Evaluation of antiplatelet effects of ticlopidine in cats

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Objective—To determine whether ticlopidine exerts an antiplatelet effect, estimate the pharmacodynamics of ticlopidine, and evaluate any acute adverse effects associated with administration of ticlopidine in cats.

Animals—8 domestic purpose-bred sexually intact male cats.

Procedure—Ticlopidine was administered orally (50 mg, q 24 h; 100 mg, q 24 h; 200 mg, q 24 h; and 250 mg, q 12 h). Each treatment period consisted of 10 days of drug administration. Platelet aggregation studies with adenosine diphosphate (ADP) and collagen and evaluation of oral mucosal bleeding times (OMBTs) were performed on days 3, 7, and 10 during each drug administration. Serotonin was measured to evaluate secretion at baseline and on day 10 for cats that received the 250-mg dosage.

Results—A significant reduction in platelet aggregation was detected in response to ADP on days 7 and 10 at 100 mg, on day 3 at 200 mg, and on days 3, 7, and 10 at 250 mg. A significant increase in the OMBT and decrease in serotonin release on day 10 at 250 mg was also detected; however, the cats had anorexia and vomiting at the 250-mg dosage.

Conclusions and Clinical Relevance—Although there was a consistent antiplatelet effect at the 250-mg dosage, there was dose-dependent anorexia and vomiting that we conclude precludes the clinical usefulness of this drug in cats. (*Am J Vet Res* 2004;65:327–332)

Systemic arterial thromboembolization (SATE) is common in cats and is usually associated with some form of underlying myocardial disease.[1-3] The emboli are composed of platelets within a fibrin network, which is characteristic of systemic arterial emboli. Additional evidence for the role of platelets in the pathogenesis of SATE includes altered platelet aggregation in cats with underlying cardiac disease and reduced collateral flow around the site of embolization in response to platelet release products such as serotonin.[4-8]

Antiplatelet drugs, such as aspirin, would appear to be an attractive choice in the prevention of SATE; however, administration of aspirin does not result in a substantial reduction in occurrence of SATE.[9,10] Ticlopidine, a thienopyridine derivative, is thought to induce irreversible inhibition of **adenosine diphosphate (ADP)** receptors along the platelet membrane, which results in its antiplatelet effects, including decreased platelet aggregation and prolonged bleeding time. Ticlopidine does not exert any direct effect on platelets and must undergo hepatic transformation to form 1 or more active metabolites. Because of this, in vivo and ex vivo studies, such as bleeding times and platelet aggregation studies, respectively, are required to detect the antiplatelet effects. In addition, plasma concentration of the parent drug does not correlate with the antiplatelet effect, so pharmacodynamic instead of pharmacokinetic studies are typically used to determine dosage and administration intervals in the species of interest.[11] Ticlopidine has resulted in significant reductions in stroke and myocardial infarction when used in humans.[12,13] Although ticlopidine has been evaluated for possible thrombolytic effects in a feline extracorporeal perfusion model,[14] antiplatelet effects have never been studied in cats to our knowledge.

The purposes of the study reported here were to determine whether ticlopidine exerts an antiplatelet effect, estimate the pharmacodynamics of ticlopidine, and evaluate any acute adverse effects associated with administration of ticlopidine in cats.

Materials and Methods

Cats—Eight domestic purpose-bred sexually intact male cats, approximately 1 year of age, were used for this study. During 4 treatment periods, ticlopidine[a] was administered PO at dosages of 50 mg, q 24 h; 100 mg, q 24 h; 200 mg, q 24 h; and 250 mg, q 12 h. Each treatment period consisted of 10 days of drug administration, followed by a drug washout period and an inter-study resting period that was at least 2 weeks in duration. Platelet aggregation studies and evaluation of **oral mucosal bleeding times (OMBTs)** were performed prior to drug administration and on days 3, 7, and 10 during each treatment period. Platelet function studies were repeated on days 3 and 7 during the washout period after the 250-mg administration period to determine duration of the antiplatelet effect. These time points were chosen because data from humans indicate that onset of action is within 2 to 4 days, maximal effect is from 4 to 6 days of drug administration, and loss of effect is detected from 4 to 8 days after discontinuation of drug administration.[15] Serotonin was measured to evaluate secretion prior to drug administration and on day 10 of administration of the 250-mg dosage. A CBC was performed, as well as determination of serum activities of **alkaline phosphatase (ALP)** and **alanine aminotransferase (ALT)** and total bilirubin concentration, prior to drug administration and on day 10 of each treatment period to monitor reported adverse effects of ticlopidine reported in humans.[16,17] Blood samples were collected, and bleeding times

