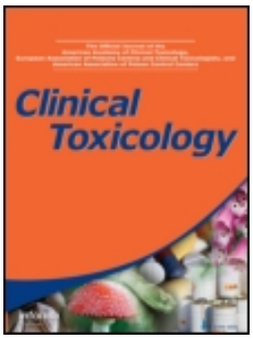

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# Letter to the Editor: "Severe neurotoxicity following oral meperidine (pethidine) overdose"

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LETTER TO THE EDITOR

# Severe neurotoxicity following oral meperidine (pethidine) overdose

*To the Editor:*

"Recreational" intravenous meperidine overdose and toxicity due to accumulated metabolites during chronic use are the usual clinical presentations of meperidine toxicity (1–5). Oral meperidine overdose has not previously been reported. We present a case of a very large oral meperidine overdose in an otherwise healthy girl who manifested severe non-opioid central nervous system toxicity.

A 17-year-old girl was found unconscious at home, 2.5 hours after last being seen. Two hundred 50 mg tablets of meperidine belonging to a relative were missing. Ambulance officers recorded pinpoint pupils, a Glasgow Coma Score (GCS) of 3, respiratory rate (RR) of 6 breaths/minute, and a heart rate of 130 beats/minute. She was given 2 mg of naloxone IV. Upon presentation to the emergency department, her GCS was 10, RR was 12 breaths/minute, heart rate was 120 beats/minute, and her pupils were mid-point. She was treated with a further 1 mg of naloxone without any significant further improvement in her conscious state. Ninety minutes later, she had a short generalized tonic-clonic seizure and her GCS dropped from 10 to 6. She was intubated, sedated with propofol, and admitted to the intensive care unit. Electrolytes, calcium, magnesium, phosphate, blood urea, and creatinine were normal. She was managed with supportive therapy and was extubated the next day. She remained delirious and agitated and had to be restrained over the next 24 hours. Her signs at this stage included tremor, hyperreflexia, myoclonus, clonus, dilated pupils, and tachycardia. She fully recovered over the next 48 hours. The serum meperidine concentration in our patient at presentation was 6.5 mg/L; normeperidine was not detectable at that time. No other toxicological analysis was performed.

There are several case reports of neurotoxicity with meperidine when used as post-operative analgesia (parenteral) (3–6). This is the first reported case of overdose of oral meperidine. Meperidine shares some of the adverse and toxic effects of other opioids, such as respiratory depression and hypotension, but also causes non-opioid CNS toxicity and excitation.

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Meperidine was originally developed as an anticholinergic agent in 1939 (7), and earlier reports have mentioned excessive anticholinergic activity of meperidine as a potential cause of delirium associated with meperidine toxicity (6). It is also known that meperidine can inhibit the presynaptic reuptake of serotonin (8). The mechanisms behind the non-opioid manifestations of meperidine/normeperidine toxicity (such as mydriasis and seizures) have not been defined, but could be due to these anticholinergic and serotonergic properties (2).

In therapeutic doses, oral meperidine has low bioavailability (50%–60%) due to extensive hepatic first pass metabolism (7). Normeperidine is the only active metabolite and has a half-life of 24 to 48 hours, compared to a half-life of meperidine which is 3–6 hours (9). Repeated meperidine use may cause toxicity through accumulation of normeperidine. Chronic meperidine-induced delirium, nervousness, tremors, myoclonus, and seizures correlates more highly with normeperidine plasma levels than with meperidine plasma levels (10).

Acute oral, as opposed to intravenous, exposures might be expected to result in relatively lower meperidine and higher normeperidine levels, and more chance of toxicity (3). However, the meperidine concentration in our patient three hours after suspected ingestion at the time of severe CNS toxicity was very high, while normeperidine was not detectable. This suggests that early acute toxicity is due to meperidine rather than metabolites, and that there is minimal first-pass metabolism following massive oral ingestions. However, the subsequent prolonged delirium in this case followed a time course more compatible with the normeperidine half-life, suggesting that conversion subsequently occurred normally as it does following intravenous meperidine. Thus, the clinical effects of oral overdose of meperidine are similar to that of intravenous meperidine except for the much larger ingested dose, which probably leads to a longer time-course.

This case also illustrates the clinical importance of recognizing and appropriately treating non-opioid symptoms of meperidine toxicity. Naloxone does not reverse CNS toxicity of normeperidine and may precipitate seizures by blocking the CNS depressant effects of meperidine (1–3), and this may have contributed in this case. Generalized seizures should respond to benzodiazepines and do not generally recur (3). Other CNS toxicity such as tremors,

restlessness, and myoclonus should be expected to subside over two to five days (3).

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