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Case Report

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A case of dog with fatal seizure caused by tranexamic acid administration to induce emesis

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ABSTRACT

The use of tranexamic acid (TXA, 20-50 mg/kg, IV) in inducing emesis has been widely used in veterinary medicine in recent years, and the safety of higher than usual dose has also been evaluated. In this case, emesis was induced using TXA in a dog (12-year-old neutered female papillon) had accidentally ingested onions. As a result after28 administration, the dog indicated tonic-clonic seizure and eventually result in death of cardiorespiratory arrest. Adverse effects at higher than usual dose, included a tonic-clonic seizure and hemostatic disorder in two different dogs, have been reported, and both of which recovered after receiving medical treatment. To my knowledge, this is the first fatal case with seizure despite medical treatment.

Keyword: accidentally ingestion, dog, emesis, seizure, tranexamic acid

Introduction

Accidental ingestions of toxic substances often occur in dogs, and in some cases they require urgent treatment such as emetic, endoscopy or surgery. If dogs accidentally ingest substances that cause poisoning, including chocolate, tobacco, raisins, onions, xylitol, pharmaceuticals, they are often removed from the gastrointestine by inducing emesis. In veterinary medicine, the most common method used to induce emesis is intravenous injection and ocular conjunctival administration of apomorphine, which stimulates CTZ centrally, and oral administration of 3% hydrogen peroxide, which stimulates the gastrointestinal sensory nerve peripherally [1, 2, 3]. Recently, in addition to these methods, intravenous injection of high doses TXA (20-50 mg/kg) have become commonplace especially in Japan [4, 5]. TXA is a lysine amino acid derivative synthesized in the 1960s.

It exerts antifibrinolytic effect by binding the lysine-binding sites on plasminogen molecules and inhibiting fibrin degradation.TXA is widely used to control bleeding in veterinary and human medicine [6, 7, 8]. Side effects include nausea, flushing, and headache, and intravenous injection of high doses of TXA may induce emesis in human [9, 10]. In veterinary medicine, the safety of multiple high doses than usual to induce emesis were revealed [4, 5]. Among them, adverse effects included a tonic-clonic seizure and hemostatic disorder in two different dogs have been reported, and both of which recovered after receiving medical treatment. And there have been no reports of deaths from seizure caused by TXA administration in veterinary medicine.

Case

A 12-year-old neutered female papillon, weighing 5 kg, accidentally ingested onions and visited our hospital. The dog was normothermic (38.5°C), with a normal heart rate (144 bpm) and a normal respiratory rate (32 /min), and had no underlying disease. After consulting with the owner, we decided to administer TXA to induce emesis. TXA (40 mg/kg, IV) administered via the cephalic vein to induce emesis, but emesis did not occur.

30 min later, the same dose of TXA was administered again

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Table 1

Parameter	The dog	Reference interval
WBC [$10^2/\mu l$]	103	60-170
RBC [$10^4/\mu l$]	736	550-850
HGB [g/dl]	16.4	12-15
HCT [%]	49.1	37-55
MCV [fl]	66.7	60-77
MCH [pg]	22.3	19.5-24.5
MCHC [g/dl]	33.4	32-36
PLT [$10^4/\mu l$]	42.8	20-50
TP [g/dl]	5	5.0-7.2
ALB [g/dl]	3	2.6-4.0
GLU [mg/dl]	243	75-128
ALT [U/l]	117	17-78
AST [U/l]	220	17-44
ALP [U/l]	345	47-254
BUN [mg/dl]	37.4	9.2-29.2
CRE [mg/dl]	1.5	0.4-1.4
NH_3 [mg/dl]	127	16-75
TCHO [mg/dl]	264	111-312
CPK [U/l]	>2000	49-166
Ca [mg/dl]	9.4	9.3-12.1
Ma [mEq/l]	152	141-152
Cl [mEq/l]	107	102-117
K [mEq/l]	4.8	3.8-5.0
CRP [mg/dl]	0.7	0-0.7

and emesis immediately. 5min after emesis, the following abnormalities appeared: tonic-clonic seizure, hyperthermia (rectal temperature, 43°C), shallow breathing. The dog was treated with oxygenation, cooling and administration of diazepam (1 mg/kg, IV), hydrocortisone (2 mg/kg, IV), diphenhydramine (1 mg/kg, IV), famotidine (1 mg/kg, IV) and lactated Ringer's solution (10 ml/kg/hr, 10min, IV). Complete blood count and Biochemical profile revealed the following abnormalities at the time of treatment for seizure (table 1).

Since disappearance of seizures could not be confirmed, diazepam (1 mg/kg, IV) was administered again. However, because no improvement in seizures was observed, midazolam (0.3 mg/kg, IV) was administered. Then the seizures disappeared and rectal temperature settled down, but after 3 hr, a decrease in heart and respiratory rate was observed. Immediately, tracheal intubation and administration of atropine (0.04 mg/kg, IV) and adrenalin (0.1 mg/kg, IV) were performed, but there was no response to the treatment and eventually the dog result in death of cardiorespiratory arrest.

Discussion

The seizure-inducing properties of TXA may be due to a direct effect on the central nervous system (CNS). γ-Aminobutyric acid (GABA) receptors and glycine receptors are major mediators of inhibition excitatory synaptic transmission in the CNS. It is suggested that TXA may induce hyperexcitability by blocking GABA-driven inhibition and of the CNS [11]. Although diazepam and midazolam administration appropriate for this mechanism, it is highly possible that cause of death is damage to CNS due to prolonged seizure in this case. It is also unclear why diazepam was ineffective while midazolam was effective. There are reports that diazepam is less effective than midazolam in human medicine, so midazolam should be the first choice in these situations [12, 13]. It is also suggested that TXA may mediate hyperexcitability induction by derepression of persistent glycine currents. Therefore, anesthetics that increase glycine receptor function, such as isoflurane and propofol, may be effective in treating or preventing TXA-induced seizures [14]. Another possibility is an anaphylactic reaction, but this diagnosis is difficult because neither histamine nor tryptase concentration was measured. In rare cases, TXA can cause anaphylaxis, and previously two reports have been reported in human medicine [15, 16]. Anaphylaxis to drug administration is a type 1 IgE-mediated acute response that occurs within min of drug administration. This response results from the binding of the IgE antibody to Fc receptors on the surface of tissue mast cells and circulating basophils previously exposed to foreign antigens. In this case, there was administration history of TXA at normal dose about 1 year ago, but causal relationship is unknown because non immunological mechanisms also exist in anaphylactic reaction to drug administration. Particularly in Japan, TXA is commonly used to induce emesis in a primary care hospital, and its safety has also been evaluated. This report describes the rare but important adverse effect of administration of TXA to induce emesis, and we should be more careful with doses and repetition.

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