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Concerning the Possible Nature of Reported Fentanyl Seizures

To the Editor:—We have read with interest reports of grand mal seizures associated with the intravenous administration of fentanyl.[1-3] The last correspondence indicated that the seizure occurred after only 100 μg of fentanyl and was so severe that the patient dislocated both shoulders. There was no electroencephalographic documentation of the reported seizure, and studies addressing whether fentanyl can produce cortical seizures documented by EEG in humans have failed to demonstrate such activity.[4,5] Furthermore, none of the patients had neurologic disorders by history or physical examination before or after their reported seizure. Nonetheless, seizure activity can be produced by all narcotic analgesics at extremely high doses (usually 100 times the anesthetic or profoundly analgesic dose) in all experimental animals.[5,6] Furthermore, the possibility of opiate-induced seizures in subcortical structures such as the hippocampus, which conceivably are undetectable by cortical leads, also has been documented.[7] An examination of recent papers in the nonanesthetic literature adds an interesting perspective to these reports.

High-dose morphine in rats (>20 mg/kg) results in a catatonic state consisting of rigidity and catalepsy (akinesia and waxy flexibility). DeRyck and Teitelbaum[8] recently examined the phenomenon of morphine catalepsy and described cortical EEG synchronization and hippocampal activation during this phenomenon. These authors raise the question of whether hippocampal seizures are a feature of the cataleptic state. Should such an association be made, one must question the relevance of narcotic-induced hippocampal activity to the myoclonic movements described in the case reports, since catalepsy is typified by the absence of movement. Given the large species differences in opiate actions, the occurrence of the above mechanisms in primates and/or humans is speculative until more definitive research is done.

Our experiences suggest that rigidity is a more likely explanation for the myoclonic movements described in the above reports. Rigidity commonly occurs with therapeutic doses of narcotics. In experimental work (unpublished), high-dose alfentanil inductions produce rigidity involving all extremities, closely resembling seizures. Like the study of Murkin *et al.*,[4] simultaneous EEG recording during such movements are devoid of seizure activity.

More ominous, perhaps, are nonopiate mechanisms of morphine seizures. This was recently well described in a series of papers beginning with a description by Frenck *et al.*[9] of tonic/clonic movements limited to the hindlimbs of rats receiving lumbar subarachnoid injections of morphine. These seizures reproduced those seen with large systemic doses and were not naloxone reversible. Injections of methadone or the opioid D-ala-methionine enkephalinamide did not result in seizures but did produce catalepsy. We feel these findings must be of concern, given the current popularity of intrathecal/epidural morphine analgesia and in light of a case report describing catatonia in a patient receiving large doses of epidural morphine.[10]

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