

Dose-dependent effects of Flumazenil on cognition, mood, and cardio-respiratory physiology in healthy volunteers.

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Objectives To assess the possible effects of flumazenil on cognitive processing, physiology, and mood.

Design A double-blind, placebo controlled, four-way cross-over study, using healthy volunteers.

Methods On each of 4 separate visits, 16 participants received 0.5mg, 2.5mg, 5.0mg of flumazenil, or normal saline. They then performed a computerised test battery assessing cognitive function. Measures of pulse rate, arterial oxygen saturation and mean arterial pressure were also taken. Finally, participants completed visual analogue scales assessing their subjective mood state.

Results The majority of cognitive tasks showed dose-dependent declines in performance. Mean arterial pressure was significantly reduced, as was pulse rate. Subjective alertness showed a similar decline.

Conclusions Flumazenil has been clinically described as an agent with few intrinsic properties, whose primary effect lies in its ability to reverse benzodiazepine-induced states. This study has shown that flumazenil does possess intrinsic activity which have a significant effect on cognition, cardiovascular physiology and mood. Clinicians need to be aware of these effects.

Benzodiazepines are known to produce anxiolytic and amnesic effects in humans across a wide range of behavioural paradigms.¹⁻² It is logical to assume that benzodiazepine antagonists should reverse such effects, and indeed, the antagonist flumazenil (formerly known as Ro 15-1788) has been shown to rapidly reverse the sedative and anxiolytic effects of benzodiazepines in a dose-dependent manner.³ In the clinical environment, flumazenil is an essential component of the emergency armamentarium and should be available whenever benzodiazepine sedation is being provided. The safety of benzodiazepine sedation in medicine and

dentistry has been significantly enhanced by flumazenil, largely because of its ability to reverse the cardio-respiratory depressant effects of the benzodiazepines.⁴⁻⁶ In acute use, flumazenil is normally reserved for use in sedation emergencies, although some clinicians may use it to expedite recovery of ambulatory patients.

At the behavioural level, the effects of flumazenil on benzodiazepine-induced amnesia remain equivocal. For example, it has been reported that flumazenil attenuated, but did not fully reverse, the amnesic effects of diazepam.⁷ Similarly, it has been found that while flumazenil reversed the psychomotor impairments induced by midazolam, it had no such effect on amnesia induced by the same compound.⁸ The latter authors argued however that flumazenil may demonstrate a differential sequence of reversal, with psychomotor impairments having a lower reversal threshold than any amnesic deficits, resulting in the differential sensitivity of these measures.

Similarly, in surgical patients, some studies have also reported that benzodiazepine-induced amnesia may be partly reversed by flumazenil administration.⁹ Furthermore, studies using healthy volunteers have shown that the amnesic effects of benzodiazepines can be fully reversed by flumazenil at appropriate doses¹⁰⁻¹¹ though both of these studies lacked placebo controls. In a well controlled double-blind study, it was reported that a dose of 1.0 mg of flumazenil administered intravenously was sufficient to completely reverse midazolam-induced amnesia.¹²

Rather more interesting is the possibility of memory enhancement following flumazenil administration alone. In a review of the possible intrinsic actions of flumazenil¹³ the authors reported that the compound does show intrinsic activity in a variety of behavioural, neurological, electrophysiological, and biochemical test situations, in both animals and humans. However, that review did not specifically address cognitive processing. Several other studies have not revealed clear behavioural effects in humans following flumazenil administration alone.^{3,11-12} Others have indicated that flumazenil administration may produce some intrinsic physiological actions¹⁴ but may have little effect on cognitive processing.^{3,14} However, it should be pointed out that the tasks described in these studies (i.e. reaction time measures, digit symbol substitution etc) do not typically assess episodic memory.

Several laboratory animal studies have indeed shown that flumazenil administration may actually enhance certain types of mnemonic processing. In one such study, rats received post-training intraseptal injections of flumazenil, and this significantly enhanced retention of working memory over a long delay. The authors argued that this facilitation was due to the interaction of flumazenil with the septohippocampal cholinergic system during a critical phase in memory consolidation.¹⁵ In another study using

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Table 1 Results from measures of attention.

