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ABSTRACT

Limited data are available regarding the use of the antifibrinolytic drugs tranexamic acid (TXA) and epsilon aminocaproic acid (EACA) in cats. This study aimed to evaluate the indications for the use of TXA and EACA in cats and to describe dosing regimens used, occurrence of adverse events, and patient outcomes. This was a retrospective multicenter study. Medical databases were searched for feline patients billed for TXA or EACA between 2015 and 2021. Thirty-five cats met the inclusion criteria; 86% received TXA and 14% received EACA. The most common indication was nontraumatic hemorrhage (54%), followed by traumatic hemorrhage (17%) and elective surgery (11%). The median dose was 10 mg/kg for TXA and 50 mg/kg for EACA. Overall, 52% of cats survived to discharge. Potential adverse events were noted in 7/35 (20%) patients. Of these, 29% survived to discharge. No standardized dosing regimen was identified; rather, dose, dosing interval, and duration of administration varied markedly between patients. Administration was potentially associated with severe adverse events, although the retrospective design makes it difficult to establish a causal association with antifibrinolytic use. This study provides a base for future prospective studies by giving an insight into the use of antifibrinolytic drugs in cats.

Introduction

Hyperfibrinolysis is accelerated clot breakdown due to congenital or acquired dysregulation of the fibrinolytic system.[1] Premature fibrin breakdown can lead to hemorrhage.[1] Tranexamic acid (TXA) and epsilon aminocaproic acid (EACA) are antifibrinolytics that inhibit fibrinolysis by blocking lysine binding sites on plasminogen.[1] This stops plasminogen from binding to fibrin and prevents its conversion to plasmin, therefore inhibiting clot breakdown.[1]

There is very little evidence regarding antifibrinolytic use in cats, but the evidence in people and dogs would suggest its use could be beneficial and safe in feline patients. TXA and EACA are frequently used in people, particularly after trauma or surgery. TXA administration within 3 hr from injury reduced all-cause mortality in patients with trauma, including risk of death from bleeding.[2–6] TXA reduces bleeding and the need for blood transfusion when used perioperatively in elective surgeries and reduces hemorrhage in immune-mediated thrombocytopenia.[4,5] EACA is frequently used to reduce blood loss and transfusion requirements in people undergoing orthopedic or cardiac surgery and to prevent or treat thrombocytopenic hemorrhage due to hematological malignancies.[7–9]

In contrast to the extensive literature in people, the clinical literature in veterinary medicine is scant. Hyperfibrinolysis has been documented by viscoelastic coagulation testing in cats with traumatic hemorrhage, cholestatic liver disease, and pregnancy and following snake envenomation (Carolina Pygmy Rattlesnake and unspecified species).[1,10–12] In cats with acute trauma, 15% developed acute traumatic coagulopathy but only 1/26 showed hyperfibrinolysis.[13] TXA has been used in cats with diseases of the blood and blood-forming organs; neoplasia; trauma; disease of the digestive tract; and diseases of the skin and subcutaneous tissue, genitourinary system, pregnancy, and parturition.[14] A literature search identified no published studies regarding the therapeutic use of EACA in cats.

In dogs, TXA and EACA have been demonstrated to decrease fibrinolysis in vitro.[15–19] Kelmer et al.[20] showed enhanced coagulation/prothrombotic effect but no clear

antifibrinolytic effect after TXA administration in healthy dogs, whereas Osekavage et al.[18] demonstrated both enhanced coagulation and decreased fibrinolysis. In vivo effects were seen in greyhounds, in whom increased postoperative bleeding is associated with weaker clot strength.[21] In this breed, EACA increased clot strength measured using thromboelastography (TEG; shorter R and K times, increased alpha angle, MA and G values) and reduced postoperative bleeding after gonadectomy or amputation due to appendicular bone tumors.[21,22] However, the administration of TXA in conjunction with hemoabdomen and packed red blood cell (pRBC) transfusions did not significantly affect pRBC transfusion requirements in dogs.[14,23] An effective therapeutic antifibrinolytic dosing regimen has not been established in veterinary patients other than greyhounds.[21,22]

