Ventilatory Responses to Hypoxia and Hypercapnia in Stable Methadone Maintenance Treatment Patients*

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Rationale: **Methadone is a long-acting μ-opioid and is an effective treatment for heroin addiction. Opioids depress respiration, and patients receiving methadone maintenance treatment (MMT) have higher mortality than the general population. Few studies have investigated ventilatory responses to both hypercapnia and hypoxia in these patients.**
Study objectives: **We measured hypercapnic ventilatory response (HCVR) and hypoxic ventilatory response (HVR) and investigated possible factors associated with both in clinically stable patients receiving MMT.**
Design and setting: **Patients receiving long-term, stable doses of methadone recruited from a statewide MMT program, and normal, non-opioid-using subjects matched for age, sex, height, and body mass index were studied with HCVR and HVR.**
Results: **Fifty MMT patients and 20 normal subjects were studied, and significantly decreased HCVR and increased HVR were found in MMT patients compared to normal subjects (HCVR [mean ± SD], 1.27 ± 0.61 L/min/mm Hg vs 1.64 ± 0.57 L/min/mm Hg [$p = 0.01$]; HVR, 2.14 ± 1.58 L/min/% arterial oxygen saturation measured by pulse oximetry [Spo_2] vs 1.12 ± 0.7 L/min/% Spo_2 [$p = 0.008$]). Respiratory rate and not tidal volume changes were the major physiologic responses contributing to both HCVR and HVR differences between the groups. Variables associated with HCVR in the MMT patients are as follows: obstructive sleep apnea/hypopnea index ($t = 5.1$, $p = 0.00001$), $Paco_2$ ($t = -3.6$, $p = 0.001$), body height ($t = 2.6$, $p = 0.01$) and alveolar-arterial oxygen pressure gradient ($t = 2.5$, $p = 0.02$). Variables associated with HVR in MMT patients are body height ($t = 3.2$, $p = 0.002$) and $Paco_2$ ($t = -2.8$, $p = 0.008$).**
Conclusions: **Stable long-term MMT patients have blunted central and elevated peripheral chemoreceptor responses. The mechanisms and clinical significance of these findings need further investigation.** ***(CHEST 2005; 128:1339–1347)***

Key words: chronic opioids; hypercapnic ventilatory response; hypoxic ventilatory response; respiratory rate; tidal volume

Abbreviations: CAI = central apnea index; DLCO = diffusion capacity of the lung for carbon monoxide; $Faco_2$ = expired fractional concentration of carbon dioxide; HCVR = hypercapnic ventilatory response; HVR = hypoxic ventilatory response; MMT = methadone maintenance treatment; OSAHI = obstructive sleep apnea/hypopnea index; $P(A\text{-}a)O_2$ = alveolar arterial oxygen pressure gradient; $Pvco_2$ = tension of carbon dioxide in the mixed venous blood when saturated with oxygen; RR = respiratory rate; Spo_2 = arterial oxygen saturation measured by pulse oximetry; $\dot{V}E$ = minute ventilation; VT = tidal volume

Illicit opiate use is a major worldwide problem. The prevalence of heroin use in the United States was 3 million in 1999[1] and 74,000 from 1997 to 1998 in Australia.[2] The population prevalence of heroin dependence is 6.9 per 1,000 adults aged 15 to 54 years in Australia and is the same as in Britain (7 per 1,000) and in the European Union (3 to 8 per 1,000).[2]

Methadone, a long-acting μ-opioid agonist blocks the narcotic effects of heroin and relieves craving

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and the abstinence syndrome.[3] Methadone maintenance treatment (MMT) is recognized as an effective treatment for heroin addiction.[3–5] Although MMT reduces the risk of death of opioid users by a factor of three to four, all-cause mortality in MMT patients is three to four times higher than that of the general population.[6,7]

μ-Opioids depress respiration, at least in part by virtue of a direct effect on the brainstem respiratory centers.[8] Acute respiratory depression occurs with most commonly used opioid anesthetics.[9–12] In humans, the primary receptors are assumed to be μ-receptor type.[13] All μ-receptor–stimulating opioids cause acute dose-dependent depression of respiration,[14] primarily through direct action on brainstem respiratory centers.[15] Acute opioid use significantly reduces the responsiveness of the brainstem respiratory centers to carbon dioxide[13] and the slopes of the hypercapnic ventilatory response (HCVR) are decreased and shifted to the right.[16] In addition, studies[16–18] have reported that acute, low-dose opioid analgesia use can acutely decrease hypoxic ventilatory response (HVR).

