Intrathecal morphine overdose in a dog

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Case Description—A healthy 6-year-old 28.5-kg (62.7-lb) spayed female Boxer undergoing surgical repair of a ruptured cranial cruciate ligament was inadvertently administered an overdose of morphine (1.3 mg/kg [0.59 mg/lb]) via subarachnoid injection.

Clinical Findings—50 minutes after administration of the overdose, mild multifocal myoclonic contractions became apparent at the level of the tail; the contractions migrated cranially and progressively increased in intensity and frequency during completion of the surgery.

Treatment and Outcome—The myoclonic contractions were refractory to treatment with midazolam, naloxone, phenobarbital, and pentobarbital; only atracurium (0.1 mg/kg [0.045 mg/lb], IV) was effective in controlling the movements. The dog developed hypertension, dysphoria, hyperthermia, and hypercapnia. The dog remained anesthetized and ventilated mechanically; treatments included continuous rate IV infusions of propofol (1 mg/kg/h [0.45 mg/lb/h]), diazepam (0.25 mg/kg/h [0.11 mg/lb/h]), atracurium (0.1 to 0.3 mg/kg/h [0.045 to 0.14 mg/lb/h]), and naloxone (0.02 mg/kg/h [0.009 mg/lb/h]). Twenty-two hours after the overdose, the myoclonus was no longer present, and the dog was able to ventilate without mechanical assistance. The dog remained sedated until 60 hours after the overdose, at which time its mentation improved, including recognition of caregivers and response to voice commands. No neurologic abnormalities were detectable at discharge (approx 68 hours after the overdose) or at a recheck evaluation 1 week later.

Clinical Relevance—Although intrathecal administration of an overdose of morphine can be associated with major and potentially fatal complications, it is possible that affected dogs can completely recover with immediate treatment and extensive supportive care. *J Am Vet Med Assoc* 2007;230:1665–1668)

A 6-year-old 28.5-kg (62.7-lb) spayed female Boxer was evaluated at the North Carolina State University VTH for surgical repair of a ruptured cranial cruciate ligament. History was unremarkable (including no previous problems with anesthesia), and results of physical examination and routine clinicopathologic analyses were within reference limits. After food was withheld for 12 hours, the dog received IM injections of hydromorphone (0.1 mg/kg [0.045 mg/lb]) and medetomidine (8 µg/kg [3.64 µg/lb]). Anesthesia was induced with 3 mg/kg (1.36 mg/lb) of propofol administered IV and maintained with isoflurane in oxygen to effect. Physiologic measurements were initially obtained via continuous ECG monitoring, capnography, and intermittent indirect oscillometric blood pressure[a] (for which continuous direct arterial blood pressure monitoring[a] was later substituted). The anesthetic plan included a caudal epidural injection of preservative-free morphine sulfate[b] (0.1 mg/kg) in combination with bupivacaine hydrochloride (1 mg/kg [0.45 mg/lb]). During placement of the epidural needle into the epidural space, CSF was detected in the needle, indicating subarachnoid placement. For subarachnoid injections, the convention in effect at the VTH at that time was to administer only morphine at a dose 50% less than that used for epidural injections (ie, 0.05 mg/kg [0.02 mg/lb]). The concentration of the preparation of preservative-free morphine typically used in the VTH was 1 mg/mL.[b] Inadvertently, the morphine preparation used in the injection administered to the dog had a concentration of 25 mg/mL.[c] Thus, instead of a subarachnoid injection of morphine at a dose of 0.05 mg/kg, the dog received a subarachnoid injection at a dose of 1.3 mg/kg (0.59 mg/lb), which was 26 times greater than the dose appropriate for this route of administration.

In the small animal section of the VTH, controlled drugs were dispensed from a password-controlled automated drug-dispensing machine, which was accessible to veterinarians every hour of every day. Single vials or ampules of drugs were dispensed pursuant to correct entry of information including an identification number of the ordering veterinarian, password, patient number and name, and drug required. There were 5 different formulations and concentrations of morphine in the

Abbreviations

VTH	Veterinary Teaching Hospital
SAP	Systolic arterial blood pressure
M3G	Morphine-3-glucuronide
M6G	Morphine-6-glucuronide

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drug-dispensing machine: morphine sulfate (concentration, 15 mg/mL [volumes of 1 and 20 mL]), preservative-free morphine sulfate (concentrations of 1 mg/mL [volume, 10 mL] and 25 mg/mL [volume, 10 mL]), and a 1% topical solution of morphine sulfate (volume, 1 mL). Each vial was stacked in a separate column and keyed to a specific key on the drug machine keyboard to ensure that the drug dispensed exactly matched the keyboard selection made by the user. The preparation of morphine dispensed by the automated machine was not checked by the user prior to administration to the dog.

