USE OF FLUMAZENIL IN THE PRODUCTION OF A DRUG FOR THE TREATMENT OF ALCOHOL DEPENDENCY

FIELD OF THE INVENTION

The invention relates to the use of pharmaceutical compositions that contain flumazenil in the treatment of alcohol dependency, more specifically to improvements in the use of flumazenil in the treatment of said dependency.

BACKGROUND OF THE INVENTION

Alcohol dependency is a syndrome that develops in alcoholics who, all at once, stop consuming alcohol. Minor symptoms include tremor, weakness, sweats, and nausea. The most severe cases include convulsions and hallucinations. If untreated, alcohol withdrawal may cause delirium tremens.

The customary treatment of alcohol dependency includes the administration of vitamin B and C complexes, benzodiazepines (to calm agitation and to help prevent dependency), and, sometimes, disulfiram (to prevent alcohol use). A review of the various pharmacological treatments existing for the treatment of alcohol dependency can be found in A Practice Guideline for the Treatment of Patients With Substance Use Disorders: Alcohol, Cocaine and Opioids, produced by the Work Group on Substance Use Disorders of the American Psychiatric Association and published in Am. J. Psychiatry 152:11, Nov. 1995 Supplement. An updated review of the treatment of alcohol dependency was made by Mayo-Smith et al., JAMA July 9, 1997, Vol. 278, No. 2, who conclude by indicating that the

benzodiazepines (alprazolam, diazepam, halazepam, lorazepam or oxazepam) are agents suitable for the treatment of alcohol dependency, whereas β-blockers (propranolol), neuroleptics (chlorpromazine and promazine), clonidine and carbamazepine, may be used in coadjuvant therapy, but their use is not recommended as a monotherapy. In none of the reviews mentioned is the use of flumazenil considered in the treatment of the alcohol withdrawal syndrome.

Flumazenil [ethyl 8-fluoro-5,6-dihydro-5-methyl-6-oxo-4H-imidazol[1,5-a][1,4]benzodiazepine-3-carboxylate] is a benzodiazepine antagonist which selectively blocks the effects exerted on the central nervous system via the benzodiazepine receptors. This active principle is indicated to neutralize the central sedative effect of the benzodiazepines; consequently, it is regularly used in anesthesia to end the general anesthesia induced and maintained with benzodiazepines in hospitalized patients, or to stop the sedation produced with benzodiazepines in patients undergoing brief diagnostic or therapeutic procedures on an inpatient or outpatient basis.

Some clinical studies have examined the role of flumazenil in the reversal of alcohol withdrawal syndrome.

Gerra et al., 1991, Current Therapeutic Research, Vol. 50, 1, pp 62-66, describe the administration to 11 selected alcoholics (who did not have cirrhosis, metabolic disorders, convulsions, addictions to other substances or psychiatric disorders) of 2 mg/day of flumazenil divided into 4 doses (0.5 mg), intravenously (IV), in saline solution, every 6 hours for 48 hours, continuing the treatment with flumazenil for 2 more days. The use

of 0.5 mg of flumazenil is based on the presentation of pharmaceutical preparations that contain said active principle, for example ANEXATE7 [sic] ROCHE, but not on studies performed in humans concerning the level of occupation of the receptors involved. Taking into consideration the fact that the half-life of flumazenil in the human body is approximately 45 minutes, the administration of 0.5 mg of flumazenil every 6 hours (i.e., 0.08 mg/hour of flumazenil) does not seem adequate to effectively cover the cerebral benzodiazepine receptors (Savic et al., Lancet, 1991, 337, 133-137), which confirms what was stated by Gerra et al., loc. cit., who, on page 64, next to last paragraph, state that they did not observe significant changes in either the blood pressure or in the heart rate of the patients after the administration of flumazenil, which is surprising when there had been an effective interaction of the fumazenil administered with the cerebral benzodiazepine receptors. The tests performed by Gerra et al. present some characteristics that are far from the actual circumstances, for example, the tests were performed on a small sample (11 individuals) of select patients not representative of the pathology considered since it is relatively customary that these patients have cirrhosis, metabolic disorders, convulsions, addictions to other substances (cocaine, heroin, etc.) and/or psychiatric disorders. Moreover, Gerra et al. do not present data concerning the evaluation of the dependency either before or after administration of the drug. The treatment with flumazenil, in accordance with the protocol developed by Gerra et al., lasts 4 days, which means a very long period of time which causes inconvenience for the patient as well as an increase in the cost and duration of the treatment.

