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Flumazenil in the outpatient

A study following midazolam as sedation for upper gastrointestinal endoscopy

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Summary

Fifty outpatients who underwent upper gastrointestinal endoscopy under midazolam sedation were allocated randomly into two equal groups of 25 in this double-blind study. After the endoscopy, and 30 minutes after administration of the sedative, patients in one group received flumazenil 0.5 mg; those in the other group received a similar volume of vehicle only. Assessments of memory function, psychomotor performance and coordination were carried out and these were repeated 3.5 hours later. Flumazenil produced a significant improvement ($p < 0.0001$) immediately but no difference could be detected between flumazenil and placebo at 3.5 hours. However, patients in the flumazenil group reported, by means of linear analogue scales, a subjective feeling of alertness at the time of discharge, which was greater than that reported by those in the placebo group ($p < 0.005$).

Key words

Gastrointestinal tract; endoscopy.
Pharmacology; midazolam, flumazenil.

Benzodiazepines are used commonly for intravenous sedation for outpatient diagnostic investigations. Midazolam produces excellent amnesia, anxiolysis and, if titrated carefully, minimal cardiorespiratory depression.[1] It also has the most suitable pharmacokinetic profile of the benzodiazepines for use in the outpatient.[2] The central effects of intravenous sedation with midazolam usually last longer than is necessary for the clinical investigation and thus recovery facilities and close nursing care may be required until the patient is fit to leave hospital. Flumazenil, an imidazobenzodiazepine, is an antagonist of the effects of benzodiazepines at the benzodiazepine receptor.[3,4] It has a short elimination half-life of 54 minutes and a partial reversal of neurological depression has been noted after its use as an antagonist.[5] Its elimination half-life is closest to that of midazolam (1.2–3.8 hours)[6,7] and considerably shorter than that of diazepam.[8] The aim of this study was to assess the efficacy of flumazenil in antagonising the effects of midazolam on psychomotor performance, coordination, short term memory loss, and the subjective feelings of pain and drowsiness. These assessments were carried out immediately after reversal of sedation and again before discharge home.

Methods

Fifty patients of ASA grade 1 or 2, aged between 18 and 76 years, who underwent elective outpatient upper gastrointestinal endoscopy at the Western General Hospital Edinburgh, participated in this prospective, double-blind trial. The patients were allocated randomly into one of two equal groups (flumazenil and placebo). The groups were stratified for sex and all patients gave informed, witnessed consent, in accordance with the Helsinki 2 declaration. The study was approved by the Lothian Health Board ethics of medical research committee. Both groups of patients were familiarised with the test battery and each patient was permitted 30 minutes of practice before baseline recordings were made;[9,10] sedation was then administered. The equipment for the tests described below was transported on a trolley of adjustable height so that an optimum position for performance of the tests could be maintained in all cases. The battery of tests took 20 minutes to complete.

Choice reaction time (CRT). Each test involved 30 responses. Total time, latency and motor time were noted (T,L,M).[9]

Critical flicker fusion frequency (CFF). Ambient light, image size, illumination and viewing distance remained constant. The CFF threshold was assessed with increasing then decreasing flicker frequency, five times in each assessment. CFF and CRT were performed using the Leeds Psychomotor Testing Equipment.[9]

Paired word association. The 27 possible correct responses were made up of three lists of three word pairs. The first list contained pairs which were all related, e.g. father–son, the second set were less closely linked, e.g.

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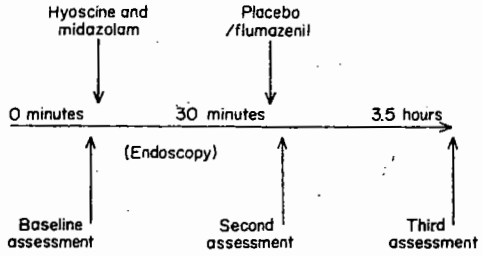

Fig. 1. Sequence of events during study.

scissors–cloth, and the final paired words were unrelated. The patient was familiarised with a new set of paired words for each assessment and was then shown one word of the pair on a television screen and asked to give the other word. Possible responses were correct, incorrect or no response; The first two were noted (paired word association correct, incorrect; PWA,C,I). The maximum possible score was 27.[11]

Wright codoc ataxia meter. This meter is an electronic revolution counter and is attached to the patient at waist level by a bulldog clip on the end of a line. The meter automatically maintains a constant tension on the line and rewinds after the patient sways forwards and backwards. The revolutions of the spindle are counted electronically and the results noted as 'sway'. The units measured are 0.33 of a degree or 20 minutes of arc.[12]

Linear analogue scales. These tests were self-rated and results recorded in millimetres. Sedation and pain were assessed in this way (LSED/LPAIN). These were assessed using scales from 0 (no pain) to 100 (worst pain) and 0 (alert) to 100 (drowsy).

