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The efficacy of flumazenil in subclinical to mild hepatic encephalopathic ambulatory patients

A prospective, randomised, double-blind, placebo-controlled study

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Summary

Objectives: Hepatic encephalopathy (HE) is a neuropsychiatric syndrome associated with fulminant hepatic failure and chronic liver disease. Its pathogenesis is unclear. One of the factors implicated is enhanced GABA-ergic tone, which is probably related to increased concentrations of cerebral benzodiazepine (BNZ). In the present study, we tested flumazenil, a cerebral BNZ antagonist, in cirrhosis patients with hepatic encephalopathy. Methods: Out of 47 patients, 7 were excluded prior to randomization for various reasons. Twenty patients were included in the flumazenil group and 20 in the placebo group in a prospective, randomized, double-blind, placebo-controlled study. Patients were given flumazenil (1 mg/h, continuous IV infusion) or an equal volume of saline solution for 5 hours. Before and after treatment, portosystemic encephalopathy (PSE) stage and number connection test (NCT) scores were checked every half hour for 5 hours. EEG was recorded 15 minutes before and 1 hour after treatment. Results: While significant improvements were determined in PSE stage and NCT score in the flumazenil group, there were no such improvements in the placebo group. There was no statistically significant difference between pre- and post-treatment EEGs in either group. Conclusion: It was concluded that continuous IV infusion of flumazenil had beneficial and safe effects in the treatment of hepatic encephalopathy patients.

Key words: hepatic encephalopathy; flumazenil

Introduction

Hepatic encephalopathy (HE) is a reversible, complex neuropsychiatric syndrome seen in patients with acute and chronic hepatic failure. According to severity of disease, mild confusion, shortened attention span, drowsiness, lethargy, personality changes, somnolence, disorientation of time and place, and deep coma may be seen in these patients. Its pathogenesis, although still unknown, is thought to be multifactorial. Among the mechanisms thought to be responsible are changes in the permeability of the blood-brain barrier, changes in cerebral metabolism, impaired neuronal Na/K-ATPase activity, and, in particular, enhanced GABA-ergic tone activity [1] which is probably related to increased concentrations of endogenous brain benzodiazepine-like substances [2–11]. If an increase in endogenous BNZ agonists plays a role in the development of HE, it is likely that patients would benefit from flumazenil. Benzodiazepine receptors are closely associated with GABA receptors that constitute the principal inhibitory network in the central nervous system, and benzodiazepine receptors activation potentiates the effect of GABA. Flumazenil diminishes GABA action by blocking the benzodiazepine receptor sites. Nonetheless, conflicting results have been obtained in studies investigating the efficacy of flumazenil in cirrhosis patients with HE, some studies finding it effective and others ineffective. In the present study, we evaluated the efficacy of flumazenil in a prospective, randomized, double-blind, placebo-controlled study.

Patients and methods

Selection of patients

Forty-seven hepatic encephalopathy patients attending the Gastroenterology Clinic at the Medical Faculty of Dicle University between December 1999 and January 2002 were recruited. When our study was designed, we received the approval of the Ethics Committee to be valid throughout the study. Prior to randomization, 7 patients were excluded according to the criteria below. Twenty patients were randomized into the flumazenil group and 20 into the placebo group; the patients in both groups had similar features prior to treatment.

Inclusion criteria

a. Age of 18–70 years
b. Cirrhosis diagnosis supported by clinical and laboratory findings, since haemostatic parameters (prothrombin time, platelet count … etc.) could contraindicate liver biopsy in any patient. Of our patients, 12 were in stage Child B and the others in stage Child C. The aetiology of cirrhosis in all patients was viral hepatitis (32 HBV, 3 HBV + HDV, 5 HCV). Of the liver function tests, ALT and AST were within normal limits in 25 cases (62.5%). The bilirubin level was high in 18 (45%) subjects. In all patients, prothrombin time (PT) was prolonged and serum albumin levels were low. In 36 of the cases (90%), there was ascites. In all of the cases, ultrasonographic findings confirmed liver cirrhosis.
c. Subclinical or stage I, II, or III hepatic encephalopathy.

The severity of hepatic encephalopathy in each patient was graded. The patients whose examination was normal but with subtle changes in psychometric or number connection tests were considered as subclinic HE, those with impaired attention, irritability, depression or personality changes as HE stage I, those with drowsiness, behavioral changes, sleep disorders and poor memory as HE stage II, and those with confusion, disorientation, somnolence and amnesia as HE stage III [12].

Of the cases in the Flumazenil group, 4 were in subclinic, 8 in stage 1, 3 in stage 2 and 5 in stage 3. In the placebo group, these findings were 6, 6, 4 and 4, respectively.