Nutt et al. [Alcohol & Alcoholism, 1993, Suppl. 2, pp 337-341. Pergamon Press Ltd.; Neuropschychopharmacology, 1994, Vol. 10, 35, part 1, Suppl., p. 85f) describe the administration to 8 alcoholics in the acute withdrawal phase of 2 mg of flumazenil, by IV, for 1 minute. This dosage was selected on the basis of studies that demonstrated that with said dose approximately 75% of the cerebral benzodiazepine receptors are occupied (Savic et al., Lancet, 1991, 337, 133-137). The results obtained after the administration of flumazenil were not completely satisfactory since in some cases, there was an immediate worsening of the withdrawal symptoms, especially of sweats and anxiety. In other cases, the withdrawal symptoms disappeared but returned a few hours later. Since flumazenil is metabolized and eliminated very quickly, the IV administration of a relatively high quantity of fumazenil in a single dose of 2 mg, for 1 minute, has several disadvantages since, on the one hand, it triggers side effects, and, on the other, some of the flumazenil administered yields no pharmacological response or a weak response which means an unacceptable expense.

The tests performed by Gerra et al. and by Nutt et al., loc. cit., with flumazenil to treat alcohol dependency do not provide representative results due to the use of a very small sample (only 19 patients tested of the approximately 600,000 patients treated annually in the United States during the years 1991-1994, years during which the work of Gerra et al. and of Nutt et al. occurred) which is not representative of said patients (the 11 patients treated in the trial of Gerra et al. were selected alcoholics who did not have cirrhosis, metabolic disorders,

convulsions, addictions to other substances or psychiatric disorders). Moreover, the results obtained are not conclusive since in some cases, no significant changes were observed in either the blood pressure or the heart rate of patients after the administration of flumazenil (Gerra et al., loc. cit.); whereas, in other cases, an immediate worsening of the withdrawal symptoms was observed, especially sweats and anxiety (Nutt et al., loc. cit.). These very discouraging results seem to have favored the abandonment of flumazenil as a therapeutic agent for the treatment of alcohol dependency, a situation which could explain the absence of publications of new trials associated with the treatment of alcohol dependency with flumazenil during the past 6 years as well as the failure to include said treatment in the aforementioned reviews concerning the treatment of alcohol dependency [A Practice Guideline for the Treatment of Patients With Substance Use Disorders: Alcohol, Cocaine and Opioids and Mayo-Smith et al.].

Consequently, it would be desirable to be able to determine without ambiguity whether flumazenil may be a suitable agent to treat alcohol dependency and, if so, to develop a protocol for administration of flumazenil for the treatment of alcohol dependency that would enable effectively eradicating the symptoms of alcohol withdrawal. It would also be desirable to reduce the quantity of flumazenil to be administered per dose during a short period of time for the purpose of reducing, on the one hand, the risk of undesirable side effects, and, on the other, to reduce or avoid unnecessary and pointless consumption of flumazenil.

BRIEF DESCRIPTION OF THE INVENTION

The invention deals with the problem of developing a new method for the treatment of alcohol dependency based on safe and effective administration of flumazenil and which requires a short period of time to effectively eradicate the symptoms of alcohol dependency.