Adverse events have been reported rarely after TXA administration in people, despite its use in several large-scale trials.[2,4,6] Kelley et al. reported hypersalivation as the only adverse events in 1/28 (3%) of cats after TXA administration.[14] There are no clinical safety data on the use of EACA in cats. TXA and EACA administration is considered safe in dogs.[20,24–26] Antifibrinolytics are easy to administer, relatively cheap, and readily available and appear to have a good safety profile in people and dogs. There is good evidence supporting their use in people. As such, they have potential for use in feline patients, particularly given the frequency of trauma in cats and its possible association with hyperfibrinolysis, in conjunction with the relative lack of availability of feline blood products.[27]

This study aimed to evaluate the indications for the use of TXA and EACA in cats and to describe dosing regimens used, occurrence of any adverse events, and patient outcomes. Our hypotheses were that antifibrinolytics would be used for similar indications and at similar doses as in dogs.

Materials and Methods

This was a retrospective, multicenter study from four referral centers in the United Kingdom and one in the United States. The inclusion criteria were feline patients that had been billed for EACA or TXA between 2015 and 2021. Exclusion criteria were incomplete medical records regarding TXA/EACA dosing regimen. The medical database of each center was searched for data including patient signalment, indication for antifibrinolytic administration, antifibrinolytic dose, route of administration, dosing interval, course duration, coagulation testing, final diagnosis, use of blood products, adverse events, and outcome (euthanasia in hospital, death in hospital, survival to discharge, long-term survival, short-term survival, and lost to follow-up). Adverse events were defined as follows: seizures, increased respiratory rate (>40 breaths per minute), increased respiratory effort, pruritus, salivation, nausea, vomiting, diarrhea, hypotension (<90 mm Hg systolic or <60 mm Hg mean arterial pressure), mentation change or other complication within 2 hr of administration, and clinical suspicion of thrombus or computed tomography or ultrasound visualization of thrombus within 24 hr of administration.[28,29] Adverse events were attributed as unrelated, unlikely, possibly, probably, or definitely related to the antifibrinolytic agents.[30]

Results are presented using descriptive statistics, with continuous variables reported as median (min–max) and categorical variables as percentages, if not stated otherwise. Informed consent was obtained from the owner or legal custodian of all animals described in this work (nonexperimental animals) for all procedure(s) undertaken. No animals or people are identifiable within this publication. Therefore, additional informed consent for publication was not required. All patients described in the study were clinically managed according to contemporary standard of care.

Results

Thirty-five cats met the inclusion criteria. No patients were excluded. The median age was 9 yr and 11 mo (7 mo to 19 yr and 10 mo). Most patients (23/35 [66%]) were males, of whom 20/23 (87%) were neutered; of the 12 female patients, 10 were neutered (83%). Breeds represented were domestic shorthair (23/35 (66%]), domestic longhair (3/35 (9%]), British shorthair (2/35 (6%]), and 1/35 (3%) each of domestic medium hair, Maine Coon, Ragdoll, Devon Rex, Birman, Bengal, and Burmese crossbreed. Median body weight was 4.2 kg (2.3–7.6 kg).

TXA was administered in 30/35 (86%) of cases, whereas 5/35 (14%) received EACA. The most common indication for administration was nontraumatic hemorrhage (19/35 (54%]), followed by traumatic hemorrhage (6/35 (17%]) and elective surgery (4/35 (11%]). Of the patients treated with antifibrinolytics, there was active hemorrhage in 26/35 (74%), and in 4/35 (11%) the treatment was pre-emptively given. In 5/35 (14%) cases, it was unclear in the records whether there was active hemorrhage.

