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Central effects of β-adrenoceptor antagonists II–Electroencephalogram and body sway

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1 Effects of the β-adrenoceptor antagonists, propranolol (40, 80 and 160 mg) and atenolol (50 and 100 mg) on the electroencephalogram and on body sway, were studied in 12 healthy male subjects. The study was double-blind, and included two placebos and an active control, oxazepam (15 mg). Medication was ingested at 11.00 h, and assessments were made before, and at 2 h and 4 h after ingestion.

2 All doses of both β-adrenoceptor antagonists modified the electroencephalogram, and the changes reported were statistically significant at probability levels of less than 5%. The circadian rise in α activity was reduced by both β-adrenoceptor antagonists as well as by oxazepam. Atenolol also decreased β activity.

3 Body sway was modified by atenolol and oxazepam ($P < 0.05$). The increase with oxazepam was most marked in the low frequency component (0.05–2.25 Hz) of the spectrum, while atenolol modified only the component of higher frequency (2.25–4.0 Hz).

4 These observations suggest that propranolol and atenolol have a sedative effect, and that hydrophilic antagonists are unlikely to be free of central activity. The changes in body sway could imply that peripheral mechanisms may be modified at least with atenolol.

Keywords β-adrenoceptor antagonists electroencephalogram body sway

Introduction

Modulation of the electrical activity of the brain by β-adrenoceptor antagonists has been the subject of several recent studies. The effects of propranolol and metoprolol generally indicate sedation (Wagner *et al.*, 1981; Matousek *et al.*, 1984), although some studies with propranolol (Itil & Itil, 1983) may be interpreted as increased vigilance at low doses and sedation at high doses. The effects of mepindolol and pindolol (Roubicek, 1976; Wagner *et al.*, 1981; Mock & Kunkel, 1982) may also be considered as either sedative or vigilance enhancing in nature.

As well as the uncertainty of the interpretation of the effects of β-adrenoceptor antagonists on the electroencephalogram, it is not clear whether hydrophilic drugs which are thought to enter the brain with greater difficulty have any central activity. Despite lower brain concentrations there is some evidence that sotalol leads to sedative changes in the electroencephalogram (Eschmann *et al.*, 1983), and other studies indicate that atenolol decreases arousal (Salem & McDevitt, 1983; Gengo *et al.*, 1987). Factors other than the ease by which these antagonists cross the blood brain barrier may determine whether they modulate central activity, such as the effective drug level at receptor sites and the possibility that receptors may be saturated at low concentrations.

It is with these issues in mind that we have studied in healthy volunteers the effects of atenolol, a hydrophilic antagonist, and pro-

pranolol, a lipophilic antagonist on the electroencephalogram and on body sway. These measures have been shown to be sensitive physiological indicators of the effects of centrally acting drugs (Saletu *et al.*, 1982; Sittig *et al.*, 1982). The studies were carried out together with observations on psychomotor activity reported previously (Currie *et al.*, 1988).

Methods

Experimental design

Details of the methodology are described in Part I of the study (Currie *et al.*, 1988). Recordings of the EEG and body sway were made before (10.00 h) drug ingestion and at 2 (13.00 h) and 4 (15.00 h) h thereafter.

Electroencephalograms (EEG)

Resting activity was recorded from P3–01, P4–02 and C3–T3 (10–20 international system), using silver-silver chloride electrodes with inter-electrode resistances less than 10 kΩ. The EEG was recorded for 2 min with eyes open while the subjects performed a mental arithmetic task, and this was followed by recording 5 min with the eyes closed, when the subjects were instructed to relax. The signals were recorded on magnetic cassettes (TDK 60) using ambulatory four-channel Medilog recorders (Oxford Medilog Systems, Model 4-24). A timing marker provided automatic detection of the start of each recording session.

The tapes were replayed at 20 times real-time using a Medilog Page Mode Display (PMD-12) controlled by a PDP11-34 computer. The analogue data were low pass filtered before digitisation at a sampling rate of 2560 Hz (equivalent to 128 Hz real-time). Epochs containing artefacts were identified and excluded from subsequent analysis. From each recording with eyes open, fifteen epochs of 4 s duration were analysed, and power spectra (0.25 Hz resolution) for each epoch computed using a fast Fourier transform. A mean power spectrum based on fifteen epochs (1 min of data) was then calculated. Sixty epochs of 4 s were analysed from each recording with eyes closed, and four mean power spectra (0.25 Hz resolution) relating to consecutive intervals of 1 min calculated. From each mean spectrum (one eyes open, four eyes closed), the total power in six bands (δ: 0.5–3 Hz, θ: 3.5–7.0 Hz, α_1: 7.5–10 Hz, α_2: 10.5–13 Hz, β_1: 13.5–21 Hz, β_2: 21.5–30 Hz) were computed.

Body sway

The subjects stood on a rigid platform which rested on three pressure transducers (one at the front, two at the back), providing measurement of lateral and anterior body sway. Data were recorded for 1 min with eyes open and then with eyes closed. For each recording, a period of 32 s was digitised off-line at a sampling rate of 32 Hz. A mean power spectrum with resolution 0.25 Hz over the frequency range 0.05–4 Hz was computed using a fast Fourier transform. Spectra from lateral and posterior channels were summed to give a single mean spectrum for each condition.