The solution provided by this invention is based on the use of pharmaceutical compositions that contain a therapeutically effective quantity of flumazenil for the treatment of alcohol dependency and the eradication of the symptoms of said syndrome in a short period of time, with said pharmaceutical compositions containing small quantities of flumazenil and being intended for sequential administration.

Thus, one object of this invention consists in a method for the effective administration of flumazenil that uses a smaller quantity of drug per dose unit to be administered, by sequential administration of small quantities of flumazenil, to eradicate the symptoms of alcohol withdrawal in a short period of time, while simultaneously reducing the side effects caused by the administration of large quantities of the drug in a single application in a short period of time.

Another object of this invention consists in a method for the administration of flumazenil by sequential administration of small doses of flumazenil, without compromising its effects of eradication of the symptoms of alcohol withdrawal, effectively and reproducibly, in a short period of time.

Another additional object of this invention consists in the use of flumazenil to produce a drug for sequential administration, at short time intervals,

of small quantities of flumazenil, until a therapeutically effective quantity to treat alcohol dependency has been administered.

Another additional object of this invention consists in a method for the treatment of alcohol dependency that includes administration, to a patient in need of said treatment, of a therapeutically effective quantity of flumazenil, broken down into small quantities of flumazenil and intended for sequential administration, at short time intervals, until said therapeutically effective quantity to treat alcohol dependency has been reached.

DETAILED DESCRIPTION OF THE INVENTION

The invention relates to the use of flumazenil to produce a drug for sequential administration, at short time intervals, of small quantities of flumazenil, until a therapeutically effective quantity to treat alcohol dependency has been administered.

More specifically, the invention relates to the use of flumazenil to produce a drug for sequential administration, at time intervals between 1 and 15 minutes, of quantities of flumazenil between 0.1 and 0.3 mg, until a therapeutically effective quantity, usually between 1.5 and 2.5 mg/day, of flumazenil has been administered, to treat alcohol dependency.

In one embodiment, the invention relates to the use of flumazenil to produce a drug for sequential administration, at intervals of 3 minutes, of 0.2 mg of flumazenil, until a therapeutically effective quantity of 2 mg/day of flumazenil has been administered, to treat alcohol dependency.

In the meaning used in this description, the term drug includes the group of pharmaceutical compositions that contain flumazenil, along with the pharmaceutically acceptable excipients suitable for the form of administration of said pharmaceutical compositions.

Although the trials described in the prior art associated with the treatment of alcohol dependency with flumazenil include the administration to the patient of an IV perfusion of 2 mg/day of flumazenil divided into 4 doses (0.5 mg/dose), every 6 hours for 48 hours, or 2 mg by IV for 1 minute, it was discovered, surprisingly, that flumazenil can be safely administered to said patients, in small quantities, applied sequentially and separated by a relatively short interval of time, until a therapeutically effective quantity of flumazenil to treat alcohol dependency has been reached.

This surprising discovery means that it is possible to administer flumazenil in smaller doses than was believed were necessary to obtain the desired therapeutic response, which reduces the risk of secondary effects in the patient (as a result of reducing the quantity of drug administered per dose applied), on the one hand, and, on the other, provides a better use of flumazenil to treat the symptoms of alcohol withdrawal and to reduce the unnecessary and pointless consumption of said drug (which increases convenience and the quality of life of the patient and reduces cost) to treat alcohol dependency in a very short period of time.

Example 1 demonstrates that the administration to patients of 2 mg/day of flumazenil divided into doses of 0.2 mg every 3 minutes eradicates the symptoms of alcohol withdrawal in a high percentage of the patients treated.

Consequently, in one embodiment, the invention relates to the use of flumazenil to produce a drug for administration, sequentially, of 0.2 mg of flumazenil every 3 minutes, up to a quantity of 2 mg/day, to treat alcohol dependency.

Flumazenil may be administered by any appropriate route of administration, for example, orally or parenterally, for which it will be formulated with the appropriate excipients for the form of administration to be used. In one embodiment, flumazenil is administered by IV.

