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Seizure activity occurring in two dogs after S-ketamine-induction

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Summary

Two healthy dogs were anaesthetized to undergo elective orthopaedic procedures. After premedication with methadone and acepromazine, general anaesthesia was induced with midazolam and S-ketamine. Immediately after anaesthetic induction, seizures occurred in both dogs. In the first dog the syndrome was characterized by tonic and clonic motor activity, muscular hypertone, hypersalivation, urination, defecation and hyperthermia. In the second dog muscular twitches of the temporal and masseter regions were observed, followed by increased skeletal muscles tone, hypersalivation, spontaneous urination and increase in body temperature. Recoveries from anaesthesia were uneventful and no seizures were observed. Considering the temporal association between anaesthetic induction and occurrence of seizures, and the fact that other causative factors could not be identified, it is hypothesized that S-ketamine played a role in determining the convulsive phenomena observed in these patients. S-ketamine might carry the potential for inducing seizures in otherwise healthy dogs, despite the concomitant use of GABA-ergic drugs.

Keywords: adverse reaction, anaesthetic induction, dog, seizures, S-ketamine

Krampfanfall bei zwei Hunden nach Einleitung der Anästhesie mit S-Ketamin

Zwei gesunde Hunde wurden anästhesiert, um sich einer elektiven orthopädischen Prozedur zu unterziehen. Nach Prämedikation mit Methadon und Azepromazin wurde eine Vollnarkose mit Midazolam und S-Ketamin eingeleitet. Unmittelbar nach der Einleitung traten bei beiden Hunden Krämpfe auf. Die Symptome des ersten Hundes waren durch tonische und klonische motorische Aktivität, erhöhten Muskeltonus, Hypersalivation, Urinieren, Defäkation und Hyperthermie gekennzeichnet. Beim zweiten Hund wurden muskuläre Zuckungen im Bereich des M. temporalis und des M. masseter gefolgt von erhöhtem Skelettmuskeltonus, Hypersalivation, spontaner Harnabgang und erhöhte Körpertemperatur beobachtet. Das Aufwachen aus der Narkose verlief normal und bis zur Entlassung aus dem Hospital wurden keine Anfälle beobachtet. In Anbetracht des zeitlichen Zusammenhangs zwischen Einleitung der Anästhesie und Auftreten der Krampfanfälle und der Tatsache, dass keine anderen ursächlichen Faktoren identifiziert wurden, wird angenommen, dass bei der Auslösung der Krampfanfälle S-Ketamin eine Rolle spielte. S-Ketamin kann trotz gleichzeitiger Verabreichung von Benzodiazepinen bei gesunden Hunden zu Krampfanfällen führen.

Schlüsselwörter: Nebenwirkung, Narkose-Einleitung, Hund, Krampfanfall, S-Ketamin

Introduction

S-ketamine has been recently introduced into clinical anaesthesia in dogs as an alternative to its racemic parent compound. In human medicine, the advantages of S-ketamine over ketamine in the clinical setting are higher potency, decreased incidence of emergence reactions and faster clearance from the body (White et al., 1985; Adams et al.,1997; Lauretti et al., 2000). Whilst there is a large body of publication concerning the pharmacodynamics of racemic ketamine (Ubogu et al., 2003; Dhote et al., 2012), less literature investigating the effects of the S+ ketamine isomer is available to date (Modica et al., 1990; Proeschold et al., 2001). This report describes the occurrence of seizures after the ad-

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ministration of anaesthetic doses of S-ketamine in two dogs.

History and anaesthesia

A 5-year old, female neutered mixed breed dog weighting 31 kg (dog 1) and a 6-year old, intact female Do-Khyi dog weighing 36 kg (dog 2) were anaesthetized for TPLO plate removal and stifle joint radiographic exam, respectively. In both dogs, indications for surgery were intermittent lameness and suspicion of low grade plate infection. Except for the cranial cruciate ligament rupture, none of the dogs had history of other pathological conditions. In both dogs, pre-anaesthetic physical examination was unremarkable and haematology and biochemistry were within normal ranges.

Both dogs were enrolled in a clinical study (for which cantonal approval and signed informed owner consent were obtained) comparing the potency of racemic ketamine and S+ketamine as induction agents. The dogs were premedicated intramuscularly with methadone (Methadon, Streuli AG, Switzerland, 0.2 mg/kg) and acepromazine (Prequillan, Fatro, Italy; 0.02 mg/kg), and in both patients the quality of sedation was judged adequate. An intravenous catheter was placed in a peripheral vein and general anaesthesia was induced with intravenous (IV) midazolam (Dormicum, La Roche, Switzerland, 0.2 mg/kg) and S-ketamine (S-Ketamine, Graeub AG, Switzerland, 1.5 mg/kg). One minute following S-ketamine administration, tracheal intubation was attempted. Because the anaesthetic depth achieved with the induction dose did not allow for tracheal intubation, dog 1 and dog 2 received two and one top up doses of S-ketamine (0.75 mg/kg each top up), respectively.

In dog 1, the syndrome began with tonic and clonic motor activity, generalized increase in muscular tone and teeth grinding, followed within a few seconds by apnoea, hypersalivation, urination, defecation and increase in rectal body temperature to 41 °C (baseline temperature recorded before anaesthesia was 38.5 °C). Diazepam (Valium, La Roche, Switzerland, 0.5 mg/kg) was immediately given IV and, since no improvement was noticed, administration was repeated after 2 minutes to reach a total dose of 1 mg/kg. After the second dose of diazepam remission of the tonic clonic activity occurred, but tracheal intubation was still not possible due to increased jaw tone. For this reason, propofol (Propofol 1 %, Fresenius Kabi, Switzerland, 1 mg/kg) was administered IV. The endotracheal tube (ETT) was then connected to a circle breathing system and 100 % oxygen delivered to the patient. In order to decrease the body temperature, wet towels and ice pads were applied on the skin and cold fluids were administered IV. These measures were taken until the rectal temperature decreased to 39 °C; during this time, isoflurane (Isoflo, Abbot Laboratories, USA) was delivered to maintain the ETT in place, in order to provide oxygen supplementation and ventilation support if needed.