Received April 23, 2003.
Accepted July 25, 2003.
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Supported by a grant from the American Association of Feline Practitioners and Academy of Feline Medicine.
Presented at the 20th Annual American College of Veterinary Internal Medicine Forum, Dallas 2002.
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were evaluated via an anesthetic protocol of ketamine[b] (15 mg/kg, IM), acepromazine[c] (0.2 mg/kg, up to 1 mg total dose, IM), and atropine[d] (0.1 mL, IM) that is reported not to affect platelet function studies.[5,18] The cats were examined at least twice a day for evidence of petechiae, ecchymoses, hematochezia, or hematuria during the treatment periods. The research protocol was approved by the Purdue Animal Care and Use Committee, and the cats were adopted at the end of the study.

OMBT—Because of anatomic limitations of the feline oral cavity, OMBT was performed in lieu of buccal mucosal bleeding time. This technique has been described elsewhere and is accurate and repeatable in cats.[18] Briefly, after the cats had been anesthetized, they were placed in lateral recumbency and the lip was reflected back and held in place by gauze that was tightly tied around the head. Spring-loaded blade cassettes[e] were used to create 1-mm-deep and 5-mm-long incisions in the oral mucosa above the premolars or molars. The OMBT was determined from the time the incision was created until cessation of bleeding was noted.

Blood aggregometry—Blood aggregometry performed with a whole-blood platelet aggregometer[f] was chosen to evaluate platelet aggregation responses because only a small volume of blood was needed to perform the studies, which allowed frequent sampling. In addition, we believe that whole-blood aggregometry is representative of platelet aggregation in vivo because all the cellular components of blood as well as plasma proteins are present. Prior to drug administration, the minimum amount of agonist for maximum platelet aggregation was determined for each cat by establishing a dose-dependency curve for ADP and collagen on 3 consecutive days. Three milliliters of venous blood was collected from the anesthetized cat by atraumatic jugular venipuncture with a 22-gauge needle and a blood tube that contained sodium citrate anticoagulant (3.8%) at 9 parts blood to 1 part anticoagulant. The cats were anesthetized to ensure atraumatic venipuncture, which is essential in minimizing platelet activation prior to aggregation studies. The OMBT determination was performed at the same time. The anticoagulated blood was kept at room temperature (21°C), gently rocked for 30 minutes as described,[5] and diluted 1:1 with saline (0.9% NaCl) solution. One milliliter of blood was placed in an aggregometer cuvette,[f] and its temperature was increased to 37°C in the aggregometer heating block. The warmed blood was placed into the aggregometer where it was stirred and baseline value was established. Platelet aggregation was induced with the addition of ADP[f] or collagen.[f] Either 5µM ADP or 10µM ADP and 1 µg of collagen/mL was determined to be the minimum concentration of agonist necessary for maximal platelet aggregation in our cats and considered as baseline concentration for that cat. Platelet aggregation was measured by documenting the percentage change in electrical resistance over time and expressed as percentage aggregation with changes recorded by use of a computer interface.[f]

Serotonin secretion—To evaluate platelet serotonin secretion, blood used for the whole-blood aggregometry study was recovered after platelet aggregation and centrifuged at 5,000 × *g* for 5 minutes at 4°C to separate the cellular elements from the plasma and serotonin. The platelet-free plasma was snap frozen in liquid nitrogen and stored at –80°C until serotonin concentrations were measured with a commercially available ELISA test kit.[g]

Statistical analyses—Statistical analyses were performed with commercially available software programs. Results were expressed as the arithmetic mean ± SD. Mean platelet aggregation percentage and OMBT within each treatment group were compared by use of an ANOVA with repeated measures with Bonferroni correction (overall type-I error, 0.05).[h] Serotonin, weight, and clinicopathologic measurements on days 0 and 10 were evaluated by use of tailed, paired *t* tests.[i] Mean platelet concentrations in groups were analyzed by use of a 1-way ANOVA.[h] Pairwise comparisons were performed by use of the least significant difference method.[i] Differences were considered significant at $P < 0.05$.

