Role of Flumazenil in Reversing the Sedative Effect of Benzodiazepines in Endoscopies: Salmaniya Medical Centre Experience

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ABSTRACT

Thirty seven patients undergoing endoscopic procedures were sedated with either midazolam 0.15mg -0.2mg/kg or diazepam 0.2 - 0.3 mg/kg intravenously. The sedative effect was reversed in 27 patients with flumazenil (Anexate) 0.2mg initially and then in incremental doses of 0.1mg. The remaining ten patients served as control group by allowing them to recover spontaneously. The efficacy of flumazenil was evaluated by the degree of sedation, comprehension and co-operation, orientation to space and time and re-sedation. The safety of flumazenil was evaluated by local and systemic tolerability. We conclude that flumazenil is a safe and effective benzodiazepine antagonist, and that the recovery of patients given this antagonist is both quick and complete.

Benzodiazepines are the most commonly used sedative-hypnotics[1]. While we already have reliable antagonist for the opiate analgesics and the non-depolarising muscle relaxant drugs, which have become essential to modern anaesthesiology, no such antagonist has so far been available to reverse the effects of benzodiazepines. There was no alternative but to wait until these effects subside spontaneously[2]. The specific antagonist has become an absolute necessity especially in total intravenous anaesthesia and in balanced anaesthesia. The discovery of flumazenil has enabled us to sedate the patients completely as we can reverse this effect post-operatively to get a well oriented patients[3].

The aim of this study is to evaluate the efficacy and safety of flumazenil in patients sedated with benzodiazepines for endoscopic procedures, at Salmaniya Medical Centre (SMC).

METHODS

Thirty seven patients of both sexes, ASA grade 1 or 2 and 25-65 years of age (Table 1) scheduled for endoscopic procedures (Table 2) were admitted as day cases to the study. All patients were visited by the Anaesthesiologist in the day case unit. An informed consent was obtained after familiarising the patient with the anaesthesia procedure.

The patients were premedicated with buscopan (Hyoscin-N-butybromide) 20 mg intramuscularly 1/2 an hour before endoscopy. The patients were randomly allocated to receive either medazolam 0.15 to 0.2 mg/kg or diazepam 0.2 - 0.3mg/kg intravenously. The endoscopy was performed. Repeated boluses of either midazolam or diazepam were administered to the patients as indicated by response to the endoscopic procedure. After the endoscopic procedure, the patients were shifted to the recovery room where the sedation effect of benzodiazepines in 27 patients was reversed with flumazenil 0.2mg

Table 1
Demographic data of the patients

Sex	*No. of patients*	*Age in Years Range & Mean*	*Weight in Kg Range & Mean*	*ASA I*	*ASA II*
Male	28	30-60 (28.2)	51-97 (74.4)	17	11
Female	9	5-50 (37.6)	50-75 (61.6)	6	3

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Table 2
Type of endoscopies

Type of endoscopy	*Duration in minute Range & Mean*	*No. of patients*	*Type of Benzodiazepine Midazolam*	*Diazepam*
Gastroscopy	5 - 15 (11.8)	19	14	5
Gastroduodenoscopy	10 - 20 (13.7)	8	3	5
Colonoscopy & Sigmoidoscopy	25 - 35 (31.2)	4	4	5
Gastroscopy & Sigmoidoscopy	25 - 30 (27.5)	2	1	1
Bronchoscopy	15 - 20 (17.5)	4	4	–
Total	5 - 35 (20.3)	37	26	11

intravenously. Additional incremental doses of flumazenil 0.1 mg/min were slowly administered intravenously until the patients were fully awake (Table 3). The remaining 10 patients were allowed to recover spontaneously.

In the recovery room, the level of sedation, orientation to time and space, patient co-operation and comprehension were assessed and scored. Tables 4, 5 and 6 show the parameters used in the assessment and scoring of the patients.

Table 3
Dose of Flumazenil received

Dose of Flumazenil (in mg)	*No. of patients*	*Percentage*
0.2	6	22.2
0.3	11	40.7
0.4	6	22.2
0.5	3	11.1
0.6	1	3.7

Table 4
Level of sedation

Level of sedation (5 - points scale)	*Patient reversed Flumazenil*	*Patients allowed to recover spontaneously*
Awake, alert of tense	27	–
Awake, not alert or tense	–	1
Drowsy	–	4
Asleep, arousable	–	3
Asleep, not arousable	–	2

Table 5
Orientation in space and time

Orientation in space & time	*Patients reversed with flumazenil*	*Patients allowed to recover spontaneously*
Full orientation	27	–
Partial orientation	–	7
Total disorientation	–	3

Table 6
Comprehension and co-operativeness

Comprehension & Co-operativeness	*Patients reversed with flumazenil*	*Patients allowed to recover spontaneously*
Response to orders	27	1
Limited response	–	6
No response	–	3

The blood pressure, heart rate, respiratory rate and also the oxygen saturation were recorded prior and during the procedure 5 and 60 minutes following the administration of flumazenil (Tables 7 and 8).