Condition	Saline (1)	Flumazenil 0.5mg(2)	Flumazenil 2.5mg(3)	Flumazenil 5.0mg(4)	Significant post-hoc Comparisons
SRT pre	259.5 (4.7)	252.9 (5.0)	263.5 (4.2)	253.1 (5.2)	
SRT post	267.5 (5.5)	267.1 (6.0)	271.0 (5.8)	266.5 (5.5)	
Post-pre	8.0 (5.6)	14.2 (5.5)	7.5 (5.1)	13.4 (6.1)	ns
CRT pre	389.6 (10.6)	377.8 (7.2)	383.8 (9.4)	381.0 (9.7)	
CRT post	387.9 (8.4)	388.1 (9.2)	406.3 (14.0)	383.2 (8.6)	
Post-pre	1.7 (7.8)	10.3 (5.2)	22.5 (10.1)	2.2 (5.4)	ns
CRTACC pre	96.4 (0.5)	94.6 (1.0)	95.5 (0.8)	95.6 (0.6)	
CRTACC post	97.4 (0.5)	97.0 (0.9)	96.9 (0.8)	96.4 (0.5)	
Post-pre	1.0 (0.8)	2.4 (0.9)	1.4 (0.8)	0.8 (0.8)	ns
DVACC pre	98.1 (0.5)	97.3 (1.3)	96.7 (1.1)	98.8 (0.5)	
DVACC post	97.5 (0.7)	96.9 (1.3)	98.2 (0.7)	99.2 (0.5)	
Post-pre	0.6 (0.8)	-0.4 (0.7)	1.5 (1.4)	0.4 (0.7)	ns
DVRT pre	382.4 (4.8)	383.1 (5.9)	388.7 (6.4)	378.6 (8.2)	
DVRT post	378.9 (6.9)	401.4 (7.4)	406.4 (8.7)	405.1 (7.3)	I Vs 2, P<0.05
Post-pre	-3.5 (4.8)	18.3 (6.3)	17.7 (7.8)	26.5 (4.3)	I Vs 4, P<0.01

The results are shown as means, with 95% confidence intervals in parentheses; ns: not significant.

The units are in milliseconds for reaction times, and percentages for accuracy. The tasks are: SRT (simple reaction time); CRT (choice reaction time); CRTACC (choice reaction time accuracy); DVACC (digit vigilance accuracy); and DVRT (digit vigilance reaction time).

rats, it was found that flumazenil enhanced spatial learning in a dose-dependent manner, this improvement being independent of the anxiolytic effects of the agent. Interestingly, enhancement was also seen following introduction of the antagonist CGS 8216 and the inverse-agonist β -CCM.¹⁶ However, such positive results are not always found.¹⁷

The data described above indicate that the administration of flumazenil may have enhancing properties with regards to certain types of cognitive processing. However, the effects of this agent have typically been evaluated in surgical patients or in terms of reversing the effects of previously administered benzodiazepines. It has been pointed out however that there are several problems in comparing results from such studies as they typically differ in the doses of benzodiazepines and flumazenil used; method of drug administration; selection of appropriate memory tests; lack of control groups; and absence of pre-treatment assessments.⁹ Thus, using a double-blind, within-subjects, placebo-controlled, crossover design, the aim of this study was to assess the possible dose-dependent effects of flumazenil on cognition, mood and cardio-respiratory physiology in healthy volunteers.

Methods

Patients

The appropriate number of participants was established by power analysis; 5 male and 11 female healthy volunteers aged between 20–23, (mean=21.6) were recruited from dental undergraduates attending the University of Newcastle Dental School. In a double-blind, pseudo-randomised order (where balanced treatment order was ensured by random allocation of patients to one cell of a Latin-Squares grid) the 16 volunteers received 0.5 mg, 2.5 mg and 5.0 mg flumazenil, and placebo (0.9% saline) on 4 separate occasions. The volume of each drug condition was standardised; the total volume in each case was 50 ml, with the drug concentrations being adjusted accordingly. These testing sessions were separated by at least 48 hours, and were equally spaced. Each participant was paid, and gave written, witnessed, and informed consent which was approved by the Joint Ethics Committee of Newcastle and North Tyneside Health Authority, and the University of Northumbria, Division of Psychology Ethics Board.

Procedure

In each testing session a 22 g intravenous cannula was sited in the

dorsum of the hand. The flumazenil (Anexate, Roche Products Ltd), was injected intravenously at one of the three doses; the same procedure being followed for the injection of the placebo (0.9% saline). Pulse, arterial oxygen saturation and blood pressure were monitored immediately prior to drug administration and at 10 minutes intervals for a total of 50 minutes. The time intervals of 10 minutes and 30 minutes were chosen for analyses as these represent blood levels of the drug just after administration and after another 20 minutes. It has been shown that between 97–99% of benzodiazepine receptor occupancy is achieved at a flumazenil dose of 0.1 mg/kg.¹⁸ The normal flumazenil dose used clinically to reverse benzodiazepine sedation is in the range 0.004–0.008 mg/kg. The test doses were selected on the basis that 0.5 mg represented a typical clinical dosage whilst 2.5 mg and 5.0 mg would show the effect of increasing receptor occupancy (approximately 35% and 70% respectively). Currently, there are no reported side-effects or adverse reactions to flumazenil administration alone, in doses of up to 100 mg IV, in healthy individuals who are not concurrently taking benzodiazepines.

Cognitive assessment

Following drug or placebo administration cognitive performance was assessed using a tailored version of the Cognitive Drug Research (CDR Ltd, Reading, UK) computerised test battery¹⁹ under both baseline (prior to drug administration), and test (5 minutes after drug delivery) conditions. Participants were tested in the same room during each visit in order to control for context-dependent influences and were tested individually to prevent covariance in the scores.