Statistical analysis

The methods of analysis are given in Part I of the study (Currie *et al.*, 1988) with the following differences. In the case of EEG data with eyes closed, a fourth factor (min) was included in the ANOVA model. For all EEG data, drug effects were estimated by calculating the difference between pre- and post-ingestion means to allow for day-to-day differences between pre-ingestion means. These differences were used to compare drug responses with the placebo value at each post-ingestion time.

In the case of body sway, principal components analysis was used to reduce the number of variables required to explain drug effects, and direct comparisons made between drug and placebo means at post-ingestion times.

Results

Electroencephalograms

The effect of drugs on the electroencephalogram meaned over dose is shown in Figures 1 and 2, and on α activity only for individual doses in Figure 3. A summary of the results is given below.

Recordings with eyes open Oxazepam reduced θ, α_1 and α_2 in all channels. δ activity was reduced in channel P3–01 and β_2 activity in channel C3–T3. Propranolol decreased δ activity in P3–01 and P4–02, θ and α_2 power in P3–01 and C3–T3, and α_1 activity in C3–T3. Atenolol reduced θ and β_1 power in all channels, α_1 and α_2 in C3–T3, and δ power in P3–01.

Recordings with eyes closed Since inclusion of the factor 'min' in the ANOVA model did not

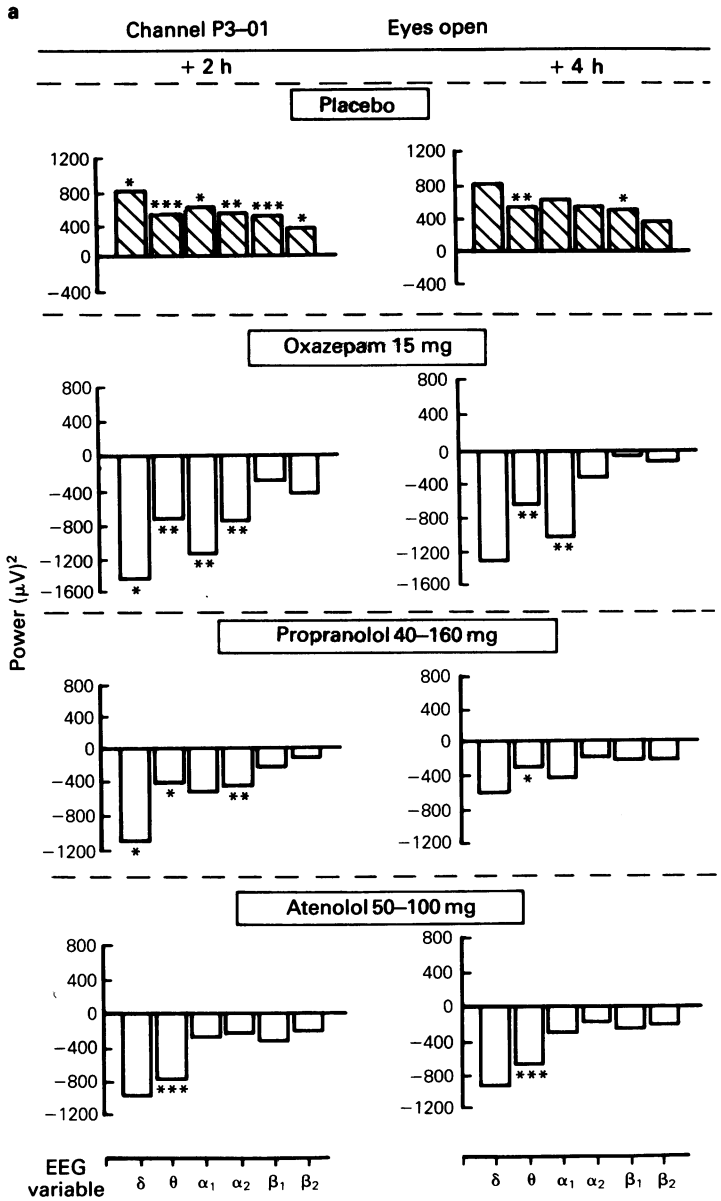
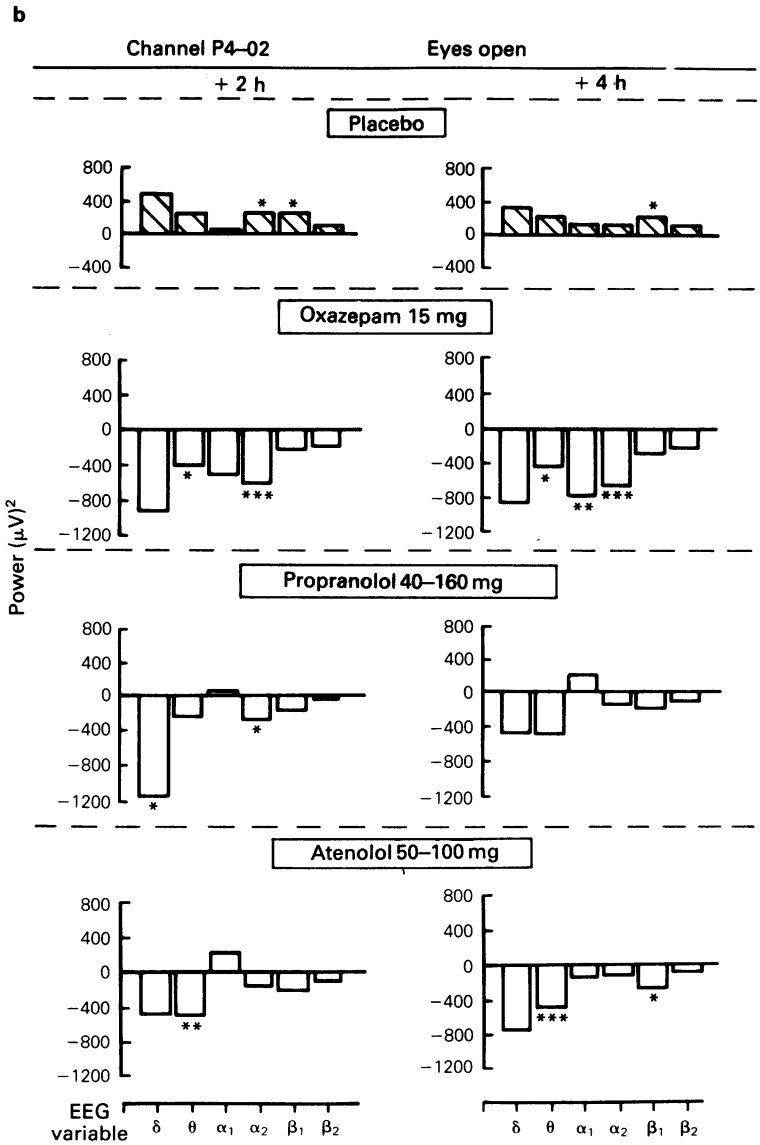
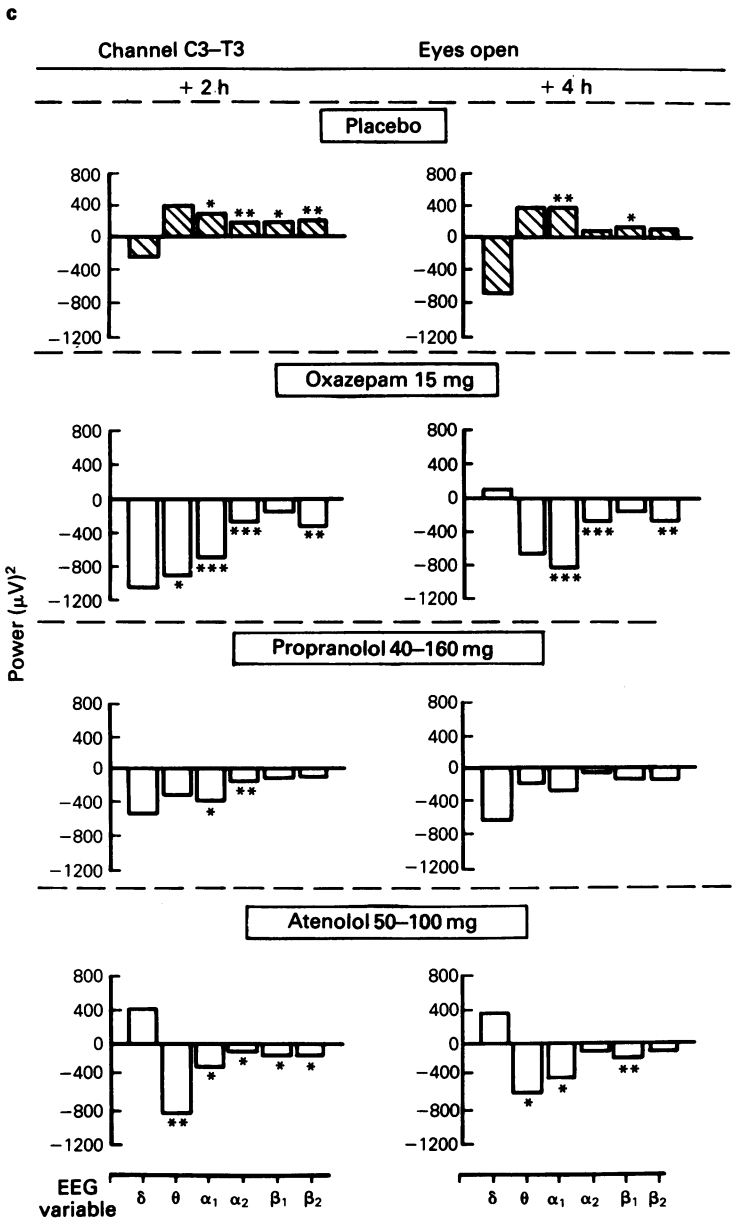


Figure 1 The effects of propranolol and atenolol (meaned over dose at 2 and 4 h after ingestion) on the EEG with eyes open, for derivations (a) P3–01, (b) P4–02 and (c) C3–T3. EEG variables are defined as δ : 0.5–3 Hz; θ : 3.5–7 Hz; α_1 : 7.5–10 Hz; α_2 : 10.5–13 Hz; β_1 : 13.5–21 Hz; β_2 : 21.5–30 Hz.
▨ Indicates change from pre-ingestion value with placebo.
□ indicates difference between the changes in placebo from pre-ingestion value and the change in drug level from pre-ingestion.
Differences are based on mean values for 12 subjects. Significance levels: * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.


b
Channel P4–02
Eyes open
+ 2 h
+ 4 h
Placebo
Oxazepam 15 mg
Propranolol 40–160 mg
Atenolol 50–100 mg
Power (μV)²
800
400
0
−400
−800
−1200
EEG variable
δ θ α1 α2 β1 β2


c
Channel C3–T3
Eyes open
+ 2 h
+ 4 h
Placebo
Oxazepam 15 mg
Propranolol 40–160 mg
Atenolol 50–100 mg
Power (μV)²
800
400
0
−400
−800
−1200
EEG variable
δ θ α1 α2 β1 β2

