NEUROPHYSIOLOGY

Effect of Flumazenil on Electroencephalographic Patterns Induced by Midazolam

VALERIE WOJNA, MD*; LIDIA GUERRERO, DMD†; JULIO GUZMÁN, DMD†; MARY COTTO, BS*

Background. **Flumazenil is a competitive benzodiazepine receptor antagonist, reverts the sedation effects of benzodiazepines and its effect on electroencephalographic (EEG) patterns is controversial. The purpose of this study was to describe flumazenil's effect on EEG patterns of patients undergoing conscious sedation.**

Methods. **Ten voluntary patients, aged 16-23, at elective oral surgery had conscious sedation with midazolam and local anesthesia. After the procedure, sedation was reversed with flumazenil. Each patient had 4 EEGs of 4 minutes each: baseline, 5 minutes after midazolam, prior to flumazenil, and 8 minutes after flumazenil. A clinical neurophysiologist interpreted EEGs blinded to time.**

Results. **Eight patients had an awake and 2 had an awake and drowsy normal EEG. After midazolam all developed a diffuse beta wave and alpha wave attenuation or dropout. Prior to flumazenil 7 presented diffuse beta and scattered theta waves, and 3 an awake pattern (procedure required >30 minutes). After flumazenil, reversal of beta and theta waves and appearance of alpha waves was noted; no changes occurred when procedure lasted more than 30 minutes. One patient presented with diffuse theta waves, 6 Hz.**

Conclusions. **Flumazenil reverts midazolam EEG changes if administered <30 minutes after midazolam administration, midazolam-induced EEG changes revert spontaneously after 30 minutes, and flumazenil may precipitate theta activity.**

Key words: Flumazenil, Midazolam, EEG, Sedation, Elective surgery

Midazolam (Versed®, Roche Laboratories, Nutley, NJ) is a well-tolerated benzodiazepine agonist with anxiolitic, amnestic, and sedative effects. Due to its rapid onset of action and short half-life it is widely used in conscious sedation at minor elective procedures and as an anesthetic inductor. As a benzodiazepine agonist its administration precipitates the known EEG changes: widespread beta activity more prominent over central and frontal regions with an attenuation or disappearance of the alpha activity (1-9). This effect is not dose dependent (4-9). Flumazenil (Romazicon®, Roche Laboratories, Nutley, NJ) is a competitive benzodiazepine receptor antagonist. It is used to revert sedation and psychomotor effects of benzodiazepines (8,10,11,12). Studies have demonstrated a reversal of EEG patterns induced by midazolam when flumazenil is administered in rats and in healthy volunteers (4,8,13,14). There is contradictory evidence regarding flumazenil's effect on the EEG patterns. Many researchers have found no EEG effects after the administration of flumazenil (7,13,15,16) but other studies have found the contrary (17-19).

The purpose of this study was to describe flumazenil effects on EEG patterns of patients undergoing conscious sedation by midazolam for an elective procedure. The return to a normal EEG patterns will reassure us of a reversal of sedation and allow for an earlier patient discharge.

Methods

Ten voluntary healthy patients (6 women, 4 men) scheduled for an elective minor oral surgery procedure, a third molar extraction, were studied after giving inform

From the *Neurology Section, Department of Medicine and the †Maxilofacial Section, Department of Surgery, University of Puerto Rico School of Medicine, San Juan, Puerto Rico.

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Address correspondence to: Valerie Wojna, MD Neurology Section, Department of Medicine University of Puerto Rico School of Medicine, PO Box 365067, San Juan, PR 00936-5067 Tel. (787) 754-0101 ext.3176; Fax (787) 751-3911

consent. All fasted for 6 hours and denied use of any medications in the last 48 hours prior to procedure. Ages ranged from 16 to 23 years old.

