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Central neurogenic hyperventilation treated with intravenous fentanyl followed by transdermal application

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Abstract
Central neurogenic hyperventilation (CNH) is a rare clinical condition that is sometimes difficult to treat. We report a 51-year-old female patient who was successfully treated with intravenous fentanyl followed by transdermal fentanyl. She had a transient epileptic episode with a temporary loss of consciousness. Immediately before her admission to the intensive care unit (ICU), her Pa_{CO_2} and pH were 6.7 mmHg and 7.64, respectively. Rebreathing from a paper bag and the intravenous administration of diazepam failed to improve the decreased Pa_{CO_2}. Therefore, we administered intravenous fentanyl, at the rate of 50 μg·h^{-1}. Two days after her admission to the ICU, the Pa_{CO_2} had increased gradually to 22.9 mmHg, and the pH to 7.50. Although infiltration of recurrent lymphoma to the brain became apparent, she remained active, without epilepsy or loss of consciousness, in a general ward for 1 month with transdermal fentanyl, treatment until she again became drowsy; she died on hospital day 58. Transdermal fentanyl seems to be a good palliative measure to treat CNH in patients who have advanced neoplasms.

Key words Central neurogenic hyperventilation · Fentanyl patch · Durotep

Introduction

Central neurogenic hyperventilation (CNH) is defined as a syndrome comprising normal or elevated arterial oxygen tension, decreased arterial carbon dioxide tension, and respiratory alkalosis, induced by lesions in the central nervous system in the absence of cardiac or pulmonary disease, stimulating compensatory hyperpnea [1]. The hyperventilation is sometimes difficult to treat. We describe our experience with a patient who had CNH that was treated effectively with fentanyl.

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Case report

A 51-year-old female patient was admitted to the intensive care unit (ICU) with severe hypocapnia. She had undergone a diagnostic biopsy for a brain tumor and had been treated with chemotherapy and irradiation for malignant lymphoma 1 year earlier. The treatment for her brain tumor had been effective, and no other systemic abnormalities were found until 1 week before her admission to the ICU, when she experienced a transient epileptic episode with a temporary loss of consciousness and was hospitalized.

On admission to the hospital, she was conscious. Neither neurological nor magnetic resonance imaging (MRI) findings showed any apparent abnormalities in the brain. Three days later, she lost her appetite and her level of consciousness decreased slightly. Her breathing was calm and regular, at 16 to 20 breaths·min^{-1}. Arterial blood gas analysis showed pH, 7.64; Pa_{CO_2}, 6.7 mmHg, and Pa_{CO_2}, 137.6 mmHg in room air. The serum ionized calcium concentration was 1.14 mEq·l^{-1}, and the lactate concentration was 4.7 mmol·l^{-1} (Table 1). Rebreathing from a paper bag and the intravenous administration of diazepam failed to increase the Pa_{CO_2}. The neurosurgeon consulted with us about the treatment for her respiratory abnormality in the ICU.

On admission to the ICU, she was drowsy, calm, and unemotional. Routine hematological and biomedical tests, as well as electrocardiogram and chest radiograph, were normal. Systemic review revealed no abnormalities in the heart, lung, liver, or kidney. Although no apparent lesion in the brain stem was detected on MRI, her history of treatment of brain malignant lymphoma prompted us to suspect that the hyperventilation was CNH. We administered intravenous fentanyl at 50 μg·h^{-1} continuously to reduce her respiratory rate. After 8 h, her respiratory rate had decreased to 12–14 breaths·min^{-1}, and the Pa_{CO_2} was 16.7 mmHg. The next morning, her level of consciousness had clearly

Table 1. The results of arterial blood gas analysis

	Before treatment	8 h after beginning administration of fentanyl	2 Days after beginning administration of fentanyl	1 Month after beginning administration of fentanyl
pH	7.64	7.53	7.50	7.45
Pa_{CO_2} (mmHg)	6.7	16.7	22.9	39.9
Pa_{CO_2} (mmHg)	137.6	96.5	99.7	104.9
HCO_3^- (mEq·l^{-1})	7	13.5	17	26.8
BE (mEq·l^{-1})	–12.9	–8.4	–5.5	2.9
Lactate (mmol·l^{-1})	4.7	2.9	1.9	2.7
K^+ (mEq·l^{-1})	3.6	3.9	3.5	4.3
Ca^{2+} (mmol·l^{-1})	1.14	1.16	0.98	1.03

Ca^{2+}, Serum ionized calcium concentration

improved. She voluntarily opened her eyes, answered our questions, and ate a meal. After 2 days in the ICU, her Pa_{CO_2} had increased to 22.9 mmHg and pH to 7.50.

After she was returned to the ward, a transdermal fentanyl patch (Durotep; Janssen Pharmaceutical, Tokyo, Japan) was used to treat her hyperventilation, instead of intravenous fentanyl administration. A 5-mg Durotep patch allows the transdermal administration of fentanyl at approximately 50 μg·h^{-1}. Immediately after switching from the intravenous to the transdermal route, her respiratory rate increased and the arterial Pa_{CO_2} decreased to 16.5 mmHg. However, 3 days later, both parameters had returned to the levels obtained at the end of her ICU stay. Although MRI showed no finding that indicated new infiltration of lymphoma during her stay in the ICU, numerous lymphoma cells were detected in the cerebrospinal fluid on hospital day 3.