The invention also relates to a method for the treatment of alcohol dependency that includes the administration to a patient in need of said treatment of a therapeutically effective quantity of flumazenil, usually between 1.5 and 2.5 mg/day of flumazenil, broken down into quantities of flumazenil between 0.2 and 0.3 mg and intended for sequential administration, at time intervals between 1 and 15 minutes, until said therapeutically effective quantity of flumazenil to treat alcohol dependency has been reached.

Flumazenil may be administered by any appropriate route of administration, for example, orally or parenterally, for which it will be formulated with the appropriate excipients for the form of administration to be used. In one embodiment, flumazenil is administered by IV.

The method for the treatment of alcohol dependency provided by this invention is applicable to any patient who, when the treatment is to begin, has no acute or uncompensated illness, or is not taking medication contraindicated with flumazenil. In

general, the method of treatment of alcohol dependency provided by this invention begins with a complete medical and psychological examination. Before and after administration of flumazenil, the symptoms of alcohol withdrawal, heart rate, and blood pressure are evaluated. If the patient presents an anxiety crisis, it is possible to administer an appropriate therapeutic agent, for example, clomethiazole, before administration of flumazenil. Likewise, if the patient presents a severe diagnosis of benzodiazepine dependency, the first administration of flumazenil is carried out under sedation, for example, with propofol, under intensive care conditions. The administration of flumazenil may be carried out orally or intravenously, for example, by boluses that contain the appropriate quantity and under observation of the patient's reaction. Once inpatient treatment has concluded, as part of the therapeutic program, the patient must continue pharmacological treatment and continue sessions with his therapist to evaluate his progress. The treatment is supplemented by a semistructured follow-up of the cognitive behavior of the patient.

The following example demonstrates the invention and must not be considered to limit the scope thereof.

EXAMPLE 1
Treatment of patients with flumazenil sequentially and at low dose

1.1 Experimental Protocol

64 alcoholics (51 males and 13 females) voluntarily entered a treatment program to discontinue the use of alcohol. Said patients were provided the appropriate information and the corresponding informed consent form was obtained

from them. The patients were warned not to drink alcohol the morning on which the treatment was to be carried out to enable better evaluation of the withdrawal symptoms.

Table 1 summarizes the characteristics of the patients treated associated with alcohol use.

Table 1

Characteristics of the patients

associated with alcohol use

	Mean	SD	Minimum	Maximum
Age (years)	42.7	10.2	20	75
Age at the beginning of daily alcohol use (years)	24.6	10.2	6	71
Daily units of alcohol intake	24.9	15.4	4	73
γ-glutamyl transpeptidase (GGT)	159.1	227.2	12	1.230
Corpuscular volume (RBC)	97.8	6.4	72	111
Number of previous detoxifications	1.6	1.2	0	5

[SD: Standard deviation]

NOTE:

85% consumed alcohol daily and 39.1% consumed benzodiazepines daily.

Before starting the treatment, the patients underwent a complete medical and psychological examination. The monitoring of the patients throughout the morning included a complete blood count, a biochemical profile [creatinine, glucose, urea, cholesterol (HDL and LDL), triglycerides, alkaline phosphatase, LDH (lactic dehydrogenase) and total proteins], hepatic function tests [GOT, GPT, GGT, bilirubin), electrocardiogram and, if need be, pregnancy test and x-ray examination. The exclusion criteria applied included acute or uncompensated illnesses, as well as the taking of any drug contraindicated with flumazenil. No patient was excluded after the pre-admission interview and the tests performed. Admission of one patient was postponed until his cardiac pathology was checked.

Before and after the administration of flumazenil, the withdrawal symptomatology was measured using the CIWA-A evaluation (Adinoff et al., Medical Toxicology 3:172-196 (1988)), as well as heart rate and blood pressure.