Conscious sedation was induced with midazolam 0.08 mg/kg IV. Once the oral surgery procedure ended, sedation was reverted with flumazenil 0.2 mg IV. Procedure was carried out at the Maxilofacial Department outpatient clinics. (Table 1) A 10-channel portable Grass EEG machine was used to perform all EEG's. Electrodes

Table 1. Patient Data

Patient	Sex	Age	Weight	Midazolam dose (0.08 mg/kg)	Flumazenil dose	Procedure duration
1	M	16	73.2 kg	5.8 mg	0.2 mg	17 minutes
2	F	17	49.5 kg	4.0 mg	0.2 mg	50 minutes
3	M	18	63.6 kg	5.1 mg	0.2 mg	23 minutes
4	F	22	74.8 kg	6.0 mg	0.2 mg	14 minutes
5	F	19	57.3 kg	4.6 m	0.2 mg	37 minutes
6	M	17	60.0 kg	4.8 mg	0.2 mg	21 minutes
7	F	23	55.0 kg	4.4 mg	0.2 mg	14 minutes
8	F	18	66.0 kg	5.3 mg	0.2 mg	13 minutes
9	F	16	82.0 kg	6.6 mg	0.2 mg	32 minutes
10	M	23	76.6 kg	6.1 mg	0.2 mg	12 minutes

were fixed with conductive paste after scrubbing the scalp with a mild abrasive solution following the International 10-20-electrode placement system. Impedance was maintained below 5 kilo-Ohms, the band pass filter was set at 0.5-70 Hz, and sensitivity at 7 mm/mV. A longitudinal bipolar montage was used. EEG's were performed taking into account the time of peak of action: for midazolam 3-5 minutes and for flumazenil 6-10 minutes. Each patient had 4 EEG's performed of 4 minutes duration at: 1) baseline, before the procedure, 2) 5 minutes after midazolam administration, 3) at the end of the procedure but prior to flumazenil administration, and 4) 8 minutes after flumazenil administration. A clinical neurophysiologist interpreted each EEG individually, blinded to the time of performance.

Results

Baseline EEGs showed that 8 patients had a normal awake study characterized by anterior low voltage fast beta waves and posterior alpha waves, 10-12 Hz. Two patients had a normal awake and drowsy study consisting of scattered over imposed diffuse theta waves, 5-6 Hz, with an alpha drop out. After midazolam administration all of the patients developed a diffuse beta wave and an alpha wave attenuation or dropout. The patients tolerated the procedure well without any complications. The duration of the oral surgery procedure varied form 12 to 50 minutes with a median time of 19 minutes. After the procedure and prior to flumazenil administration, seven of the ten patients presented a diffuse beta and scattered theta, 5-6 Hz, waves. These patients oral surgery procedure lasted less than 30 minutes. The remaining three patients presented an awake EEG pattern. Their procedure lasted more than 30 minutes (32, 37, and 50 minutes). After flumazenil administration the EEG showed a reversal of beta and theta waves and a reappearance of alpha waves in the patients whose procedure lasted less than 30 minutes (Figure 1). No change in the EEG activity was noted on those patients whose procedure lasted more

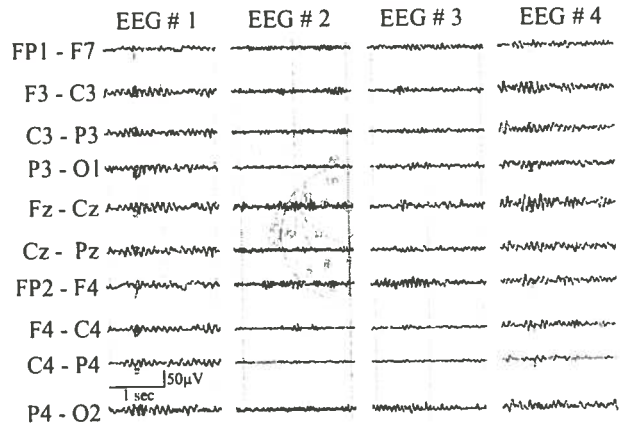

Figure 1. Flumazenil induced EEG findings. Flumazenil administration reverts the midazolam-induced EEG patterns. All EEGs were performed on a 10 channel Grass machine using a longitudinal montage (FP_1-F_7, F_3-C_3, C_3-P3, P3-O1, Fz-Cz, C_z-P_z, FP2-F4, F_4-C_4, C_4-P_4, P_4-O_2). EEG #1 represents baseline study and shows a normal awake pattern with anterior low voltage beta and a posterior alpha waves. EEG #2 was obtained 5 minutes after midazolam administration and shows the midazolam-induced EEG patterns characterized by diffuse beta waves. EEG #3 was obtained at the end of the procedure, prior to flumazenil administration. It shows less prominent beta waves with scattered theta waves. EEG #4 was done 8 minutes after flumazenil administration and shows a reversion of the midazolam-induced EEG patterns with a return of a posterior alpha waves.

