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Clinical efficacy of gamma-hydroxybutyric acid in treatment of opiate withdrawal

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Abstract This paper describes the role of gamma-hydroxybutyric acid (GHB) in the treatment of opiate withdrawal syndrome. In the two patients described, after having abruptly withdrawn from long-term methadone treatment, GHB was orally administered (each dose given every 4–6 h) for 8–9 days. The GHB showed both a high efficacy (some mild and transient symptoms attributable to opiate withdrawal were observed, but only in the first days of therapy) and a good tolerability (no clinical phenomena interpreted as GHB side effects were found). These results could be of interest in improving the pharmacological treatment of drug addiction.

Key words Gamma-hydroxybutyrate · Opiate dependence · Opiate withdrawal · Drug addiction

Introduction

In opiate addiction pharmacological treatment of withdrawal symptoms is often the first approach. The more effective this initial treatment is and the fewer its side effects, the more the patient will be induced to continue treatment. Gamma-hydroxybutyric acid (GHB) is a normal component of the nervous system in mammals. It was first marketed in Italy (under the name of Alcover, by Laboratory C.T. of San Remo) in 1992 as a sodium salt. Preclinical pharmacological studies had shown that in its lactone form GHB inhibits voluntary ethanol consumption in a rat line selectively bred for high preference for ethanol, and that GHB suppresses ethanol withdrawal syndrome in rats made physically dependent on ethanol by forced ethanol administration [1–3].

In humans these results were supported by our group. In a randomized double-blind study [4] a sample of patients showing alcohol-withdrawal syndrome were treated either with GHB (150 mg/kg/day in a syrup preparation; 11 patients) or with a syrup placebo (12 patients). The GHB treatment led to a prompt reduction in withdrawal symptoms such as tremor, sweating, nausea, depression, anxiety and restlessness. The only side effect was dizziness.

More recently the effect of GHB on alcohol consumption and craving in alcoholics was investigated in a randomized double-blind study [5]. A total of 71 outpatients completed the 3-month trial, either with GHB (50 mg/kg/day) or placebo. During the 3-month treatment period, in the placebo group there were no significant variations in either the number of daily drinks or in the abstinent days. The GHB-treated patients, on the other hand, showed a decrease by one-half in the number of daily drinks, and a 3-fold increase in the number of abstinent days. The GHB treatment significantly decreased alcohol craving during the 3 months of treatment. Transient side effects (dizziness and headache in the first days of treatment) were noted by a few patients on GHB.

Some of our previous (unpublished) observations on patients with both alcohol and multiple-drug abuse were so encouraging that we wished to try out GHB treatment on opiate-dependent subjects. This paper reports two clinical cases in which GHB treatment was effective in controlling opiate-withdrawal syndrome. In Italy GHB may only be given to alcohol addicts, therefore a special authorization was obtained from the Italian Ministry of Health for the prescription of GHB to opiate addicts. Both patients were informed about this experimental-drug trial and gave their informed written consent.

Patients and methods

Case 1

The first patient, a 30-year-old unmarried female, began injecting heroin at the age of 15 years. On many occasions she had unsuc-

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cessfully tried to reduce or suspend the use of opiates and had marked tolerance to them. Moreover, in early adolescence she had often been truant from school, told lies and stole. On examination she was found to be impulsive, could not hold a job, was irritable and aggressive and had frequently come into conflict with the law. According to the DSM-III-R she fit the diagnostic criteria for opiate addiction and antisocial-personality disorder. Since January 1991 she had been on methadone (mean dose 60 mg/day) with only partially successful results: Urine tests showed the frequent presence of morphine. She was then hospitalized for "washing out" preparatory to entering a residential therapeutic community.