Because intrathecal overdose of morphine in dogs had not been described in the veterinary literature to our knowledge, no treatment was instituted and the dog was monitored for adverse effects. Approximately 50 minutes after subarachnoid injection and prior to the start of the surgical procedure, mild focal myoclonic contractions were detected at the level of the dog's tail. The duration of each contraction was 1 to 2 seconds, and they occurred spontaneously every 5 to 10 minutes or after local pressure stimulation. During this time, the dog's level of anesthesia was assessed as being at an adequate surgical plane, and the contractions were diagnosed as myoclonic movements. Surgery began approximately 1 hour after the injection, and the stimulus of surgery did not appear to affect the frequency or intensity of the myoclonic activity. Midazolam (0.1 mg/kg) was administered IV and was somewhat effective in inducing muscle relaxation, decreasing the severity of the contractions, and prolonging the interval between spasms. However, during the following 30 minutes, the myoclonic movements increased in intensity and frequency and began to develop in more cranial regions. At 120 minutes after the injection, myoclonia was evident at the level of the hind limbs. Midazolam treatment (at the same dose) was repeated 3 times at 5-minute intervals, but the spasms were refractory to treatment. Neuromuscular blockade was instituted with administration of multiple boluses of atracurium (0.1 mg/kg, IV) and was effective in diminishing the intensity and frequency of the myoclonic movements. Positive pressure ventilation was simultaneously instituted.

The surgical procedure was completed successfully within approximately 2 hours, after which time the dog (still anesthetized) was transferred into another area for monitoring and treatment of the myoclonus. Approximately 4.5 hours after administration of the morphine overdose, the myoclonic movements worsened. Multiple boluses of naloxone hydrochloride (0.8 mg, IV) were administered without effect. Phenobarbital sodium (2.25 mg/kg [1.02 mg/lb]) and pentobarbital sodium (2.08 mg/kg [0.95 mg/lb]) were administered IV in response to the severity of the myoclonic movements and to evaluate whether any component of the spasms was possibly seizure activity. Neither drug was effective in achieving complete relaxation of the dog or stopping the myoclonic movements; thus, the decision was made to transfer the dog to the intensive care unit for further treatment.

The dog was admitted to the intensive care unit at approximately 5 hours after the overdose. Continued treatment attempts with midazolam, pentobarbital, and naloxone failed to control the myoclonus; myoclonic activity worsened, and hyperthermia (41.6°C [107°F]) and hypercapnia (end-tidal carbon dioxide concentration, 59 mm Hg) developed. Control of hyperthermia was attempted with movement of air over the dog by use of a fan and application of ethanol and ice to its skin, close to the large vessels. Hypercapnia was treated by use of manual intermittent positive pressure ventilation provided via an anesthesia circuit. Hyperthermia resolved with these treatments and did not recur. At 5.5 hours after the overdose, inhalant anesthesia was discontinued, but the dog received continuous rate IV infusions of propofol (1 mg/kg/h) and diazepam (0.25 mg/kg/h [0.11 mg/lb/h]), and the dog was ventilated by use of a mechanical ventilator.[d] Additionally, the dog received continuous rate IV infusions of naloxone (0.02 mg/kg/h [0.009 mg/lb/h]) and a crystalloid solution (2× maintenance fluid rate; 120 mL/kg/24 h [54.55 mL/lb/24 h]). During the first several hours of mechanical ventilation, there were continued signs of myoclonus, and treatment was attempted with intermittent IV administrations of atracurium (0.1 mg/kg) every 15 to 30 minutes, pentobarbital (1 mg/kg) as needed, and a single dose of methocarbamol (40 mg/kg [18.2 mg/lb], IV). Transient cessation of myoclonic movements was achieved following each atracurium administration, but the clinical duration of action was only 15 to 20 minutes, and no notable clinical improvement resulted from administration of either pentobarbital or methocarbamol.

A constant rate IV infusion of atracurium (0.1 mg/kg/h) was started. This dosage initially controlled the myoclonus effectively, but needed to be increased over the next few hours to a final rate of 0.3 mg/kg/h (0.14 mg/lb/h) to prevent movement. Ventilation parameters were monitored periodically via arterial blood gas analyses and were within reference limits at all assessments. Beginning at approximately 15 hours after the overdose, the dog developed mild hypertension (SAP, 186 mm Hg; reference range, 100 to 120 mm Hg) and bradycardia (51 beats/min; reference range, 75 to 90 beats/min); it was speculated that these abnormalities had developed as results of increased intracranial pressure (Cushing's reflex), and treatment with mannitol (15 g, IV; duration of administration, 15 minutes) was provided. Following mannitol administration, the heart rate increased, but the blood pressure did not change appreciably. Approximately 4 hours later, heart rate had decreased to < 40 beats/min and SAP had increased to approximately 190 mm Hg. Mannitol (30 g, IV; duration of infusion, 20 minutes) was administered again with no change in either variable, and a constant rate IV infusion of sodium nitroprusside (2 µg/kg/h [0.91 µg/lb/h]) was started in an attempt to control hypertension.

