Meperidine-induced serotonin syndrome is a very rare adverse event that may occur during anesthesia that is often missed or treated inadequately. Untreated serotonin syndrome can be fatal. The mortality rate of severe serotonin syndrome ranges from 2% to 12% [1]. The syndrome usually occurs in the context of usage of antidepressants or other medications that increase serotonin prior to surgery. However, a previous report described the occurrence of meperidine-induced serotonin syndrome in a patient with a past history of clomipramine-induced serotonin syndrome [2]. The present report is the first case of meperidine-induced serotonin syndrome in a patient with no use of other serotonergic medication and also with no history of susceptibility. Furthermore, an unexpected paradoxical rapid reversal of the neurologic symptoms of serotonin syndrome was observed in this case in association with the administration of famotidine.

**Case Report**

A 70-year-old male was admitted for the ureteroscopic removal of ureter stones. He had been receiving treatment with glimepiride for diabetes; atorvastatin for hyperlipidemia; and aspirin, thiazide, valsartan, and carvedilol for hypertension and...
Famotidine in serotonin syndrome

The present report describes a case of serotonin syndrome induced by meperidine alone in a patient with no history to suggest a susceptibility to serotonin syndrome. This is the first case report of serotonin syndrome induced by meperidine alone because of the close temporal relationship between meperidine injection and the onset of serotonin syndrome. Although serotonin syndrome is a potentially life-threatening situation, specific treatment for serotonin syndrome has not yet been established. Serotonin syndrome is caused by hyperactivity of central and/or peripheral serotonin receptors [4]; therefore, several previous treatment attempts have aimed to suppress serotonergic transmission using chlorpromazine [5], cyproheptadine [6], risperidone [7], propranolol [8], or even electroconvulsive therapy [9]. However, the efficacy of these treatments has not been proven, and none are routinely recommended because of side effects and the availability of the above-mentioned pharmacological agents only in the oral form.

The present report describes a case of serotonin syndrome exhibiting immediate paradoxical reversal of unconsciousness and neurological symptoms following the intravenous administration of famotidine. Famotidine is a histamine receptor.
antagonist with high selectivity for histamine 2 (H2) receptors. It has been reported to be associated with several unexpected central nervous system (CNS) effects such as delirium, mania, and seizures [10]. Delirium associated with famotidine has been reported in several cases, possibly associated with central anticholinergic effects [11].

The mechanisms underlying famotidine-mediated reversal of serotonin syndrome are a matter of speculation. Perhaps this H2-selective blocker increases the histamine concentration at CNS synapses, resulting in hyperactivation of histamine H1 receptors and mental arousal. Another possible explanation is that histamine H2 antagonists may have an effect on reduction of blood serotonin levels [12].

Famotidine, a drug that has been the subject of attention at times, has been reported to result in a paradoxical treatment response via an unknown mechanism in the CNS. The present case did not confirm whether the pharmacological effects of famotidine alone caused a dramatic recovery of neurologic symptoms or whether the interaction of famotidine and the patient's individual genetic specificity resulted in an improvement of the symptoms. However, it is useful to note that this is the first report that famotidine may be an effective treatment for serotonin syndrome. It is also worthwhile to note that the intravenous formulation of famotidine enables rapid medication administration in non-cooperative patients. In addition, famotidine is known to be a relatively safe drug with few drug interactions. Further preclinical and clinical studies are necessary to confirm the efficacy and safety of this treatment.

This case had two idiosyncratic features. First, the patient's mental and neurological state improved immediately following famotidine administration. The half-life of meperidine is 2.5–4 h. The patient's neurological symptoms recovered beginning approximately 60 min after the administration of meperidine. In addition, the recovery from moderate to severe serotonin syndrome takes 24 h to several days. Therefore, the course in this case is not thought to represent the natural course of recovery.

Although the mechanisms are uncertain, the close temporal relationship between the administration of the medication and the recovery of the neurological symptoms strongly suggests that famotidine contributed to symptom reversal in this case. While metoclopramide was also administered, it is unlikely to have contributed to recovery because metoclopramide has been reported to actually cause or exacerbate serotonin syndrome [13,14]. Second, the recovery of individual symptoms followed a distinct time course, with mental condition showing immediate improvement, followed by mitigation of neurologic symptoms and the more gradual remission of autonomic symptoms. In contrast, recovery from serotonin syndrome is generally gradual, spanning a period of over several hours.

In summary, anesthesiologists should keep in mind that meperidine alone can induce serotonin syndrome and the administration of famotidine, a relatively safe drug with few drug interactions, may be useful in critical patients with suspected serotonin syndrome.

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