma concentrations were measured only over 8 h, it was not appropriate to calculate the apparent oral clearance of diazepam. However, the results are in agreement with other studies showing impairment of clearance of orally administered drugs in the presence of lipophilic β -adrenoceptor antagonists (Bax *et al.*, 1981; Conrad & Nyman, 1980).

For drugs eliminated entirely by the liver, the plasma concentration time curve after oral administration is dependent upon both the fraction of drug unbound in the plasma and the intrinsic hepatic clearance of free drug (Wilkinson & Shand, 1975). An alteration in the percentage of diazepam that is protein-bound is unlikely to account for the pharmacokinetic changes observed after propranolol administration, since this would require a positive co-operative binding interaction between two drugs which are both extensively protein bound. In addition, the high affinity binding component for propranolol involves binding to α_1 -acid glycoprotein, not albumin. Metoprolol is not extensively bound to plasma proteins.

The alternative theory of decreased intrinsic clearance being responsible for the increased

Table 10 Percentage inhibition of diazepam metabolism *in vitro* in the presence of β -adrenoceptor antagonists.

	Octanol/buffer partition coefficient ^a	% inhibition metabolism	
		200 μM β -adrenoceptor antagonist	10 μM β -adrenoceptor antagonist
Propranolol	20.2	65	20
Metoprolol	0.98	35	7.5
Atenolol	0.02	0	0

^a Woods & Robinson (1981)

AUC_{0-8h} is supported by the results of studies *in vitro*, where the inhibition of diazepam metabolism was proportional to the lipophilicity of the β -adrenoceptor antagonist (Table 10). A positive correlation between β -adrenoceptor antagonist lipophilicity and the percentage inhibition of lignocaine metabolism has also been shown by Deacon *et al.* (1981). An increased AUC_{0-8h} for diazepam *in vivo* was accompanied by an increase in the plasma concentrations of *N*-desmethyldiazepam, suggesting that the inhibition in metabolism might be due to inhibition of the 3-hydroxylation of diazepam. This was not confirmed *in vitro*, where the most significant effect was on oxazepam formation, *N*-desmethyldiazepam and 3-OH diazepam being present as minor metabolites. Inhibition of drug metabolism *in vivo* by propranolol may involve two mechanisms, non-competitive inhibition involving covalent binding of a reactive metabolite of propranolol to a specific form of cytochrome P-450 (Schneck & Pritchard, 1981), and competitive inhibition by propranolol.

Even if intrinsic clearance is decreased, altered pharmacokinetics do not necessarily produce a change in pharmacological effect. For diazepam, KVA appears to be a more sensitive indicator of drug effect than CRT. Comparison of mean KVA values between treatments showed that a combination of diazepam and metoprolol led to significantly lower KVA values than those obtained for placebo or atenolol alone. CRT allowed discrimination only between subjects on diazepam or on placebo. Impairment of KVA was also correlated with plasma concentrations of diazepam, although since *N*-desmethyldiazepam is equipotent with diazepam, KVA values will be due to both diazepam and *N*-desmethyldiazepam concentrations. Improved correlations would also be expected using drug tissue concentrations, rather than plasma concentrations of diazepam.

Two subjects who showed a greater than two-fold increase in plasma diazepam and *N*-desmethyldiazepam concentrations in the

presence of lipophilic β -adrenoceptor antagonists did not show the most marked impairment of KVA in the presence of propranolol or metoprolol. The mean small increase (22%) in diazepam AUC_{0-8h} and *N*-desmethyldiazepam concentrations would not appear to account totally for the altered pharmacodynamics, since it is likely that at least a two-fold increase in dose is necessary to show a change in KVA for any individual. The results also suggest that plasma concentrations of diazepam or *N*-desmethyldiazepam cannot be used to predict adverse reactions in the presence of β -adrenoceptor antagonists. From this study in normal subjects no advantage seems to be gained by mixing diazepam with a β -adrenoceptor antagonist. Although clinically anxious patients may react differently, the present study does suggest that if β -adrenoceptor antagonists must be prescribed with diazepam, use of a hydrophilic β -adrenoceptor antagonist would appear to minimise the incidence of adverse side effects.

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Group discussion

J. M. Cruickshank

Regarding Dr Betts' data, on the response of volunteers to the combination of a β -adrenoceptor blocker plus diazepam, how would your findings relate to a group of patients with chronic anxiety?

T. A. Betts

Anxiety is one of the clinical psychiatric conditions in which one can cautiously extrapolate from 'normal' anxiety in volunteers to 'pathological' anxiety in patients. It is true that the response to an anxiolytic, whether it be benzodiazepine or β -adrenoceptor blocker is the more impressive the nearer to 'normal' a subject approaches. Hallstrom and colleagues who combined propranolol and diazepam, found the same thing. In Tyrer's monograph on the role of bodily feelings in anxiety, which reviewed the use of β -adrenoceptor blocking drugs in anxiety, a relationship could be seen between the results

in the 'patient' population and those in the 'normal' subject population. I would therefore feel fairly happy that we can extrapolate a little to a patient population from our tentative results which suggest that the combination of β -adrenoceptor blocker and benzodiazepine impairs subjective measures of anxiety, mood and arousal. However, I have strong doubts about those clinical studies in which anxiety lasts for longer than a week. Chronic anxiety is an unusual condition, because if you try to find it in order to treat it in a controlled crossover trial it tends to get better permanently before the end of the trial. In Hallstrom's study, to ensure enough numbers in the trial, patients were taken from both Southampton and London. The results were modest in these patients with chronic anxiety, and the patients were largely unaffected by treatment. In such chronic studies, I suspect that we are probably examining the effects of drugs on personality rather than on chronic anxiety itself.