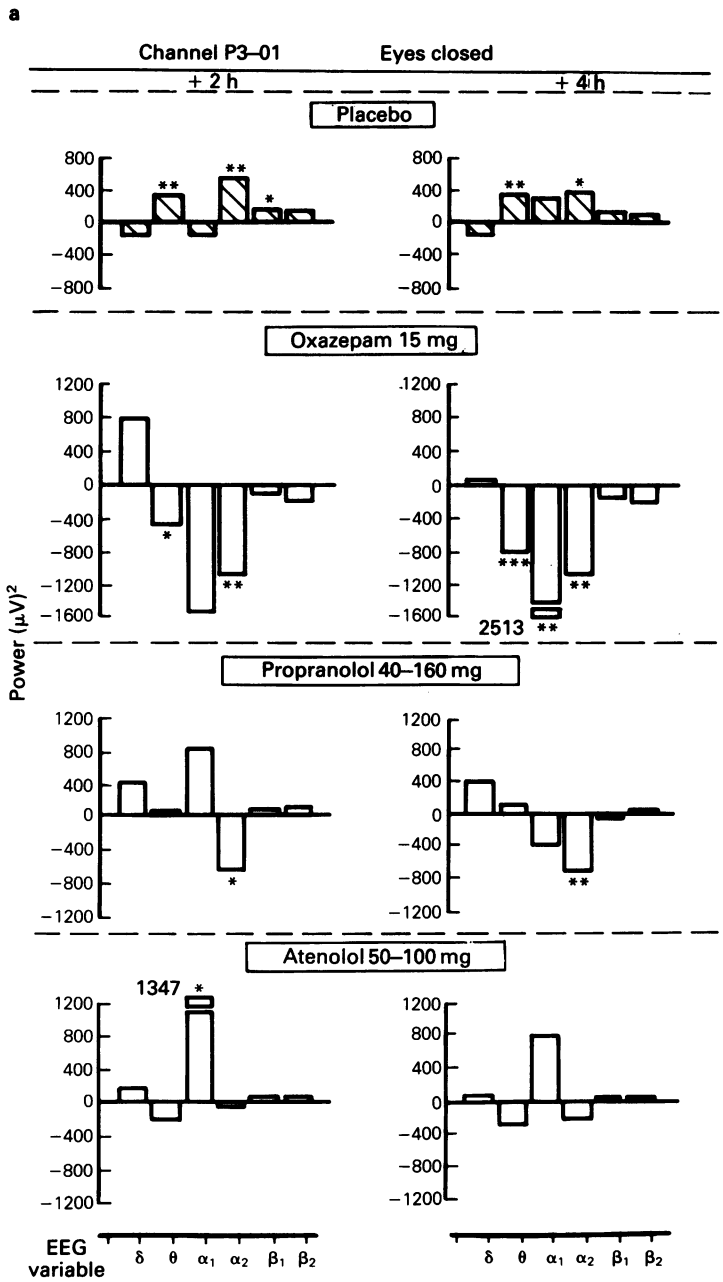
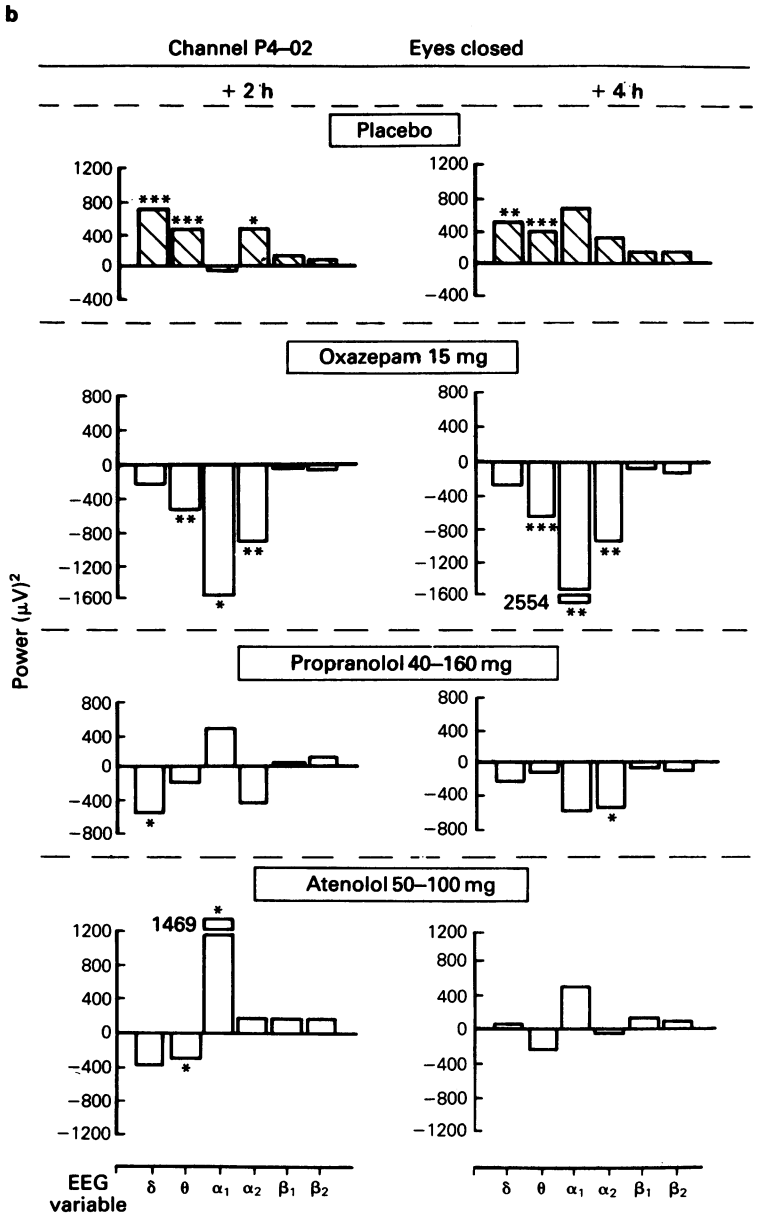
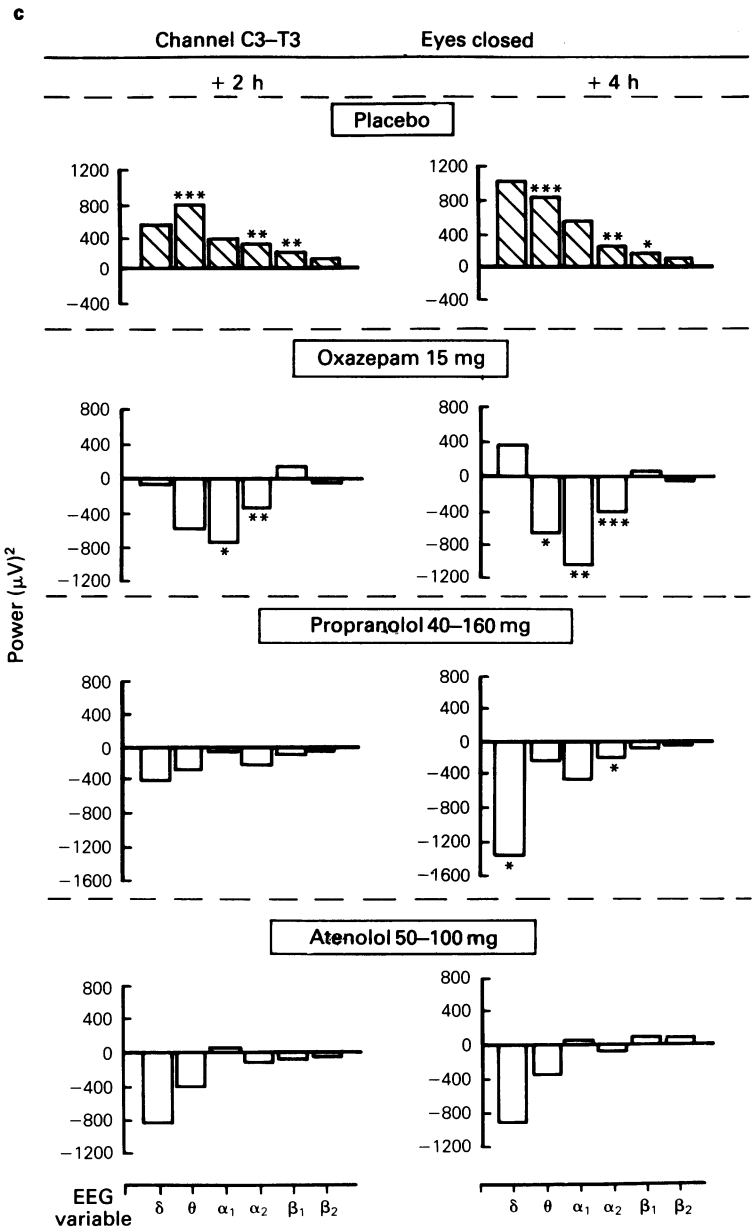