Table 2 presents the treatment protocol followed during hospitalization.

Table 2

Protocol followed during hospitalization

Time	Day of admission	Day 2	Day of discharge
9:00 a.m.		Clomethiazole 192 mg Vitamin B Complex Piracetam 3 g (oral) Drink with vitamins, minerals, proteins, and amino acids	Clomethiazole 192 mg Vitamin B Complex Piracetam 3 g (oral) Drink with vitamins, minerals, proteins, and amino acids
11:00 a.m.		Flumazenil 2 mg	
1:00 p.m.	Clomethiazole 192 mg Vitamin B Complex Piracetam 3 g (oral)		
4:30 p.m.	Flumazenil 2 mg		
7:30 p.m.	Vitamin B Complex	Vitamin B Complex Disulfiram 250 mg	
9:30 p.m.	Clomethiazole 384 mg	Clomethiazole 384 mg	

Flumazenil was administered at a dose of 0.2 mg every 3 minutes (up to a total of 2 mg/day), because of the fact that the effects of flumazenil can be detected after 1-2 minutes after their administration. This quantity per dose was established to minimize the adverse side effects associated with withdrawal or interactions with other pharmaceuticals or psychopathologies. By administration of 2 mg of flumazenil per day, more than 55% of the GABA B receptors were occupied.

Patients who presented marked anxiety were administered an additional dose of 192 mg of clomethiazole 30 minutes before administration of flumazenil. In those patients who presented a severe diagnosis of benzodiazepine dependency, the initial administration of

flumazenil was performed under sedation with propofol under intensive care conditions.

Before discharge from the hospital, the following medications were prescribed:

Vitamin B complex: 1 month 1-1-0 (breakfast-lunch-dinner);

Piracetam 3 g: 1 week 1-0-0; piracetam 800 mg: 1 month 1-1-0;

Fluoxetine 20 mg: 2 months 1-0-0;

Clomethiazole 192 mg: 1 week 1-0-1, and reduction to 0-0-0 during the second week; and

Disulfuram 250 mg 1-0-0.

As part of the treatment program, the patients were instructed to attend the outpatient treatment center for 9 months with decreasing frequency [once a week for the first three months, once every two weeks during the second three months, and once a month during the third three months].

Likewise, a semistructured follow-up of cognitive behavior was implemented. Individual and family psychotherapy was focused on 4 major interventions (cognitive restructuring, work therapy, prevention of relapse, and stress reduction) aimed at rehabilitating the social, family, work, personal and leisure life of the patient.

1.2 Results

Of the 64 patients treated, in 3 cases, the first administration of flumazenil was interrupted and postponed to the following day: one of them, who was obviously intoxicated with alcohol, demonstrated a distressing increase in confusion, another had a significant increase in distal tremors, and the other, who was also addicted to

benzodiazepines, demonstrated a significant increase in anxiety. Another group of 3 patients received the first dose of flumazenil under sedation with propofol in the intensive care unit.

Approximately 10% of the patients suffered headache during or immediately following the administration of flumazenil, which disappeared after a few minutes, or after administration of metamizole magnesium.

Results after the first administration of flumazenil

The CIWA-A scoring of 55 patients showed that:

47.3% had a significant reduction (t: -7.713; p<.000);

40.0% experienced no change; and

12.7% had a significant increase (t: 2.511; p<.046) [in the three cases presenting the greatest increase, the treatment was discontinued].

The heart rate values of 55 patients showed that:

50.9% had a significant reduction (t: -8.820; p<.000);

40.0% experienced no change; and

9.1% had a significant increase (t: 4.750; p<.009).

The systolic blood pressure values of 53 patients showed that:

47.2% had a significant reduction (t: -9.908; p<.000);

37.7% experienced no change; and

15.1% had a significant increase (t: 4.314; p<.004).

