

Cardiac arrhythmia during anaesthesia of a cat on long-term treatment with selegiline

#1405 words

Introduction

A cat anesthetized for the surgical treatment of a diaphragmatic hernia exhibited sudden cardiac arrhythmia detected by auscultation. During the surgery, the cat received acepromazine, thiopental, isoflurane and morphine, and an interaction between these drugs and selegiline that the cat received as a long-term treatment for a behavioural problem was suspected to be the cause of the arrhythmia.

Problem list

- Ability of selegiline to induce cardiac arrhythmia
- Pharmacodynamic/pharmacokinetic interactions between selegiline and anaesthetic and analgesic drugs
- Other potential causes of cardiac arrhythmia

Ability of selegiline to induce cardiac arrhythmia

Selegiline is a monoamine oxidase (MAO) inhibitor approved for use in veterinary medicine in elderly dogs for the treatment of cognitive dysfunction. The use in cats for the same indication is an extra-label use which implies that there is little information available on the pharmacokinetic and pharmacodynamic properties and toxicity of selegiline for this species.

The mode of action of selegiline is to selectively inhibit type B MAO. MAO A and B are intracellular enzymes responsible for the oxidative deamination of endogenous and xenobiotic amines. MAO A preferentially deaminates norepinephrine, serotonin, and dopamine. MAO B deaminates dopamine but not serotonin or norepinephrine.

Selegiline, an irreversible selective MAO B inhibitor, inhibits dopamine degradation and so extends the effects of dopamine in the organism. The principal activity of dopamine is mediated by binding to different families of dopamine receptors. However, at high doses, dopamine also binds to alpha- and beta-adrenergic receptors and releases neuronal stores of endogenous norepinephrine and has sympathomimetic activity (Papich, 2009). Thus, at low doses of selegiline, the effects of dopamine on its receptors predominate, but at higher doses, selegiline also exhibits sympathomimetic activity in humans and in cats (Finberg & Youdim, 1985). Dopamine excess can lead to tachycardia and vasoconstriction and selegiline, which decreases dopamine breakdown, can lead to the same consequences.

Cardiac arrhythmia has been reported to occur more often in human patients with Parkinson's disease receiving selegiline compared with those receiving placebo (Yamada & Yasuhara, 2004). In rabbits, selegiline has been shown to be cardiotoxic, altering the QT interval (Uzun, Alp et al., 2009). Severe arrhythmias requiring cessation of selegiline treatment have not been described in human patients.

These two studies suggest that selegiline alone could induce cardiac arrhythmia in the cat. However, there is not a large body of evidence suggesting that selegiline is cardiotoxic and, although the metabolism of selegiline has not been studied in detail in cats, it would seem unlikely that selegiline alone was the cause of the arrhythmia in this case.

Pharmacodynamic interaction of selegiline with anaesthetic and analgesic drugs

Toxic effects of selegiline alone appears to be rare or mild but some authors suspected some toxic interactions of selegiline when administered with anaesthetic drugs (el-Ganzouri, Ivankovich et al., 1985; Dodam, Cohn et al., 2004).

It has been reported that human patients treated with MAO inhibitors may be difficult to manage under anaesthesia and that hemodynamic instability (hypertension or hypotension) may be a problem (Insler, Kraenzler et al., 1994). Before 1980, it was recommended that MAO inhibitors be withdrawn two weeks before surgery to avoid potential adverse effects under anaesthesia (Rogers & Thornton, 1969; el-Ganzouri, Ivankovich et al., 1985). The hypothesis for instability under anaesthesia for patients treated with MAO inhibitors was that the decrease in the presynaptic metabolism of catecholamines and serotonin increases the intraneuronal storage of catecholamines and serotonin, which could be massively released when another drug that stimulates its release is administered, such as meperidine (pethidine), fentanyl or phenylephrine (Noorily, Hantler et al., 1997). One study reported an acute toxicity (decrease of LD50) of meperidine (an opioid) after administration of a MAO inhibitor (tranylcypromine) in mice (Rogers & Thornton, 1969) and this might suggest that there could be a similar a toxic interaction between the opioid morphine and the MAO inhibitor selegiline administered to this cat. However, meperidine and tranylcypromine have quite different modes of action from morphine and selegiline that need to be taken into account before concluding that an interaction between these agents led to the development of cardiac arrhythmia in this case. Indeed, meperidine, unlike morphine, is able to induce the release of serotonin and, tranylcypromine, unlike selegiline, is a non-selective inhibitor of MAO targeting both MAO A and MAO B. So, the combination of tranylcypromine and meperidine can lead to toxicity by inducing the release of serotonin that is not removed by metabolism due to the inhibition of MAO. Morphine would not induce release of catecholamines and selegiline is a selective inhibitor of MAO type B and would not increase the storage of serotonin, thus an interaction between selegiline and morphine would not likely induce toxic effects (Noorily, Hantler et al., 1997).

MAO inhibitors, in addition to increasing the intraneuronal storage of catecholamines and dopamine through the inhibition of MAO activity, have been suspected to interfere with the hepatic metabolism of anaesthetic drugs (Dodam, Cohn et al., 2004) thus potentially modifying the pharmacokinetics of these drugs. Potentiation and prolongation of the effects of meperidine, morphine, pentazocine, pentobarbital and thiopental have been reported occasionally in old studies in patients treated with selegiline (Rogers & Thornton, 1969; el-Ganzouri, Ivankovich et al., 1985). However, even if this cat was also treated with morphine and thiopental, the prolongation of the effects of these two drugs should not have led to cardiac arrhythmia but more probably to increased sedation and respiratory depression. So, the involvement of selegiline by pharmacodynamic and pharmacokinetic interactions

in the arrhythmia appears to be quite unlikely, supported further by the fact that most studies in humans and dogs have shown no interference of MAO inhibitors with anaesthetic and analgesic drugs (el-Ganzouri, Ivankovich et al., 1985; Dodam, Cohn et al., 2004). Despite this, the lack of data on the metabolism and excretion of selegiline in cats and particularly in anesthetized cats prevents selegiline toxicity from being excluded definitively in this case.