All patients received hyoscine butylbromide 20 mg after the baseline assessment. They were then given a variable dose of midazolam through an indwelling needle intravenously on the dorsum of the hand to produce a level of sedation titrated carefully to point 3 on a five-point scale: 1, fully awake; 2, drowsy; 3, asleep but rousable to command; 4, rousable only to mild stimulation; 5, unrousable. Any patient who could not be roused by command was eliminated from the trial. Thus all patients were sedated to the same end-point and received an equipotent dose of midazolam. The endoscopy was then performed. Thirty minutes later, the patients received either vehicle only or flumazenil 0.5 mg intravenously over 2 minutes. The battery of tests was repeated immediately, and again after 3.5 hours. This time was chosen as the time at which patients were normally deemed fit to return home. The order to be performed was selected randomly on each occasion that the tests were performed. Figure 1 summarises the sequence of events.

The results were analysed using the Mann–Whitney *U*-test for between-group analysis and Wilcoxon Signed-ranks test for within-group analysis.

Table 2. Results at 30 minutes.

	Flumazenil		Control		Two-tailed p
	Mean	SD	Mean	SD	
CRTT	1104.3	745.2	1847.3	1205.5	0.00001
CRTL	715.4	676.5	1131.2	725.3	0.00001
CRTM	396.7	129.6	712.7	544.8	0.0003
CFF	26.2	2.7	25.2	3.9	0.354
PWAC	18.0	3.6	10.6	6.8	0.0001
PWAI	5.1	2.1	8.7	5.8	0.0613
SWAY	46.0	31.0	90.9	63.8	0.0023
LPAIN	17.1	21.4	21.8	23.8	0.4574
LSED	46.2	27.2	65.5	28.0	0.0113

Choice reaction time total, latency and motor (milliseconds); CRT, T, L, M. Critical flicker fusion frequency (Hz); CFF. Paired word association, correct and incorrect; PWAC, I. Wright codoc ataxia meter; SWAY (1 unit = 20 minutes of arc). Linear analogue scale pain/sedation (mm); LPAIN/LSED.

Table 3. Results at 3.5 hours.

	Flumazenil		Control		Two-tailed p
	Mean	SD	Mean	SD	
CRTT	876.9	209.6	888.0	232.1	0.8234
CRTL	532.2	147.0	528.8	139.1	0.7859
CRTM	349.7	96.4	367.6	165.5	0.6908
CFF	26.4	3.0	30.3	13.3	0.0594
PWAC	22.0	3.1	21.4	4.5	0.8453
PWAI	3.2	2.4	3.7	3.3	0.7767
SWAY	18.9	9.7	22.1	20.4	0.7707
LPAIN	17.2	20.3	14.0	22.4	0.364
LSED	30.9	26.7	50.2	18.6	0.0072

Abbreviations as above.

Results

Both groups were well matched for demographic data and total dose of midazolam administered (Table 1).

All patients received hyoscine butylbromide 20 mg (to relax the gastrointestinal smooth muscle) immediately before the injection of midazolam. Only one patient, in the control group, received local anaesthetic spray (lignocaine 60 mg). Her results were analysed along with the others in that group.

Analysis of baseline tests revealed no differences between groups. Between-group analysis for all variables demonstrated that patients in the flumazenil group were significantly better at most of the tests in the battery than were the control group at 30 minutes (Table 2). CRTT in the control group (1847 milliseconds) was long and demon-

Table 1. Demographic data.