than 30 minutes. One patient presented diffuse theta waves, 6 Hz, (Figure 2) but didn't show any signs of drowsiness, confusion, nor disorientation. Individual EEG findings at the different stages of the study: baseline; 5 minutes after midazolam administration; end of the procedure and prior to flumazenil administration, and 8 minutes after flumazenil administration are described (Table 2). All patients tolerated well flumazenil administration except for one patient (patient #7) that developed nausea and vomits that resolved spontaneously.

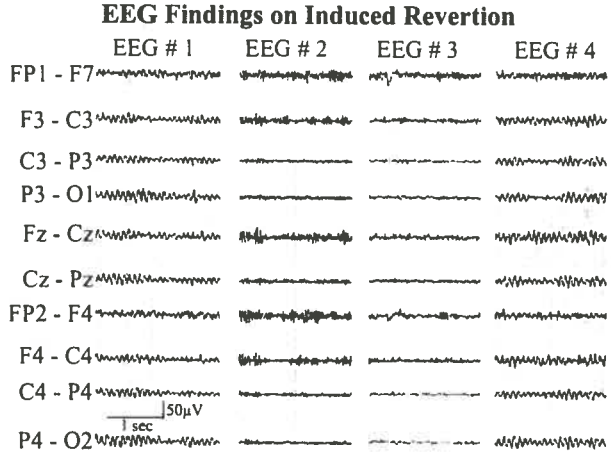

Figure 2. Flumazenil administration induced theta waves. EEGs was performed of a 10 channel Grass machine using a longitudinal montage (FP_1-F_7, F_3-C_3, C_3-P3, P3-O1, Fz-Cz, C_z-P_z, FP2-F4, F_4-C_4, C_4-P_4, P_4-O_2). EEG #1 represents baseline study and shows a normal awake pattern with anterior low voltage beta and a posterior alpha waves. EEG #2 is obtained 5 minutes after midazolam administration and shows the midazolam-induced EEG patterns characterized by diffuse beta waves. EEG #3 was obtained at the end of the procedure and prior to flumazenil administration, it shows a less prominent beta waves with scattered theta waves. EEG #4 was done 8 minutes after flumazenil administration and shows diffuse theta waves at 6 Hz. This patient didn't show any signs of drowsiness, confusion, nor disorientation

Discussion

In this study we have shown that midazolam precipitates EEG changes as seen after benzodiazepine administration: widespread beta waves with attenuation or disappearance of alpha waves and scattered theta, 5-6 Hz. This activity persisted up to 30 minutes after midazolam administration. Three patients whose oral surgery procedure lasted >30 minutes (patients # 2, 5, and 9) presented a spontaneous reversal of the midazolam-induced EEG pattern. This effect could be related to the low dose of midazolam used (0.08 mg/kg), as well as, to it's short action time and half-life. Therefore, patients weaned off midazolam without the need of flumazenil administration (16).

Seven patients whose oral surgery procedure lasted <30 minutes (patients # 1, 3, 4, 6, 7, 8, and 10) persisted with the benzodiazepine-induced EEG changes. Induced reversion was obtained 8 minutes after flumazenil administration in 6 of those 7 patients. One patient (patient #1) did not have a reversal of the EEG pattern; instead, flumazenil precipitated a diffuse theta at 6 Hz intermixed with beta activity. This patient didn't show any signs of drowsiness, confusion, nor disorientation. The theta

Table 2. Summary of EEG results.

