Clotiapine Toxicosis in a Puppy

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ABSTRACT

A 3.5-month-old, 1.5 kg Shih-Tzu puppy ingested 120mg of clotiapine – a neuroleptic drug used for treatment of schizophrenia in human medicine. Upon presentation the dog was mentally depressed, flaccid, with miotic pupils and a supraventricular tachycardia. It was treated with gastric lavage and supportive care. The dog recovered uneventfully and was discharged within 48 hours. This is the first veterinary report describing the clinical manifestation of clotiapine intoxication in a dog.

Keywords: Clothiapine; Etumine; Dibenzothiazepine; Intoxication.

INTRODUCTION

Clotiapine is a dibenzothiazepine drug used in human medicine as a neuroleptic as well as for the treatment of schizophrenia (1). Clotiapine acts mainly on receptors in the serotonergic and dopaminergic neurotransmitter systems, though it interacts with many other receptors in the central nervous system (2). In an experimental study performed on tissues of rats and guinea pigs, clotiapine was shown to act as a noncompetitive antagonist of norepinephrine, dopamine and histamine, and as a competitive antagonist of serotonin (2).

Clotiapine is not approved for pediatric use and its use has not yet been reported in veterinary medicine.

In humans, adverse effects are considered uncommon (1, 3-4). Reported adverse reactions include transient anticholinergic effects (e.g. dry mouth, blurred vision and constipation), dopaminergic and CNS-related effects (e.g. sedation, confusion, abnormal movement), and orthostatic hypotension. Life threatening arrhythmias, increased risk for stroke and seizures, reversible leukopenia and agranulocytosis as well as neuroleptic malignant syndrome have been rarely reported (3, 4).

To the best of the authors' knowledge, there is no available data regarding the use of clotiapine in veterinary medicine, nor are there reports describing the clinical manifestation of its wrongful ingestion. This is the first report to describe a case of acute clotiapine intoxication in a dog.

CASE SUMMARY

A 3.5-months-old, 1.9 kg intact female Shih-Tzu puppy was presented to an emergency center with severe mental depression. The owners reported that the dog ingested 3 tablets of Etumine™, (Clotiapine 40mg tablets, Juvise Pharmaceuticals, Famar L'Aigle, France), a total amount of 120mg of clotiapine, 1.5 hours prior to presentation.

Upon initial physical examination the puppy was mentally dull, tachycardic with an irregular heart rate ranging from 160-240 BPM, accompanied by pulse deficits. The dog was mildly hypothermic (36.9°C), with normal respiratory rate (24), and pink mucus membranes. Neurological examination revealed obtunded mentation, ventral strabismus, miosis, and muscle flaccidity. No additional abnormalities were noted. Electrocardiogram (ECG) monitor showed a supraventricular tachycardia of 160 BPM with short, self-limiting bursts reaching 220 to 240 beats per minute (Figure 1) (Philips CMS Patient Monitoring System V24/26, model M1204A,

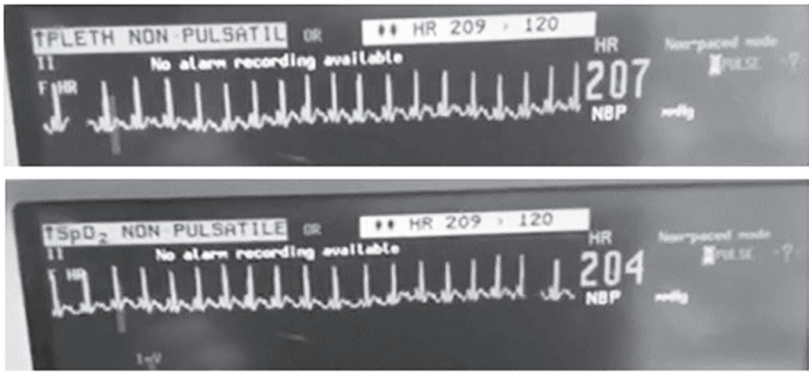

Figure 1. Recording of a ECG monitor screenshots in a 3.5-months-old, intact female Shih-Tzu puppy with clotiapine toxicosis. A tachyarrhythmia of heart rate over 200 BPM is evident on arrival

Philips Medical Systems, Andover, USA), which resolved spontaneously about 6 to 8 hours post presentation. Blood pressure was noted to be normal upon arrival but the numerical value was not recorded (petMAP+II, Ramsey Medical, Inc., USA).