Exclusion criteria

– the use of psychotropic medicine, including BNZ, during the past 3 days (BNZ levels were not monitored; and determination of use was based on anamnesis) [13];
– HE-specific treatment other than lactulose within the past 24 hours;
– use of alcohol within the past month;
– BUN >75 mg/dL, creatinin >5 mg/dL;
– severe pulmonary insufficiency (in case of pO_2 <60 mm Hg and/or pCO_2 >50 mm Hg);
– blood pH <7.30;
– previous history of neurological, cardiac or other systemic diseases;
– failure of attempts to stabilise haemodynamic status for 12 hours;
– gastrointestinal haemorrhage (in case of haematemesis and/or melaena);
– cerebral oedema.

Study design

After admission to the hospital, patients were haemodynamically stabilised, and if there was electrolyte unbalance, hypoglycaemia of patients tried to be corrected. Those who could be corrected were included in the study. During 12 hours of stabilisation period, all patients received lactulose (30 ml every 6 hours) and a diet of approximately 2000 cal/day containing 20 g protein. After the stabilisation period, 7 patients were excluded from the study; 3 patients due to renal failure, 1 patient due to severe pulmonary insufficiency, 1 patient due to gastrointestinal hemorrhaging, and 2 patients due to haemodynamic unstability. Before treatment, HE stage and Glasgow coma and number connection test (NCT) [14] scores were determined. NCT is one of the most adequate diagnostic psychometric tests and gives a value as to the severity of onsetting chronic hepatic encephalopathy, which is independent of tester. Hepatic disease staging was carried out according to Child's classification. Blood ammonia levels were assessed.

"EEG was recorded 15 minutes before treatment. EEG traces were evaluated and scored in blind fashion by an independent neurologist using Parsons et al.'s classification" [15]. In this respect, the subjects who had generalised suppression of alpha rhythm were accepted as Grade A; unstable alpha rhythm with paroxysmal waves at 5 to 7 per second or occasional underlying fast activity were accepted as Grade B; runs of medium voltage 5 to 6 per second waves bilaterally over front and temporal lobes or alpha rhythm seen occasionally were accepted as Grade C; constant 5 to 6 per second waves in all areas were accepted as Grade D, and bilaterally synchronous 2 to 3 per second waves, predominating over frontal lobes and spreading backward to occipital lobes or occasional short-lived appearance of faster rhythms (5 to 6 per second) were accepted as Grade E.

After a stabilisation period, patients were randomized into a flumazenil group and a placebo group. They received an IV infusion of either flumazenil (1 mg/h) or an equal volume of saline solution for 5 hours. The physicians performing the evaluation had no knowledge of the nature of the treatment. NCT and PSE staging were repeated every half hour for 5 hours, and EEG was recorded 1 hour after infusion.

Statistical analysis was performed with SPSS 10.0 by using the Chi-squared test, Mann-Whitney U, Wilcoxon Signed Ranks, Friedman, and regression analysis. To compare frequencies between subject and control groups in terms of sexes, we used the Chi-squared test. The Mann-Whitney U test was used to compare the differences between control and subject groups according to age, EEG, NCT, PSE and blood ammonia levels. The Wilcoxon Signed Ranks test was used for comparing the differences between pre- and post-treatment levels of EEG, NCT, PSE for each group. The Friedman test was used for analysis of the differences of PSE stage and NCT value changes in the course of time. Regression analysis was used for measurement of the correlation between PSE stage and blood ammonia level. The power of the study was accepted at 95%. The level of significance was 0.05.

Results

Of the 40 patients included in our study, HBV was found to be the responsible agent in 32 cases, HBV + HDV in 3 and HCV in 5.

Table 1

Patient characteristics in both groups.

Characteristics	flumazenil group	placebo group
Age	44.5 ± 12.85	43.65 ± 11.89
Sex (M/F)	14/6	15/5
Marital status (Maried/single)	16/4	12/8
Economic status		
low	12	13
moderate	6	7
high	2	–
Aetiology		
HBV	17	15
HBV + HDV	1	2
HCV	2	3

Patient characteristics in both groups are shown in table 1.

The overall results of both groups are documented in tables 2 and 3.

a. Change in PSE stage: No statistically significant difference was determined between the groups prior to treatment. A statistical difference was found between pre-treatment and 5-hour values in the flumazenil group, but no such difference was observed in the placebo group (figure 1).

b. Change in NCT: There was a very significant difference between pre-treatment and 5-hour values in the flumazenil group. There was no such difference in the placebo group (figure 2).

c. Change in EEG traces: There was no statistically significant difference between pre-treatment and 1-hour EEG traces in either group.