Table 7
Haemodynamic parameters

Haemodynamic parameters	*Before benzodiazepine* (Range & Mean)	*After benzodiazepine* (Range & Mean)	*Following injection of flumazenil* 5 min (Range & Mean)	60 min
Systolic B P	100 - 160 (117.3)	90 - 130 (116.0)	110-140 (119.0)	100-130 (121.7)
Diastolic B P	70 - 100 (73.5)	60 - 90 (73.3)	60-100 (78.2)	70-90 (77.0)
Heart rate	60 - 94 (77.8)	62 - 99 (80.5)	60-96 (77.9)	64-98 (76.2)

Table 8
Respiratory parameters

Respiratory	*Before BZD* (Range & Mean)*	*After BZD (Range & Mean)*	*After inj. Flumazenil* 5 min. (Range and Mean)	60 min.
Sp 02	94 - 99 (97.7)	90 - 98 (94.3)	95-99 (97.2)	93-99 (96.4)
Resp.rate	14 - 20 (15.8)	13 - 18 (14.2)	14-21 (15.3)	13-16 (13.8)

*BZD: Benzodiazepine

The adverse local and systemic reactions following the administration of flumazenil were observed (Table 9).

Table 9
Adverse Reactions

Adverse reaction to Flumazenil	*Number of patients*
Hypotension	1
Hallucination	1
Nausea	1

RESULTS

Twenty six patients received midazolam and 11 patients received diazepam as sedative agent. Six patients in the midazolam group and 4 patients in the diazepam group were allowed to recover spontaneously (Table 2).

The group of patients who received flumazenil were compared with the group of patients allowed to recover spontaneously. Five minutes after the administration of flumazenil, all patients were fully awake, alert and oriented in space and time. They were also co-operative and obeying the commands (Tables 4,5 and 6). Re-sedation was observed in 4 control patients mainly in the diazepam group.

With the exception of one patient (in the group given flumazenil) who developed hypotension, there was no

significant difference with regard to the blood pressure and heart rate after the administration of flumazenil. The mean value of heart rate was 77.9 after 5 minutes and 76.2 after 60 minutes. Blood pressure was 119/78.2 after 5 minutes and 121.7/77 after 60 minutes.

Slight reduction in the oxygen saturation was noticed during the sedation period and returned to the base line after the administration of flumazenil (Table 8).

No pain was experienced by the patient at the site of injection of flumazenil or along the course of the vein. Nausea occurred in one patient and another one developed hallucination. No other adverse side effects were observed (Table 9). The patients who received flumazenil did not require close nursing care and the time to discharge from the day case unit was shorter than the control group.

DISCUSSION

Benzodiazepines are widely used as a sedation for patients undergoing endoscopies as a day case procedure[3]. Benzodiazepines enhance the transmission at the GABA-ergic synapses in the CNS, modifying the GABA receptor chloride channel coupling. The result is the well known hypnotic, sedative anxiolytic effects of benzodiazepines[4].

Diazepam has a long elimination half-life of approximately 20 hours and it yields active metabolites. Therefore, there is a risk of cumulation when repeated doses are given. Midazolam has a short elimination half-life of approximately 2 hours and no active metabolites[5]. The speed of recovery for benzodiazepines is also dependent upon the distribution of the drugs. The total volume of distribution for midazolam is 0.8 - 1.2 mg/kg b.w., and for diazepam 0.7 - 1.2 mg/kg b.w[6].

Sometimes, long duration of action of benzodiazepines is unwanted and so the discovery of a specific antagonist is highly welcome. Flumazenil, an imidazobenzodiazepine, has a high affinity for the benzodiazepine receptors, and act as a competitive antagonist of the benzodiazepines[7]. The duration of the effect of flumazenil is short; it varies from 1-2 hours, the elimination half-life of flumazenil is 1.0 +– 0.2 hours[8].

In this study it was found that the patients who received flumazenil were fully awake, alert and oriented in space and time. They were also co-operative and responding to the commands. The side effects were minimal without serious adverse reactions.

In a study of the effect of flumazenil during stead state infusion of midazolan in anaesthetic doses, serum concentration 0.6 mcg/ml, all patients who received 10mg of intravenous flumazenil were awke within 30-60 seconds, but after 145 minutes they slept again[9]. In another study, the re-sleeping were not observed in patients who were sedated with midazolam 0.3 mg/kg for CAT scanning and cystoscopy when the sedation effect was reversed by flumazenil in the same dose[10]. In our study the occurrence of re-sedation was observed in 4 patients. Despite the re-sedation, the vital signs, the performance of psychomotor tests, the ability to execute orders and the improvement in the degree of orientation were sustained longer. The patients who became re-sedated after the administration of flumazenil could be aroused sufficiently for tests to be performed. In contrast, the patients allowed to recover spontaneously, gradually became less sedated but still could not be aroused sufficiently to perform the tests or execute orders.

CONCLUSION

We concluded from this study that flumazenil is well tolerated and effectively reduces the sedation and hypnosis produced by benzodiazepines. It also reduced the stay and after care of the patients in the recovery room.

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