"Could it be the shots?"

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Harold's case

Harold, 41, is brought to the ED after a witnessed seizure at home and another *grand mal* seizure witnessed by Emergency Medical Services on transport.

Examination

On arrival, Harold's vital signs are as follows:

- Temperature: 37.0°C
- Pulse: 120 bpm
- Respiratory rate: 24 breaths per minute
- Oxygen saturation: 97%

At the scene, his blood glucose was 4.2 mmol/L.

In the ED, Harold is drowsy and becomes increasingly combative when stimulated. He has a laceration on his lower lip and a contusion over his left scapula; the rest of his physical examination is normal.

Medical history

Harold has no history of epilepsy, although his spouse states that he had a similar, but less severe, "spell" earlier in the week.

He had back surgery 4 weeks prior to this presentation, which was complicated by severe post-operative pain and treated with increasing doses of meperidine. Over the past few days, he has been self-administering intramuscular injections of 100 mg of meperidine every 2 to 3 hours.

He (and his spouse) deny alcohol or other recreational drug use. A CT scan of his head (Figure 1) is normal.

Turn to page 4 for more on Harold

Questions & Answers

1. What is the most likely cause of Harold's seizures?

In the setting of large doses of meperidine in a patient without localizing signs on clinical examination, no history of epilepsy and a normal CT scan, new onset seizures are most likely caused by meperidine toxicity.

Meperidine is a synthetic opioid that is frequently prescribed for acute pain management. Compared to other opioid analgesics, such as morphine and hydromorphone, meperidine is less potent, has a shorter duration of action and is not well absorbed orally. Meperidine is metabolized to an active metabolite, normeperidine, that is only half as effective as the parent compound as an analgesic; however, meperidine is neurotoxic and can cause significant excitatory central nervous system (CNS) adverse effects. Studies of CNS toxicity, secondary to normeperidine, report:

- nervousness,
- hallucinations,
- tremors,
- myoclonus and
- generalized seizures.

2. What are the risk factors for normeperidine-induced seizures?

Normeperidine is primarily eliminated renally. Its half-life is five to 10 times longer than that of meperidine (which is 15 to 30 hours), depending on renal function. Therefore, the accumulation of normeperidine in a patient with renal dysfunction can be substantial. If excessive doses are used, seizures and other CNS side-effects can also occur in those with normal renal function.

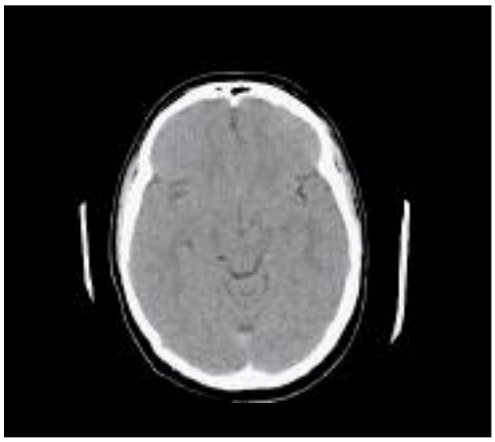

Figure 1. Harold's normal CT scan.

Meperidine is neurotoxic and can cause significant excitatory CNS adverse effects.

3. What other problems can be found with the use of meperidine?

In addition to the excitatory CNS adverse effects associated with normeperidine, meperidine can also cause side-effects similar to all other opioids, which include:

- Sedation
- Confusion
- Hypotension
- Vomiting
- Rash
- Dizziness
- Respiratory depression
- Nausea
- Constipation
- Urinary retention

Drug interactions are also of concern when using meperidine. Concurrent use with other CNS and respiratory depressants can result in additive effects. The most serious drug interaction occurs when meperidine is concurrently used with a monoamine oxidase inhibitor (MAOI), such as phenelzine and tranylcypromine. This interaction can result in serotonin syndrome and may be life-threatening.

4. What should be done in Harold's case?

In Harold's case, meperidine should be discontinued immediately and withdrawal symptoms and further seizures should be managed with benzodiazepines. In cases of meperidine neurotoxicity, naloxone should not be used. Naloxone does not reverse the CNS stimulatory effects of normeperidine and may actually precipitate seizure activity as the sedative effects of meperidine are reversed, allowing the full effect of normeperidine to exert effects on the CNS. Alternative analgesics should then be considered.

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Harold's case cont'd...

Harold's meperidine is stopped and his subsequent agitation is managed with lorazepam. Attempts to manage his pain with NSAIDs are only partially effective and he is discharged after a period of observation on a combination of naproxen and twice daily controlled-release hydromorphone.

The concerns of inappropriate opioid use spawned by this presentation are discussed with the patient; thus he and his spouse are referred to a specialist in chronic pain management.

In cases of meperidine neurotoxicity, naloxone should not be used as it does not reverse the CNS stimulatory effects of normeperidine and may actually precipitate seizure activity.

5. When should alternatives to meperidine be considered?

Meperidine should not be considered as a first-line agent due to its:

- adverse effects associated with its toxic metabolite,
- potential for drug interactions,
- short duration of action and
- the availability of safer and equally effective opioids.

Meperidine should also be avoided in patients:

- with a planned treatment duration > 48 hours,
- taking doses > 600 mg q.d.,
- who are elderly,
- with renal dysfunction and
- who concurrently use MAOIs.

6. What alternate analgesics should be considered for Harold?

Non-opioid analgesics should be used whenever possible. These may include the use of acetaminophen, NSAIDs or COX-2 inhibitors. If opioid analgesics are required, an alternate agent should be considered and may be safely administered to most patients. The most common agents available for oral use include:

- codeine,
- oxycodone
- morphine and
- hydromorphone.

Although all opioids may cause CNS and respiratory depression, as well as adverse GI and cardiovascular effects, unlike meperidine, none of these agents produce a neurotoxic metabolite which may result in neuroexcitation and so may be considered. Dx

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