Comprehensive blood analysis was advised but not preformed due to owner's financial constraints. The dog had a complete blood count (CBC) done a week earlier which was within normal reference interval (RI). Partial blood work upon admission showed mildly decreased packed cell volume (34%, RI 37-55%) which was estimated normal for her age, with normal total plasma proteins (5.3 g/dL, RI: 5-8). Blood glucose (100 mg/dL, RI: 65-112 ,Accu-chek®, model nc, Roche Diagnostics GmbH, USA), and electrolytes (IDEXX VetLab, Catalyst DX, IDEXX Laboratories, Inc., Westbrook, Maine USA) were within normal reference range.

The puppy was treated with an intravenous crystalloid bolus 21 ml/kg (Lactated ringer's solution, Teva Medical, Ashdod, Israel) followed by 5ml/kg/hr IV constant rate infusion (CRI). As no data was available about clotiapine absorption time, and in an attempt to clear unabsorbed tablets particles, gastric lavage was performed under a very short general anesthesia (propofol 1% 1 mg/kg IV, Propofol Injectable Emulsion 1%, Fresenius Kabi, Austria and diazepam 0.5 mg/kg IV, Assival®, Teva pharmaceutical industries Ltd., Petah-Tikva, Israel). A small amount of grayish substance was recovered from the stomach. The puppy was hospitalized for further monitoring and supportive care. During its hospitalization the puppy was treated with CRI of Lactated Ringer's solution with added dextrose (2.5%, Glucose Monico 50%, Monico Spa, Venice/Mestre, Italy), metoclopramide (1 mg/kg/day IV CRI, Pramin, Salf S.p.A, Cenate Sotto, Italy), and maropitant (1mg/kg IV q24hr, Cerenia®, Fareva Amboise, France).

Following initial treatment the puppy appeared hemodynamically stable. Mentally it was still markedly depressed but vital signs were consistently within normal range and blood pressure was normal. Six hours post presentation (approximately 8 to 9 hours from exposure) the puppy began eating. Activated charcoal (Toxicarb®, SERB specialty pharmaceuticals, Paris, France) was administrated with the food. The puppy's mental status improved gradually during hospitalization and 48 hours from admission, the puppy behaved normally and was discharged.

Discussion

This is the first reported case of clotiapine intoxication in a dog. In the human literature, information regarding acute overdose of clotiapine is scarce. A single case report describes the intoxication of a toddler that was rushed to the emergency service after falling asleep without being able to be awakened, two hours following the ingestion of 200 mg of clotiapine (5). Upon initial presentation the child was stuporous, responded only to painful stimuli, hypertensive with pinpoint pupils. ECG demonstrated normal sinus rhythm. Partial blood work showed no abnormalities. The child was admitted for observation and supportive care. The hypertension spontaneously resolved within 4 hours and complete recovery was achieved 36 hours post admission. Serial blood sampling for clotiapine concentrations revealed the elimination half-life (T½) to be 9.2 hours – within the range previously reported by the manufacturer, Novartis (7.1±3.8 hours (6)). It is known that in humans, 25% of the drug is eliminated unchanged in the urine, and 10% as conjugated metabolites with no available antidote (5).

A pharmacokinetics study done on mice by Michaelis *et al.* in 1969 (7) shows that 2 hours after clotiapine ingestion over 30% of the administered dose was still present in the stomach. Peak concentrations in target organs was reached 8 hours from ingestion (at which time only 1.8% of administered dose was still present in the stomach). Though the absorption of clotiapine in dogs and mice might be different, this data suggests that gastric lavage may be beneficial

if performed early after ingestion. As the puppy reported herein was presented to the emergency service 1.5 hours post ingestion, gastric lavage was indicated and was potentially beneficial. Emesis might be contraindicated since the rapid absorption could result in changes in consciousness and high risk of aspiration. The dilemma, whether administration of activated-charcoal and cathartic medications for prevention of entero-hepatic reabsorption is indicated, remains unanswered.

