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The effect of buprenorphine *vs* methadone on sleep breathing disorders

Abstract

Opioids are used widely as analgesics and can play an important role in agonist maintenance therapy for opium dependence. Despite their benefits, the negative effects on the respiratory system remain an important side effect to be considered. Ataxic breathing, obstructive sleep apnea, and most of all central sleep apnea are among these concerns. Obstructive sleep apnea leads to various metabolic, cardiovascular, cognitive, and mental side effects and may result in abrupt mortality. Buprenorphine is a semisynthetic opioid, a partial mu-opioid agonist with limited respiratory toxicity preferably used by these patients, as it is accompanied by significantly lower risk factors in the development of obstructive and central sleep apnea. In this manuscript, the case of a patient is reported who underwent methadone maintenance therapy which was shifted to buprenorphine in order to observe possible changes in sleep-related breathing disorders. The results of this study indicate a reduction in these problems through the desaturation and apnea hypopnea index of methadone substituted by buprenorphine while no change in sleepiness was observed.

Key words: opioid, methadone, buprenorphine, sleep breathing disorders

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Introduction

Opioids are compounds that affect opioid by G-protein receptors. Three main subgroups of these G protein receptors are mu, kappa, and delta. Although these receptors are present in the respiratory system, the important point to consider about their respiratory effect is the influence of the respiratory center located on the brain stem, precisely in pre-Botzinger complex, which seemingly is the area with respiratory rhythm-generating neurons [1]. These receptors are mainly of the mu-type and their stimulation by drugs such as chronic use of methadone is at risk because of breathing disorders of complicated and potentially lethal nature, including central and obstructive apneas, hypopnea, ataxic breathing and nonapnoeic hypoxemia during sleep [2]. Opioids were used in order to relieve pain and also, to act as a main part of opioid (e.g. methadone or buprenorphine) agonist maintenance therapy [3]. Buprenorphine is a semisynthetic opioid, i.e., a partial mu-opioid agonist with limited respiratory toxicity. But it has an antagonistic effect on kappa and delta receptors and through the effect of the opioid receptor-like (ORL-1). Meanwhile, it is an agonist that induces the analgesic effects [4]. Nowadays, ORL1 is the same as Nociceptine/orphanin FQ receptors which are widely used because of the contributing result of their function, the treatment of opioid dependency and chronic nonmalignant pain. Although buprenorphine maintains an analgesic dose response across all levels, it appears to have flat or inverted U-shaped biological response on respiratory suppression via mu receptors.

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The more the dosage, the lower the incidents of breathing disorders, that is, higher doses do not lead to higher effect in both animal and human studies, for example, the ventilatory response to hypercapnia does not continually decrease with progressively greater doses, while the analgesic effect is maintained. In analgesic effect, it does not follow a U-shaped curve in dose-response pattern. The incidence of tolerance to the analgesic effects of buprenorphine is relatively low in high doses [5].

On the other hand, the estimated yearly death rate (1994–1998) for methadone was at least threefold greater than the death rate related to buprenorphine. There are two well-known treatments to harm reduction in opioid dependent patients, maintenance therapy with methadone (MMT) and buprenorphine (BMT) [3]. However, their risk of sleep apnea with these alternative therapies still exists. Research suggests increased central sleep apnea due to chronic opioid use, although few studies have reported obstructive sleep apnea [5, 6]. In another study by Grote *et al.* which investigated the results of 14 clinical trials in remifentanil, benzodiazepine, only mild deteriorations in overnight oxygenation and apneic events have been shown; no systematic increases in the apnea hypopnea index (AHI) have been observed [6]. It should be emphasized that evidence based on facts and meta-analyses does not always explain us everything. It is noteworthy that in 3,325 case reports of sleep apnea syndrome (SAS) as adverse drug reaction (ADR), the polysomnography record couldn't have been verified. This is necessary for true diagnosis of central sleep apnea (CSA) and obstructive sleep apnea (OSA). The data wasn't systematically recorded in VigiBase [7].

Concerning the harm reduction approach with opioid agonist in opioid users, it is necessary to select a drug with a minimum risk of developing respiratory depression. In this paper, the case of a patient is discussed with more prominently marked decrease in central than obstructive sleep apnea when changing the therapeutic plan from MMT to BMT.