Results

50-mg dosage—No significant changes were detected in platelet aggregation induced with ADP or collagen or in OMBT (**Table 1**). The cats appeared to tolerate the drug well and had no adverse effects. However, there was a significant reduction in body weight during the treatment period (**Table 2**). There was a significant increase in Hct, WBC, and neutrophil concentrations at the end of the treatment period. The minor increase in Hct could have been secondary to shifts in water between intravascular and extravascular spaces, which were supported by a minor increase in plasma protein concentration, or splenic contraction from epinephrine release. None of the cats appeared clinically dehydrated so the loss in body weight seemed unlikely to be caused by water loss alone, and anorexia was not noted. The increases in WBC and neutrophil concentrations could also be secondary to epinephrine release that can occur during blood sampling in cats or from the IM injection of the anesthetic agents. Although increased for individual cats, the values were all within reference ranges and not considered to be clinically important.

100-mg dosage—A significant reduction in platelet aggregation induced by ADP on days 7 and 10 was detected (Table 1). However, there was no significant reduction in platelet aggregation induced by collagen or prolongation of the OMBT on any day during the treatment period. Two of the cats had mild anorexia for 1 day each, and 3 cats vomited on 1 day each within 1 hour after administration of drug. There was a significant decrease in body weight similar in degree to that seen at the 50-mg dosage (Table 2). There was a significant increase in WBC concentration that was characterized by neutrophilia and could have been secondary to a stress response or epinephrine release. There was also a significant increase in bilirubin concentration, which could have been secondary to increased RBC turnover, minor cholestatic disease, or alterations in bilirubin binding such that the Δ fraction was responsible for this increase. Cholestatic disease was considered less likely because there was no increase in serum activity of ALP. The individual fractions of bilirubin were not measured, so it was unclear what was responsible for the increase. Despite the significant changes, all values were within reference ranges and the abnormal values were not considered clinically important.

200-mg dosage—One cat was removed from the study during the beginning of this treatment period because of upper airway disease that was diagnosed as stenotic choanae not related to administration of the drug. This cat's data were not included in the analysis during this treatment period. There was a significant reduction in

platelet aggregation induced by ADP on day 3, but this was not detected on days 7 or 10 (Table 1). There was no significant change in platelet aggregation induced by collagen or OMBT on any day of the treatment period. There was a significant increase in Hct similar in degree to that seen with the 50-mg dosage (Table 2). There was a mild increase in anorexia in 3 cats on at least 1 day during drug administration. Four cats had sporadic vomiting immediately after drug administration. There was also a significant reduction in body weight similar in degree to that seen at the 50-mg and 100-mg dosages.

250-mg dose—One cat was removed from the study prior to this treatment period when it died suddenly during the interstudy resting period with no apparent cause or premonitory illness. Necropsy findings included minimal myocardial fibrosis and no identifiable cause of death. There was no evidence of hemorrhage or hepatocellular injury. In the remaining 6 cats, there was a significant decrease in platelet aggregation induced by ADP on all days of the treatment period (Table 1); there were no significant differences among values obtained on days 3, 7, and 10. However, although there was a gradual reduction in platelet aggregation induced by collagen, this never reached significance on any day during the treatment period. Similarly, the OMBT became progressively prolonged during the treatment period but only became signifi-

Table 1—Variables (mean ± SD) associated with platelet function in 8 cats treated with various dosages of ticlopidine