At approximately 22 hours after receiving the overdose, the dog was weaned from mechanical ventilation by slow discontinuation of the propofol, atracurium, naloxone, and diazepam constant rate infusions. As the dog recovered, spontaneous ventilation was resumed and the ventilatory support was discontinued. The dog was able to breath spontaneously with no ventilatory abnormalities detectable via arterial blood gas analyses. Following extubation, myoclonus was no longer present, although the dog was stuporous.

Approximately 29 hours following the overdose, the dog became dysphoric, constantly vocalized, and developed hypertension (SAP, 227 mm Hg) despite continued sodium nitroprusside infusion. A constant rate IV infusion of naloxone was resumed (0.02 mg/kg/h), and midazolam (0.5 mg/kg/h [0.23 mg/lb/h]) was added with no reduction in the frequency of vocalization or decrease in SAP. A constant rate IV infusion of medetomidine (1 µg/kg/h) was initiated, which provided control of the dysphoria and decreased SAP to approximately 160 mm Hg.

The dog continued to receive this treatment combination until 42 hours after the overdose; at that time, the dosage of naloxone was decreased to 0.01 mg/kg/h (0.0045 mg/lb/h) and then discontinued, and the dosage of midazolam was decreased to 0.25 mg/kg/h. Within 1 hour, the dog became dysphoric and hypertensive again, and all of the constant rate infusions were resumed (naloxone, 0.02 mg/kg/h; midazolam, 0.5 mg/kg/h; and medetomidine, 1 µg/kg/h).

At 49 hours after the overdose, the sodium nitroprusside infusion was discontinued, and the SAP was maintained at approximately 170 mm Hg. At 60 hours after the overdose, the dog's mentation improved, including recognition of caregivers and response to voice commands. Over the following 6 hours, the remaining infusions were slowly tapered and discontinued, at the conclusion of which the dog was no longer dysphoric, responded appropriately to stimuli, ate and drank readily, and was able to walk outside. No neurologic abnormalities were detectable at the time of discharge from the VTH (approx 68 hours after the overdose), and no abnormalities were evident at a recheck evaluation 1 week later.

Discussion

In the dog of this report, several adverse effects resulted from the intrathecal morphine overdose and also possibly from subsequent treatments. The dog's clinical signs included myoclonus, hypertension, dysphoria, hyperthermia, and hypercapnia. The development of myoclonus after intrathecal administration of morphine (whether as an overdose or presumably idiosyncratically with appropriate dosages) is well documented.[1-5] In the human and veterinary medical literature, a clear description of the mechanisms of the myoclonus and its treatment is lacking, although disinhibition of postsynaptic γ-aminobutyric acid and glycine receptors via nonopiate mechanisms has been suggested.[6,7] In humans, intrathecal administration of morphine can cause myoclonus, ventilatory depression, myosis, and decreased pulmonary compliance.[8] There is evidence that in sufficiently high doses, all opioids likely potentiate convulsant activity.[1] Many different hypotheses exist to explain these adverse effects, although a complete understanding of the mechanisms is unknown.

Morphine has 2 major metabolites, M3G and M6G, that are produced in the liver.[5] Following administration of morphine, concentrations of these morphine metabolites exceed the concentration of morphine in CSF in humans and rats,[5,9] and M6G is cleared approximately 10 times more slowly than morphine from CSF in rats.[9] These metabolic products are formed approximately 1.5 to 2 hours after introduction of morphine into the circulatory system and have been associated with the neuroexcitatory effects of large doses of morphine.[10,11] There is also evidence that these metabolites may indirectly activate N-methyl-D-aspartate receptors, resulting in nonopioid receptor responses, which may be a pathway promoting myoclonus.[11] In dogs, M6G is known to induce ventilatory depression, whereas M3G causes myoclonus, hyperalgesia, and allodynia.[12] In addition, although the ratio of M3G to M6G concentrations in plasma or CSF after morphine administration that would be considered normal is unknown,[13] it had been suggested that abnormalities in those ratios may contribute to the metabolite-associated adverse effects. In an experimental setting, rats developed myoclonus after intrathecal administration of morphine,[2] and it was concluded that there was an increase in serotonergic activity in the spinal cord that could be blocked by serotonin inhibitors. In the dog of this report, similar myoclonic activity developed, suggesting that it was a result of spinal serotonin activity. In a case report[3] of myoclonus and urinary retention that developed in a dog following intrathecal administration of an appropriate dose of morphine, it was suggested that the opioid or its metabolites were responsible for inhibition of central inhibitory neurotransmitter activity, but the authors did not address whether activation of serotonin or N-methyl-D-aspartate receptors was the more likely mechanism. Thus, the lack of effect of the naloxone administered to the dog of this report may have occurred because the adverse effects of morphine were not opioid receptor mediated. Alternatively, the ineffectiveness of naloxone as an antagonist may have been because the receptors that were bound by morphine and its metabolites were primarily neuraxial and the naloxone was administered IV; administration of naloxone intrathecally may have provided relief from the morphine-associated adverse effects.