The CDR system includes a number of measures specific to particular aspects of 'attention' (simple reaction time: SRT, choice reaction time: CRT and digit vigilance: DV); 'working memory' (spatial memory: SM, immediate word recall: IWR); and 'long-term memory' (delayed picture recognition: PR, delayed word recognition: WR, and delayed word recall: DWR). These tests can also be analysed in terms of the factors onto which they load. 'Speed of memory processes' reflects the time taken to recall an item from episodic memory. 'Quality of episodic memory' is a measure of the ability to store, hold and retrieve episodic information. 'Power of attention' reflects the intensity of effortful concentration. 'Continuity of attention' reflects the ability to sustain concentration. Finally, 'quality of working memory' reflects the attributes of working memory

Table 2 Results from measures of working memory.

Condition	Saline (1)	Flumazenil 0.5mg(2)	Flumazenil 2.5mg(3)	Flumazenil 5.0mg(4)	Significant post-hoc Comparisons
IWR pre	8.3 (0.6)	7.9 (0.6)	8.2 (0.4)	7.9 (0.5)	
IWR post	8.5 (0.6)	7.0 (0.5)	7.6 (0.6)	7.0 (0.6)	
Post-pre	0.2 (0.6)	-0.9 (0.5)	-0.4 (0.6)	-0.9 (0.6)	ns
SMSI pre	0.9 (0.0)	0.9 (0.4)	0.9 (0.0)	1.0 (0.0)	
SMSI post	0.9 (0.0)	0.9 (0.0)	0.9 (0.0)	0.9 (0.0)	
Post-pre	-0.0 (0.0)	-0.0 (0.0)	-0.0 (0.0)	-0.1 (0.0)	ns
SMRT pre	730.9 (54.2)	687.7 (70.3)	665.8 (37.1)	621.3 (20.3)	
SMRT post	630.7 (28.1)	709.2 (93.0)	610.1 (93.0)	606.3 (24.4)	
Post-pre	-100.2 (41.4)	21.5 (77.4)	-55.7 (28.4)	-15.0 (21.0)	ns

The results are shown as means, with 95% confidence intervals in parentheses; ns: not significant.

The units are in milliseconds for reaction times, and percentages for accuracy. The tasks are: IWR (immediate word recall); SMSI (spatial memory sensitivity index); and SMRT (spatial memory reaction time).

processes.

Responses are made using a 2-button response box labelled ‘yes’ and ‘no’, the use of which enables performance to be accurately measured even in sedated patients. The battery has been shown to be sensitive to the temporary amnesic effects of benzodiazepines^{2,20} and is specifically designed to be sensitive to improvements in cognitive function, as well as impairments. Full details of these tasks and their administration have been published before.¹⁹⁻²⁰

Mood assessment

‘Visual analogue scales’ assess subjective emotional state and have been found to be effective in measuring change over time in response to drug treatment.²¹ Their reliability and validity have also been well-documented.²² Participants rate their current subjective feelings on 16 scales by making a perpendicular mark across a 100 mm horizontal line lacking gradation. The line is anchored by two adjectives representing contrasting states of mind. The ratings are measured in mm, transformed, and weighted according to three factor loadings of ‘alertness’, ‘contentedness’, and ‘relaxation/calmness’.

Physiological measures

Monitoring of pulse rate, arterial oxygen saturation and mean arterial pressure was performed throughout testing using an automated

monitor (Datascopie Acutoplus), and for 30 minutes post-drug administration.

Statistical analysis

Drug-induced performance changes in the cognitive and mood variables under consideration were derived by subtracting the pre-dose (baseline scores on each visit) from the subsequent post-dose scores. These differences were examined across conditions using repeated-measures (the within-subjects factor being the three drug conditions) analyses of variance (ANOVA) using the Minitab for Windows statistical package. Post-hoc comparisons were conducted using Bonferroni-corrected, repeated-measures *t*-tests. Changes in the physiological measures were similarly analysed by comparing the groups at baseline, and at 10 minutes and 30 minutes post-drug treatment.

Results

Cognitive Assessment

As is conventional with studies using the CDR test battery, the variables tested were organised into four main categories:

i. Attention

Table 1 contains the means for pre-drug (baseline) and post-drug

Table 3 Results from measures of long-term memory.

Condition	Saline (1)	Flumazenil 0.5mg (2)	Flumazenil 2.5mg (3)	Flumazenil 5.0mg (4)	Significant post-hoc Comparisons
DWR pre	6.9 (0.5)	6.4 (0.6)	6.4 (0.5)	6.8 (0.6)	1 Vs 2, P<0.01
DWR post	8.5 (0.6)	5.0 (0.4)	5.3 (0.6)	4.5 (0.6)	1 Vs 3, P<0.001
Post-pre	1.6 (0.5)-1.4	(0.8)	-1.1 (0.4)	-2.3 (0.5)	1 Vs 4, P<0.001
WRSI pre	0.9 (0.0)	0.8 (0.0)	0.8 (0.0)	0.8 (0.0)	
WRSI post	0.9 (0.0)	0.7 (0.1)	0.8 (0.0)	0.8 (0.0)	
Post-pre	-0.0 (0.0)	-0.1 (0.1)	0.0 (0.0)	-0.0 (0.0)	ns
WRRT pre	746.1 (44.9)	785.0 (53.5)	692.9 (23.5)	668.5 (19.1)	
WRRT post	730.6 (35.5)	785.5 (48.7)	691.3 (23.1)	707.0 (29.3)	
Post-pre	-15.5 (25.0)	0.5 (43.9)	-1.6 (19.7)	38.5 (28.0)	ns
PRSI pre	0.7 (0.1)	0.8 (0.0)	0.8 (0.0)	0.8 (0.0)	
PRSI post	0.8 (0.0)	0.7 (0.1)	0.7 (0.0)	0.7 (0.0)	
Post-pre	0.1 (0.0)	-0.1 (0.1)	-0.1 (0.0)	-0.1 (0.0)	ns
PRRT pre	819.9 (35.8)8	11.4 (32.1)	825.7 (39.9)	775.8 (31.5)	
PRRT post	812.0 (23.2)	854.4 (43.6)	790.0 (29.9)	772.7 (26.4)	
Post-pre	-7.9 (21.1)	43.0 (22.9)	-35.7 (38.1)-	3.1 (34.9)	ns