Dose and treatment period	ADP (%)	COL (%)	OMBT (s)	Serotonin ADP (ng/mL)	Serotonin Col (ng/mL)
50 mg, q 24 h					
Baseline	38.7 ± 6.0	48.4 ± 3.0	96.6 ± 27.9	NP	NP
Day 3	42.0 ± 13.0	50.4 ± 4.4	113.7 ± 30.6	NP	NP
Day 7	32.3 ± 13.5	42.4 ± 3.3	76.1 ± 15.7	NP	NP
Day 10	40.4 ± 9.1	46.4 ± 7.9	86.1 ± 13.6	NP	NP
100 mg, q 24 h					
Baseline	39.2 ± 6.0	47.8 ± 3.0	96.6 ± 27.9	NP	NP
Day 3	31.4 ± 8.3	48.0 ± 9.0	84.5 ± 11.0	NP	NP
Day 7	27.3 ± 9.3[a]	49.0 ± 8.8	131.6 ± 46.6	NP	NP
Day 10	30.9 ± 5.2[b]	42.0 ± 13.4	118.0 ± 26.5	NP	NP
200 mg, q 24 h					
Baseline	32.1 ± 4.8	46.4 ± 5.3	90.8 ± 18.7	NP	NP
Day 3	15.3 ± 9.3[b]	45.5 ± 4.5	107.6 ± 51.3	NP	NP
Day 7	22.9 ± 11.4	44.5 ± 13.4	80.9 ± 17.9	NP	NP
Day 10	25.3 ± 13.3	47.3 ± 8.1	102.8 ± 24.4	NP	NP
250 mg, q 12 h					
Baseline	39.3 ± 8.2	50.8 ± 5.2	79.5 ± 30.1	515.03 ± 99.84	608.04 ± 104.00
Day 3	17.2 ± 15.2[c]	40.2 ± 23.5	120.5 ± 34.4	NP	NP
Day 7	15.2 ± 10.1[b]	32.8 ± 19.0	139.8 ± 45.0	NP	NP
Day 10	13.5 ± 11.5[b]	36.5 ± 17.1	190.7 ± 80.3[b]	317.42 ± 270.63	279.22 ± 206.13[b]
Washout day 3	26.0 ± 22.6	44.3 ± 16.7	76.3 ± 14.6	NP	NP
Washout day 7	37.4 ± 5.2	56.6 ± 2.9	70.0 ± 16.5	NP	NP

[a]Significantly ($P < 0.001$) different from baseline value. [b]Significantly ($P = 0.01$) different from baseline value. [c]Significantly ($P < 0.05$) different from baseline value.

ADP = Platelet aggregation induced by use of adenosine diphosphate. COL = Platelet aggregation induced by use of collagen. Serotonin ADP = Serotonin concentration obtained after ADP-induced platelet stimulation. Serotonin Col = Serotonin concentration obtained after collagen-induced platelet stimulation. OMBT = Oral mucosal bleeding time. NP = Not performed.

Table 2—Blood and serum biochemical values (mean ± SD) in 8 cats treated with various doses of ticlopidine

	50 mg, q 24 h		100 mg, q 24 h		200 mg, q 24 h		250 mg/cat q 12 h		
Variable	Baseline	Day 10	Baseline	Day 10	Baseline	Day 10	Baseline	Day 10	Reference
Hct (%)	31.1 ± 2.7	38.3 ± 2.7[a]	31.1 ± 2.6	32.3 ± 4.0	31.6 ± 4.0	37.8 ± 3.0[c]	29.8 ± 2.4	36.5 ± 2.4[a]	30–45
WBCs (×10³/µl)	7.00 ± 2.77	13.02 ± 3.49[b]	7.00 ± 2.77	10.80 ± 2.44[a]	9.52 ± 1.71	9.39 ± 2.98	7.26 ± 3.40	8.98 ± 3.75	600–18.00
Neutrophils (×10³/µl)	4.53 ± 1.73	8.99 ± 1.71[b]	4.53 ± 1.73	6.76 ± 1.80	6.40 ± 1.96	5.93 ± 1.58	4.72 ± 2.53	5.99 ± 2.45	3.00–12.00
Platelets (×10³/µl)	TCTC-Adq	TCTC-Adq	TCTC-Adq	TCTC-Adq	319.5 ± 152.0	389.7 ± 155.4	311.7 ± 107.1	361.7± 60.7[d]	300.0–700.0
ALT (U/L)	98.8 ± 28.4	82.4 ± 25.1	98.8 ± 28.4	117.3 ± 43.8	91.9 ± 20.1	109.1 ± 51.0	91.7 ± 35.5	79.8 ± 63.1	20–108
ALP (U/L)	48.0 ± 7.3	51.0 ± 8.1	48.0 ± 7.3	51.8 ± 12.6	53.0 ± 14.5	42.0 ± 11.3	52.8 ± 9.3	47.2 ±17.2	23–107
Bilirubin (mg/dL)	0.10 ± 0.00	0.13 ± 0.05	0.10 ± 0.00	0.19 ± 0.08[c]	0.15 ± 0.05	0.29 ± 0.2	0.22 ± 0.08	0.52 ± 0.12[a]	0.1–0.4
Weight (kg)	4.38 ± 0.64	4.28 ± 0.60[a]	4.40 ± 0.62	4.23 ± 0.55[a]	4.80 ± 0.63	4.31 ± 0.60[b]	4.61 ± 0.76	3.80 ± 0.58[a]	