Other potential causes of cardiac arrhythmia

As the arrhythmia detected in this cat was not probably the consequence of selegiline treatment, the use of anaesthetic drugs or the surgery itself was suspected to be the cause of the arrhythmia. A study in a university hospital in 683 cats that had undergone different surgeries revealed that cardiac arrhythmias were observed in 2% of the cats and that cardiac arrest occurred in 0.4% of the cats (Gaynor, Dunlop et al., 1999).

The cat here underwent surgery for diaphragmatic hernia implying an invasive procedure with access to the cardiopulmonary area. This surgery quite often induces several complications including hypotensive episodes, multifocal ventricular premature contractions and loss of palpable pulses (Reimer, Kyles et al., 2004). These complications have often been associated with reduction of the herniated viscera and may have been the result of release of endotoxin or free-radicals from liver lobes that had undergone long-standing compromised perfusion. A study investigating the outcome of cats treated surgically for diaphragmatic hernia reported that one (3%) of the 37 cats developed multifocal ventricular premature contractions, that one (3%) of the 37 cats died of a cardiopulmonary arrest 4 days after the surgery and that hypotension and loss of palpable pulse were detected in 24% and 3% of the cats, respectively (Reimer, Kyles et al., 2004). In another study, three (9%) cats out of 34 died of a sudden cardiac arrest within 48 hours after the surgery for the traumatic diaphragmatic hernia (Schmiedt, Tobias et al., 2003). Due to the quite frequent cardiovascular adverse effects of such a surgery, some authors recommended that cats undergoing surgical repair of peritoneopericardial diaphragmatic hernia should be monitored carefully during anaesthesia, particularly during reduction of abdominal viscera, to allow for rapid treatment of complications (Reimer, Kyles et al., 2004). By taking into account all these considerations highlighting the high potential of the surgery to induce itself cardiac arrhythmia, it could be suspected that the arrhythmia observed in this cat was a direct consequence of the reduction of hernia.

Conclusion

There is very little information about selegiline pharmacodynamic and pharmacokinetic properties in the cat. No studies on the selectivity of selegiline for MAO subtypes or metabolism of selegiline have been carried out in this species so it is impossible to exclude selegiline toxicity during anaesthesia in this species definitively. However, the high frequency of cardiac arrhythmia during surgery for diaphragmatic hernia in cats non receiving selegiline indicates that the arrhythmia observed in this cat was more probably a consequence of the pathology and the surgery than the selegiline treatment.

References

- Dodam, J.R., Cohn, L.A., Durham, H.E. & Szladovits, B. (2004). Cardiopulmonary effects of medetomidine, oxymorphone, or butorphanol in selegiline-treated dogs. *Vet Anaesth Analg*, **31**(2), 129-137.
- el-Ganzouri, A.R., Ivankovich, A.D., Braverman, B. & McCarthy, R. (1985). Monoamine oxidase inhibitors: should they be discontinued preoperatively? *Anesth Analg*, **64**(6), 592-596.
- Finberg, J.P. & Youdim, M.B. (1985). Modification of blood pressure and nictitating membrane response to sympathetic amines by selective monoamine oxidase inhibitors, types A and B, in the cat. *Br J Pharmacol*, **85**(2), 541-546.
- Gaynor, J.S., Dunlop, C.I., Wagner, A.E., Wertz, E.M. & Golden, A.E. (1999). Complications and mortality associated with anesthesia in dogs and cats. *Journal of the American Animal Hospital Association*, **35**(1), 13-17.
- Insler, S.R., Kraenzler, E.J., Licina, M.G., Savage, R.M. & Starr, N.J. (1994). Cardiac surgery in a patient taking monoamine oxidase inhibitors: an adverse fentanyl reaction. *Anesth Analg*, **78**(3), 593-597.
- Noorily, S.H., Hantler, C.B. & Sako, E.Y. (1997). Monoamine oxidase inhibitors and cardiac anesthesia revisited. *South Med J*, **90**(8), 836-838.
- Papich, B.L.S.a.M.G. (2009). *Drugs affecting animal behavior*. In *Drugs affecting animal behavior* Ed Papich, J.E.R.a.M.G. pp. 509-538. Wiley-Blackwell.
- Reimer, S.B., Kyles, A.E., Filipowicz, D.E. & Gregory, C.R. (2004). Long-term outcome of cats treated conservatively or surgically for peritoneopericardial diaphragmatic hernia: 66 cases (1987-2002). *J Am Vet Med Assoc*, **224**(5), 728-732.
- Rogers, K.J. & Thornton, J.A. (1969). The interaction between monoamine oxidase inhibitors and narcotic analgesics in mice. *Br J Pharmacol*, **36**(3), 470-480.
- Schmiedt, C.W., Tobias, K.M. & Stevenson, M.A. (2003). Traumatic diaphragmatic hernia in cats: 34 cases (1991-2001). *J Am Vet Med Assoc*, **222**(9), 1237-1240.
- Uzun, M., Alp, R., Uzlu, E., Alp, S., Cital, M., Topcu, B. & Erdogan, H.M. (2009). Investigation of oral selegiline and rasagiline administration on QT interval in conscious rabbits. *Eur Rev Med Pharmacol Sci*, **13**(2), 95-98.
- Yamada, M. & Yasuhara, H. (2004). Clinical pharmacology of MAO inhibitors: safety and future. *Neurotoxicology*, **25**(1-2), 215-221.