Gamma-Hydroxybutyric Acid for Treatment of Opiate Withdrawal Syndrome

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In a double-blind placebo-controlled trial, gamma-hydroxybutyric acid (GHB) (25 mg/kg orally) suppressed most of the withdrawal symptomatology in 14 heroin addicts and 13 methadone-maintained subjects. The GHB effect was prompt (within 15 minutes) and persisted for between 2 and 3 hours. Subsequently, the same patients received GHB in an open study every 2 to 4 hours for the first 2 days and 4 to 6 hours for the following 6 days: most abstinence signs and symptoms remained suppressed and patients reported felling well. Urine analysis failed to detect any presence of opiate metabolites. No withdrawal symptomatology recurred after 8 days of treatment when GHB was suspended, and patients were challenged with an intravenous injection of 0.4 mg naloxone. The results indicate that GHB may be useful in the management of opiate withdrawal.
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KEY WORDS: *Gamma-hydroxybutyric acid; Heroin; Methadone; Opiates; Withdrawal syndrome; Opiate dependence*

Gamma-hydroxybutyric acid (GHB), an endogenous constituent of the mammalian brain, is found in the highest concentrations in the hypothalamus and basal ganglia (Snead and Morely 1981). Because there are specific high-affinity binding sites for GHB in the central nervous system (CNS), and the compound is located principally in synaptosomes—from which it is released in a Ca^{2+}-dependent process—GHB is considered to function either as a neurotransmitter or neuromodulator rather than as an incidental metabolite of gamma-aminobutyric acid (GABA) (Mandel et al. 1987).

Gamma-hydroxybutyric acid has been used as an intravenous hypnotic and anesthetic agent (Mamelak et al. 1977) and in the treatment of narcolepsy. In the latter condition, GHB is given orally at bedtime to improve nocturnal sleep quality, thus reducing cataplexy episodes during the day (Mamelak et al. 1986). Previous work in animals has shown that GHB both inhibits voluntary ethanol consumption in rats having a strong preference for ethanol and suppresses the ethanol withdrawal syndrome in rats physically dependent on ethanol (Fadda et al. 1989a, 1989b).

More recently, in a double-blind study we found that GHB, given orally in nonhypnotic doses, is highly effective in suppressing the withdrawal symptomatology in alcoholics; the GHB effect being rapid and devoid of negative side effects (Gallimberti et al. 1989). By using GHB in the management of the withdrawal syndrome in a number of alcoholics who concomitantly abused heroin, we observed that GHB not only suppressed the alcohol withdrawal symptomatology

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but, even more effectively, that of heroin. The present study was undertaken to clarify, in a double-blind condition, whether GHB was effective in suppressing the withdrawal syndrome in heroin- and methadone-dependent subjects.

SUBJECTS AND METHODS

The subjects participating the study were 22 male heroin users, with a mean age of 27.3 years (range 22 to 33 years), with a clear history of daily use of heroin for over 3 years (3 to 6 years) claiming a high degree of opiate dependence; and 19 male subjects, with an age ranging from 24 to 31 years (mean 28 years) undergoing a methadone maintenance treatment program at the Addiction Treatment Service (SERT, USL 21), Cagliari.

Methadone-maintained subjects were receiving a stabilized dose of 30 to 60 mg/day of methadone for at least 6 months prior to hospitalization. All subjects were interested in discontinuing opiate consumption and gave informed consent to the study. The present study required hospitalization for a period of 8 days. Subjects were hospitalized on the morning of the day following their last consumption of opiates. On admission each subject underwent a medical and psychiatric examination, routine laboratory tests, urine screening analysis for opiate metabolites, amphetamine, cocaine, benzodiazepines, barbiturates, cannabinoids, and alcohol.

The first test revealed that all heroin-dependent subjects had urinary opiate metabolites. All subjects under methadone maintenance presented methadone metabolites, three of whom revealed also other opiate metabolites. Small concentrations of alcohol and benzodiazepine metabolites were found in the urine of both groups of patients. After admission, methadone-maintained subjects were left with no opiate administration for 24 hours and the rating of withdrawal symptomatology was started at 8 AM on the second day of hospitalization. Fifteen of the 22 heroin-dependent subjects showed overt signs of abstinence on the morning of the day of admission; therefore, the rating of withdrawal symptomatology for these subjects was made on the morning of the same day of admission. The other seven heroin-dependent subjects, who showed objective signs of abstinence after 6 PM on the day of admission, received 1 or 2 intramuscular doses of 15 mg of morphine to ease their discomfort (no morphine was given after midnight) and their withdrawal symptomatology was scored on the second day of hospitalization starting at 8 AM as for methadone-maintained subjects.