Figure 2 Effects of propranolol and atenolol on the EEG with eyes closed (see Figure 1 for symbols).


b
Channel P4–02
Eyes closed
+ 2 h
+ 4 h
Placebo
Oxazepam 15 mg
Propranolol 40–160 mg
Atenolol 50–100 mg
Power (μV)²
1200
800
400
0
−400
−800
−1200
−1600
1469
2554
EEG variable
δ θ α1 α2 β1 β2


c
Channel C3–T3
Eyes closed
+ 2 h
+ 4 h
Placebo
Oxazepam 15 mg
Propranolol 40–160 mg
Atenolol 50–100 mg
Power (μV)²
EEG variable
δ θ α1 α2 β1 β2

show any systematic drug effects, a single mean power spectrum representing the 5 min recording was calculated. Oxazepam reduced θ, α_1 and α_2 in all channels. α_2 power was reduced by propranolol in all channels. Atenolol increased α_1 power in P3–01 and P4–02.

Body sway

The results are given in Tables 1 a, b and c. The spectra for body sway with eyes open and eyes closed were analysed separately, and in each case two principal components accounted for 84% of the variance. The structure of the components indicated that the spectra could be represented by a low (0.05–2 Hz) and a high (2.25–4 Hz) frequency variable. The weights of the components were negative, and therefore a decrease in score represented an increase in body sway. Analysis of the spectra using four variables (0.05–1 Hz, 1.25–2 Hz, 2.25–3 Hz and 3.25–4 Hz) did not provide any additional information.

