The Use of GHB in Treating Narcolepsy

CLINICAL PRACTICE REVIEW COMMITTEE
AMERICAN ACADEMY OF SLEEP MEDICINE

Rationale

The following position statement was commissioned by American Academy of Sleep Medicine (AASM) Board of Directors and provides a review of the evidence on gammahydroxybutyrate (GHB) as well as recommendations for its classification schedule. The report focuses on proven scientific and therapeutic uses of GHB; potential for abuse; and how GHB might best be classified if it becomes a controlled substance. The best, published evidence from peer-reviewed, scientific journals about GHB was considered and primary observations rather than reviews, editorials, letters, or reports in newspapers and magazines were concentrated on.

Proven Therapeutic Use of GHB in Narcolepsy

Several independent investigators have reported beneficial effects in narcolepsy with GHB but only 2 double-blind studies have been published (Scrima et al, 1989 and 1990; Lammers et al., 1993). The first was performed by Scrima (1989 and 1990) in 20 patients using 50 mg/kg/night. A significant decrease in cataplexy was observed but no significant effects on daytime sleep attacks were reported when compared to placebo. The second study was performed by Lammers (1993). Twenty-four patients received GHB, 60 mg/kg/night. Hypnagogic hallucinations and daytime sleep attacks decreased significantly. Cataplexy was also reduced by 50 percent, but the effect was not significantly different from placebo due to large inter-individual variation. In both studies, sleepiness as measured using MSLT sleep latencies was only slightly affected (maximum difference in mean sleep latency: 1 minute).

Based on these two reports, there is little doubt that the drug is helpful to narcoleptic patients. Several other independent investigators have confirmed the findings in open labeled studies (Broughton and Mamelak, 1979; Mamelak et al., 1986). The most consistent and least controversial effects are improved cataplexy and improved nocturnal sleep disruption with GHB treatment (Scrima et al., 1990; Broughton and Mamelak, 1980: Bedard et al., 1990). Further investigations would be needed to confirm a possible beneficial effect for daytime sleepiness. Importantly, GHB anti-cataplectic effects are clearly mediated by a different mode of action when compared to those produced by antidepressant compounds. As such, patients who do not tolerate classical antidepressant treatment because of side effects, tolerance or contraindications would not have any other choice if GHB were not available to them.

Therapeutic Use of GHB in Other Medical Disorders

Besides its demonstrated efficacy in narcolepsy, GHB has proved useful when evaluated in controlled trials for anesthesia (Kleinschmidt et al., 1997; Kleinschmidt et al., 1998) and for treatment of withdrawal syndromes (Gallimberti et al., 1989; Gallimberti et al., 1992; Gallimberti et al., 1993).

Use of GHB in Basic Neuroscience Research

GHB is a unique tool in neuroscience research. Maitre (1997) just reviewed the neurobiology of GHB. The compound is a natural metabolite of GABA; it is synthesized and accumulated in neurons in the brain. Investigators have shown that GHB behaves as a genuine CNS neurotransmitter distinct from GABA. GHB receptors have been identified and a pharmacological antagonist of the compound (NCS-382) has been synthesized. The most established pharmacological effect of the compound is to dramatically decrease the firing rate of mesocorticolimbic dopaminergic neurons in the brain while activating dopamine synthesis. This effect produces an acute increase in dopamine stores. Higher doses are also believed to activate GABA-B receptors.

One of the most interesting properties of the compound is its ability to increase both REM and Slow Wave Sleep (SWS). Almost all other hypnotic compounds available to us suppress REM and SWS, thus GHB produces a more "natural" sleep architecture. This difference in profile has been established in several animal species including humans. It is also clear that not only the hypnotic profile of GHB but also its mode of action is distinct from all other commonly prescribed hypnotic compounds. No other known compound has the paradoxical effect on dopaminergic transmission described above. As such, it is not only an interesting compound but research in the area may lead to the discovery of novel hypnotics that may have clinical application far beyond narcolepsy.

Prevalence and Severity of GHB Abuse

GHB, also known as sodium oxybate, is a naturally-occurring fatty acid derivative that is neuroactive and has abuse potential. GHB has powerful depressant effects on the central nervous system and has been used as an anaesthetic, however in lower doses it can produce a state of euphoria which has led to popular recreational use (Li et al, 1998). Also, GHB has been used by bodybuilders because of its anabolic effects. Physical dependence can occur. In addition, prolonged abuse may result in seizures and withdrawal symptoms. The withdrawal syndrome includes insomnia, anxiety and tremor that usually resolves in 3 - 12 days.

GHB has been referred to as a "date rape" drug when combined with flunitrazepam, because of the tendency to induce initial euphoria and subsequent CNS depression. Excessive

intake of GHB has led to serious sequelae including respiratory arrest and death.

Typically, profound unconsciousness occurs in severe GHB toxicity, and despite full (and often rapid) recovery, most patients require medical intervention, including intubation and mechanical ventilation. Interestingly, GHB has hypoxia-sparing effects that may aid the total recovery seen in the majority of cases of severe toxicity. The adverse effects are more serious when GHB is used with other illicit drugs and alcohol (Ryan et al., 1997). Of the 10 deaths reported with GHB all have been associated with the use of mixed drugs (Li J, personal communication). However, in lower doses, the drug has been used to aid withdrawal from opiate and alcohol addiction. GHB has led to abstinence of alcohol in 78% of 179 alcohol dependent subjects (Addorato et al., 1996).

Although available since 1990, the current prevalence of GHB use is not known, however it is believed that it is relatively low compared with cocaine and marijuana. In 1995-1996, poison control centers in New York and Texas reported 69 acute poisonings and one death attributed to GHB (JAMA, 1997).

Since the recent widespread publicity about GHB there have been numerous sources of information available on how to make GHB, particularly on the internet. GHB can be easily synthesized from Lactone (gamma hydroxybutyral lactone), also a potent euphoric drug that is inexpensive and occasionally sold as GHB. Lactone is widely used and available in industry with little prospects of regulation of its availability. Two states have made GHB a schedule I drug, and 20 states have made it a misdemeanor or felony to distribute GHB (Li J, personal communication). Most states have legislation pending.

Recommendations of the AASM

GHB has demonstrated therapeutic usefulness in narcolepsy, cardiac anesthesia, and withdrawal syndromes. GHB abuse is a problem, but there is no documented evidence that supplies of GHB from the medical and scientific community have been diverted for illegal uses. Classification of GHB as a Schedule I drug is likely to impede further research into clinical and scientific applications of GHB. The AASM opposes a Schedule I classification of GHB.

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