Use of auditory evoked responses as a measure of recovery from benzodiazepine sedation

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Summary
The amplitude of the P_{300} component of auditory evoked responses was found to be depressed by benzodiazepine sedation and was subsequently used to monitor the recovery of volunteers sedated with midazolam. The amplitude of the evoked responses was found to be highly correlated with blood midazolam levels but to be no more sensitive than standard psychomotor testing in assessing recovery from sedation.

Introduction
Evoked potentials are electrical potentials generated by the cerebral cortex in response to auditory, sensory or visual stimuli presented to the subject. These potentials can be used to test the integrity of specific neural pathways and to elicit specific responses and can be detected using suitable scalp electrodes and appropriate recording apparatus. A light flashed in the eye will produce a small electrical response which can be recorded over the occipital cortex - a 'visual evoked response'. An auditory stimulus will produce a similar cortical response. The stimuli must be repetitive so that the signals detected can be averaged to separate them from background EEG activity. Once this is achieved evoked responses are very reproducible and appear similar in different subjects. In recent years auditory evoked responses have been used as a measure of depth of anaesthesia[1,2], the latency of the response increasing and its amplitude decreasing with increasing depth of anaesthesia.

This study was carried out to examine the possibility of using auditory evoked potentials as a means of assessing patient recovery from CNS depressant drugs using midazolam sedation as a model. The study was carried out in two parts. In the first part auditory evoked potentials (AEPs) were assessed before and after oral midazolam was administered to volunteers. The changes produced by the midazolam were examined and the most significant selected for further study in the second part of the investigation. In this part a large intravenous dose of midazolam was administered and AEPs recorded for several hours. The resultant CNS depression was assessed using both AEPs and standard psychomotor testing and the results correlated with blood midazolam levels.

Methods
Study 1
Following University Medical Research Ethical Committee approval 20 healthy male volunteers were recruited into the study. They were aged 21-27 years, weighed 55-85 kg and were taking no other medications. Silver/silver chloride electrodes were attached to the scalp at the standard sites FP_Z, F_Z, C_Z and P_Z as well as to the mastoid processes. Baseline AEPs were recorded from midline sites referred to linked mastoids.

Recordings were carried out using an 'oddball' paradigm in which occasional low pitched tones of 1000 Hz, the responses to which were measured, were randomly interspersed among frequent high pitched tones of 2000 Hz. A total of 32 low pitched tones were presented, the average proportion of these being 15%. To prevent the subject becoming refractory to the stimulus a button press response was required for the rare tones. Trials contaminated by eye movement were automatically rejected.

The evoked signals were amplified and recorded using a Grass Neurodata Acquisition system and were processed using the Data Acquisition in Neurophysiology (DAN) system with an Apple II microprocessor and ancillary hardware.

The subjects were then randomly allocated to receive either midazolam 15 mg or placebo orally, in a double-blind manner. One hour later the AEPs were again recorded by an observer who was unaware of which tablet the subject had received. The results were then analysed using independent and paired *t*-tests to examine differences between the groups.

Study 2
In this part of the study the use of P_{300} amplitude as a measure of recovery from sedation was investigated in greater detail (see below) and compared with standard psychomotor techniques.

Seven healthy male volunteers aged 30-35 years and weighing 45-90 kg were recruited into the study. Scalp electrodes were attached as in method 1 and baseline auditory evoked responses recorded. Psychomotor testing was then carried out using a four choice reaction timer (CRT)[3] and a critical flicker fusion frequency (CFFF) apparatus[4]. The CRT consisted of an array of coloured lights which illuminated on a random basis. Immediately a light illuminated the subject had to press a button to extinguish it, the latency of the response being an accurate measure of sedation[5]. The responses were recorded on magnetic tape and subsequently decoded using a computer programme. The CFFF was measured by the subject viewing a flashing light, the frequency of which was gradually increased until the subject perceived it as a constant source. The frequency at

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which this occurs decreases with increasing sedation and can be used as a measure of alertness. All subjects underwent a minimum of 20 rehearsals in an effort to eliminate practice effects from the testing.

Once baseline psychomotor values had been obtained midazolam 0.3 mg/kg was administered intravenously to all subjects at a rate of 1 mg/min. AEPs, CRTs and CFFFs were repeated 1 h after the start of the infusion and hourly thereafter for the next five hours. A blood sample for estimation of blood midazolam levels by gas liquid chromatograph was taken at the start of each test session and correlated (Pitmann Rho correlation) with AEP, CRT and CFFF measurements.

Results

Study 1

The placebo and midazolam groups were similar with regard to the subjects' age and weight (Table 1). There were obvious changes in both the amplitudes and latencies of the AEPs produced by the group treated with midazolam; the results for one subject are shown in Figure 1. It was found that although both the amplitude and latency of several components of the AEP were significantly altered, the amplitude of P_{300}, a positive wave (by convention a downward deflection is positive) occurring 300 ms after the stimulus showed the greatest change (Table 1). The P_{300} represents the cortical response to the auditory stimulus and was defined as the maximum positivity occurring between 250 ms and 450 ms post-stimulus relative to the pre-stimulus baseline and was selected for further study.