Body sway with eyes open was unaffected by all drugs. In the recordings with eyes closed, oxazepam meaned over time increased ($P < 0.05$) low frequency activity, while atenolol increased the high frequency component ($P < 0.05$). The value for atenolol differed ($P < 0.05$) from propranolol, but not from oxazepam. For individual doses, atenolol (100 mg) was higher than placebo ($P < 0.05$), while at individual sessions, atenolol (100 mg) differed from placebo only at 4 h post-ingestion ($P < 0.05$). At individual times, oxazepam increased both components at 2 h post-ingestion ($P < 0.05$).

Discussion

The present studies with the electroencephalogram suggest that both propranolol and atenolol have a depressant effect on the central nervous system. All doses of both antagonists modified electrical activity, and the majority of the changes were consistent with sedation. With

Table 1a Effect of β-adrenoceptor antagonists on body sway – means over dose and post-ingestion times (means for 12 subjects)

Measure		*Placebo*	*Oxazepam*	*Propranolol*	*Atenolol*
† Body sway					
Eyes open	0.05–2 Hz	0.0061	0.2309	–0.1015	0.0258
	2.25–4 Hz	–0.0068	0.0658	0.0988	–0.0373
Eyes closed	0.05–2 Hz	0.3015	–1.0087*	–0.1288	–0.0829
	2.25–4 Hz	0.1833	–0.2752	0.0847	–0.5147*

Significance levels: * $P < 0.05$.
† For body sway, the values tabulated are scores on the principal components, which have negative weights. A decrease in score therefore represents an increase in sway.
The pooled estimates of standard error from the analysis of variance for the following variables were:
Eyes open (0.05–2 Hz) = 0.2896; eyes open (2.25–4 Hz) = 0.1395
Eyes closed (0.05–2 Hz) = 0.6274; eyes closed (2.25–4 Hz) = 0.4228

Table 1b Effects of β-adrenoceptor antagonists on body sway – means over post-ingestion times (means for 12 subjects)

			Oxazepam	*Propranolol*			*Atenolol*	
Measure		*Placebo*	*15mg*	*40mg*	*80mg*	*160mg*	*50mg*	*100mg*
† Body sway								
Eyes open	0.05–2 Hz	0.0061	0.2309	–0.3436	0.1099	–0.0709	0.1960	–0.1444
	2.25–4 Hz	–0.0068	0.0658	0.1182	0.1395	0.0388	0.0091	–0.0837
Eyes closed	0.05–2 Hz	0.3105	–1.0087*	0.1870	0.1029	–0.6762	0.5682	–0.7341
	2.25–4 Hz	0.1833	–0.2752	0.1499	0.3615	–0.2573	–0.1289	–0.9006*

Significance levels: * $P < 0.05$.
† Values for body sway variables are scores on the principal components, which have negative weights. A decrease in score therefore represents an increase in sway.

Table 1c Effect of β-adrenoceptor antagonists on body sway (eyes closed) (means for 12 subjects)

Measure	*Time after ingestion (h)*	*Placebo*	*Oxazepam 15mg*	*Propranolol 40mg*	*Propranolol 80mg*	*Propranolol 160mg*	*Atenolol 50mg*	*Atenolol 100mg*
0.05–2 Hz	2	0.2198	-1.7502*	-0.4041	-0.2024	-0.9976	0.8876	-1.0432
	4	0.3833	-0.2671	0.7780	0.4082	-0.3548	0.2489	-0.4251
2.25–4 Hz	2	0.2176	-0.8338*	-0.0282	0.2905	-0.2868	0.3391	-0.5979
	4	0.1490	0.2835	0.3282	0.4326	-0.2278	-0.5969	-1.2032*

Significance levels: * $P < 0.05$.

eyes open the increase in α activity during the day associated with the rising phase of alertness related to the circadian rhythmicity of the individual was diminished by all drugs, though the magnitude of the effect was less with the antagonists than with oxazepam. Atenolol also reduced the circadian rise in the power of the low frequencies of the β band (13–20 Hz), and subjective assessments with this drug reflected decreased alertness. These findings of sedation are in general agreement with previous studies (Roubicek, 1976; Wagner *et al.*, 1981; Eschmann *et al.*, 1983; Matousek *et al.*, 1984).

The observations with eyes closed, when the subjects were not required to perform any mental activity, are more difficult to interpret. Propranolol, but not atenolol, reduced the circadian rise in the intensity of the higher frequencies of the α band, though the effect was less obvious than that with oxazepam. However, oxazepam and the antagonists affected the lower α frequencies differently. Oxazepam decreased