In the active hemorrhage group, indications for antifibrinolytic administration were nontraumatic hemorrhage (19/26 (73%]), traumatic hemorrhage (6/26 (23%]), and postoperative bleeding after supravalvular mitral stenosis correction (1/26 (4%]). The nontraumatic hemorrhage group included 6/19 (32%) patients with neoplasia, 5/19 (26%) with bleeding disorders, 4/19 (21%) with bleeding from other known causes (ulcerative eosinophilic and lymphocytic stomatitis, hepatic mass, immune-mediated hemolytic anemia, and hepatic lipidosis), 2/19 (10%) with hematuria of unknown cause, and 2/19 (10%) with hemorrhage of unknown etiology.

In the pre-emptive treatment group, the indication for administration was elective surgery (4/4 [100%]). Elective surgery included one patient undergoing cholecystocentesis, liver biopsies, and gastrointestinal tract biopsies. The remaining surgeries were nasal biopsies, cholecystectomy, and nasopharyngeal polyp removal.

In the group in which the records were unclear regarding active hemorrhage, the indications for administration were bone marrow hypoplasia/aplasia in conjunction with thrombocytopenia (2/5 (40%]), and 1/5 (20%) each of cholangiohepatitis, hepatic lipidosis, and unknown cause of coagulopathy.

Only 2/35 (6%) patients had viscoelastic testing[a,b] performed. Both patients received EACA; one patient was hyperfibrinolytic based on LI30 and LI40 before EACA and showed normal fibrinolysis after EACA, whereas the other patient had normal fibrinolysis before EACA and hyperfibrinolysis after EACA (Supplementary Tables).

Twenty-three patients (23/35 (66%]) required blood product transfusion, and 43 transfusions were administered in total. Of these, 15/43 (35%) received pRBC, 12/43 (28%) received plasma (not recorded whether fresh or frozen), 7/43 (16%) received canine packed red blood cell xeno-transfusions, 5/43 (12%) received fresh whole blood, and 4/43 (9%) received auto-transfusions.

The median dose was 10 mg/kg (5–35 mg/kg) for TXA and 50 mg/kg (35–100 mg/kg) for EACA. TXA was administered *q* 8 hr (12/30 (40%]), *q* 12 hr (9/30 (30%]), *q* 24 hr (2/30 (7%]), or as a single dose (7/30 (23%]). EACA was given *q* 6 hr (2/5 (40%]), *q* 8 hr (2/5 (40%]), or *q* 24 hr (1/5 (20%]). No cats received a constant rate infusion of TXA or EACA. The median duration of administration was 2 days for TXA (single treatment–270 days) and 3 days for EACA (single treatment–3 days).

The route of administration was IV in 21/30 (70%) TXA cases, *per os* (PO) in 9/30 (30%) TXA cases, and IV in 5/5 (100%) EACA cases. IV TXA was administered slowly (10–30 min) in

18/21 (86%) cases and at an unknown speed of injection in the rest of the cases (3/21 (14%]). IV TXA was administered diluted in 6/21 (29%) patients, with dilution unknown in the remaining cases (15/21 (71%]). TXA was diluted with water for injection in 3/6 (50%) patients and unspecified in 3/6 (50%) patients. EACA was administered slowly and diluted in 2/5 (40%) cases; in 3/5 (60%) cases the speed of injection and dilution were not noted in the medical record. One patient had a single subcutaneous TXA injection before starting IV medication, and one patient had a single subcutaneous TXA injection before starting PO medication. Two TXA patients had later PO administration of TXA at home after IV administration in the hospital.