The dog was brought to the operating room as soon as its conditions were judged stable by the anaesthetist. Surgery lasted 30 minutes. During recovery phase, return to consciousness and tracheal extubation were smooth, although some muscular twitches and vocalization occurred. Rectal temperature was 37.6 °C. A neurological examination performed the day after surgery did not reveal any abnormality, and the owner reported that no signs of convulsive activity were observed within the following 6 months.

In dog 2, the syndrome was less severe and commenced during endotracheal intubation with muscular twitches of the temporal and masseter regions, followed by generalized increase in skeletal muscles tone, purposeless movements and tonic and clonic activity. Hypersalivation and spontaneous urination followed. Rectal temperature increased to 39 °C (basal temperature recorded prior to anaesthesia was 38.2 °C). The ETT was connected to a circle breathing system delivering isoflurane in 100 % oxygen; intravenous diazepam administration (0.5 mg/kg) resulted in prompt improvement of the symptoms. The same measures described for dog 1 were taken also in dog 2. Surgery lasted 21 minutes, and the recovery phase was smooth and uneventful. Rectal temperature at recovery was 37.8 °C. No signs of seizure activity were observed overnight, and one day after surgery the dog was discharged from the hospital. Within 9 weeks following anaesthesia, the owner did not observe any convulsive activity. During this period, the dog was anaesthetized other 3 times, twice with IV ketamine (2 mg/kg) and propofol to effect, and once with propofol only, each time after premedication with acepromazine (0.02 mg/kg) and methadone (0.2 mg/kg). On all occasions the anaesthetist reported a smooth and uneventful induction and recovery.

Discussion

This report describes the occurrence of seizures after S-ketamine administration in two dogs.

The neurological symptoms observed in these two dogs could have been provoked by other causes, namely electrolytes imbalances, idiopathic epilepsy and several types of brain lesions, either of inflammatory, traumatic or neoplastic nature (Platt et al., 2002). Serum electrolytes were within normal ranges in both cases. Concerning the above mentioned types of brain lesions, these cannot be completely ruled out. However, on the basis of the history of both dogs, the presence of pre-existing brain diseases seems to be unlikely. Other pathological conditions commonly implicated in the pathogenesis of convulsive phenomena, such as poisoning and kidney or liver failure (Platt et al., 2002), could be excluded on the basis of anamnesis as well as clinical and laboratory findings.

Both dogs were premedicated with acepromazine, a compound whose clinical use has been traditionally implicated in the occurrence of seizures. However, more recent literature indicates that this assumption lacks of scientific evidence. The potential for convulsive phenomena, historically attributed to phenothiazines but demonstrated only for chlorpromazine, should not be extended to other compounds belonging to this class of sedatives (Tobias et al., 2006; Drynan et al., 2012). Indeed, a retrospective study (Tobias et al., 2006) showed a lack of association between acepromazine administration and the occurrence of seizures in dogs with a history of epilepsy. Although the contribution of the above mentioned factors cannot be completely ruled out, considering the temporal association between anaesthetic induction and occurrence of seizures, and since more probable causes could not be identified, the authors hypothesize that S-ketamine played a central role in determining the convulsive phenomena observed in both dogs.

In the two cases presented here, the S+ isomer could have provoked seizures acting through mechanisms similar to those described for the racemic compound. One experimental study (Deleforge et al., 1991) reported the occurrence of seizures after both ketamine and S-ketamine administration in non-premedicated beagles. However, to the best of the authors' knowledge, S-ketamine-induced convulsive phenomena have never been described in dogs in which benzodiazepines had been administered prior to anaesthesia induction. There is experimental evidence that racemic ketamine can induce cortical and subcortical stimulation and cortical cells spiking, as well as electrical seizure activity in the limbic and thalamic regions (Ferrer-Allado et al., 1973; Bowyer et al., 1983). Historically, these findings suggested cautions in the clinical use of this anaesthetic agent in patients with corticoreticular epilepsy (Black et al., 1980). Moreover, several studies suggest that subanaesthetic doses of ketamine and other NMDA receptor antagonists may increase the release of endogenous excitatory aminoacids glutamate and aspartate (Bustos et al., 1992; Liu et al., 1995), making the interaction of cyclohexamines and NMDA receptors much more complex than a pure reduction of glutamatergic activity. As a result, administration of ketamine may enhance, rather than inhibit, glutamatergic transmission at AMPA and kainite non-NMDA receptors, leading to cortical hyperexcitability and increased repetitive pyramidal cell discharge (Di Lazzaro et al., 2003). It is worth to notice that, despite diazepam was found effective in treating the convulsions, the administration of midazolam prior to ketamine did not prevent the phenomena. Diazepam and midazolam have been found comparable in terms of effectiveness against seizures (McMullan et al., 2010), which seems to indicate that the dose, rather than the drug used or the timing of administration, played a central role in determining the different outcome in both cases.

In conclusion, the enantiomer S-ketamine, similarly to the racemic compound, might carry the potential for inducing seizures in otherwise healthy canine patients despite the concomitant use of GABA-ergic compounds. Further investigations are needed to demonstrate S-ketamine's pro-convulsivant activity, and to determine the incidence of such drug-related complication.

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