USE OF FLUMAZENIL IN THE PRODUCTION OF A MEDICAMENT FOR THE TREATMENT OF COCAINE DEPENDENCY

FIELD OF THE INVENTION

The invention relates to the use of pharmaceutical compositions that contain flumazenil in the treatment of cocaine dependency.

BACKGROUND OF THE INVENTION

Cocaine is a drug with a powerful stimulating effect that increases alertness (reduces fatigue), increases concentration, reduces appetite, increases physical resistance, and may induce a state of well being or euphoria.

Cocaine may be taken orally, inhaled nasally in powdered form, or injected, usually, directly in a vein. When heated with sodium bicarbonate, it is converted into a base called crack, which may be smoked.

Cocaine increases the blood pressure and the heart rate and may cause a fatal heart attack. Other effects include gastrointestinal disorders, intestinal damage, intense nervousness, a sensation that something is moving under the skin, epileptic attacks, hallucinations, sleep disorders, paranoid delirium, and violent behavior.

Due to the fact that the effects of cocaine are of short duration, ca. 30 minutes, cocaine users usually take repeated doses of the drug. To reduce some of the extreme nervousness caused by cocaine, many addicts use heroin or nervous system depressants, for example, alcohol.

Cocaine withdrawal syndrome is a syndrome which develops in cocaine addicts who stop using cocaine. The reactions typical of this syndrome include extreme fatigue and depression, i.e., reactions opposite the effects of the drug, and, frequently, suicidal tendencies appear upon discontinuation of use of the drug.

Cocaine dependency is usually treated, initially, by a psychosocial treatment. However, patients or individuals with severe forms of cocaine dependency that do not respond to said psychosocial treatment may be subjected to a pharmacological treatment. Currently, no truly effective treatment is available for cocaine withdrawal syndrome.

A review of the various pharmacological treatments to reduce the symptoms of cocaine dependency and to combat cocaine withdrawal syndrome can be found in "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, pp. 36-39.

This publication states that approximately 20 different pharmaceutical products have been studied for the purpose of finding an effective pharmacological treatment for cocaine dependency, although there is still no truly effective treatment available. The most promising results seem to have been obtained with desipramine and amantadine although there are studies that could not confirm the positive expectations created, possibly due to differences in the cocaine addict population and the route of administration of the drug. Other pharmaceuticals tested have been carbamazepine, pergolide, carbidopa/L-dopa, fluoxetine, flupenxitol, bupropion, maprolitine, phenelzine, buprenorphine, and methadone.

Likewise, the above referenced publication states that treatment with dopamine agonists, for example, amantadine, reduces the symptoms of cocaine withdrawal syndrome, although two later studies could not confirm these results. Initial studies with bromocriptine yielded some results in the treatment of cocaine withdrawal syndrome

that were also not subsequently confirmed. In fact, Moscoviz et al., J. Gen. Intern. Med. 1993, 8:1-4, did not find a significant reduction between bromocriptine and placebo in outpatients.

In none of the reviews mentioned is the use of flumazenil considered in the treatment of cocaine dependency.

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.

BRIEF DESCRIPTION OF THE INVENTION

The invention deals with the problem of developing a method for the treatment of cocaine dependency.

The solution provided by this invention is based on the use of flumazenil in the treatment of cocaine dependency.

Thus, one object of this invention consists in the use of flumazenil to reduce or eradicate the symptoms of cocaine dependency.

An additional object of this invention consists in the use of flumazenil to produce a medicament for the treatment of cocaine dependency.

Another additional object of this invention consists in a method for the treatment of cocaine dependency that

includes administration of a therapeutically effective quantity of flumazenil to a patient in need of said treatment.

DETAILED DESCRIPTION OF THE INVENTION

The invention relates to the use of flumazenil in the production of a medicament for the treatment of cocaine dependency. In the sense used in this description, the term "cocaine dependency" includes cocaine abuse, cocaine withdrawal syndrome, and relapse.