Withdrawal symptomatology was evaluated by one of the investigators (either RP or PPP) blind to the treatment conditions. Twenty-one items associated with the withdrawal syndrome were rated as present (1) or absent (0), according to Gold et al. (1978); the maximum score attainable was 21. Symptoms considered included: craving, nausea, anorexia, anxiety and restlessness, aching bones and muscles, insomnia or yen sleep, and hot and cold flashes. Signs considered comprised: tremors, yawning, vomiting, diarrhea, perspiration, lacrimination, rhinorrhea, increased respiration rate and depth, goose flesh, mydriasis, spontaneous orgasm, increased temperature, tachycardia, and increased blood pressure.

Withdrawal scoring was made every 30 minutes for 3 hours prior to treatment (baseline period) and at various times afterwards, as indicated in the Results Section. The experiment was randomized and double blind; subjects, nurse, and physician observer were unaware of the substance administered. Active medication, consisting of GHB 17% solution in a black cherry syrup, and an identical placebo were provided by CT (San Remo, Italy). Subjects took GHB orally at the dose of 25 mg/kg or the placebo syrup. Treatments were given by a nurse who was not otherwise involved in the study. The Mann-Whitney U-test was used to test differences between placebo and GHB treatment. A modified Wilcoxon test (Pratt's test) was applied for within-patient comparison.

RESULTS

All methadone- and heroin-dependent subjects showed signs and symptoms of abstinence that increased during the 3 hours preceding treatment. Table 1 shows the reported withdrawal scores obtained during the 30 minutes preceding treatment and at various times after treatment. The administration of GHB (25 mg/kg) reduced most of the withdrawal signs and symptoms both in heroin- and methadone-dependent subjects. The GHB effect had a rapid onset but short duration. Thus, the global withdrawal score was significantly reduced within 15 minutes and remained maximally suppressed between 30 minutes and 2 hours after treatment. At the third hour, withdrawal scores tended to increase once again. Table 2 shows the effect of GHB on specific items of the opiate withdrawal scale. It appears that GHB was effective in reducing all the signs and symptoms of opiate withdrawal, except for diarrhea and insomnia, which were resistant to the GHB effect. All patients on GHB referred to relief of subjective distress. Placebo had no significant effect on any of the withdrawal items; therefore, at the end of the double-blind trial, these patients were assigned to a more conventional detoxification treatment with clonidine or methadone.

On the other hand, patients on GHB continued

Table 1. Effect GHB on Opiate Withdrawal Syndrome

Drug Withdrawn (No. Subjects)	Treatment	Before Treatment	Total Withdrawal Score (Minutes After Treatment)						8th Day of Treatment[d]	
			15	30	60	90	120	180	Prior to Naloxone	After Naloxone
Heroin (14)	GHB	15.1 ± 1.5	4.8 ± 0.9[a]	2.5 ± 1.9[a]	2.1 ± 0.8[b]	1.6 ± 1.2	1.3 ± 0.1[b]	5.1 ± 1.9[b]	1.2 ± 0.3	2.3 ± 0.2
Heroin (8)	Placebo	16.7 ± 1.0	15.3 ± 1.8[c]	13.7 ± 2.1[c]	18.1 ± 2.1[c]	16.1 ± 2.4[c]	20.0 ± 3.1	19.3 ± 2.1[c]		
Methadone (13)	GHB	13.4 ± 2.0	5.1 ± 2.3[a]	2.8 ± 2.4[a]	1.4 ± 1.6[b]	2.1 ± 2.1	1.9 ± 1.2[b]	3.3 ± 1.3[b]	2.1 ± 0.2	2.2 ± 0.1
Methadone (6)	Placebo	12.3 ± 1.7	12.7 ± 1.4[c]	13.4 ± 1.2[c]	12.7 ± 2.5[c]	15.2 ± 1.1[c]	16.1 ± 1.8[c]	15.9 ± 1.7[c]		

[a] $p < .01$; [b] $p < .001$ (Pratt's test for comparison of scores before and after treatment).
[c] $p < .01$ (Mann-Whitney test for comparison of placebo and GHB group).
[d] Tested 30 minutes prior to and 10 minutes after naloxone, 0.4 mg (IV).
Total withdrawal scores are mean ± SEM.

this treatment receiving the drug in an open study every 2 to 4 hours on the first 2 days and every 4 to 6 hours the following 6 days, as indicated by the pharmacokinetics of GHB (Lettieri and Fung 1979, Ferrara et al. 1992). Every day, withdrawal signs and symptoms were recorded before each dose. The withdrawal score remained reduced throughout the trial. On the eighth day, GHB administration was suspended, subjects were observed during a period of 5 to 6 hours, and then received an intravenous injection of 0.4 mg of naloxone. No withdrawal signs and symptoms occurred before and after naloxone treatment (see Table 1). Urine analysis performed every other day during the trial failed to detect the presence of opiate metabolites. Three methadone-dependent and two heroin-dependent subjects reported transient dizziness or vertigo on the second and/or third day following the first morning dose of GHB; these symptoms were usually well tolerated. No other side effects attributable to this compound were noted either by the observer or the subjects themselves. None of the subjects reported somnolence after GHB.