The results are shown as means, with 95% confidence intervals in parentheses; ns: not significant.

The units are in milliseconds for reaction times, and percentages for accuracy. The tasks are: WR (word recognition sensitivity index); WRRT (word recognition reaction time); PRSI (picture recognition sensitivity index); PRRT (picture recognition reaction time).

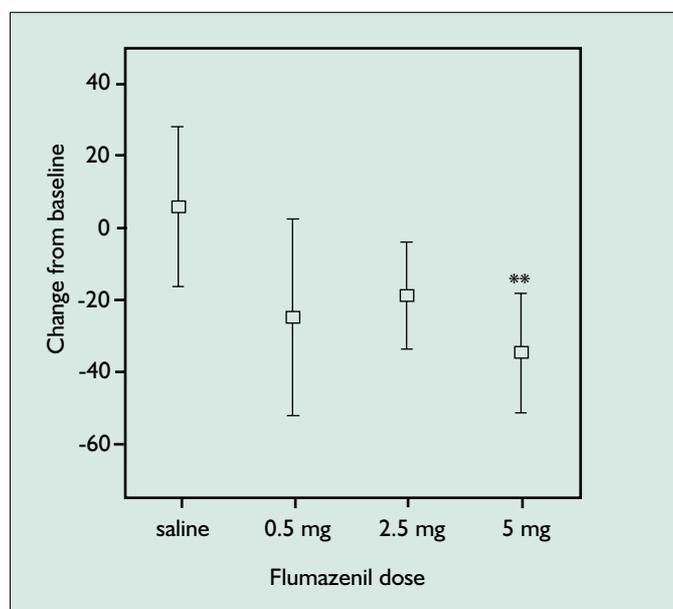


Figure 1 'Quality of episodic memory' factor following administration of 0.5 mg, 2.5 mg and 5.0 mg of flumazenil. Values represent mean changes from baseline with 95% confidence intervals (**, $P < 0.01$ compared with saline condition).

performance on measures of attention. The statistical analyses revealed no significant differences between saline and drug conditions simple reaction time (SRT) speed ($F < 1$); Choice Reaction Time (CRT) speed ($F_{3,45} = 2.47$, $P = 0.074$); and CRT accuracy ($F < 1$). To assess possible effects on the cognitive component of CRT (i.e. decision time), SRT responses were subtracted from CRT responses for each session. This analysis revealed no significant effect of condition ($F_{3,45} = 2.04$, $P = 0.122$). While digit vigilance (DV) accuracy showed no significant effect of condition ($F < 1$), the reaction time measure of this task did show a significant effect ($F_{3,45} = 4.52$, $P = 0.007$). A series of repeated measures *t*-tests revealed that the 0.5 mg and 5.0 mg flumazenil groups were both significantly slower post-drug compared with baseline performance, than the saline group ($t_{15} = 2.94$, $P = 0.010$; and $t_{15} = 3.87$, $P = 0.0015$ respectively). The 2.5 mg flumazenil group was also slower than the saline group, but this difference did not quite reach significance ($t_{15} = 1.91$, $P = 0.075$).

ii. Working memory

Table 2 contains the means for pre-drug (baseline) and post-drug performance on measures of working memory. These analyses revealed no significant effects in any of the cognitive measures. So, performance on the Spatial Memory (SM) task both in terms of sensitivity and reaction time did not differ significantly between conditions with respect to baseline ($F_{3,45} = 1.29$, $P = 0.289$; $F_{3,45} = 1.34$, $P = 0.275$ respectively). Finally, although there was a trend for a dose-dependent decline in Immediate Word Recall (IWR), performance on this task did not differ significantly between conditions ($F_{3,45} = 2.24$, $P = 0.097$).