Few studies have investigated HCVR[19–21] and HVR[20] in long-term opioid users such as MMT patients. To our knowledge, only one study[20] assessed both HCVR and HVR in the same group of patients, and the gender distribution in the three other studies was skewed to male MMT patients.[19–21] MMT patients often ingest other drugs that may significantly confound HCVR and HVR, and the previous studies[3,19–21] did not assess blood toxicology of the patients studied. The combination of concomitant opioid, alcohol, antidepressants, or benzodiazapine use in this patient group may present a greater risk of respiratory depression.[8]

We have previously shown that MMT patients have a high prevalence of central sleep apnea.[22,23] As part of a project addressing the potential mechanisms of central sleep apnea in stable MMT patients, we wished to assess the HVR and HCVR in this patient group. The hypotheses for this study are as follows: (1) HVR and HCVR findings are abnormal in clinically stable MMT patients compared to normal, non-opioid-using subjects; and (2) physiologic and toxicologic factors explain these abnormalities.

Materials and Methods

This study forms part of a project assessing sleep architecture and sleep-disordered breathing in stable MMT patients.

Subject Selection

MMT patients and normal, non-opioid-using subjects were recruited through advertisements placed in pharmacies licensed for distributing methadone across the inner suburbs of Melbourne, Australia. The advertisement did not mention the research topic. The patients had been receiving MMT for ≥ 2 months with a stable dose of methadone. The normal subjects did not have a history of substance abuse, and none were using opioids at the time of study. All subjects underwent a screening examination by a physician skilled in the diagnosis of respiratory and sleep-disordered diseases. A detailed medical history was obtained with particular reference to respiratory illness, cigarette use, current substance abuse, medication use, sleep patterns, and snoring history. Exclusion criteria for study were significant cardiorespiratory, neurologic, liver, and psychotic disorders, and pregnancy. The institutional Research and Ethics committee approved the protocol. All subjects gave written informed consent prior to participation.

Procedures

MMT patients underwent echocardiography, ECG, and chest radiography. All subjects underwent acclimatization polysomnography on night 1. At 8 AM the next morning, MMT patients underwent respiratory function tests, and arterial blood was sampled at rest and when breathing air for arterial blood gas analysis. All subjects returned at 4 PM for the HVR and HCVR tests, having fasted for 4 h prior to the test procedure. Blood was taken for toxicology and methadone concentration 30 min prior to tests and within 6 h of medication with methadone. HCVR and HVR were separately tested from 4 to 6 PM, and the HVR was always performed first with at least 30 min between the tests. Polysomnography was performed for analysis on each subject on the night of the ventilatory response tests.

HVR: A modification of the Rebuck and Campbell[24] hypoxic, isocapnic rebreathing method was used. The subjects breathed via a closed circuit (bag in a box system) consisting of a 15-L rebreathing bag filled with 6 L of 7% CO_2, 23% O_2, and balance N_2. With nose clip *in situ*, subjects breathed room air through a mouthpiece for 3 min before the circuit was closed via a three-way valve. The subjects then took three deep breaths and breathed at tidal volume (VT) after that. Rebreathing continued until the oxygen saturation measured by pulse oximetry (Spo_2) [Ohmeda Biox 3740; Louisville, CO] dropped to 80% or if the subject became distressed. End-tidal CO_2 percentage was measured by a rapid CO_2 analyzer (model 17630; VacuMed; Ventura, CA). Soda lime in the inspiratory limb of the circuit was used to keep expired fractional concentration of CO_2 ($FACO_2$) at $< 7\%$ for all subjects. There was no evidence of hypercapnia on expired gases on this test procedure for patients and normal subjects.

HCVR: A modification of Read's rebreathing method[25] was used. The equipment was similar to that of the HVR test. The differences were as follows: (1) gas in the rebreathing bag contained a mixture of 7% CO_2, 50% O_2, and balance N_2; (2) the carbon dioxide absorber was absent; (3) a fuel-cell rapid oxygen analyzer (Fisher & Paykel Healthcare; Victoria, Australia) was connected to the circuit to measure fractional inspired oxygen. The subjects were connected to the circuit as per the HVR test. They were asked to rebreathe on the circuit to a minimum fractional inspired oxygen of 22% or if the subject became distressed, whichever occurred first.

For both the HVR and HCVR tests, breath-by-breath minute ventilation ($\dot{V}E$), VT, respiratory rate (RR), and the time stamp for each breath were measured (RSS100HR Research Pneumotach System; Hans Rudolph; Kansas City, MO) and recorded (RSS100HR software; Hans Rudolph) through the digital output of the system. The pneumotach system also had an analog output connected to an analog-to-digital card. The oximeter and CO_2 analyzer were also connected to the card. The software for the analog-to-digital card (Logger; Total Turnkey Solutions; Sydney,