Potential adverse events were noted in 7/35 (20%) patients (**Tables 1, 2**). In total, 10 adverse events were seen, of which 8/10 (80%) occurred after TXA and 2/10 (20%) after EACA. Both adverse events seen after EACA administration occurred in a single patient (mentation change followed by cardiopulmonary arrest [CPA]). The adverse events were attributed as unlikely related to the EACA administration. Three patients had two adverse events: 2/3 (66%) had received TXA and 1/3 (33%) had received EACA. In 1/10 adverse events (10%), retroperitoneal thrombus formation was confirmed by ultrasound after 80 days of 16 mg/kg *q* 24 hr PO TXA administration. The patient was being treated for a coagulopathy of unclear origin with bleeding in the subcutaneous tissue of the abdomen and neck. At the start of the TXA treatment, the platelet count was within the reference interval and activated partial thromboplastin time and prothrombin were unremarkable. No viscoelastic testing was performed. The thrombus and the concurrent hypotension were attributed by the primary clinician as probably related to the extended TXA administration, although the fact that the thrombus was within the retroperitoneal space rather than a vessel suggests an appropriate clot in response to hemorrhage rather than a pathological clot. The remaining 9/10 (90%) potential adverse events occurred within 2 hr of administration and included hypotension 5/10 (50%), mentation changes 2/10 (20%), transient mild tachycardia 1/10 (10%), and CPA 1/10 (10%). The transient tachycardia was attributed as possibly related to EACA administration, whereas the remaining 7/10 (70%) events were attributed as unlikely related to this.

No other adverse events, including seizures, salivation/nausea, or vomiting, were noted. The antifibrinolytic (TXA) was continued in 1/7 (14%) patients after the adverse event (transient tachycardia). Euthanasia was elected in 4/7 (57%) cases; all these patients were euthanized on the same day as the events were noted. The patient with CPA was resuscitated but had a repeat CPA later that day.

Twenty-seven (27/35 (77%]) patients were treated with antifi-brinolytics in hospital only, 2/35 (57%) were treated both in hospital and at home, and 6/35 (17%) were treated only at home (**Figure 1**). All the EACA patients were treated in hospital only.

Outcomes of cats treated with antifibrinolytic drugs.

Of the patients that survived to discharge after being treated in hospital, 2/13 (15%) were euthanized but dates or reason for euthanasia were not recorded, 1/13 (8%) was euthanized 17 days after stopping TXA administration because of an unknown reason, and 1/13 (8%) had CPA 2 days after discharge because of worsening triaditis. The owners reported that 1/13 (8%) patients was doing well 6 days after discharge and 1/13 (8%) was fine after 1 mo; both patients were then lost to follow-up.

Of the 8/35 (23%) patients treated partially in hospital and at home, the median survival time was 19 days (1–80 days). One of the patients treated at home was euthanized after 80 days of TXA administration owing to complications associated with a thrombus. One patient was undergoing chemotherapy, although the exact cause for euthanasia is not available. One patient was still alive after ~270 days of TXA treatment and was still receiving ongoing TXA at the time of writing this manuscript.

Of the patients with adverse events, 4/7 (57%) were euthanized, 1/7 (14%) died in hospital, and only 2/7 (29%) survived to discharge.

Discussion

This retrospective study sought to give insight into the indications, dosing, and potential adverse events of antifibrinolytics in cats, as reports of their use in this species have been minimal.

Antifibrinolytics are occasionally administered to cats in the centers involved in this study. There are no studies regarding the pharmacokinetics, pharmacodynamics, or clinical efficacy in this species. Thus, the use of antifibrinolytics in cats remains based on clinicians' experience and opinions. There is no standardized dosing regimen, and in our study, dose, dosing interval, and duration of administration varied markedly between patients including in the same hospital, although doses typically appear to be extrapolated from either human or canine data. In people, TXA doses of 10–50 mg/kg and EACA doses of 100 mg/kg are recommended.[5,31] The following recommended dosages for dogs are extrapolated from people: TXA 10–20 mg/kg subcutaneous, intramuscular, or slow IV followed by 1 mg/kg constant rate infusion for 5–8 hr; EACA 50–100 mg/kg IV or PO *q* 6 hr depending on the cause for administration.[1,14,15,24] In a retrospective study by Kelley et al. on cats admitted to critical care units, a median TXA dose of 10 mg/kg was used.[14] There are no available studies regarding EACA dosing regimens in cats. Adverse effects in cats reported after higher doses of TXA were fibrinolysis and collagen deposition in the myocardium, and lung pathology was seen in experimental studies after very high doses (single dose of 100 mg/kg and 200 mg/kg daily for 7 days).[32,33] An accidental overdose of 10 times of TXA in one cat did not result in any appreciable adverse effects.[14]

