

DOI: 10.21767/2472-5048.100013

## Sodium Oxybate and Respiration

Ortega-Albás JJ<sup>1\*</sup>, Martínez Martínez A<sup>1</sup>, Ortega-Gabás SP<sup>2</sup>, Carratalá S<sup>1</sup> and Leal DE<sup>1</sup>

<sup>1</sup>Sleep Disorders Unit, Hospital General Universitario de Castellón, Spain

<sup>2</sup>Universidad Politécnica de Valencia, Spain

\*Corresponding author: Ortega-Albás JJ, Sleep Disorders Unit, Hospital General Universitario de Castellón, Spain, E-mail: jjoral@ono.com

Received date: March 07, 2016; Accepted date: May 17, 2016; Published date: May 20, 2016

Citation: Ortega-Albás JJ, Martínez Martínez A, Ortega-Gabás SP, Carratalá S, Leal DE (2016) Drug Resistant Epilepsy: Current Challenges and the Path Forward. Dual Diagn Open Acc 1:13. doi: 10.21767/2472-5048.100013

Copyright: © 2016, Ortega-Albás JJ, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

### Short Commentary

Gamma-Hydroxybutyric acid (GHB) is a short-chain fatty acid, an endogenous metabolite of the gamma-aminobutyric acid (GABA), a known major neurotransmitter inhibitor. GHB acts mainly on the CNS, with an enhanced affinity for receptors that are located in the cerebral cortex and the medulla oblongata.

From the 90s onwards, GHB has been widely used as a recreational drug. GHB poisoning leads to adverse effects including bradycardia, hypothermia, coma and depression/respiratory arrest. It is responsible for around 1,000 to 2,000 visits to emergency rooms in the USA [1].

From a respiratory standpoint, there are Emergency Services reports in which GHB overdoses have led to apnoea, hypopnoea or respiratory failure [2,3]. There have even been published cases of death [4]. On the other hand, there are also published articles involving comas, with normal breathing, induced by a GHB overdose [5,6]. The problem lies in the difficulty to link serious respiratory issues to GHB, bearing in mind the frequent concomitant ingestion of alcohol and/or other types of drugs in these cases.

Morse et al. [7] have demonstrated the effects of GHB on breathing. A decrease in respiratory rate occurs, accompanied by a compensatory increase in tidal volume, allowing minute volume to be maintained until doses approach lethality. The concomitant ingestion of ethanol typically alters the concentration-effect relationship, leading to respiratory depression when the compensatory increase in tidal volume is avoided as seen in cases where GHB is administered alone. This deleterious effect from combining GHB and ethanol could be avoided through the administration of GABA-B receptor antagonists. These receptors seem to be involved in its development.

Ethanol, in this regard, enhances the sedative and respiratory effects of GHB through the compensatory increase in tidal volume. Its concomitant administration therefore increases the risk of death due to respiratory depression in cases of GHB overdose.

On the other hand, the sodium salt in GHB (sodium oxybate, SO) is the treatment of choice in type 1 narcolepsy cases [8].

There is debate over its use in patients with narcolepsy who also suffer from sleep apnoea syndrome. The matter is complicated as we know that the apnoea-hypopnea index (AHI) during sleep is elevated in many patients who suffer from narcolepsy. Some 31% of patients show an apnoea-hypopnea index (AHI)>5 [9] and some 24.8% show an AHI> 10 [10]. In 1986, Chokroverty[11] warned about this common link, suggesting a neural dysfunction in those areas of the brain where respiratory and sleep-waking systems are interrelated, such as the nucleus tractus solitarius and ponto-medullary reticular formation.

Currently, it is believed that sodium oxybate does not worsen sleep apnoea as there is no increase in the number and/or duration of breathing pauses. There is even a case with an improvement in AHI [12,13]. This case seems to be related to the increase in slow-wave sleep and the decrease in REM sleep caused by SO [14] and the subsequent improved stability in breathing.

With regard to pharmacokinetics, SO is quickly absorbed through the oral route. It has a short half-life and it is metabolised through the tricarboxylic acid cycle (Krebs cycle) with H<sub>2</sub>O and CO<sub>2</sub>. During sleep, particularly during NREM sleep, breathing is controlled almost exclusively by the metabolic control system. CO<sub>2</sub> plays an important role in maintaining respiratory rate during sleep. We believe that the metabolisation of SO and the subsequent production of CO<sub>2</sub> stimulate breathing and increase the "sleep apnoea threshold". That is to say, CO<sub>2</sub> levels are under the levels at which central sleep apnoea occurs.