One month after beginning administration of fentanyl, her arterial blood gases were maintained within the normal range in room air (Table 1). However, multiple lymphoma infiltrations became apparent in the brain on MRI on hospital day 28. Subsequently, she again became drowsy, and she died on hospital day 58.

Discussion

This case report describes a patient with central neurogenic hyperventilation (CNH) who was treated successfully with intravenous fentanyl and subsequently with transdermal fentanyl.

CNH in conscious patients is a rare condition, first described by Plum and Swanson in 1959 [1]. The diagnostic criteria for this abnormal pattern of breathing are hyperventilation that persists during sleep, low arterial Pa_{CO_2}, high arterial Pa_{CO_2}, and high arterial pH in the absence of drug-induced or metabolic causes [2]. The diagnosis of CNH requires the exclusion of pulmonary, cardiac, and metabolic disorders that can result in hyperventilation [3].

Our patient had neither pulmonary nor cardiac abnormalities that cause hyperventilation. Although she had marked lactic acidosis and a low base excess (BE), she had no metabolic cause of hyperventilation, such as hepatic or renal failure, or diabetes mellitus. Her increased lactate level normalized without any specific corrective action after the administering of fentanyl. The lactic acidosis and low BE were thought to be the result rather than the cause of the CNH, a notion which is suggested in other reports [4].

Despite her marked respiratory alkalosis and hypocapnia, the decrease in consciousness in our patient was modest, although she experienced a transient loss of consciousness and an epileptic seizure. Severe hypocapnia may induce constriction of the brain vessels and subsequent ischemia of the brain that would result in a loss of consciousness; the decrease in Pa_{CO_2} and increase in pH might induce epilepsy. One case of a conscious patient with CNH similar to ours has been reported [5], and several studies have described patients with severe CNH, with a normal level of consciousness [1,2,6,7]. A compensatory mechanisms might counteract the hypocapnia-induced vasoconstriction of the brain.

The mechanism underlying CNH is not fully understood. Tarulli et al. [2] stated that the majority of reported CNH patients had infiltrative tumors involving the pontine tegmentum and medulla, and they proposed that slowly infiltrating neoplastic lesions activated central respiratory pathways that produced CNH. The infiltration of lymphoma cells into the pons and medulla is the most frequently reported cause of CNH, and this was suspected in our patient, based on the findings in the cerebrospinal fluid (CSF) and the last magnetic resonance imagining (MRI) scan. Johnston et al. [8] described chronic dyspnea and hyperventilation in an awake patient with small subcortical infarcts in the medial thalamus bilaterally, and they suggested a role for the thalamus in regulating ventilation. Dysfunction of the reticular formation of the midbrain and upper pons might be associated with the syndrome. Systemic

lactic acidosis, thought to arise from medullary respiratory chemoreceptors, was once proposed as the mechanism underlying CNH; however, this mechanism is not thought to be the sole cause of CNH, because in vivo measurements of the pH in brain neoplasms, using positron emission tomography (PET), have demonstrated that the pH was higher there than in the rest of the brain [9].

Hyperventilation is not a sign of a fatal brain tumor, although hypocapnia could, theoretically, decrease the threshold of seizure activity and induce an abnormal electrolyte balance. Our patient's serum calcium concentration was somewhat low ($8.2\,mg \cdot dl^{-1}$), although the ionized calcium concentration was maintained, despite her alkalemia (Table 1). She developed no neurological abnormality, such as tetany, despite the extremely low carbon dioxide tension. The hyperventilation-induced decrease in acute systemic ionized calcium concentration was reported to be too small to account for the signs and symptoms of hypocapnic tetany [10]. No relationship between the ionized calcium concentration and CNH has been reported, and our patient had no abnormal laboratory result other than the blood lactate level.

Treatment of the primary cerebral neoplasm is essential for inducing a remission of CNH [4]. However, it is sometimes difficult to treat CNH in patients with advanced neoplasms. Palliative measures that alleviate the CNH are required in those who are refractory to chemotherapy, irradiation, or corticosteroids [11]. Rebreathing from a paper bag, and the intravenous administration of diazepam are reported to be ineffective [4], as was also the case in our patient. In contrast, opioids, such as morphine and methadone, are reported to be effective [12].

In this case report, we have described the successful use of fentanyl that was first administered intravenously and then subsequently given transdermally at a rate of approximately $50\,\mu g \cdot h^{-1}$. Transdermal fentanyl seemed to alleviate CNH in this patient with an advanced neoplasm. Fentanyl is usually administered intravenously, although a transdermal patch has recently been made available, based on fentanyl's lipid solubility. A common indication for the use of the transdermal fentanyl patches is for weaning a person from the excessive use of morphine. In our patient, the change in the route of administration from intravenous to transdermal was easy and acceptable. Our patient required no intravenous fluid therapy, and the transdermal patch allowed her to remain active while in the ward. Ultimately, our patient died from multiple lymphoma infiltrations in the brain, although her respiratory function and activities of daily living were maintained effectively with the application of the fentanyl patches.

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