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Clinical Note

Clonazepam treatment of myoclonic contractions associated with high-dose opioids: case report

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Summary A 30-year-old man with chronic abdominal pain was treated with high doses of hydromorphone intravenously and developed severe and frequent myoclonic contractions. Several medications including lorazepam failed to control the contractions; however, clonazepam in normal doses reduced the myoclonus dramatically.

Key words: Clonazepam; Opioid-induced myoclonic contractions; Chronic pain treatment, High-dose opioids

Introduction

The treatment of chronic pain with increasing doses of opioids is sometimes associated with increased myoclonic activity. This is manifested by uncontrollable twitching and jerking of various muscle groups of the spine, neck, face, and most frequently the extremities. There is an associated increased sensitivity to touch and noise which can trigger muscle contractions that may last several seconds or longer. The occurrence and severity of this opioid-associated myoclonic activity is not predictable, but it does appear to be dose related. It is not seen during standard opioid treatment of acute pain, and it is clinically different from the hypermotor or tremor activity associated with opioid withdrawal.

Case report

Patient G.B. is a 30-year-old male with AIDS and an associated mycobacterium avium-intracellular (MAI) infection involving the retroperitoneal and intestinal lymphatics. Following an extensive small bowel resection and anastomosis he developed increasingly severe lower abdominal pain. The pain had been treated with escalating doses of opioids administered via a pump through a perma-

nent intravenous line. When first seen by the University Pain Service he was receiving hydromorphone (Dilaudid) in doses of 50–70 mg/h without evidence of oversedation; however, he had frequent myoclonic contractions, mostly in the arms, legs, and trunk, at a rate of almost 1/5 sec. This muscular jerking was continuous during sleep. Both the patient and his family had become accustomed to these contractions, yet they were distracting, and we were concerned that the movements would make it impossible to perform a celiac plexus block for pain control. The patient gave a history of intolerance to morphine, and methadone was not tried, possibly due to its unpredictable accumulation.

Lorazepam (Ativan) made the patient excessively sedate, and haloperidol was tried for several weeks with no reduction of myoclonic activity. Then, because of its reported anti-myoclonic effects (see below), 0.5 mg clonazepam t.i.d. was tried, and within 72 h the myoclonic contractions were less than 1/min. Also, the intensity of the contractions was noticeably reduced and, within 5 days, the contractions occurred less than 1/10 min. There was, however, no change in the opioid requirement. The elimination of the myoclonus enabled us to proceed with a celiac plexus injection of phenol, which reduced his abdominal pain, and his opioid requirement to less than 1 mg/h of Dilaudid.

Discussion

Clonazepam (Klonopin) is a benzodiazepine compound useful alone or as an adjuvant in the treatment of akinetic and myoclonic seizures such as infantile spasms, progressive myoclonic epilepsy, spinal myoclonus, palatal myoclonus, and post-encephalitic myoclonus (Hoehn and Cherington 1977; Gauthier et al. 1981). It is reported that clonazepam and nitrazepam

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are more potent in treating myoclonus than other benzodiazepines (Coletti et al. 1980).

Skeletal muscle contractions and rigidity have been observed, although unpredictably, during rapid intravenous injection of opioids for the induction of general anesthesia (Comstock et al. 1981). In this situation, abnormal muscle movements range from extremity flexion and/or tonic-clonic movements of the extremity to global tonic-clonic activity, which some observers have interpreted as seizures. Opioid-induced muscle contractions may be related to the catatonic state which has been studied in animals and humans (Benthuisen et al. 1986). Some investigators have suggested that brain-stem sites containing serotonergic and GABAergic pathways play an important role in opioid-induced rigidity (Weinger et al. 1987, 1988a). It is generally believed that the neuropharmacology of opioid-induced rigidity is complex and differs from the rigidity produced by other drugs, such as the phenothiazines and drugs producing parkinsonian-like activity (Weinger et al. 1988b).

Metabolites of opioids such as normeperidine can cause neurotoxicity, including delirium, myoclonus, and seizures. With morphine neuroexcitatory symptoms are unusual, and it has been reported that no correlation exists between the incidence of myoclonus and plasma morphine measured by high performance liquid chromatography. However, morphine metabolites were not measured (Potter et al. 1989). Recently, normorphine has been identified in 2 cancer patients on high doses of morphine who demonstrated myoclonus in the setting of renal impairment (Glare et al. 1990). It is possible that analogous metabolites of hydromorphone (Dilaudid) exist and could be responsible for the marked myoclonus seen in this case.

Continuous myoclonic activity induced by opioids can be a serious side effect whereupon other opioids should be tried, preferably compounds that are not closely related such as fentanyl transdermally. Combining benzodiazepines and opioids may produce excessive sedation, drowsiness, and respiratory depression

that can develop with chronic usage. Also, if discontinuing clonazepam it must be done over weeks because of the possibility of adverse reactions such as involuntary movements and mental confusion (Busto et al. 1986).

This case and several subsequent cases treated by the authors suggest that a trial of clonazepam using normal doses may be valuable in treating opioid-related myoclonus including nocturnal myoclonus.

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