In humans, respiratory depression is a well-known adverse effect associated with opioid agents; although this effect is far less pronounced in veterinary patients, overdose or continuous rate infusions can induce ventilatory depression, which may have been the cause of hypercapnia in the dog of this report. In addition, it is possible that the hypercapnia was simply a consequence of hyperthermia that developed within the same time frame. Hyperthermia was likely a direct result of the dog's prolonged, uncontrolled myoclonic movements because it resolved with treatment and control of the myoclonus. In addition, morphine and other opioids have direct effects on the thermoregulatory centers that appear to be dependent on species, dose, route of administration, body temperature, and several other factors.[14]

Hypertension is a recognized adverse effect of naloxone administration that develops via the rapid reversal of opioid receptor agonist effects, which leads to increased sympathetic tone. Naloxone was administered to the dog of this report as a continuous rate IV infusion for a prolonged period of time and may have been the cause of the hypertension.[15] Because of the administration of multiple agents during anesthesia and the sub-

sequent treatment period prior to discharge from the VTH, it is difficult to determine whether dysphoria was a direct result of the morphine or, more likely, a result of multiple infusions of drugs such as midazolam, phenobarbital, and pentobarbital.

Atracurium is metabolized via Hoffman elimination to laudanosine. Laudanosine is able to cross the blood-brain barrier and can promote seizure activity in dogs under experimental conditions.[16] It is possible that accumulation of laudanosine contributed to CNS excitement in the dog of this report. However, CNS excitement does not explain the increased need for atracurium because nondepolarizing neuromuscular blockers work at the neuromuscular junction and are not affected by CNS stimulation.

From a subsequent review of the human medical literature, alternative treatment options for the dog of this report were identified. Because the fact that an overdose of morphine had been administered was realized almost immediately, treatment measures should have been instituted at that point, rather than waiting for clinical signs to develop. In 1 report[4] of a woman who received an overdose of morphine intrathecally during caesarian section, IV administration of naloxone was started promptly after the overdose occurred. Unlike morphine overdose–associated effects reported[4,8] for other patients, that woman did not develop myoclonus and did not require mechanical ventilation; however, the magnitude of that overdose was much smaller than the dose administered to the dog of this report. In another report,[17] an intrathecally administered overdose of morphine in a human who was receiving long-term treatment with the drug was described. For that person, a technique of CSF aspiration and irrigation to remove the drug and minimize the direct neurotoxic effects was used (which was also described in another report[18] in the human medical literature). The success of that technique was questionable because the patient still had to be placed in a pentobarbital-induced coma and required supportive care for recovery. Although the technique may decrease the direct neurotoxic effects of morphine, it increases the risk of inflammation and the possibility of meningitis.[17] In a report[5] of the development of myoclonus secondary to an appropriate dose of morphine administered intrathecally in a dog, the myoclonic movements were eventually controlled via a single bolus of pentobarbital administered IV. The reason for the effectiveness of pentobarbital in that dog and its inability to improve clinical signs in the dog of this report is unclear but may be associated with the difference in doses administered. Although it has not been reported to our knowledge, 1 possible treatment of the dog of this report would have been to introduce a spinal needle into the subarachnoid space in the L5-6 region and elevate the dog's head relative to the body. Morphine is a hyperbaric drug, and by elevating the dog's head relative to the body, the pressure gradient within the cerebrospinal column would have been increased caudally, presumably promoting drainage of the drug via the spinal needle.

Since the accidental overdose event in the dog of this report, several changes were implemented in the VTH to prevent occurrence of such errors. Preservative-free morphine sulfate at the concentration of 25 mg/mL was no longer stocked in the automated drug-dispensing machine located in the small animal section of the VTH, and it became mandatory that all drugs be labeled with both the name and the concentration of the substance. In addition, only the person who prepared a drug injection may administer it. As this case report highlights, intrathecal administration of an overdose of morphine (26 times the appropriate dose) in a dog can be associated with major and potentially fatal adverse effects; however, with immediate treatment and extensive supportive care, complete recovery can be achieved.

a. Dinamap Plus, Critikon, Tampa, Fla.
b. Morphine sulfate PF (1 mg/mL), Hospira, Lake Forest, Ill.
c. Morphine sulfate PF (25 mg/mL), Hospira, Lake Forest, Ill.
d. Servo 300, Siemens-Elema AB, Solna, Sweden.

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