Approximately 25 h after the first dose of methadone (60 mg) withdrawal symptoms of moderate severity appeared (gooseflesh, sweating, psychomotor agitation, alternate hot flushes and cold sweats, muscle contraction and mydriasis), scoring 30 on Wang's scale [6]. She was given an initial GHB dose of 50 mg/kg, and 15 min later all symptoms had completely disappeared (score: 0 on Wang's scale; overall feelings of subjective well-being). This dose was repeated every 4 h for 7 days, and then every 6 h for 2 days. The GHB treatment was suspended on the 9th day, and a naloxone test (0.4 mg i.v.) was given: No symptoms were observed. The patient began naltrexone therapy (50 mg/day orally) on that day and was discharged in good physical condition, suitable for entry into the therapeutic community. During her hospital stay she never reported particularly important withdrawal symptoms or fits of opiate craving, as measured daily by a 10-cm visual analogue scale (where 0 was absence of craving and 10 its maximum), except on one occasion (day 3 of GHB therapy, 2 h after a dose), when indomethacin had to be injected i.m. for extensive muscle pain. Urine tests during hospitalization never revealed any intake of psychoactive substances extraneous to the treatment procedure.

Case 2

The second patient, a 24-year-old male, began using heroin continuously at the age of 19 years. Since July 1989 he had spent most of his time trying to obtain the drug, had greatly reduced his social and work activities, and had marked tolerance. According to the DSM-III-R he fit the diagnostic criteria for opiate addiction, but did not meet any diagnostic criteria on axis 2. Since January 1992 he has been on methadone (fixed dose of 50 mg/day), and urine tests have occasionally been positive for morphine, but not for other psychotropic substances. He was hospitalized for a brief "washing out" preparatory to entering a residential therapeutic community.

Approximately 30 h after the last dose of methadone, when withdrawal symptoms appeared (sweating, psychomotor agitation, gooseflesh, extensive muscle pain, diarrhea and abdominal cramps of moderate severity; score of 25 on Wang's scale), an initial GHB dose of 30 mg/kg was given. Approximately 20 min later all withdrawal symptoms had completely disappeared (score: 0 on Wang's scale; overall sensation of subjective well-being and no craving for opiates). This dose was repeated every 4 h. Two days after the beginning of GHB treatment three evacuations (semiliquid faeces) were observed, but no antidiarrhea treatment had to be given. During his hospital stay no fits of opiate craving (measured as in case 1) or other disturbances linked to opiate withdrawal symptoms were observed. The GHB treatment was suspended on the 8th day of therapy and a challenge test with naloxone (0.4 mg i.v.) was given: No symptoms were observed. During the entire hospital stay urine tests did not reveal any opiates or other substances of abuse. The patient was then discharged and entered the therapeutic community in good physical condition.

Discussion

The previously mentioned clinical cases indicate that GHB can satisfactorily control withdrawal symptoms and opiate craving, both frequent causes of early drop-out during hospitalization. Treatment with GHB, with careful consideration of its pharmacokinetic properties [7], thus deserves attention, because its control over withdrawal symptoms and craving is not associated with the side effects often produced by other drugs more frequently used on a clinical basis (e.g. clonidine causes hypotension; benzodiazepines and neuroleptics have marked sedative effects; nonsteroid analgesics cause gastric pain). With regard to the dosage for the two patients described (300 mg/kg/day, subsequently reduced to 200 mg/kg/day in case 1, and 180 mg/kg/day in case 2) it seems that under our controlled clinical use the same dose of GHB caused different responses in different patients and different responses in the same person at different times. Again, it must be emphasized that the dosage that can satisfactorily control opiate withdrawal symptoms seems, from these preliminary observations, higher than the dose (150 mg/kg/day) needed to control alcohol-withdrawal symptoms [4].

There could be doubts as to the possible abuse liability of GHB. In this respect, the United States Food and Drug Administration (FDA) issued an advisory warning that GHB use outside of FDA-approved physician-supervised protocols was unsafe and illicit [8], given that some acute (but not lethal) poisonings attributed to GHB had been reported to the FDA, and that GHB has been marketed illicitly to bodybuilders for weight control, as a sleeping aid and as a food supplement instead of L-tryptophan. However, our long-term clinical experience with this drug in alcoholics confirms findings in these two patients: abrupt cessation of GHB administration even after long-term use does not involve the occurrence of symptoms attributable to withdrawal phenomena [5]. We have also never recorded any patient behaviour attributable to GHB abuse. Further preclinical and clinical trials may clarify the pharmacodynamics of GHB so as to shed some light on the biology of drug addiction [9].

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