Case report

A 36-year-old man with symptoms of insomnia and daily hypersomnolence (ESS = 16) visited the Sleep Clinic of Masih Daneshvari Hospital in Tehran. Given his long history of opium use, he consumed 25 mg of methadone equivalent to 75 mg oral morphine per day. The patient had a history of mood disorder and consumption of citalopram 40 mg, 400 mg sodium valproate, and clonazepam 1 mg on a daily basis. Neck circumference and body mass index (BMI) were 42 cm, and 31.1 kg/m^2, respectively, while the PCO_2 was 37 mm Hg. After one night of adaptation, polysomnography was performed, by G3 Phillips Respironic software. The analysis was carried out considering the AASM 2017 manual of sleep scoring (Table 1). Concerning the continuation of events during titration, BiPAP-S/T (S/T bilevel positive airway pressure — spontaneous/timed) was ultimately applied, set on 24/20/2/12. Compliance of the patient was acceptable. During one year the man used the device 4 hours and 45 min, and AHI is equal to 4/h.

One year after the last visit, the patient was advised by his psychiatrist to add 100 mg of quetiapine and 50 mg of lamotrigine to his previous medications and also to replace methadone with sublingual buprenorphine 4 mg (equivalent dose of 160–320 mg of oral morphine) over the last three months. The patient's weight rose by 9 kg and his BMI to 34.3 kg/m^2, he could not tolerate the BIPAP st device. Considering the fact that his drugs and dosage were changed, polysomnography was repeated. The comparative polysomnography results related to methadone and buprenorphine are presented in Table 1 and Figures 1, 2.

Discussion

The major finding of this report was the complete elimination of obstructive and central sleep apnea and partial decrease of hypopnea by replacing methadone with buprenorphine.

Despite the fact that a certain dosage of buprenorphine had manifold effect compared with methadone, it is a partial agonist of the mu-receptor. Although the mortality risk related to buprenorphine overdose is lower than that of methadone, the rate of sleep breathing disorders, especially central apnea, have been reported to be higher in patients who underwent methadone and buprenorphine maintenance therapy rather than the control group [8]. However, the occurrence of sleep apnea was not affected by such factors as buprenorphine dosage, benzodiazepine and quetiapine use, or other apnea risk factors [9, 10]. Nociceptine/orphanin FQ receptors (NOP) receptor activation has a clear modulatory role on mu opioid receptor-mediated actions and thereby affects opioid analgesia positively, while leading to the tolerance of respiratory suppression. Buprenorphine can act through this receptor [8, 10].

Table 1. Polysomnographic findings on methadone and buprenorphine maintenance therapy

Polysomnography items	Methadone	Buprenorphine
Recording duration [min]	528.0	375.5
Total sleep time [min]	450.0	325.0
Sleep onset latency [min]	5.0	18.2
Sleep efficiency%	95.9	88.3
Wake after sleep onset	14	25.0
Sleep stages		
N1 [%]	20.8	6.6
N2 [%]	58.3	72.6
N3 [%]	6.4	2.0
REM [%]	15.4	18.8
REM sleep latency [min]	86.0	90.5
Number of REM	5	8
Respiratory events		
Number of events/hour		
Central sleep apneas	69 (9.2)	0 (0)
Obstructive sleep apneas	4 (0.5)	0 (0)
Mixed sleep apnea	7 (0.9)	0 (0)
Hypopnea	183 (24.4)	94 (17.4)
RERA	1 (0.1)	12 (2.2)
Apnea/hypopnea index	**263** (35.1)	94 **(17.4)**
Respiratory disturbance index	264 **(35.2)**	106 **(19.6)**
Oximetry		
Average $SatO_2$ [%]	95	92
Lowest Detected $SatO_2$ [%]	85	83
$SatO_2 < 90\%$ (duration %TIB)	5.7	
$SatO_2 < 88\%$ (duration %TIB)	0.1	
Desaturation index	290 (37.6)	102 (18.0)
Arousals		
Number index	29 (4.0)	30 (5.7)
Arousals associated with leg movement	0	0
Arousals with respiratory events and desaturation	17	15
Periodic leg movement	0 (0.0)	0 (0.0)
PCO_2 mmHg	37	39
HCO_3	20.7	23

REM — rapid eye movement sleep; RERA — respiratory effort–related arousal; SatO2 — oxygen saturation

This is a stunning result that can be helpful in prescribing less harmful opioid medication during maintenance therapy and other treatment processes. Given the high number of patients treated with these morphine agonists, it is important to know which of the two drugs is associated with a lower risk of developing sleep breathing disorders. In the only available case report so far, it was suggested that significant reduction in CSA together with improved hypoxia and normalized awake ventilatory control following a change from methadone to buprenorphine-naloxone therapy occurred [11].