	Flumazenil			Control		
	Mean	SD	Range	Mean	SD	Range
Age (years)	53.8	13.8	20–76	50.8	17.3	22–75
Height (cm)	167.3	8.1	153–186	165.6	8.0	152–183
Weight (kg)	67.2	8.9	52–85	69.2	12.4	50–105
Dose of midazolam (mg)	8.8	1.3	6–10	8.6	1.3	5–10

Table 4. Within-group analysis, baseline and 3.5 hours.

	Flumazenil				Placebo			
	Time 0.0 hours		Time 3.5 hours		Time 0.0 hours		Time 3.5 hours	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
CRTT	765.1	160.8	876.9	209.7	801.5	239.0	888.0	232.1
CRTL	468.5	111.2	532.2	147.0	467.8	109.7	528.2	139.1
CRTM	296.2	74.5	349.7	96.4	328.0	143.5	367.6	165.4
CFF	28.7	2.5	26.4	3.0	28.8	3.0	30.3	13.3
PWAC	23.2	4.9	22.0	3.1	24.5	2.3	21.4	4.5
PWAI	2.2	4.9	3.2	2.4	1.2	1.1	3.7	3.3
SWAY	16.3	8.6	18.9	9.7	16.1	8.8	22.2	20.4
LPAIN	19.4	24.1	17.2	20.3	24.1	10.6	16.3	22.5
LSED	21.8	21.5	30.9	26.7	24.1	22.1	50.2	18.6

Abbreviations as in Table 2.

strated significant impairment. Similarly the mean value for 'sway' in the control group (90.9) was high, and three patients in the control group required help to prevent a fall. Thus, the control group were compromised (coordination, psychomotor performance and short term memory) 30 minutes after the administration of midazolam and therefore required supervision. However, there was a wide range in the responses to the battery of tests.

Linear analogue scales for pain showed no statistically significant difference between groups at any time. Pain assessment was included since it may have biased the performance of the other psychomotor tests. The only test that differentiated between the groups at 3.5 hours was the linear analogue score for sedation; patients in the flumazenil group were subjectively more alert than those in the placebo group (Table 3).

Analysis of results within groups and between times 30 minutes and 3.5 hours demonstrated that neither group deteriorated in performance. Both groups improved in most aspects of performance (with the exception of CFF and LPAIN); patients in the placebo group showed greater improvement than those who had received flumazenil. The self-rated pain score did not change significantly in either group throughout the study period and therefore did not contribute to any of the differences demonstrated.

The results of all tests at 3.5 hours had not reached baseline values in either group (Table 4) despite possible learning of the tests. Learning during the study was minimised by adequate practice before the baseline assessment was made. There was a significant difference between baseline scores and those at 3.5 hours in both placebo and flumazenil groups for CRTT (flumazenil group $p < 0.0004$, placebo group $p < 0.0047$) and PWAC (flumazenil group $p < 0.0186$ and placebo group $p < 0.0006$). Thus, a number of patients had impairment of mental function at 3.5 hours. The other tests failed to demonstrate a significant difference.

Discussion

Outpatient clinical investigations under intravenous sedation are undertaken with increasing frequency in older and less fit patients. The recovery facilities in many units are less than ideal and early recovery of neurological function is desirable. Flumazenil has been shown to antagonise the effects of benzodiazepines in outpatients[13,14] and our study confirms these findings. Flumazenil 0.5 mg resulted in significantly better recovery than placebo, although there was no significant difference in CFF, one of the most sensitive tests for measuring benzodiazepine activity on the central nervous system.[9] Control of the variables that affect CFF (ambient illumination, size of image, viewing distance and pupil size) were standardised by fixing the conditions under which the measurement took place. Unfortunately, random change in the order of the six tests over three sessions does not cancel out order effects. Results from each test were compared with results in the same test at another session, and it would have been better for the order to be retained so that the test was performed under similar conditions on each occasion. The effect of alteration in the order of tests is to add to the variance and mask within-group differences. The flumazenil group reported a significantly greater subjective feeling of alertness, at the time of discharge home, 3.5 hours after sedation. This was not borne out by any of the objective assessments and may have dangerous consequences. A feeling of improved alertness might encourage patients to participate in daily tasks, such as driving, for which they are not fit. Neither group had reached baseline values by the time of discharge and all patients were accompanied home.

It is possible that some of the residual effects of sedation were due to hyoscine butylbromide.

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