DISCUSSION

The standard method used in the management of heroin withdrawal is the substitution of methadone for heroin and gradual dose reduction until complete abstinence is obtained. More recently the alpha-2 agonist, clonidine, has been introduced to facilitate withdrawal from opioids. Although clonidine is effective in reducing many of the autonomic components of the withdrawal syndrome, it fails to suppress its subjective components, such as craving, lethargy, insomnia, and restlessness. Moreover, it is not uncommon for clonidine to produce major side effects, such as sedation and severe hypotension (see Jaffe 1987). Consequently, finding a nonopioid drug capable of suppressing withdrawal symptomatology without causing negative side effects is of prime importance. Our results indicate that GHB is effective in suppressing the opiate withdrawal syndrome in humans. The GHB effect has a rapid onset but short duration. These features are in accordance with the pharmacokinetics of GHB, indicating that the compound is readily absorbed after oral administration and is rapidly eliminated (Lettieri and Fung 1979; Ferrara et al. 1992). Due to the short duration of its effect, GHB should be administered at frequent intervals. This is a limitation of an otherwise effective and well-tolerated compound.

The mechanism by which GHB suppresses opiate withdrawal syndrome is not known. A number of mechanisms may be invoked but none can be convincingly accepted. It is possible to discount the sedative effect of the compound because no sedation was pro-

Table 2. Effect of GHB on Specific Signs and Symptoms on Gold's Withdrawal Scale

	Percent of Subjects Presenting a Given Sign/Symptom at Various Times After GHB		
Sign/Symptom	**Before Treatment**	**1 Hour**	**3 Hours**
Craving	100	26	37
Nausea	89	15	23
Anorexia	59	33	21
Anxiety/restlessness	92	46	58
Aching bones and muscles	96	38	31
Insomnia or yen sleep	96	70	83
Hot and cold flashes	74	18	22
Tremors	71	15	7
Yawning	81	0	0
Vomiting	18	0	0
Diarrhea	51	43	53
Perspiration	78	0	0
Lacrimation	52	0	0
Rhinorrhea	39	0	0
Increased respiration rate and depth	63	0	0
Goose flesh	71	15	28
Mydriasis	50	0	0
Spontaneous orgasm	0	0	0
Increased temperature	41	8	13
Tachycardia	85	15	21
Increased blood pressure	96	15	30

Data for heroin- (n = 14) and methadone- (n = 13) dependent subjects were pooled. The 21 items of the scale were rated as present (1) or absent (0) according to Gold et al. (1978).

duced by those doses of GHB suppressing opiate withdrawal. Experimental evidence indicates that GHB interferes with the activity of serotonin (Spano and Przegalinski 1973), acetylcholine (Sethy et al. 1976), GABA (Snead and Nichols 1987), and dopamine (DA) (Gessa et al. 1968) in the CNS. The interference of GHB with DAergic transmission might be more relevant for its suppressant effect on the withdrawal syndrome. Indeed, recent studies have shown that both ethanol and morphine withdrawal syndromes are associated with profound inhibition of DA output in the nucleus accumbens and in the ventral caudate nucleus, as measured by brain microdialysis (Rossetti et al. 1990, 1991; Acquas et al. 1991).

Contrary to what was observed following anesthetic doses of GHB (Walters et al. 1973), we have recently found that nonanesthetic doses of the compound activate the firing rate of DAergic neurons (Diana et al. 1991), and Cheramy et al. (1977) have reported that GHB increases DA release from the caudate nucleus of cats. Because the increase in DA output is considered to play an important role in the rewarding effects of morphine and alcohol (Di Chiara and Imperato 1988), it is reasonable to hypothesize that the fall in DA output might be involved in the negative symptoms of withdrawal and, vice versa, a stimulation of DA output might be implicated in the suppressant effect of GHB on withdrawal symptomatology.

Alternatively, it should also be considered that GHB is a normal brain constituent, which seems to function as a neurotransmitter or neuromodulator (Mandel et al. 1987). Therefore possible changes in the endogenous content and activity of this compound in the pathogenesis of withdrawal from opiates and alcohol are worth specific investigation. Whatever the mechanism of action of GHB, its efficacy in suppressing both opiate and alcohol withdrawal syndrome is of practical importance, because a combination of opiate and alcohol abuse is not uncommon. Results in preparation from our group have shown that GHB prevents the emergence of opiate withdrawal signs and symptoms evoked by naloxone in opiate-dependent patients.

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