Nociceptin opioid peptide receptors include MOP (μ), KOP (κ), and DOP (δ) discovered so far. They are found in many parts of the body, especially in breathing control centers. These areas include pre-Bötzinger complex, retro-trapezoid, and para-facial respiratory group (RTN/pFRG) located in PONS which contribute to the con-

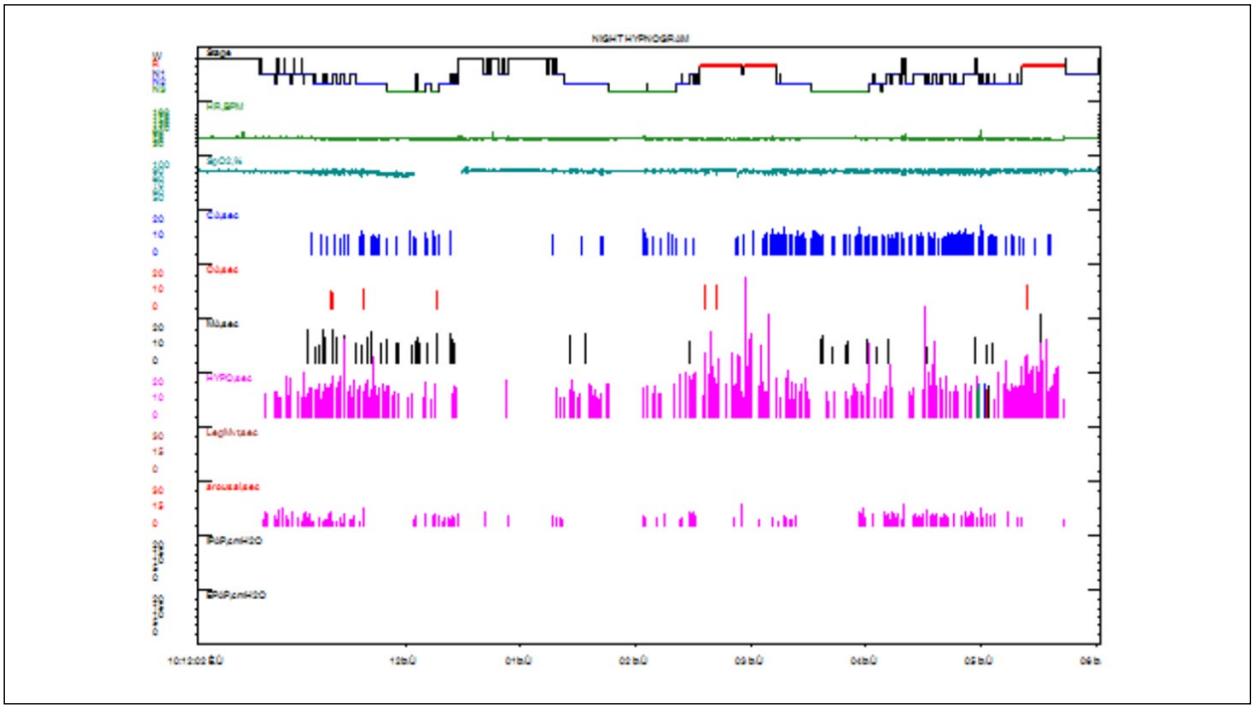

Figure 1. Patient on methadone

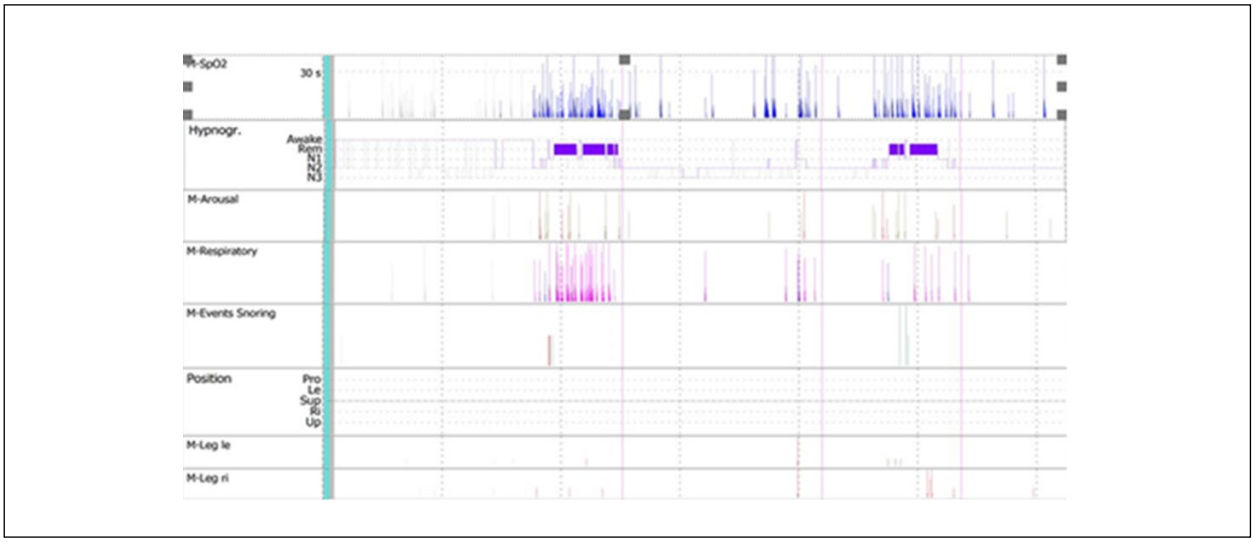

Figure 2. Patient on buprenorphine

trol of the breathing rhythm and are affected by wakeful stimulants and central and peripheral chemoreceptors [12].

While NOP receptors activation tends to synergize with mu-receptor-mediated actions, it sometimes tends to oppose them. Accordingly, gaining an insight into NOP receptors pharmacology in the context of these interactions with the opioid receptors shall significantly contribute to the development of novel and innovative therapeutic methods that engage the NOP receptors. Buprenorphine, despite methadone, is an agonist of this receptor.

The affinity of these receptors to bind with the opioid agonists (buprenorphine) is extremely low; therefore, a high concentration of opioid drugs can stimulate them while inhibiting them can be achieved by a high concentration of naloxone. These receptors have a regulatory effect on morphine receptors; their activity is so that they have minimum effect on the breathing system [12].

That is why a high dosage of buprenorphine in this patient led to a reduction in terms of the effect of the mu-receptors and also to a decrease in ventilation suppression, CSA, and OSA. This is a case in point when it comes to reverse pharmacology effect.