iii. Long-term memory

Table 3 contains the means for pre-drug (baseline) and post-drug performance on measures of long-term memory. Analyses of performance on the word recall (WR) task revealed no significant differences, either for the sensitivity index or for the reaction time measures ($F_{3,45} = 1.24$, $P = 0.306$; and $F < 1$ respectively). Performance on the picture recognition (PR) task, in terms of both sensitivity and accuracy also showed no significant group differences ($F_{3,45} = 2.05$, $P = 0.120$; and $F_{3,45} = 1.30$, $P = 0.285$ respectively). However, performance on the delayed word recall (DWR) showed a

highly significant group effect ($F_{3,45} = 8.58$, $P = 0.000$). A series of repeated measures *t*-tests revealed that the saline condition differed significantly from all three flumazenil conditions ($t_{15} = 3.24$, $P = 0.0055$; $t_{15} = 4.74$, $P = 0.0003$; and $t_{15} = 6.97$, $P = 0.0000$ respectively). There were no other significant differences.

iv. Factors

Figures 1–2 represent the significant findings when the individual measures are further defined in terms of factors onto which the tasks load. Analysis of 'speed of memory processes' revealed no significant group difference ($F_{3,45} = 1.10$, $P = 0.359$). Analysis of 'quality of episodic memory' revealed a significant effect of condition ($F_{3,45} = 3.13$, $P = 0.035$). A series of repeated measures *t*-tests revealed that the saline condition differed significantly from the 5.0 mg drug condition ($t_{15} = 4.08$, $P = 0.001$), and showed a non-significant trend to differ from the 0.5 mg and 2.5 mg conditions ($t_{15} = 1.81$, $P = 0.09$, and $t_{15} = 1.92$, $P = 0.07$ respectively). There were no other significant differences. Similarly, for 'power of attention' the analyses revealed a significant effect of condition ($F_{3,45} = 3.72$, $P = 0.018$). A series of repeated measures *t*-tests revealed that the saline condition differed significantly from the 0.5 mg, 2.5 mg and 5.0 mg drug conditions ($t_{15} = 3.30$, $P = 0.0049$; $t_{15} = 2.50$, $P = 0.024$; and $t_{15} = 2.71$, $P = 0.016$ respectively). There were no other significant differences. No significant effects of condition were revealed for both 'continuity of attention' ($F_{3,45} = 1.12$, $P = 0.350$), and 'quality of working memory' ($F_{3,45} = 1.14$, $P = 0.341$).

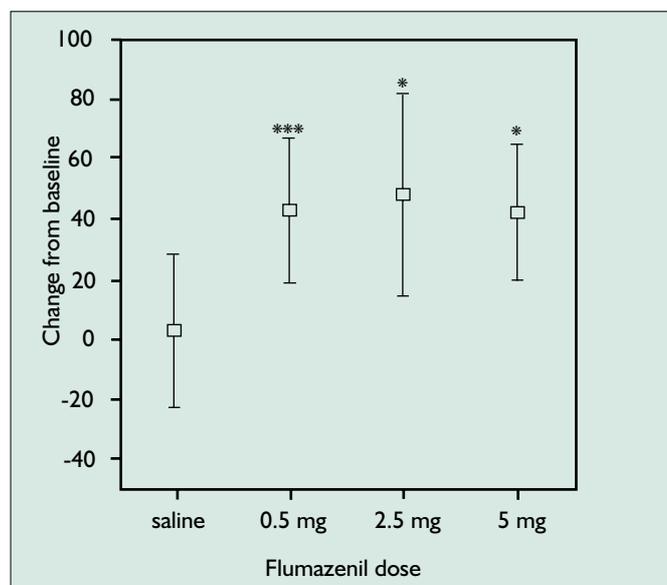


Figure 2 'Power of attention' factor following administration of 0.5 mg, 2.5 mg and 5.0 mg of flumazenil. Values represent mean changes from baseline with 95% confidence intervals (*, $p < 0.05$; ***, $P < 0.005$ compared with saline condition). A positive change from baseline represents a decrement (slowing of performance).

Mood

Figure 3 show the means for pre-post drug performance on measures of mood for each drug condition. While the mood measures of 'calmness' and 'contentedness' did not show any effects of condition ($F_{3,45} = 0.33$, $P = 0.803$, and $F_{3,45} = 1.16$, $P = 0.335$ respectively), the 'alertness' measure did show a significant effect ($F_{3,45} = 20.29$, $P = 0.000$). A series of repeated measures *t*-tests revealed that the saline condition differed significantly from all three flumazenil conditions ($t_{15} = 2.14$, $P = 0.049$; $t_{15} = 13.86$, $P = 0.0000$; and $t_{15} = 3.96$, $P = 0.0013$ respectively). Furthermore, the 0.5 mg and 5.0 mg flumazenil conditions differed significantly from the 2.5 mg flumazenil condition ($t_{15} = 5.60$, $P = 0.0001$, $t_{15} = 2.90$, $P = 0.011$

respectively). The 0.5 mg and 5.0 mg did not differ from one another ($t_{15}=1.69, P=0.11$).