The relationship between PSE stage and blood ammonia level was calculated through re-

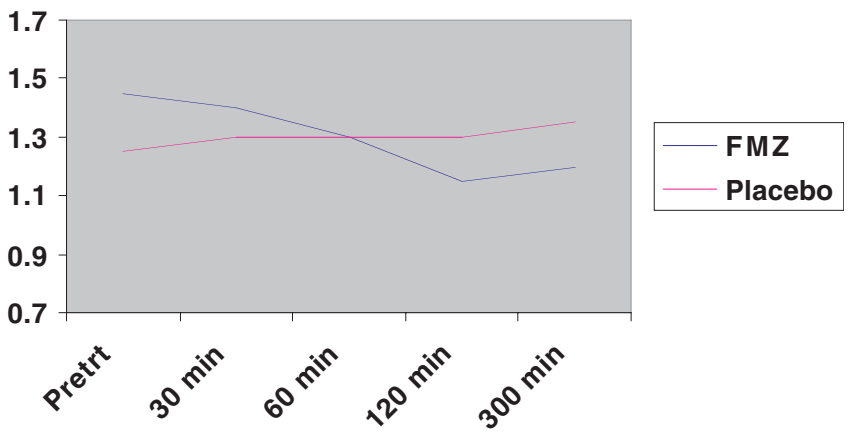
Table 2.

Results obtained in the flumazenil group.

No	age	sex	Glasgow coma sc.	Child-Pugh	PSE stage		EEG tracing		NCT value (sec)	
					Pretrt.	Posttrt.5.h	Pretrt	Posttrt.5.h	Pretrt	Posttrt.5.h
1	45	M	13	C	3	2	B	A	180	148
2	47	F	13	B	3	2	D	D	168	161
3	43	F	14	C	2	1	C	B	126	118
4	51	M	14	C	3	3	E	E	*	156
5	44	M	15	C	subclinic	subclinic	B	A	96	31
6	62	F	15	C	subclinic	subclinic	B	A	69	62
7	39	M	15	C	1	1	A	B	62	52
8	70	F	15	B	subclinic	subclinic	A	A	67	49
9	32	F	15	C	1	1	A	A	78	63
10	50	M	15	C	subclinic	0	B	B	68	43
11	42	M	15	C	1	subclinic	C	B	74	65
12	30	M	15	C	1	subclinic	A	B	211	170
13	53	M	15	C	2	2	A	B	93	65
14	32	M	12	C	3	4	E	E	*	*
15	22	M	15	B	2	1	C	B	67	56
16	52	M	14	C	3	2	D	C	*	*
17	40	F	15	C	1	1	A	A	139	129
18	67	M	15	C	1	1	A	A	149	166
19	25	M	15	C	1	1	B	A	55	59
20	45	M	15	B	1	1	A	A	63	65

Figure 1

Change in PSE stage.

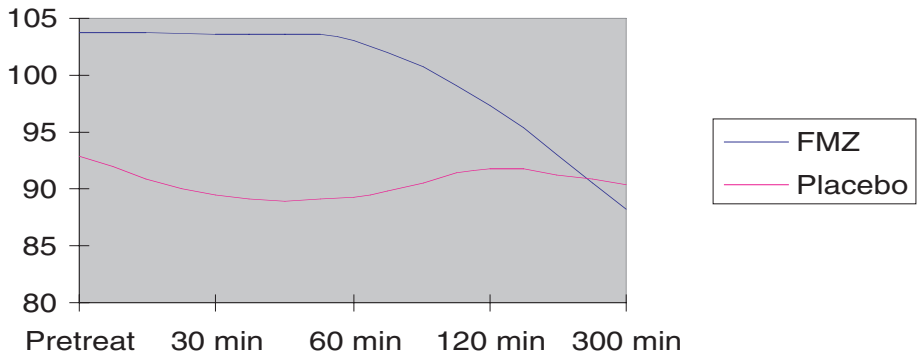


gression analysis. Standardised coefficients beta value was found to be 0.30 (t = 4.72, p = 0.00). According to this finding, it was concluded that there was a weak correlation between PSE stage and blood ammonia level.

Table 3.
Results obtained in the placebo group.

No	age	sex	Glasgow coma sc.	Child-Pugh	PSE stage		EEG tracing		NCT value (sec)	
					Pretrt.	Posttrt.5.h	Pretrt	Posttrt.5.h	Pretrt	Posttrt.5.h
1	50	M	13	B	2	2	A	C	170	192
2	45	F	15	C	Subclinic	Subclinic	A	A	167	165
3	44	M	15	C	1	1	C	C	80	78
4	19	M	15	B	subclinic	subclinic	B	A	35	45
5	70	F	15	C	subclinic	subclinic	A	C	125	92
6	37	M	15	B	subclinic	subclinic	A	A	74	50
7	44	M	15	C	subclinic	subclinic	A	A	55	40
8	69	M	15	B	1	1	B	C	83	87
9	50	M	15	B	1	1	C	C	62	47
10	47	M	15	C	1	1	B	A	162	173
11	27	M	15	C	subclinic	subclinic	A	A	38	32
12	31	M	15	C	2	2	A	A	127	82
13	45	F	13	C	3	3	D	D	98	102
14	48	M	15	B	2	2	D	D	97	105
15	36	M	15	C	3	3	E	E	102	105
16	40	F	15	C	3	3	E	E	88	98
17	42	F	13	B	1	2	A	B	105	106
18	37	M	15	C	3	3	C	C	78	80
19	43	M	14	B	2	2	A	A	62	60
20	49	M	15	C	1	1	A	A	60	68

