CASE REPORT

Cerebellar and oculomotor dysfunction induced by rapid infusion of pethidine

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SUMMARY

Pethidine is an opioid that gains its popularity for the effective pain control through acting on the opioid-receptors. However, rapid pain relief sometimes brings about unfavourable side effects that largely limit its clinical utility. Common side effects include nausea, vomiting and hypotension. In patients with impaired renal and liver function, and those who need long-term pain control, pethidine may cause excitatory central nervous system (CNS) effects through its neurotoxic metabolite, norpethidine, resulting in irritability and seizure attack. On the contrary, though not clinically apparent, pethidine potentially causes inhibitory impacts on the CNS and impairs normal cerebellar and oculomotor function in the short term. In this case report, we highlight opioid's inhibitory side effects on the cerebellar structure that causes dysmetria, dysarthria, reduced smooth pursuit gain and decreased saccadic velocity.

BACKGROUND

Opioid drugs, typified by morphine, produce profound analgesia primarily through their pharmacological actions on receptors present on the neuronal cell membranes. They act systemically on the central nervous system (CNS) and peripheral nervous system to exert their pain modulatory effects. Three major types of opioid receptors, μ , κ and δ , have been defined pharmacologically and have varied biochemical actions. These receptors are coupled to the intracellular signalling pathways through G-proteins on the cell membranes, and the type of G-proteins they bind to exerts inhibitory effects on the neurons, either the presynaptic terminals or the postsynaptic ones. Based on this mechanism, the opioids generate analgesia primarily through the inhibition of neurotransmitter release from afferent neurons in the spinal cord. However, in the complex central nervous structure where opioid receptors are densely expressed, the final effects are the results of overall neurons involved. If the output is inhibitory, then the feeling of pain is alleviated in the cerebral cortex. On the other hand, with the activation of neurons in the periaqueductal area, the descending inhibitory pathway modulates the release of substance P and glutamate from the primary afferent neurons in the spinal cord.

The opioid-induced adverse drug effects, however, are not simply the result of the activated opioid receptors that transmit analgesic signals. Although side effects such as nausea, vomiting and hypotension, may be partly explained by the activated μ -receptors in the brain, the mechanisms

underlying more severe respiratory depression is complicated and may involve serotonin receptors in the ventrolateral medulla.¹ In addition, the predisposing factors for these side effects are variable and are largely associated with a patient's physical sensitivity, repetitive dosing and the target organs that are primarily affected. To illustrate the importance of different locations in the CNS that contributes to varied clinical manifestations, we report a case of cerebellar and oculomotor dysfunction that is induced by rapid infusion of pethidine, an opioid drug that is widely prescribed for analgesia. Their clinical association may shed light on the pharmacological actions of opioids on the cerebellum and should be regarded as one of the opioid-induced adverse drug effects.

CASE PRESENTATION

A 41-year-old woman was admitted to our hospital for scheduled laparoscopy-assisted hysterectomy due to squamous carcinoma of the cervix. After the operation, she received intravenous infusion of 50 mg pethidine for postoperative analgesia. The drug was diluted in the volume-control burette (100 mL normal saline) and the dripping rate was slow. There was no nausea, vomiting, dyspnoea, hypotension or any neurologic deficit observed. On the second day, she complained of another episode of vaginal pain and pethidine (50 mg) was administered in the same way. The patient felt better and, similarly, there was no discomfort reported. However, 10 h later that night, the third ampoule of pethidine was given on the patient's request and the infusion was carelessly completed within 15 min. The patient felt sudden onset of nausea and beckoned for help.

On physical examination, her consciousness was clear. Her body temperature reached a peak of 37.8°. The oxygen saturation shown on the pulse oxymeter read 93% and with the use of nasal oxygen supplement, it was increased to 98%. There was no dyspnoea or cyanosis observed. The neurological examinations revealed isocoric pupils with positive light reflex (2 mm for each). There was no facial paralysis or decreased muscle power except for mild dysarthria. The finger-to-nose examination showed dysmetria with intention tremor of bilateral hands. When she was instructed to move the eyeballs and follow our signals, she demonstrated impaired smooth pursuit and decreased saccadic velocity. The rest of the neurological examinations were normal.