The diastolic blood pressure values of 53 patients showed that:

34% had a significant reduction (t: -9.220; p<.000);

47.2% experienced no change; and

18.9% had a significant increase (t: 5.511; p<.000).

Results after the second administration of flumazenil

The CIWA-A scoring of 58 patients showed that:

36.2% had a significant reduction (t: -5.363; p<.000);

55.2% experienced no change; and

8.6% had a significant increase (t: 4.000; p<.016).

The heart rate values of 55 patients showed that:

41.8% had a significant reduction (t: -8.523; p<.000); and

58.2% experienced no change.

The systolic blood pressure values of 56 patients showed that:

28.6 had a significant reduction (t: -7.596; p<.000);

55.4% experienced no change; and

16.1% had a significant increase (t: 4.612; p<.002).

The diastolic blood pressure values of 56 patients showed that:

28.6% had a significant reduction (t: -6.325; p<.000);

51.8% experienced no change (n = 29); and

19.6% had a significant increase (t: 6.640; p<.000).

Table 3 statistically summarizes the results obtained before and after the treatment (at the end of 18 hours).

Table 3
Statistical summary of the results
obtained before and after the treatment (at the end of 18 hours)

X			N	SD
			EM	T
			Sig.	
CIWA-A		4.13		54
		4.28	0.58	
Before treatment				
			6.190	
			0.002	
CIWA-A		0.76		54
		1.52	0.21	
After treatment				
Systolic blood pressure	135.20		51	
	18.22	2.55		
Before treatment				
			5.256	
			0.000	
Systolic blood pressure	126.67		51	
	13.99	1.96		
After treatment				
Diastolic blood pressure	86.27	51	10.76	
	1.51			
Before treatment				
			3.273	
			0.002	
Diastolic blood pressure	82.75	51	9.13	
	1.28			
After treatment				
Heart rate	81.42	53	13.83	
	1.90			

Before treatment				
				4.273
				0.000
Heart rate	75.02	53	9.93	
	1.36			
After treatment				

[X: Mean; N: Number of samples; SD: Standard deviation
EM: Mean error; T: Student's t factor; Sig.: Significance]

Table 4 summarizes the follow-up data.

Table 4

Summary of Follow-up

		Month 1	Month 3	Month 6	Month 9
	(%/n)	67.2/43	34.4/22	18.8/12	12.5/8
Therapy and Disulfiram		95.3%	86.4%	75.0%	75.0%
Therapy without Disulfiram				4.5%	
				12.5%	
Dropouts		4.7%	9.1%	25.0%	12.5%

The psychophysiological functions such as appetite and sleep were regained very rapidly during hospitalization.

The second day of hospitalization, the patients were permitted to spend a few hours outside the clinic during the afternoon. Some patients had dinner outside the clinic.

Probably, the most striking result is the spontaneous verbal report from the majority of the patients concerning the absence of anxiety and of the desire to drink alcohol.

CLAIMS

1. Use of flumazenil for the manufacture of a pharmaceutical composition for the treatment of alcohol dependency wherein the pharmaceutical composition comprises a dosage of flumazenil between about 0.1 and 0.3 mg for sequential administration at time intervals between 1 and 15 minutes until an effective amount is administered to treat the alcohol dependency.

2. Use according to claim 1, wherein said dosage of flumazenil to treat alcohol dependency is between 1.5 and 2.5 mg/day of flumazenil.

3. Use according to claim 1 or 2, wherein said pharmaceutical composition contains individual doses of 0.2 mg of flumazenil.

4. Use according to claim 3, wherein the sequential administration of said individual doses is carried out at intervals of 3 minutes.

5. Use according to any of claims 1 to 4, wherein said dosage to treat alcohol dependency is 2 mg/day.

6. Use according to any of claims 1 to 5, wherein said pharmaceutical composition is suitable for oral or parenteral administration.

7. Use according to claim 6, wherein said pharmaceutical composition is suitable for intravenous administration.