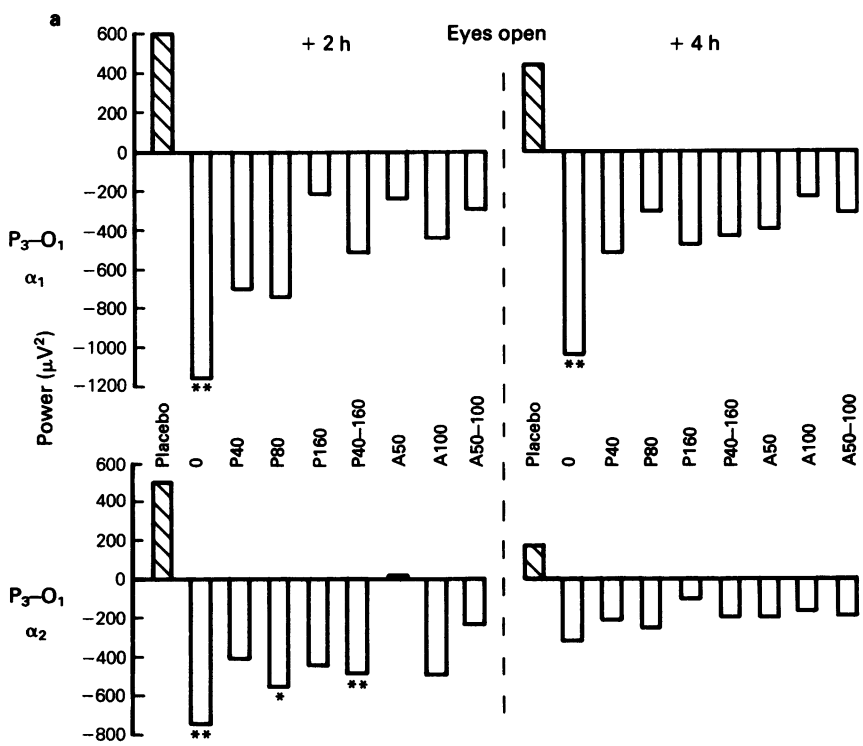
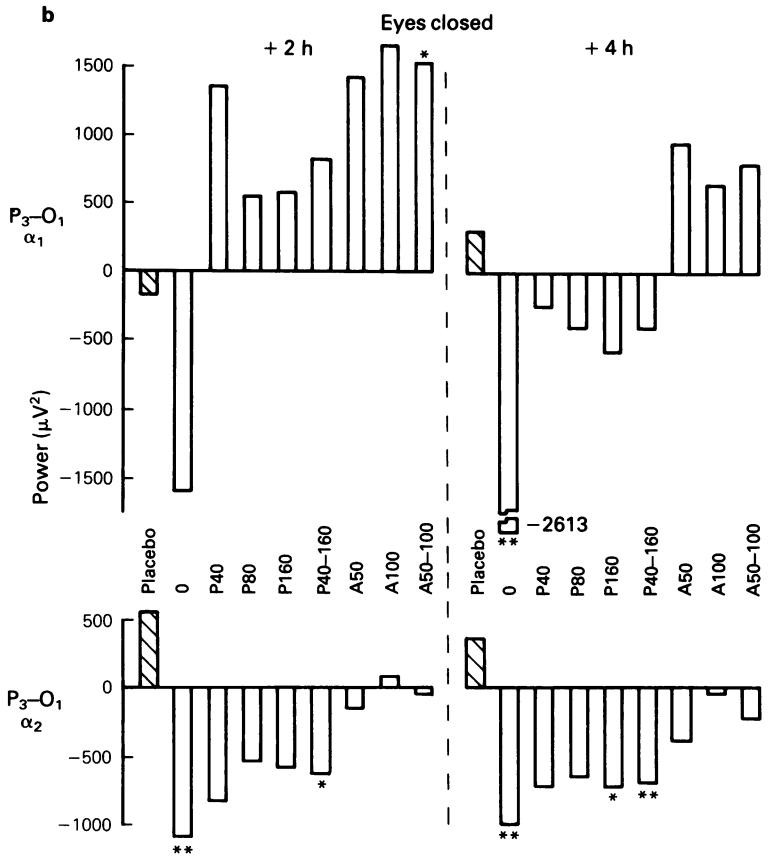


Figure 3 Effect of individual doses of propranolol (P) and atenolol (A) on α activity (see Figure 1 for symbols).



7.5–10 Hz activity in the occipital derivation, and this was consistent with subjective sedation, while atenolol increased power in this range. An effect of propranolol could not be established statistically, although inspection of the data suggests an effect cannot be excluded. The effect of the antagonists on the lower α frequencies would suggest activation, though, in view of the consistent evidence of a depressive effect on the higher frequencies, the behavioural significance of the changes at lower frequencies is not clear.

The conflicting effects of the β-adrenoceptor antagonists on α activity suggest that the activity of these drugs cannot be interpreted simply in terms of sedation or arousal. Increased α activity could reflect a reduced tendency to fall asleep with eyes closed, since drowsiness is associated with decreased α activity. In this way the increases in lower α frequencies would be interpreted as vigilance-stabilising. Such a mechanism has been suggested from studies with propranolol in narcoleptic patients (Kales *et al.*, 1979; Meier-Ewert *et al.*, 1985). On the other hand, the apparently sedative effects in the EEG with eyes open with both antagonists may be interpreted as a reduced ability to concentrate, which was reflected in the subjective assessments. This could imply impaired attention since the subjects were required to perform mental arithmetic during the recordings with eyes open.

The sedative action of both β-adrenoceptor antagonists implied by changes in the EEG is supported by decreased subjective alertness in the case of atenolol, but not with propranolol (Currie *et al.*, 1988). It could be that the complexity of the effect of these drugs on the EEG is reflected in the difficulty which subjects experience in defining their behavioural impressions, and that in turn this difficulty leads to inconsistent subjective responses between individuals. It is possible that the EEG is particularly sensitive, and in this way may indicate more readily the potential effects of a drug. Indeed, changes in the EEG which could be interpreted as sedative

were seen more consistently between subjects than were subjective assessments of reduced alertness.