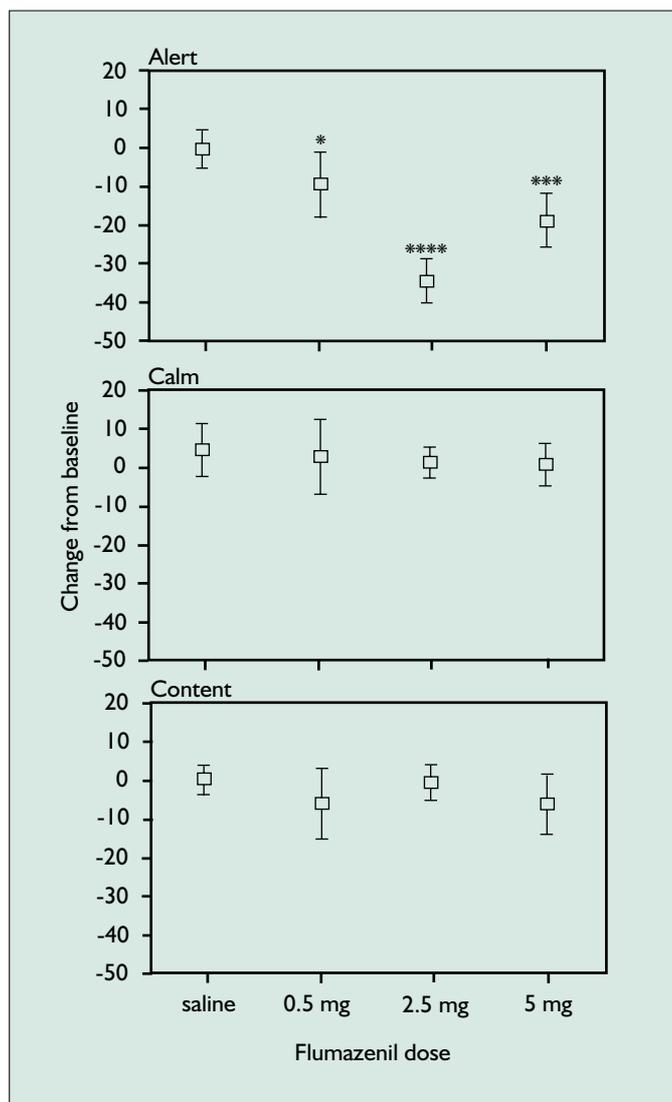


Figure 3 Results of subjective mood measures following administration of 0.5 mg, 2.5 mg and 5.0mg of flumazenil. The dimensions are: Alert 'alertness'; calm 'calmness'; and content, 'contentedness'. Values represent mean changes from baseline with 95% confidence intervals (*, $P<0.05$; ***, $P<0.005$; ****, $P<0.0001$ compared with saline condition).

Physiological measures

Figures 4a and 4b show the mean pre-post drug changes in mean arterial pressure for each condition at 10 minutes and 30 minutes respectively. Blood pressure at 10 minutes showed a significant effect of condition ($F_{3,45}=2.91, P=0.044$). A series of repeated measures *t*-tests revealed that the saline condition differed significantly from the 0.5 mg and 2.5 mg flumazenil conditions ($t_{15}=2.31, P=0.035$ and $t_{15}=2.34, P=0.033$ respectively) but not from the 5.0 mg flumazenil condition ($t_{15}=1.61, P=0.13$). There were no other significant differences. Blood pressure at 30 minutes showed no effect of condition ($F<1$).

Figures 5a and b show the mean pre-post drug changes in pulse rate for each condition at 10 minutes and 30 minutes respectively. Pulse rate at 10 minutes showed a significant effect of condition ($F_{3,45}=3.06, P=0.038$). Post-hoc *t*-tests revealed that the saline condition differed significantly from the 2.5 mg and 5.0 mg flumazenil conditions ($t_{15}=2.95, P=0.0099$, and $t_{15}=2.40, P=0.030$ respectively). The difference between 0.5 mg and 2.5 mg drug conditions almost reached significance ($t_{15}=2.08, P=0.055$). Pulse rate at 30

minutes showed a very similar pattern as the 10 minutes measure ($F_{3,45}=3.19, P=0.032$) with the saline condition differing significantly from the 0.5 mg, and 2.5 mg drug conditions ($t_{15}=2.31, P=0.035$; $t_{15}=2.65, P=0.018$ respectively); this comparison almost reached significance for the 5.0 mg drug condition ($t_{15}=1.96, P=0.069$). Finally, no significant effects were revealed for oxygen saturation at 10 minutes ($F_{3,45}=1.02, P=0.391$), and 30 minutes ($F<1$).