EEG done	EEG findings
Baseline (EEG #1)	8 patients presented a normal awake pattern* 2 presented normal wake and drowsy pattern
5 min. after midazolam (EEG #2)	All patients developed a diffuse beta wave and alpha wave dropout or attenuation
End of procedure, prior to flumazenil (EEG #3)	• 7/10 patients presented diffuse beta activity with or without scattered alpha and theta waves (procedure lasted < 30 minutes) • 3/10 patients presented a spontaneous reversal to normal awake pattern (procedure lasted > 30 minutes)
8 min. after flumazenil (EEG #4)	• Procedure < 30 min. (7/10) -6 reverted completely to normal awake -1 developed diffuse theta wave, 6 Hz, with an alpha wave dropout (patient #1) • Procedure > 30 min. (3/10) No change in the EEG pattern was observed

* Normal awake pattern: well-modulated reactive posterior alpha and anterior low voltage fast beta.
All EEGs were interpreted by a clinical neurophysiologist blinded to the time of performance.

activity precipitated by flumazenil needs further analysis. Possible explanations include re-sedation or flumazenil direct effect on the central benzodiazepine receptor. Re-sedation is a common occurrence since the half-life of flumazenil is shorter than that of midazolam and once flumazenil is cleared the effects of midazolam become evident. Re-sedation could also be precipitated by midazolam's active metabolites that may act up to 1.5-2 hours precipitating EEG changes (2,4,7,8,12). Although re-sedation is a possibility in explaining these EEG findings, it is less likely, since the time the EEG was performed coincided with the peak of action of flumazenil, 6-10 minutes, not giving time for its metabolism. Therefore, we conclude that these EEG findings could be attributed to direct flumazenil effect (2, 13).

Few studies have observed direct flumazenil-induced EEG changes in rats or in healthy human volunteers. Those findings vary greatly from increased beta waves, increased mean alpha frequency, decreased theta waves, and increased sleep latency and wakefulness 17, 18, 19). The diffuse theta and over-imposed beta waves observed should be further investigated. We encourage additional studies to analyze our findings taking into account a greater number of patients, serum levels of midazolam and flumazenil, quantitative EEG analysis, and longer study period (i.e. 2-3 hours). The development of nausea and vomits in one patient after the administration of flumazenil is described in the literature as a side effect of the medication and resolves spontaneously as occurred

in our patient. Meanwhile, we recommend observation of patients for up to 2 hours after any conscious sedation procedure until further data is obtained.

Resumen

El flumazenil es usado para revertir los efectos sedativos de las benzodiazepinas por ser un antagonista competitivo del receptor. Tiene efectos controvertibles en el electroencefalograma (EEG). El propósito del estudio es describir los efectos de flumazenil en el EEG de pacientes bajo sedación consciente. Diez pacientes voluntarios, entre los 16 y 23 años de edad, citados para cirugía oral ambulatoria fueron sometidos a sedación consciente con midazolam y anestesia local. Luego del procedimiento la sedación se revirtió con flumazenil. A cada paciente se le hicieron 4 EEGs de 4 minutos cada uno: en descanso, 5 minutos luego de administrarle midazolam, antes de, y 8 minutos después de administrarle flumazenil. Un neurofisiólogo clínico "ciego" interpretó los EEG's al ser efectuados. Los EEGs fueron normales: 8 despiertos y 2 despiertos y somnolientos. Luego de administrarle midazolam: todos los pacientes desarrollaron actividad beta difusa con atenuación o desaparición del alpha. Antes de administrar el flumazenil: 7 pacientes presentaron actividad beta difusa y theta esporádica y 3 pacientes presentaron un patrón normal despierto (procedimiento duró >30 minutos). Luego de administrar el flumazenil se revirtió la actividad beta difusa y theta esporádica y reapareció el alpha. No hubo cambios en el EEG en los pacientes cuyo procedimiento duró >30 minutos. Un paciente presentó actividad theta difusa, 6 Hz. Los autores concluyen que el flumazenil revierte los cambios del EEG precipitados por midazolam administrando durante los primeros 30 minutos, los patrones precipitados por midazolam revierten espontáneamente luego de 30 minutos, y flumazenil puede precipitar actividad theta difusa en el EEG.

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