CLINICAL REPORT

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Treatment of zolpidem poisoning with flumazenil in a cat

Tratamento da intoxicação por zolpidem com flumazenil em um gato

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ABSTRACT: This report aims to describe the case of a cat intoxicated with zolpidem that was treated with flumazenil. Flumazenil is an imidazodiazepine that effectively reverses the central effects of benzodiazepines. In humans, it is used to treat zolpidem poisoning. Zolpidem is a sedative hypnotic agent, non-benzodiazepine, that is used to treat patients with insomnia. A 2-year-old Bengal cat weighing 2.5 kg showed signs of ataxia, incoordination and diarrhea after accidental ingestion of 10 mg zolpidem (Stilnox®). The cat was administered with 0.1 mg/kg of flumazenil intravenously, and after 20 minutes all clinical signs disappeared. To our knowledge, this is the first report of the use of flumazenil for the treatment of zolpidem poisoning in cats. Discussion regarding the treatment of zolpidem poisoning is necessary owing to the increased prescription of this drug in humans and, consequently, to a greater possibility of accidental poisoning in domestic animals.

KEYWORDS: Benzodiazepine antagonist; feline; intoxication; pharmacology; stilnox.

RESUMO: Este relato tem como objetivo descrever o caso de um gato intoxicado por zolpidem que foi tratado com flumazenil. O flumazenil é uma imidazodiazepina eficaz na reversão dos efeitos centrais dos benzodiazepínicos. Em humanos, é usado para tratar a intoxicação por zolpidem. Zolpidem é um agente hipnótico sedativo, não benzodiazepínico, utilizado para pacientes com insônia. Um gato Bengal de 2 anos, pesando 2.5 kg, apresentou sinais de ataxia, incoordenação e diarreia após ingerir 10 mg de zolpidem (Stilnox®) de forma acidental. O gato recebeu 0.1 mg/kg de flumazenil por via intravenosa, e após 20 minutos todos os sinais clínicos desapareceram. Esta é a primeira publicação relatando o uso de flumazenil no tratamento de intoxicação por zolpidem em gatos. A discussão sobre o tratamento da intoxicação por zolpidem se faz necessária devido ao aumento da prescrição desse medicamento em humanos e, consequentemente, à maior possibilidade de intoxicação acidental de animais domésticos.

PALAVRAS-CHAVE: Antagonista benzodiazepínico; felino; farmacologia; stilnox.

INTRODUCTION

Zolpidem is a sedative hypnotic agent derived from imidazopyridine, non-benzodiazepine (PATAT et al., 1994), and is used to induce sleep in humans with insomnia (LHEUREUX et al., 1990). Zolpidem poisoning has been reported in dogs (RICHARDSON et al., 2002; LANCASTER et al., 2011) and cats (CZOPOWICZ et al., 2010). Cats intoxicated with zolpidem may experience stupor, vomiting and hypersalivation (CZOPOWICZ et al., 2010).

Flumazenil is a benzodiazepine antagonist with weak agonist and inverse agonist activity (HAEFELY, 1988), classified as imidazodiazepine (PATAT et al., 1994). This drug binds competitively, reversibly and specifically to the same central nervous system sites as benzodiazepines (HAEFELY, 1988). The doses of flumazenil in cats vary from 0.05 to 0.1 mg/kg (ILKIW, 1992; EBNER et al., 2007; NAOTAMI; YOSHIAKI, 2015) and have little intrinsic pharmacological activity (ILKIW, 1992). It is used to reverse the sedative, anxiolytic, muscle relaxant and amnesic properties of benzodiazepines (ILKIW, 1992), and to shorten the recovery of anesthetized cats in protocols that use midazolam (ILKIW, 1992; EBNER et al., 2007).

In humans, flumazenil is used to treat zolpidem poisoning (PATAT et al., 1994; THORNTON et al., 2013). To date, there have been no reports on the use of flumazenil in the treatment of zolpidem poisoning in cats. This report aims to describe the case of a cat intoxicated with zolpidem that was treated with flumazenil.

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CASE REPORT

A two-year-old, entire female Bengal cat weighing 2.5 kg was presented to a private veterinary clinic in Rio de Janeiro with signs of ataxia, incoordination, diarrhea and normal physiological parameters. The cat had a history of chronic inflammatory bowel disease and was administered prednisone (5 mg PO twice a day) and mesalazine (10 mg/kg PO daily). The owner reported that 10 mg of zolpidem (Stilnox®, Sanofi-Aventis; 10-mg tablet) was administered instead of prednisone, and after 15 minutes, clinical signs were observed. Based on the patient's history and clinical signs, zolpidem poisoning was diagnosed.

Physical examination was performed at the veterinary clinic, and a 22-gauge catheter was aseptically placed in the cat's cephalic vein. Subsequently, 0.1 mg/kg of flumazenil (Flumazenil®, União Química) was administered intravenously (IV), 170 minutes after administration of zolpidem. Clinical signs disappeared 20 minutes after flumazenil administration.

DISCUSSION

The discussion on the treatment methods for zolpidem poisoning is valid because this medicine is increasingly prescribed in humans, increasing the chance of accidental poisoning in companion animals (CORTINOVIS et al., 2015). The main limitation of this study was the small number of animals included in this case report. To the best of our knowledge, this is the first study to report the use of flumazenil for the treatment of zolpidem poisoning in cats. Although zolpidem has no structural similarity to benzodiazepines, it binds to the omega-1 receptor, which is a subtype of the benzodiazepine receptor (LLOYD; ZIVKOVIC, 1988; THORNTON et al., 2013). Flumazenil can reverse the effects of zolpidem because it antagonizes the site of the omega-1 receptor (DARRAGH et al., 1981, THORNTON et al., 2013).

In dogs, the toxic dose of zolpidem ranges from 0.24 to 21 mg/kg (RICHARDSON et al., 2002). In cats, a dose of 1.25 mg/kg of zolpidem results in intoxication (CZOPOWICZ et al., 2010). In this report, the dose administered to the cat was 4 mg/kg.

Zolpidem is rapidly absorbed by the gastrointestinal tract in rats (GARRIGOU-GADENNE et al., 1989) and humans (PATAT et al., 1994). In the present study, the appearance of signs of intoxication 15 minutes after zolpidem administration indicates that absorption is also fast in cats. In cats, a zolpidem dose of 1.25 mg/kg resulted in clinical signs of intoxication 30 minutes after administration (CZOPOWICZ et al., 2010). Thus, we believe that the higher the dose administered, the faster the toxic effects are observed.

Stupor, vomiting and hypersalivation have been observed in cats intoxicated with zolpidem (CZOPOWICZ et al., 2010); however, in this report, these symptoms did not occur. Symptomatic treatment of zolpidem poisoning in cats can result in prolonged recovery, with the complete disappearance of clinical signs within 36 hours (CZOPOWICZ et al., 2010). In this report, 20 minutes after flumazenil administration, the cat showed no signs of intoxication.

CONCLUSION

This case report indicates that an intravenous dose of 0.1 mg/kg of flumazenil can be used to treat cats poisoned by zolpidem.

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