Body sway was modified with oxazepam and atenolol, but not with propranolol. Changes in body sway could reflect modulation of either the central or peripheral control of posture. In the present experiment oxazepam increased mainly the lower frequency component of body sway which is believed to reflect control by the vestibular system and fine postural readjustment of muscular origin, while atenolol affected only the higher frequency component which is believed to be associated with fine control only.

Though the overall control of body sway involves inputs from both the central and peripheral nervous systems, it is likely that disturbance of central control would determine largely whether body sway is affected. Drugs which impair performance, such as oxazepam and diazepam, modify body sway, whereas similar drugs without obvious behavioural effects, such as clobazam, dipotassium chlorazepate and desmethyldiazepam tend to leave body sway unaffected (Baron *et al.*, 1977; Sittig *et al.*, 1982; Patat & Foulhoux, 1985). However, the effect of atenolol could have been mediated through the peripheral control of posture, since impaired psychomotor performance is not an obvious effect of this drug (Nicholson & Wright, 1980; Currie *et al.*, 1988).

In conclusion, the present study suggests that the β-adrenoceptor antagonists, propranolol and atenolol, modulate the central nervous system of healthy subjects, though the changes are apparently less severe than those induced by a relatively low dose of a benzodiazepine. There is no evidence to indicate that hydrophilic drugs are free of such central effects, though changes in body sway suggest that modulation of the peripheral nervous system may also be involved. Obvious changes in psychomotor performance have not been detected with propranolol or atenolol (Currie *et al.*, 1988), but changes in the electroencephalogram, body sway and memory suggest the presence of more subtle effects than with other drugs, such as benzodiazepines. In this way the β-adrenoceptor antagonists should be used with caution by individuals involved in skilled work, particularly those whose skills involve memory and vigilance.

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References

Baron, J. B., Ushio, N., Takeya, T. & Wittington, F. (1978). Action de deux anxiolytiques sur la posture et le reflexe d'Hoffmann. *Psychologie Medicale*, **10A**, 165–173.

Currie, D., Lewis, R. V., McDevitt, D. G., Nicholson, A. N. & Wright, N. A. (1988). Central effects of β-adrenoceptor antagonists I – performance and subjective assessments of mood. *Br. J. clin. Pharmac.*, **26**, 121–128.

Eschmann, G., Irrgang, V. & Ruther, E. (1983). Effects of beta-receptor blockers in pharmacology EEG. *Neuropsychobiology*, **10**, 190–192.

Gengo, F. M., Huntoon, L. & McHugh, W. B. (1987). Lipid-soluble and water-soluble beta-blockers. Comparison of the central nervous system depressant effect. *Arch. Intern. Med.*, **147**, 39–43.

Itil, T. M. & Itil, K. Z. (1983). Central mechanisms of clonidine and propranolol in man. Quantitative pharmaco-EEG with antihypertensive compounds. *Chest*, **83**, Supplement, 411–416.

Kales, A., Soldatos, C. R., Cadieux, R., Bixler, E. I., Tan, T.-L. & Scharf, M. B. (1979). Propranolol in the treatment of narcolepsy. *Ann. Intern. Med.*, **91**, 732–743.

Matousek, M., Hjalmarson, A., Koch, J. & Petersen, I. (1984). The use of the EEG for assessment of vigilance changes caused by beta-blockers. *Neuropsychobiology*, **12**, 55–59.

Meier-Ewert, K., Matsubayashi, K. & Benter, L. (1985). Propranolol: long-term treatment in narcolepsy – cataplexy. *Sleep*, **8**, 95–104.

Mock, H. & Kunkel, H. (1982). EEG-profile of mepindolol as compared to diazepam and placebo. In *Electroencephalography in drug research*, ed. Herrmann, W. M., pp. 509–521. New York: Gustav Fischer.

Nicholson, A. N. & Wright, C. M. (1980). β-adrenoceptor antagonists: studies on behaviour (delayed differentiation) in the monkey (*Macaca mulatta*). *Br. J. clin. Pharmac.*, **68**, 75–82.

Patat, A. & Foulhoux, P. (1985). Effect on postural sway of various benzodiazepine tranquillizers. *Br. J. clin. Pharmac.*, **20**, 9–16.

Roubicek, J. (1976). Effect of β-adrenoceptor blocking drugs on EEG. *Br. J. clin. Pharmac.*, **3**, 661–665.

Salem, S. A. & McDevitt, D. G. (1983). Central effects of beta-adrenoceptor antagonists. *Clin. Pharmac. Ther.*, **33**, 53–57.

Saletu, B., Grunberger, J., Taeuber, K. & Nitsche, V. (1982). Relation between pharmacodynamics and -kinetics: EEG and psychometric studies with cinolazepam and nomifensine. In *Electroencephalography in drug research*, ed. Herrmann, W. M., pp. 89–111. New York: Gustav Fischer.

Sittig, W., Badian, M., Rupp, W. & Taeuber, K. (1982). Performance tests and pharmaco EEG after

1, 4 and 1, 5 benzodiazepines. In *Electroencephalography in drug research*, ed. Herrmann, W. M., pp. 113–129. New York: Gustav Fischer.

Wagner, W., Ott, H., Herrmann, W. M., McDonald, R. J. & Berzewski, B. (1981). A multi-dimensional concept for measuring CNS effects of beta-adrenoceptor blocking agents in human pharmacology. *Int. J. clin. Pharmac., Ther. Tox.*, **19**, 23–33.

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