Table 1. Mean (±SD) age, weight, and P_{300} amplitudes and latencies

	Midazolam	*Placebo*
Age (years)	22.1±2.03	22.1±1.10
Weight (kg)	69.2±8.77	71.7±8.38
Baseline P_{300} (μV)	−13.62±3.28	−12.29±6.41
1 h P_{300} (μV)	−7.70±5.44■	−13.18±5.73
Baseline P_{300} latency (ms)	311±15.9	308±26.9
1 h P_{300} latency (ms)	331±27.1●	309±29.1

●$P<0.05$, ■$P<0.01$ (difference from baseline)

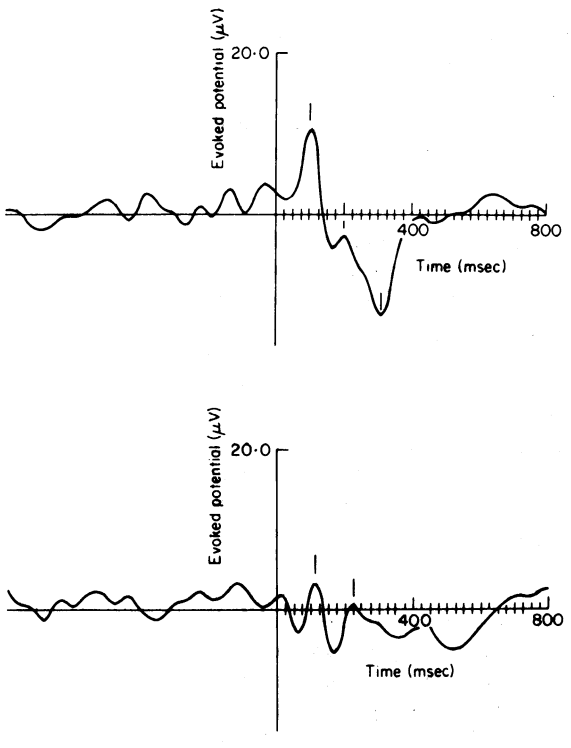

Figure 1. Upper graph, auditory evoked response prior to midazolam. Lower graph, evoked responses one hour after oral midazolam 15 mg

Table 2. Mean (±SD) blood midazolam levels, P_{300} amplitude, CRTs and CFFFs

Time (h)	*Blood levels (ng/ml)*	*AEP (P_{300}) (μV)*	*CRT (ms)*	*CFFF (Hz)*
0	—	−12.9±3.26	397±47	26.6±5.66
1	248±50	−2.6±1.16	951±325	13.4±0.79
2	167±65	−6.5±2.54	758±274	18.8±2.50
3	112±57	−7.7±2.58	553±161	22.5±5.15
4	87±49	−9.4±2.75	515±160	24.6±4.71
5	62±41	−10.5±1.62	433±48	26.1±4.49
6	40±11	−12.2±2.90	401±31	26.9±4.93

Study 2

The infusion of midazolam was successfully completed in all cases and AEPs, pyschomotor tests and blood samples obtained from all subjects. The results are summarized in Table 2 and show that both the P_{300} amplitude and psychomotor testing showed marked impairment which gradually recovered over the next 6 h. Only three subjects were alert enough to enable them to complete the first set of tests but all subjects completed all subsequent testing. At the end of the 6 h period all parameters had returned to within 5% of baseline levels. Despite this, measurable blood levels of midazolam were still present in all subjects at times when both objectively and subjectively they were fully recovered. In this respect the tests showed no difference in discrimination.

The blood midazolam levels were highly correlated with P_{300} amplitude ($r=0.81$, $P<0.001$). Analysis of individual results showed that this correlation was significant for all patients ($P<0.05$). The analysis showed a similar degree of correlation between CRTs, CFFFs and midazolam blood levels.

Discussion

The AEPs, CFFFs and CRTs showed a high correlation with blood midazolam levels and achieved baseline levels at a similar time suggesting that they are of similar sensitivity in detecting midazolam sedation although CFFF appeared to be least affected. This is in keeping with other work that has suggested that CRTs recover more slowly than CFFFs[6]. The positive findings of this study were that CRTs were as sensitive a measure of sedation as AEPs although the latter avoids the long and often impractical rehearsal required to eliminate psychomotor practice effects. It should be noted, however, that for the P_{300} component of AEPs to be reproducible the subject's attention is required[7] and hence the need to respond by pushing a button. The method would probably be unreliable in patients anaesthetized or too sedated to co-operate.

The major disadvantage of the AEPs were the complexity and expense of the equipment required and the expertise required to record and interpret the results. Despite both subjective and psychomotor recover, measurable amounts of midazolam were still

present in the blood at 6 h and the AEPs proved no more sensitive than the CRT in detecting any residual subclinical effect that this was still exerting. It is therefore concluded that the advantages of the AEPs are small in comparison to the complexity of the method.

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