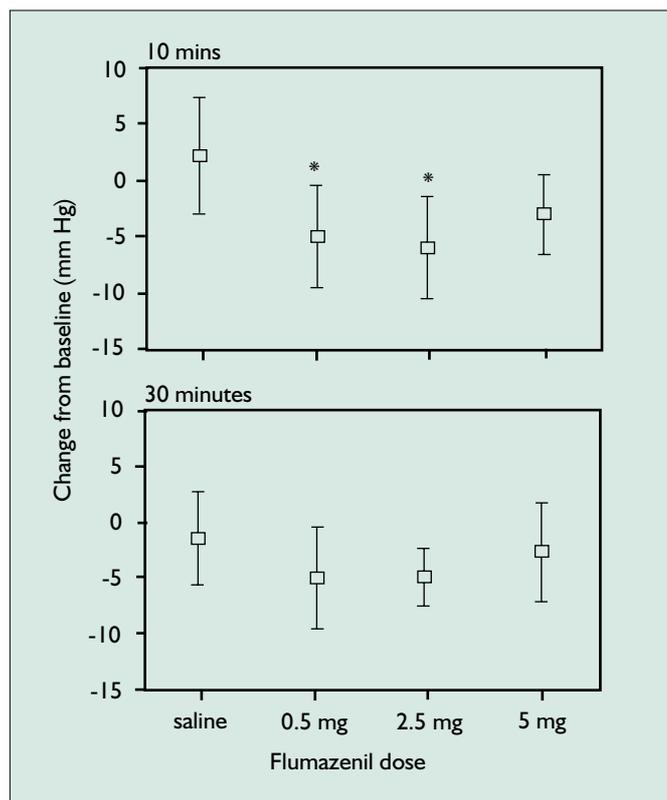


Figure 4 Changes in arterial pressure at 10 minutes and 30 minutes following administration of 0.5 mg, 2.5 mg and 5.0 mg of flumazenil. Values represent mean changes from baseline with 95% confidence intervals (*, $P<0.05$ compared with saline condition).

Discussion

The aim of this study was to assess possible dose-dependent effects of intravenously-administered flumazenil on cognition, mood and cardio-respiratory physiology in healthy volunteers. The majority of cognitive tasks showed either no significant effects, or dose-dependent declines in performance.

On the measure of simple reaction time, while all groups were slightly slower in the post sessions compared with the baseline sessions, (in particular the 0.5 mg and 5.0 mg conditions were slightly slower than the saline and 2.5 mg conditions), this did not reach significance. This is in accord with the lack of a significant effect on simple-reaction time performance of flumazenil administration.³ The measure of choice reaction time produced similar findings in that there was a slight pre-post speeding in the saline group and the 0.5 mg and 2.5 mg conditions were slower than the 5.0 mg condition, again these differences did not reach significance.

Reaction times were similarly slowed in the digit vigilance test (an attentional task producing an accuracy and reaction time measure) in a dose-dependent manner, but this time significant differences were found between the 0.5 mg and 5.0 mg conditions and the saline control (differences between the 2.5 mg condition and saline only just missed significance). However, in this task, while reaction times were impaired, accuracy of attention was not. Given that the digit

vigilance task makes higher demands on the supervisory attentional system than serial- and choice-reaction time tasks, these findings suggest that as task difficulty increases then so does reaction time in a dose-dependent manner (i.e. flumazenil leads to a speed-accuracy trade-off in cognitively-demanding tasks). As previous studies have not used the digit vigilance task then it is difficult to equate these findings.

Neither of the measures of working memory (immediate word recall and spatial memory) showed significant differences between drug conditions. Although previous tasks involving humans have not typically used these measures, the animal literature has provided evidence that some aspects of spatial working memory are enhanced following flumazenil administration.¹⁵⁻¹⁶ However, in these studies the flumazenil was given during the post-learning period (consolidation) and so differential time of administration may account for the discrepancies across human and animal studies.

In a similar manner, none of the recognition measures of long-term memory revealed significant differences between conditions, however, delayed word recall did show a clear drug effect as all doses of flumazenil reduced the number of words recalled following a delay. The significant impairments in delayed word recall and the quality of episodic memory with a sparing of word recognition following flumazenil administration may suggest a deficit involving the ability to access previously stored information. This is in contrast to the acquisition-type deficit (consolidation processes) characterised by benzodiazepine administration.

The factor 'quality of episodic memory' (ability to store, hold and retrieve episodic information which in 'real-world' situations would include recalling a specific name, an appointment, an object, for example) was significantly impaired but only so in the 5.0 mg condition. Similarly, 'power of attention' (intensity of concentration at a particular moment i.e. listening intently to what someone is saying) was significantly impaired with flumazenil, even at the lowest dose. This result was not in accord with previous findings.