In one embodiment, flumazenil is administered sequentially, at short time intervals, in small quantities, until a therapeutically effective quantity for the treatment of cocaine dependency has been administered.

More specifically, the invention relates to the use of flumazenil to produce a medicament 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 to treat cocaine dependency has been administered.

Although the therapeutically effective daily dose of flumazenil could be administered in a single administration, it was discovered, surprisingly, that flumazenil can be safely administered to patients with cocaine dependency, in small quantities, applied sequentially and separated by a relatively short interval of time, until a therapeutically effective quantity of flumazenil to treat cocaine dependency is reached. This surprising discovery means that it is possible to administer flumazenil in small successive doses to treat cocaine dependency in a very short period of time, which reduces the risk of secondary effects in the patient and provides a better

use of flumazenil to treat the symptoms of cocaine dependency.

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 cocaine dependency in a high percentage of the patients treated.

Consequently, in a specific embodiment, the invention relates to the use of flumazenil to produce a medicament for administration, sequentially, 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 cocaine 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 cocaine 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.

In one embodiment, the method for the treatment of cocaine dependency provided by this invention 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 0.1 and 0.3 mg and intended for sequential administration, at intervals of time between 1 and 15 minutes, until said therapeutically effective quantity of flumazenil to treat cocaine dependency is reached.

In a specific embodiment, the invention provides a method for the treatment of cocaine dependency that includes the administration to a patient in need of said

treatment of 2 mg/day of flumazenil, broken down into quantities of 0.2 mg of flumazenil intended for sequential administration every 3 minutes until said quantity of 2 mg/day of flumazenil is reached.

The method for the treatment of cocaine 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 cocaine dependency provided by this invention begins with a complete medical and psychological examination. Normally, before and after administration of flumazenil, the symptoms of cocaine 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 significant disphoric reaction, 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, optionally, continue sessions with his therapist to evaluate his progress.

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

3 cocaine addicts (2 men and 1 woman) voluntarily entered a treatment program to discontinue the use of cocaine. Said patients were provided the appropriate information and the corresponding informed consent form was obtained from them. The patients were warned not to use cocaine 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 cocaine use.

Table 1

Characteristics of the patients

associated with cocaine use

	Patient code	
Age (years)	P01 P02 P03	27 31 35
Age at the beginning of daily cocaine use (years)	P01 P02 P03	25 30 33
Quantity used in mg during the last 30 days prior to treatment	P01 P02 P03	6,000 5,000 500
Number of previous detoxifications	P01 P02 P03	0 0 0

Before starting the treatment, the patients underwent a complete medical and psychological examination. The monitoring of the patients throughout the morning included exhaustive blood analysis with a complete count of all series (red, white and platelets), 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 included acute or uncompensated

illnesses. No patient was excluded after the pre-admission interview and the tests performed.

Before and after the administration of flumazenil the withdrawal symptomatology was evaluated using clinical criteria 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 am.		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 in a period of time less than 1 hour, 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. Before beginning the initial administration of flumazenil, a test was performed consisting of the administration of a bolus of 0.1 mg of flumazenil to evaluate the subject's reaction. In those patients who had a significant disphoric reaction, 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; and

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

1.2 Results

Of the 3 patients treated, in 2 cases the initial test was positive and the first administration of flumazenil was carried out under sedation with propofol in the intensive care unit.

Results after the first administration of flumazenil

The withdrawal symptomatology of the patients revealed that it was not possible to find a single physical or psychological symptom in any of the 3 patients.

The heart rate values of the patients, normal at the beginning [67 $\pm$ 5 beats per minute (b.p.m.)], remained stable during the entire administration of flumazenil, with the exception of an increase of 15 $\pm$ 5 b.p.m. after the administration of the first and second bolus of flumazenil in the 2 patients who required the use of sedation.