Despite the weight gain of 9 kg, the CSA index dropped to zero, and a good response to titration was observed over methadone consumption. Noticeably, the equivalent morphine dose of buprenorphine was higher than that of methadone.

Moreover, the patient's drowsiness was still present; the intensity of sleepiness related to methadone and buprenorphine was 16 and 18, respectively.

Sleepiness continued although taking modafinil with buprenorphine could be attributed to the concomitant use of quetiapine. Despite the increase in taking sedative medications, he still complained of early insomnia, however, sleep latency and sleep efficiency were within the normal range. Slow wave sleep was reduced when the patient was taking buprenorphine and methadone, but it could also be attributed to the concurrent use of benzodiazepine. The relative reduction of REM in addition could be explained by taking citalopram. Lamotrigine, quetiapine and benzodiazepine can increase obstructive apnea. In the Mason's study, it was noted that the pharmacological effects of these drugs haven't had deleterious effect on severity of AHI and ODI, but in the case of remifentanil, benzodiazepine in the OSA subgroup, minimum oxygen saturation was reduced [13], but in this case, diminishing of both type of apnea was noted.

Conclusions

In this case, a marked decrease in CSA and OSA was observed after switching from methadone to buprenorphine.

Considering the importance of sleep apnea and the widespread use of methadone and buprenorphine, controlled clinical trials are required to assess sleep-related breathing disorders in buprenorphine MT. Safe and beneficial prescription of MMT depends greatly on a careful patient selection and treatment follow-up.

Conflict of interest

None declared.

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