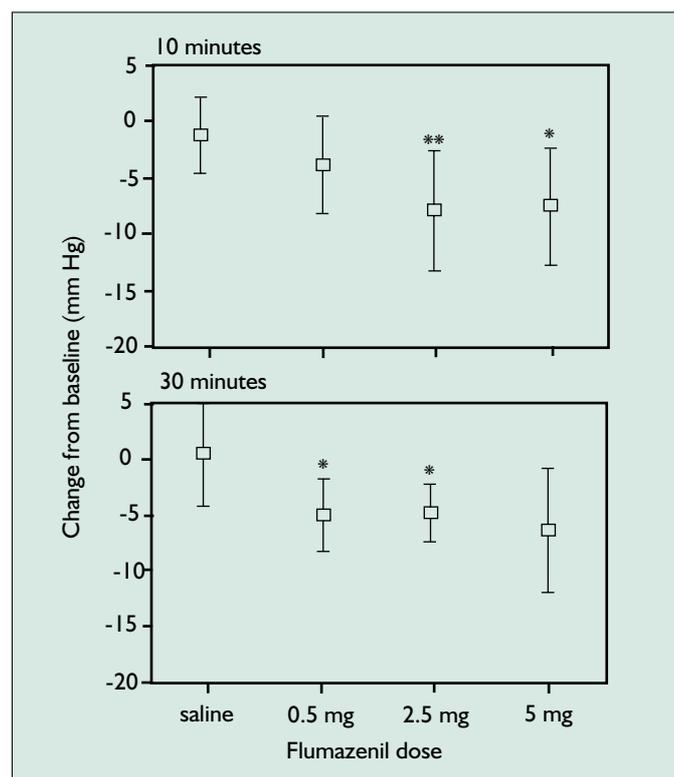


Figure 5 Changes in pulse rate at 10 minutes and 30 minutes after administration of 0.5 mg, 2.5 mg, 5.0 mg of flumazenil. Values represent mean changes from baseline with 95% confidence intervals (*, $P < 0.05$; **, $P < 0.01$ compared with saline condition).

For example, one study examined the effects of low doses of flumazenil (0.5 mg in total) on event-related brain potential indicators of selective attention, and reported that flumazenil significantly improved this form of processing.²³ As the methodologies used in that study (and others using EEG techniques) differ markedly to that used in this current study, it is difficult to address this discrepancy.

The same study also measured subjective mood and reported that participants felt more 'activated' and 'extraverted' but no more anxious following flumazenil administration.²³ Consistent with this, the present study found no differences on the measures of 'contentedness' and 'calmness' due to condition, but all drug conditions did show a significant reduction in alertness compared with the saline condition. The 2.5 mg group showed the biggest drop, and this was significantly larger than that shown in 0.5 mg and 5 mg conditions. As different mood measures were used however, these results are not directly comparable. However, the subjectively rated decreases in the level of alertness in this current study are consistent with the objectively identified reductions in the power of attention. It is unclear however to what extent the effects of flumazenil on certain tasks are mediated via its sedative actions or by the subjective reduction in alertness.

Previous studies have reported that flumazenil administration significantly reduced systolic blood pressure and heart rate²⁴ and our findings reflected this. In our study, flumazenil caused significant reductions in mean arterial pressure under all three drug conditions, compared with control, an effect that was particularly pronounced at 10 minutes following administration. In addition, there was a dose-dependent reduction in pulse rate. The benzodiazepine agonists (e.g. midazolam, diazepam) are well known to produce a hypotensive effect, thought to be caused by a reduction in sympathetic activity and peripheral vasodilatation.²⁵ The fall in blood pressure is usually compensated by an increase in pulse, thus maintaining a consistent cardiac output.

It is interesting that flumazenil, hereto thought to be devoid of pharmacological activity induced both hypotension and bradycardia. Such an effect has been demonstrated using animal models but the underlying mechanism is unclear. It has been suggested that flumazenil acts centrally in the CNS to modify sympathetic outflow. Possible sites of action include those parts of the CNS where GABA pathways are involved in cardiovascular control.²⁶ The compensatory tachycardia found with the sedative benzodiazepines did not occur with flumazenil, further supporting the theory that flumazenil acts centrally. Certainly it would seem that flumazenil displays weak agonist actions, especially on the cardiovascular system. However, as arterial oxygen saturation remained largely unchanged during all drug conditions, flumazenil appears to have no detrimental effect on the respiratory system.

Hitherto flumazenil has been marketed as a pure antagonist, with no intrinsic activity of its own (Roche Product Ltd, Anexate Data Sheet). Its primary application in clinical practice has been as a reversal agent for use in over-sedated patients, especially those who suffer respiratory depression.^{4-5,27} This current study has shown that flumazenil does have intrinsic activity and displays weak agonist actions. It is important therefore that clinicians are aware of the cardio-depressant effects of flumazenil and its ability to reduce patient awareness and attention. In particular, the present study provides further evidence to support the view that flumazenil should not be used as a routine reversal agent in an attempt to expedite recovery and discharge of ambulatory patients undergoing procedures under benzodiazepine sedation. As flumazenil itself appears to impair long-term memory processing, which in turn would effect the ability to understand and adhere to post-operative instructions, it is essential that any ambulatory patient who has been reversed using flumazenil should not only be allowed to recover for a sufficient time to cover the half-life clearing period of the drug, but should also be

discharged under the responsibility of an adult escort.

Previous reports addressing the possible intrinsic effects of flumazenil administration in humans have been sparse, and have not so far used a cognitive test battery of the sensitivity of that described in this study. We conclude that administered alone, flumazenil induces some cognitive impairments that are qualitatively different to those produced by the benzodiazepines at the highest dose in young healthy volunteers. Furthermore, mild sedative effects were evident at all dose levels. The beneficial effects of flumazenil on cognitive performance appear limited to the reversal of benzodiazepine-induced impairment (in humans at least). Studies investigating cognitive/physiological effects of flumazenil might usefully be directed at other age groups before general conclusions can be drawn. Finally, planned future studies in this laboratory include addressing the time-dependency of the profile of cognitive impairment following flumazenil administration alone, and in combination with other interventions.

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