TREATMENT

Adequate hydration with normal saline for dilution and excretion of pethidine.

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OUTCOME AND FOLLOW-UP

Those symptoms and signs disappeared 20 min later after adequate hydration. The patient's smooth pursuit recovered without jerks or nystagmus seen. The order of pethidine administration was discontinued and the patient was discharged 2 days later without another episode of such manifestation.

DISCUSSION

Pethidine is the first synthetic opioid agonist that is subsequently identified to have potential analgesic effects. However, a high incidence of adverse effects such as nausea, vomiting, respiratory depression and excitatory CNS effects such as seizure attack limits its clinical utility.^{2–5}

Like most of the opioids, pethidine has pharmacologically active metabolite, norpethidine. Norpethidine is the metabolite of pethidine that is neurotoxic and acts as a central nervous stimulant. Prolonged use of pethidine for chronic pain control is related to the accumulation of norpethidine, especially when there is impaired liver and renal function.^{6–8} While pethidine's central nervous effects aforementioned may be attributed to its higher accessibility to the CNS and the neurotoxic norpethidine, it should be emphasised that those unfavourable consequences mostly occur when there is repetitive dosing, long-term use with norpethidine accumulation, concomitant use of monoamine oxidase inhibitors (MAOI) and the patient's vulnerability.⁹ In our case, the patient, without significant underlying diseases, presented with transient disturbance of ocular movement soon after the rapid infusion of pethidine. It is possibly the plasma pethidine, rather than its toxic metabolite, that exerts its effects through the μ -receptors. The findings of dysmetria, reduced smooth pursuit gains and the decreased saccadic velocity indicated cerebellar dysfunction. We believe it is mediated through pethidine's inhibitory effect on the cerebellum that caused abnormal oculomotor findings in the absence of central nervous excitation. The opioid receptors are also found in the cerebellar structure in addition to previously defined cerebral area, and the activation of μ -receptors contributes to the oculomotor dysfunction via its inhibitory effects that support our findings.¹⁰ In the cerebellum, the activated μ -receptors inhibit the release of glutamate from the parallel fibres, diminishing activation of the Purkinje cells. The disturbed postsynaptic signals on the vestibular nuclei then cause vestibulo-ocular dysfunction. In a study conducted by Rottach *et al*, the intravenous administration of fentanyl (0.1 mg) and pethidine (100 mg) caused consistent and temporary ocular disturbances including the downbeat nystagmus, square wave jerks, ocular flutter and decreased velocity of saccades.¹¹ The fact that lesions in the vestibulocerebellum causes downbeat nystagmus also supports the idea that pethidine impaired the cerebellar and ocular function.

Therefore, the quick surge of plasma pethidine likely activated large amounts of μ -receptors in the cerebellum before being metabolised to norpethidine, resulting in cerebellar and ocular dysfunction. Although the impaired smooth pursuit,

decreased saccadic velocity and dysmetria are temporary physiological disturbances, these clinical manifestations suggest pethidine's inhibitory side effects on the CNS.

Learning points

- ▶ Pethidine is an opioid agonist that is widely prescribed for pain control.
- ▶ Its adverse effects such as nausea, vomiting and respiratory depression limit pethidine's clinical utility.
- ▶ Norpethidine, the neurotoxic metabolite of pethidine, has stimulant effects on the central nervous system (CNS), especially when there is impaired renal or liver function.
- ▶ Pethidine itself may have inhibitory effects on the CNS, based on the radiological evidence and the abnormal neurological findings.
- ▶ Inappropriate route of administration may potentiate pethidine's inhibitory effects on the CNS.

Contributors Y-HD wrote the manuscript and carried out the submission. K-LO helped search the reference and modified sentences. P-WC performed the final edition.

Competing interests None.

Patient consent Obtained.

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