In 2002 Fransson *et al.*(8) reported intoxication in a dog following the ingestion of clozapine, a dibenzothiazepine drug also used as an antipsychotic in human medicine. Despite the chemical similarities between clozapine and clotiapine, the clinical manifestation reported in this case is slightly different than the one described herein. In both cases, the dogs exhibited mental depression and tachycardia; however, in the clozapine case the dog also showed hyperexcitation in response to auditory and tactile stimulus, tremors, hyperthermia and tachypnea. Fransson *et al*. (8). also reported blood work abnormalities 10 hours post presentation which included stress leukogram, metabolic acidosis, increased liver enzymes, lipemia, and electrolyte disturbances. The authors mentioned the association of clozapine intoxication with metabolic acidosis and elevated liver enzymes found in humans. The reason for hyperlipidemia and electrolyte disturbances remains unexplained. Clinical signs in the case reported by Fransson *et al*. (8) resolved 24 hours post admission. Most blood abnormalities resolved within days of discharge, except for mild thrombocytopenia of unknown origin at 7 and 40 days post admission and elevated alanine phosphatase which persisted and was not further evaluated. Unfortunately, in the case reported herein, complete blood work was not performed due to owner's financial constraints and clotiapine's blood concentration was not measured. Nevertheless, the clinical description and disease course of what seems like a potentially massive overdose may be of future help in the management of similar cases.

While the toxidrome of different drugs from the dibenzothiazepine family may cause different clinical signs, CNS depression seems to be a significant feature and was reported in all of the above cases. Tachyarrythmia was reported in clozapine intoxication in a dog (8), but not in the clotiapine intoxication of a toddler (5). Like clotiapine, clozapine affects many receptors in the central and peripheral nervous system, including cholinergic and adrenergic receptors. Clozapine can cause cardiac muscarinic receptor blockade, inhibition of noradrenaline reuptake in post-ganglionic terminals and increased noradrenaline vesicle fusion (9-11). Cardiac signs are common adverse effect of clozapine – mild tachycardia (9-11) was reported most commonly, though a case of supraventricular tachycardia had also been reported (12). Rarely, clozapine might cause conduction abnormalities and myocarditis (9-11). Although the initial tachycardia (160 BPM) described in the case reported herein might be attributed to the dog's signalment as a toy breed puppy, bursts of 220-240 BPM in a stuporous puppy lacking other hemodynamic instability signs, represent a pathological tachyarrhythmia, and supports that tachyarrhythmias are part of the clinical manifestation of dibenzothiazepines toxicity in dogs.

The recommended daily dose of clotiapine for human adults is 120 to 200 mg total [about 2.2mg/kg for an average adult American male, (13)]. The toddler reported by Lurie *et al.*(5) ingested roughly 18 mg/kg [based on 'boys weight for age' 50th percentile for the age of 18 month according to standard WHO growth charts (14)], and was free of clinical signs 36 hours post ingestion. The puppy reported herein ingested a total of 63 mg/kg and was clear of clinical signs within 48 hours of ingestion. Both reports support that clotiapine's life threatening side effects are indeed uncommon, even in severe overdoses, and that the drug's safety margin appears to be wide. However, further studies on clotiapine's toxicokinetics and toxicodynamics are required.

In conclusion, the information regarding clotiapine toxicity is scarce. In light of the existing data and the case presented here, dogs exposed to the drug should have their vital and neurological statues assessed upon admission. Blood pressure and ECG monitoring is recommended. The clinical signs in all the described cases resolved with supportive care within a similar time frame of 24-48 hours. Asymptomatic dogs should be observed for at least 9 hours (1 elimination half-time) while dogs showing clinical signs should be admitted for further monitoring and supportive care until clinical signs resolve, expectedly within 48 hours. Comprehensive blood work is advisable as part of the general assessment and due to unknown possible complications. Prognosis seems to be excellent with detoxification and supportive care.

The authors declare no conflict of interests.

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