Sodium Oxybate and Sleep Apnea: A Clinical Case

Sarah Hartley, B.M., B.Ch.; Maria-Antonia Quera-Salva, M.D.; Mourad Machou, M.D.

AP-HP Hôpital Raymond Poincaré, Sleep Unit, Physiology Department, Versailles-St Quentin en Yvelines University, France

Sodium oxybate (GHB, Xyrem, Jazz Pharmaceuticals) is used to treat cataplexy in patients with narcolepsy. We report the case of a middle aged, normo-ponderal narcoleptic woman without risk factors who developed reversible sleep apnea and objective sleepiness when treated by sodium oxybate, with an apnea-hypopnea index (AHI) of 19.7 on sodium oxybate and AHI 4.8 without treatment. Despite a subjective improvement

in vigilance, mean sleep latency on MWT decreased from 21 minutes to 8 minutes on sodium oxybate.

Keywords: Narcolepsy with cataplexy, sleep apnea, sodium oxybate, periodic leg movements

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Sodium oxybate (GHB, Xyrem, Jazz Pharmaceuticals) is used to treat cataplexy in patients with narcolepsy. It is a central nervous system depressant causing sedation and respiratory depression in overdose (> 50 mg/kg), leading to the concern that the drug may trigger or worsen sleep apnea.¹ A recent study of the acute effects of sodium oxybate (9 g/night in 2 doses) in patients suffering from obstructive sleep apnea with AHIs from 10-40 did not find any increase in obstructive events, although there was an increase in central events, and 3 patients developed significant nocturnal oxygen desaturations.² A 2-week study at 4.5 g/night in 2 doses was reassuring.³ However, recent clinical case reports described increased AHI in a 60-year-old woman with a BMI of 26, and development of severe sleep apnea (AHI 45) in a 58-year-old man with a BMI of 32.⁴ Improvement of sleep apnea has also been reported, possibly linked to increases in slow wave sleep.⁵

REPORT OF CASE

Mrs H, aged 39, of African origin, 1.75 m and 65kg (BMI 21.2 kg/m²) first presented symptoms of narcolepsy at the age of 16 years with excessive daytime sleepiness, cataplexy, and frequent hypnagogic hallucinations. Narcolepsy was diagnosed in 1999 following polysomnography and MSLT, with reduced mean sleep latency, 2 REM sleep onset episodes (SOREM), and HLA typing of DRB1*15 DQB1*0602. Initial treatment was with modafinil 200 mg and fluoxetine 20 mg (see **Table 1** for results of polysomnograms, daytime sleepiness testing, and treatment from 2003–2010). Cataplexy persisted, as did sleepiness (Epworth Sleepiness score 13) despite treatment; and in 2004, fluoxetine 20 mg was discontinued and venlafaxine 37.2 mg was initiated. Mrs. H continued to work and drive.

PSGs in May 2004 and January 2005 found periodic leg movements and sleep fragmentation, but sleep latency on the maintenance of wakefulness tests (MWT) was satisfactory. Ferritin was normal, and no secondary cause of the leg movements apart from antidepressant treatment was found. Modafinil was increased to 300 mg/day, and 0.3 mg clonazepam was added to

control leg movements. Venlafaxine was replaced by clomipramine 10 mg in 2006, and a trial of a dopamine agonist in 2008 (ropinirole) was poorly tolerated.

In 2009 Mrs. H underwent a thyroidectomy and started on levothyroxine 100 µg/day; her BMI increased to 23.5 kg/m². Because of increased cataplexy, antidepressant treatment was withdrawn and sodium oxybate started at a dose of 4.5 g/day in 2 divided doses. Mrs. H was able to stop her clonazepam and felt that her sleep and daytime vigilance improved, although the ESS was stable. PSG showed a marked improvement in leg movements but sleep remained fragmented with the development of non-desaturating central and obstructive hypopneas (AHI 19.7) triggering arousals, and a marked reduction in mean sleep latency on the MWT to 8 minutes. Treatment by sodium oxybate was stopped, and repeat PSG 5 months later found a return of leg movements and disappearance of sleep apnea (AHI 4.8).

DISCUSSION

Mrs H has narcolepsy with cataplexy complicated by periodic leg movements, which improved when antidepressants were replaced by sodium oxybate, with the development of reversible sleep apnea. Could our finding be due to error? All PSGs were read by the same physician using the same equipment (Medatec, Brussels). Apneas were scored according to the AASM alternative scoring system (with $> 50\%$ airflow reduction and $> 3\%$ oxygen desaturation or arousal). Identical hypopnea scoring criteria were used for all PSGs. Mrs. H is compliant with treatment, and accidental overdose of treatment was ruled out. Were there clinical signs which could have alerted us to a potential risk of sleep apnea? Weight gain prior to starting sodium oxybate was moderate, and at no point was the BMI abnormal. ENT examination was normal. Of concern was the development of impaired vigilance on MWT despite an improvement in subjective sleepiness.

Other cases of sleep apnea triggered by sodium oxybate have been reported but in older patients with elevated BMI.⁴ Our pa-

Table 1—Treatment, clinical data, and results of PSG and MWT 2003-2010

Date of PSG	Treatment	BMI	ESS	Micro-arousals/h	Stage 1&2 sleep % TST	SWS % TST	REM % TST	Index of periodic leg movements/h	AHI	Mean sleep latency MWT (min)
2003	modafinil 200 mg fluoxetine 20 mg	21.2	13	28	86	7	7	23	0	11.5
2004	modafinil 200 mg venlafaxine 37.5 mg	21.2	16	27.7	76	8	16	11.3	0.6	23
2005	modafinil 200 mg venlafaxine 37.5 mg	21.2	16	41.5	87	10	3	33	Not reported	Not performed
2007	modafinil 200 mg clomipramine 10 mg clonazepam 0.6 mg	21.2	16	21.5	81	9	10	16	0	18.5
2009	modafinil 200 mg clomipramine 10 mg clonazepam 0.6 mg	20.9	16	32	69	6	25	13.4	0.2	21
April 2010	modafinil 300 mg sodium oxybate 4.5 g levothyroxine 100 µg	23.5	15	43.3	70	5	25	2.1	19.7	8
September 2010	modafinil 300 mg clomipramine 10 mg levothyroxine 100 µg	22.5	19	34.5	65	10	25	16	4.8	Not performed

BMI, body mass index; ESS, Epworth Sleepiness Scale; AHI, apnea-hypopnea index; MWT, maintenance of wakefulness test.

tient, who was young and slender, lacked signs which would have alerted us to a potential risk of sleep apnea. Monitoring by oximetry has been suggested every two years for non obese patients treated by sodium oxybate,⁶ but as Mrs. H did not present desaturations, her sleep apnea would not have been detected. Our case shows that reversible sleep apnea induced by sodium oxybate can occur even in patients considered at low risk, and prescribers should remain vigilant.

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Address correspondence to: Dr. Sarah Hartley, Sleep Unit, Hôpital Raymond Poincaré, 104 Bd Raymond Poincaré, 92380 Garches, France; Tel +331 47 10 79 40; Fax +331 47 10 79 43; E-mail: sarah.hartley@rpc.aphp.fr

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