The systolic blood pressure values of the patients also underwent no significant changes that would reflect suffering on the part of the patient. With an initial value of 110 ± 10 mm Hg, throughout the administration of flumazenil, there was a decrease of 10 ± 5 mm Hg in these values in the 3 cases.

The diastolic blood pressure values of the patients, 75 ± 5 mm Hg at the beginning, developed the same as the former values, with a slightly more pronounced decline (15 ± 5 mm Hg).

Results after the second administration of flumazenil

The withdrawal symptomatology of the patients revealed, as with the first administration, that it was not possible to find a single physical symptom in any of the patients, with the 3 stating that "ideas" and "memories" associated with the drug had a markedly lower intensity.

The heart rate values of the patients (65 ± 5 b.p.m.) remained stable throughout the entire administration of flumazenil, with no elevated peaks at any time.

The systolic blood pressure values of the patients also underwent no significant changes, with values virtually identical to those of the first administration: with an initial value of 115 ± 5 mm Hg, throughout the administration of flumazenil, there was in the 3 cases a decrease of 10 ± 5 mm Hg in these values.

The diastolic blood pressure values of the patients, 75 ± 5 mm Hg at the beginning, developed the same as the former values, again with a slightly more pronounced decline (15 ± 5 mm Hg).

The psychophysiological functions such as appetite and sleep came back very rapidly during hospitalization, progressively from the first night and were

virtually normal at the time of discharge.

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

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

CLAIMS

1. Use of flumazenil to produce a medicament for the treatment of cocaine dependency.

2. Use according to claim 1, to produce a medicament 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 of flumazenil to treat cocaine dependency has been administered.

3. Use according to claim 2, wherein said therapeutically effective quantity of flumazenil for treatment of cocaine dependency is between 1.5 and 2.5 mg/day of flumazenil.

4. Use according to claim 2, wherein said medicament contains 0.2 mg of flumazenil.

5. Use according to claim 2, wherein the sequential administration of said medicament is carried out at intervals of 3 minutes.

6. Use according to claim 2, wherein said therapeutically effective quantity of flumazenil to treat cocaine dependency is 2 mg/day.

7. Use according to claim 2, wherein said flumazenil-based medicament is administered orally or parenterally.

8. Use according to claim 7, wherein said flumazenil-based medicament is carried out intravenously.

9. Use of flumazenil to produce a medicament for administration, sequentially, of 0.2 mg of flumazenil at time intervals of 3 minutes, up to a quantity of 2 mg/day, to treat cocaine dependency.

10. Method for the treatment of cocaine dependency that includes the administration of a therapeutically effective quantity of flumazenil to a patient in need of said treatment.

11. Method according to claim 10, for the treatment of cocaine dependency that includes the administration of a therapeutically effective quantity of flumazenil to a patient in need of said treatment, broken down into quantities of flumazenil between 0.1 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 cocaine dependency has been reached.

12. Method according to claim 11, wherein said therapeutically effective quantity of flumazenil to treat cocaine dependency is between 1.5 and 2.5 mg/day of flumazenil.

13. Method according to claim 11, wherein the quantity of flumazenil that is administered in each sequential application is 0.2 mg.

14. Method according to claim 11, wherein the sequential administration of flumazenil takes place at intervals of 3 minutes.

15. Method according to claim 11, wherein said

therapeutically effective quantity to treat cocaine dependency is 2 mg/day.

16. Method according to claim 11, wherein the administration of the flumazenil takes place orally or parenterally.

17. Method according to claim 16, wherein the administration of flumazenil takes place intravenously.

18. Method for the treatment of cocaine dependency that includes the administration, to a patient in need of said treatment, of a therapeutically effective quantity of flumazenil of 2 mg/day of flumazenil, broken down into quantities of 0.2 mg of flumazenil and intended for sequential administration, at intervals of 3 minutes, until said therapeutically effective quantity of flumazenil to treat cocaine dependency has been reached.