Figure 2
Change in NCT.



Discussion

Much attention has been given to the role of enhanced GABA-ergic neurotransmission [2, 3], which is theoretically associated with enhanced affinity or density of the BNZ receptor complex, or increased endogenous BNZ ligands. There are many studies in animals and humans showing such increases occur in HE [4–11, 16]. If enhanced GABA-ergic neurotransmission does play a role in the pathogenesis of HE, then the pharmacological antagonism of the GABA/BNZ receptor complex may be expected to improve the HE patient's status. This may be achieved with BNZ antagonists, the most commonly used of which is flumazenil. Studies on the efficacy of flumazenil in HE have produced conflicting results [8, 17–25].

We assessed the efficacy of flumazenil in HE in a prospective, randomized, double-blind, placebo-controlled study. We found improvements in PSE stage and NCT scores between pretreatment and 5-hour values. In the flumazenil group, improvements of 1 stage occurred in 3 of 5 patients of stage III, 2 of 3 patients of stage II, 2 of 8 patients of stage I, and 1 of the 4 subclinical patients; no such improvements occurred in the placebo group. These results are incompatible with many other published reports [22, 23, 26, 27].

It is clear that flumazenil has greater efficacy in patients at advanced stages; this may be due to increases in BNZ ligand concentration with advancing HE stage, as pointed out by Basile et al. [6].

In a study carried out on cirrhosis patients, Amodia et al. [17] suggested that flumazenil did not cause any changes in NCT scores. However, we found significantly lower 5-hour NCT values in the flumazenil group than in the control group. One patient, despite unsuccessful NCT performance before treatment, achieved a successful score 5 hours after treatment. Neuropsychiatric assessment showed that flumazenil improved performance on the NCT, which is a very sensitive test [14], demonstrating its efficacy in treating HE.

Although EEGs showed a minimal improvement in the flumazenil group and a minimal worsening in the placebo group, the difference was not statistically significant. This result may be due to the low dosage used, the low number of patients involved, or the high standard deviation. Some studies on the effects of flumazenil on EEG have found it to be effective [8, 21, 22, 26, 29] and others ineffective [18, 30].

Although all patients in the study group received a total of 5 mg flumazenil during the study, no significant side effects were experienced, indicating that continuous IV infusion of flumazenil is reliable.

Conclusion

In the treatment of HE, short term beneficial effects were observed with flumazenil therapy. Furthermore, it showed that flumazenil at a total dose of 5 mg seemed to be safe in the treatment of subclinical to mild HE. Therefore, we are of the opinion that the addition of flumazenil to conventional treatment of patients with HE could improve cognitive symptoms. However, it will be possible through development of more active and selective analogs of BNZ receptors antagonists to achieve more effective results in patients with chronic episodes of HE.

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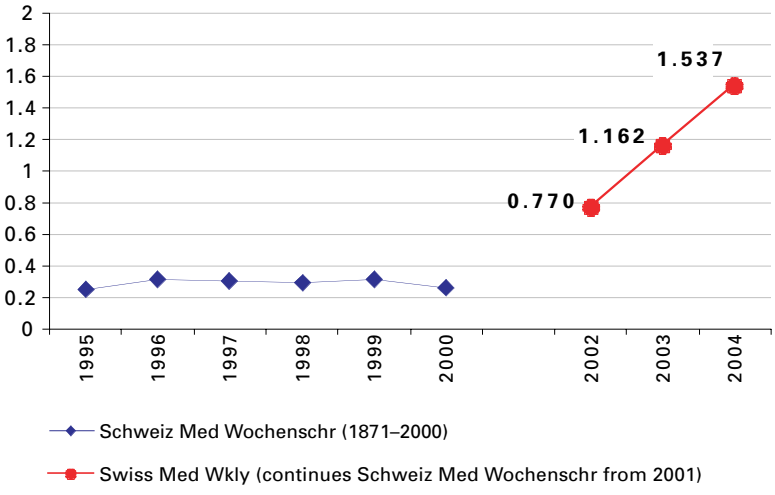

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