We have not identified a clear relationship between indication and dosing regimen. This suggests the variability observed was due to primary clinicians' preferences and not due to indication for administration and/or hospital protocols. In people, there are clear recommendations on dosing regimens based on indications, which could be an area for future research in feline medicine.[5]

In our study, potential adverse events were noted in 20% of cats receiving antifibrinolytics. However, given the retrospective nature of the study combined with the severity of the underlying conditions, it is impossible to determine causality. Most patients had underlying diseases that were deemed a likely cause or contributor to the documented adverse event (for example, ongoing bleeding and severe trauma were highly likely to have caused or contributed to hypotension and mentation changes). One of the patients with hypotension had a TXA IV injection delivered at an unknown speed; in people, hypotension has been correlated with rapid IV infusions.[34] One cat underwent CPA after EACA administration. This patient had presented in severe hypovolemic shock secondary to peritoneal hemorrhage, and respiratory arrest occurred before EACA administration. Therefore, the underlying condition was deemed to be the likely cause of CPA, although one case of suspected anaphylactic shock after TXA administration is reported in a Maltese and a similar reaction cannot be excluded in this case.[35] Hypersensitivity reactions after TXA are rarely reported in

people.[36] Rare adverse events associated with the use of EACA in people include nausea, vomiting, malaise, myalgia, renal impairment, seizures, hypotension, bradycardia, edema, and injection site reactions.[31] Possible adverse events noted in dogs after EACA include one case each of diarrhea, decreased appetite, and presumptive lupoid onychodystrophy.[24]
One patient developed transient mild tachycardia (tachycardia was noted in the patient record, but data on the heart rate were missing) after subcutaneous administration of TXA. Whether this was due to the stress of the injection, other patient pathology, or an adverse reaction to the TXA is undetermined, so the event was attributed as possibly due to TXA administration. The same patient had prior IV and subsequent oral administration of TXA, without displaying adverse events.
One patient treated for an undetermined coagulopathy and bleeding diathesis developed a thrombus after TXA administration. There was no final diagnosis for the cat's coagulopathy. Therefore, a possible underlying predisposition for clot formation cannot be ruled out. In our study, this was the only cat to develop a confirmed thrombus. Vascular occlusive complications have not been reported in dogs. In humans, the incidence of thrombus formation is reported at 1.7%,[3] 5.9%,[37] and 6.6%[38] after TXA use and 4.6%[8] after EACA use. Recent studies indicate TXA use in human patients with trauma might be associated with more thrombotic events than previously reported.[37,38] However, EACA was not associated with a higher incidence of thrombotic events when used in orthopedic surgery or when used in patients with liver cirrhosis.[7,39,40]
Given the small patient population and nonstandardized post-administration monitoring in our study, it was not possible to categorize the severity, duration, or long-term effects of adverse events. Of the patients with potential adverse events, 5/7 did not survive to discharge. However, all but one of these patients had an acute life-threatening illness at the time of administration, so it is difficult to draw meaningful conclusions from the high mortality. Most of the adverse events, 7/10 (70%), were attributed as unlikely to be related to the antifibrinolytic agents.
No nausea or vomiting was reported in any of the cases. Hyper-salivation has been reported in 1/28 (3%) of cats after TXA administration (dosing regimen 10 mg/kg *q* 6 hr IV), and nausea and vomiting are known dose-dependent side effects of IV TXA in dogs.[41] Slow, diluted injection is thought to mitigate this.[34,41] Absence of vomiting could be due to a species difference or the fact that IV administration was slow in most cases. Maropitant has been reported to reduce the frequency of vomiting after TXA.[41] The frequency of maropitant administration was not investigated in this study.
There were no neurological adverse events reported other than mentation change. Experimental induction of epileptic seizures has been reported in cats after cortical topical application of TXA.[42] Case reports and small observational studies have reported seizures in humans at high doses of TXA, possibly due to its effect on GABA and glycine receptors.[43]
The relatively high occurrence of potential adverse events in our study is in stark contrast to a study by Kelley et al. in which 1/28 (3%) cats had an adverse event (hypersalivation) due to TXA administration.[14] The study does not define adverse effects and possibly had a stricter definition than that used in our study. Disease severity was not measured in our study, although the survive to discharge rate was 52% compared with 75% in the study by Kelley et al., possibly indicating a sicker population. Further studies in cats with a higher illness severity score should be considered.
Relatively few patients, 2/35 (6%), had viscoelastic testing performed in conjunction with administration. One of the two patients had viscoelastic monitoring (VCM) performed

