Sodium Oxibate and Breathing
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The gamma-hydroxybutyrate acid (GHB) is a short chain fatty acid, an endogenous metabolite of gamma-aminobutyric acid (GABA), known major inhibitor neurotransmitter. The GHB presents an action fundamentally at Central Nervous System (CNS) level, and possesses a high affinity for specific receptors located in the cerebral cortex and in the medulla. Sodium Oxibate (SO) is the sodium salt of the GHB. Its character as inhibitor neuromodulator, with the possibility of inducing respiratory depression, and the potential risk of abuse/misuse forces clinicians to be constantly monitoring for signs of misuse.

This molecule has been known for more than 50 years, and its therapeutic use and the interest of investigators has had ups and downs, and in such way we could speak of three fundamental periods:

1) In the 70s and 80s it was used as a general anesthetic, either in the induction or in the anesthesia maintenance. Although there was a first publication that defended that SO provoked a dose-dependent decrease in ventilation per minute and in blood pH [1], subsequent research revealed that GHB, contrary to GABA, depressed neither the respiratory frequency nor the tidal volume. The GHB provoked a dose-dependent increase of respiratory frequency, which lead to an increase in the volume/minute [2], therefore proving to be a protective drug against hypoxia. It was the anesthetic choice of the event of respiratory insufficiency [3,4]. For this reason it was also used in the ICUs for years, to provide suitable sedation in those patients under controlled ventilation or fighting against the respirator, who were to be converted to spontaneous breathing [5].

a. It was clear that the effects of GHB were not comparable to those of GABA, and that it was not the same molecule [6]. GHB binds with specific receptors, and has a weak affinity for GABA-B receptors, and no affinity for GABA-A receptors.

2) In the 90s, GBH is widely used as recreational drug. There are publications regarding GBH overdoses treated in Emergency Rooms, where there were communications of apneas, bradypneas or respiratory insufficiency [7,8]. Nevertheless, overdosing appeared as the fundamental factor; in addition to this, patients had regularly consumed other substances with known CNS depressor effect, such as alcohol or other drugs. What’s more, there were also reports of GBH overdose coma with spontaneous breathing [9,10].

3) OS (Xyrem) is approved by the FDA (Food and Drug Administration) for the treatment of narcolepsy with cataplexy in patients over 16 years of age [11]. It is an effective drug for the three symptoms which dramatically decrease the quality of life of patients with narcolepsy: excessive daytime sleepiness, cataplexy and nocturnal sleep fragmentation.

a. Its prescription in patients with breathing disorders during sleep, together with narcolepsy is controversial. In the Sleep Apnea Syndrome (SAS), the significant increase of slow-wave sleep (SWS) that OS induces [12] should theoretically improve the hypopnea-apnea-index (HIA), as most of the obstructive events happen during the N1 and N2 phases, and during the REM sleep.

4) In 2009 we find two published cases of narcolepsy associated to moderate sleep apnea where there is an increase in the respiratory disorders related to sleep when OS is introduced [13] while the following year there is a similar case published where there is a marked improvement after OS treatment is initiated [14]. In a safety postmarketing study including 60 patients taking the maximum recommended dose of OS (9 gr), it was shown there was no worsening of the HIA or of the oxygen saturation (O₂) in cases of slight or moderate SAS, although there was a relative increase of central apneas [15]. In the only randomized, placebo-controlled study, the use of OS was statistically (although not clinically) associated to a significant improvement of HIA in some patients [16].

a. Regarding pharmacokinetics, OS is a short-chain fatty acid that is rapidly absorbed after the oral dose. It has a short half-life (30-60 minutes) and is metabolized in the tricarboxylic acid cycle (Krebs’s cycle) to H₂O and CO₂. During sleep, particularly during the NREM sleep, breathing is regulated almost exclusively by the metabolic control system. CO₂ plays a prominent role in this metabolic control and in the maintenance of the breathing rhythm during sleep [17]. We believe that the metabolization of OS and its subsequent production of CO₂ stimulates breathing and increases the “apnea threshold”, i.e. the CO₂ level below which the apnea occurs. On the other hand, with therapeutic levels of 9 gr or in those cases where there is an OS overdose, the dose-dependent increase of ventilation leads to a decrease of CO₂ and to an inhibition of the inspiratory effort and to the central apneas observed in some of these cases.

b. Although there is a need for prospective studies to confirm these facts, we suggest that OS can be used in cases by slight or moderate SAS, with control from the clinical point of view. Those more serious cases need nocturnal respiratory support before the administration of the drug.

References

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