There are published reports of cases in which central sleep apnoea has been treated with SO. It is possible that the onset of these events may be dose-dependent [15], with the appearance linked to maximum therapeutic doses of 9 g [12]. However, there have been isolated cases that were triggered by lower doses [16]. It seems reasonable that the increase in CO<sub>2</sub> production due to the metabolisation of high doses of SO triggers an increase in breathing during sleep, with a decrease in CO<sub>2</sub> levels, an inhibition of respiratory effort and the onset of central apnoeas.

Lastly, it would be advisable to include a series of recommendations in cases of a dual diagnosis of narcolepsy and sleep apnoea syndrome:

- If the sleep apnoea syndrome is mild, begin clinical monitoring after treatment begins.
- If the sleep apnoea syndrome is moderate or severe, before treatment with SO, conduct a polysomnography with a CPAP and a MSLT (multiple sleep latency test). At this point, assess the occurrence of central apnoeas or arterial desaturation
- Beforehand, assess adherence to treatment with CPAP
- Avoid administering SO if CPAP is not used
- Prohibit the use of sedatives, particularly alcohol
- Comprehensively monitor the administered SO dose, time of administration, etc.
- Monitor the presence of arterial desaturation immediately after initiating SO, through the use of a home pulse oximeter, outpatient studies or, preferably, polysomnography.
- Provide special assessment and observation for patients who are obese, have neuromuscular disorders, etc.

It is imperative that systematic studies be carried out as they will help assess the risk factors and predictors of adverse respiratory effects secondary to SO treatment in cases involving patients with both narcolepsy and sleep apnoea syndrome.

## References

1. Substance Abuse and Mental Health Services Administration-Center for Behavioral Health Statistics and Quality (2011). Drug Abuse Warning Network 2008: National Estimates of Drug-Related Emergency Department Visits. HHS Publication No. SMA 11-4618. Rockville, MD.
2. Engelsen J, Christensen HR (1999) Gamma-hydroxybutyrate-an endogenous substance and a new central nervous system stimulant. *Clinical aspects of acute poisoning. Ugeskr Laeger* 161: 6903-6907.
3. Boyce SH, Padgham K, Miller LD, Stevenson J (2009) Gamma hydroxybutyric acid (GHB): an increasing trend in drug abuse. *Eur J Emerg Med* 2000; 7: 177-181.
4. Zvosec DL, Smith SW, Hall BJ. Three deaths associated with use of Xyrem. *Sleep Med* 10: 490-493.
5. Herbrand R, Greminger P, Schurter G, Pletscher W, Kupferschmidt H (2000) Sudden coma in a 20-years-old man. *Praxis* 89: 1326-1330.
6. Lapostolle F, Benaissa A, Meuleman C, Jammes D, Buizine A, et al. (2001) Acute involuntary intoxication with gamma-hydroxybutyric acid. *Ann Fr Anesth Reanim* 20: 485-487.
7. Morse BL, Morris ME (2013) Toxicokinetics/toxicodynamics of gamma-hydroxybutyrate-ethanol intoxication: evaluation of potential treatment strategies. *J Pharmacol Exp Ther* 346: 504-513.
8. Billiard M, Bassetti C, Dauvilliers Y, Dolenc-Groselj L, Lammers GJ, et al. (2006) EFNS guidelines on management of narcolepsy. *Eur J Neurol* 13: 1035-1048.
9. Pizza F, Tartarotti S, Poryazova R, Baumann CR, Bassetti CL (2013) Sleep-disordered breathing and periodic limb movements in narcolepsy with cataplexy: a systematic analysis of 35 consecutive patients. *Eur Neurol* 70: 22-26.
10. Sansa G, Iranzo A, Santamaría J (2010) Obstructive sleep apnea in narcolepsy. *Sleep Med* 11: 93-95.
11. Chokroverty S (1986) Sleep apnea in narcolepsy. *Sleep* 9: 250-253.
12. George CF, Feldman N, Inhaber N, Steininger TL, Grzeschik SM (2010) A safety trial of sodium oxybate in patients with obstructive sleep apnea. Acute effects on sleep-disordered breathing. *Sleep Med* 11: 38-42.
13. Ortega-Albás JJ, Lopez-Bernabé R, Diaz JR, Serrano AL (2010) Sodium oxybate and breathing. *Sleep Breath* 14: 259.
14. Mamelak M, Webster P (1981) Treatment of narcolepsy and sleep apnea with gamma-hydroxybutyrate: a clinical and polysomnographic case study. *Sleep* 4: 105-111.
15. Kovacevic-Ristanovic R (2010) Use of sodium oxybate (Xyrem®) in patients with dual diagnosis of narcolepsy and sleep apnea. *Sleep Med* 5: 6.
16. Frase L, Schupp J, Sorichter S, Randelschofer W, Riemann D, et al. (2013) Sodium oxybate-induced central sleep apneas. *Sleep Med* 14: 922-924.