before EACA administration and TEG after, making the results difficult to compare. VCM and TEG have shown poor correlation in healthy cats.[44] Viscoelastic testing is not routinely recommended before antifibrinolytic administration in humans.

Dogs are reportedly hyperfibrinolytic compared with humans, and thus, higher doses of TXA and EACA may be required for clinical efficacy. TXA inhibits fibrinolysis in vitro in a concentration-dependent fashion in both canine and human plasma, requiring an estimated concentration of 144.7 μg/mL in dogs, versus 14.7 μg/mL in humans.[45] There are no comparative data in cats, but there is some evidence indicating that healthy cats have weaker clots than humans and possibly increased clot lysis.[46] The efficacy of antifibrinolytic administration was not evaluated in this study, and prospective studies examining dose and efficacy are warranted.

TXA is excreted through the kidneys, and in people with renal disease, dose reduction is recommended.[47] Given the small study population and the fact that serum biochemical analysis was not always performed in these patients, data on renal function were not collected.

However, chronic kidney disease and acute kidney injury are common in feline critically ill patients. Dose reduction could, therefore, be considered in these patients, although further information is required before a definitive recommendation can be made.

Our retrospective study presents multiple limitations. The indication for antifibrinolytic administration was not always clearly described in the medical records and there were frequently multiple possible reasons for administration. Monitoring after administration varied between centers and patients, and transient adverse events could have been missed or not noted in the medical records. Dilution and speed of IV injection were not always recorded. All the EACA patients were treated in a single center in the United States, whereas TXA patients were treated in multiple centers in Europe, and this could have led to a bias in patient selection. The sample size was small. Finally, as previously mentioned, the retrospective nature of the study makes it impossible to establish a causality link between the observed adverse events and the antifibrinolytics administered.

Conclusions

The most common indication for TXA and EACA administration in cats was nontraumatic hemorrhage. No standardized dosing regimens were identified in this study; rather, dose, dosing interval, and duration of administration varied markedly between patients. No dosing regimen can be recommended from this study. Although adverse events, including some severe adverse events, were noted after antifibrinolytic administration, the retrospective design of this study makes it difficult to establish whether these were due to antifibrinolytic administration or the underlying disease. It seems most likely, however, that most adverse events were due to the underlying disease.

CPA

(cardiopulmonary arrest);

EACA

(epsilon aminocaproic acid);

PO

(*per os*);

pRBC

(packed red blood cell);

TEG

(thromboelastography);

TXA

(tranexamic acid)

FOOTNOTES

[a]

Viscoelastic Monitoring, VCM vet; Entegrion, Inc., Durham, North Carolina

[b]

TEG 500 Thromboelastograph; Haemonetics Corp., Boston, Massachusetts