[a]Significantly ($P < 0.01$) different from baseline value. [b]Significantly ($P < 0.001$) different from baseline value. [c]Significantly ($P < 0.05$) different from baseline value. TCTC-Adq = Too clumped to count, adequate numbers estimated. ALT = Alanine aminotransferase. ALP = Alkaline phosphatase.

cantly prolonged on day 10. The ADP- and collagen-associated platelet aggregation and OMBT values returned to baseline values within 3 days after discontinuation of drug administration. There was a significant increase in Hct similar in degree to the 50-mg and 200-mg doses and a significant increase in platelet concentration, but these were within reference ranges and not considered clinically important (Table 2). There was a significant increase in bilirubin; 4 cats had values that were minimally greater than the reference range, although none appeared icteric. Supportive evidence for cholestasis was lacking because serum activity of ALP was within reference range, although the fractionated concentrations were not measured. The majority of cats (5/6) had some degree of anorexia on at least 1 day at this dose. Vomiting immediately after drug administration was seen in all cats, although the incidence decreased during the treatment period. There was also a significant loss of body weight at this dosage.

There was a significant reduction in serotonin concentration in response to collagen-induced platelet stimulation. Although there was also a reduction in serotonin concentration in response to ADP-induced platelet stimulation, this did not reach significance.

Discussion

The thienopyridines, including ticlopidine and clopidogrel, irreversibly inhibit activation of the ADP P_{2Y12} receptors along the platelet membrane, reducing both primary and secondary platelet aggregation.[19] Ticlopidine reduces platelet aggregation in response to many agonists, including ADP, collagen, thrombin, epinephrine, arachidonic acid, and platelet activating factor.[16,20,21] There is also an inhibition of the ADP-induced conformational change of the glycoprotein IIb/IIIa complex, preventing its binding of fibrinogen and von Willebrand factor.[20] This latter effect prevents the interaction of the GPIIb/IIIa complex with the subendothelial surface and progression of the thrombus.[22,23]

These compounds do not exert any direct antiplatelet effects but must undergo extensive hepatic metabolism to 1 or more active metabolites, many of which have not been identified. This precludes in vitro analysis, therefore ex vivo and in vivo assays such as platelet aggregation and bleeding times, respectively, have traditionally been used to evaluate their antiplatelet effects.[20] These have also been the standard assays used in veterinary medicine to evaluate platelet function in response to disease or antiplatelet drugs.[4,5,18,24-27] Although cats have high sensitivity to drugs that are cleared by the hepatic route, the feline liver does have the ability to metabolize ticlopidine via the 2 main pathways, N-oxidation and N-dealkylation.[28] Secretion of the metabolites and unchanged ticlopidine is primarily by the renal route, with small amounts found in the feces in various species.[16,28-30]

Although there were significant reductions in ADP-induced platelet aggregation at different time points within the 100-mg and 200-mg administration periods, this effect did not become consistent until the 250-mg dosage was used, which is the standard human dosage. In addition, collagen-induced platelet aggregation never became significantly reduced. There was also no significant prolongation in the OMBT until day 10 in the 250-mg administration period, although there was a noticeable prolongation during the performance of the bleeding times at all time points during this administration period. Small sample size and large interindividual variation could have precluded a significant effect from being recognized. Post hoc power estimates for ADP-induced platelet aggregation and OMBT analyses (day 0 vs day 10) were 19% and 72%, respectively. It should also be noted that the adverse gastrointestinal effects could have masked some of the antiplatelet effects of the drug. Absorption of ticlopidine is enhanced with food, so the variable anorexia could have had a negative influence. In addition, the vomiting associated with drug administration could have resulted in incomplete or inconsistent administration. Under typical conditions in other species, ticlopidine is rapidly absorbed and maximal plasma concentration is obtained within 2 hours after administration.[30]

There is a large amount of evidence that a platelet release product such as serotonin plays a primary role in the clinical signs associated with SATE. Experimental models reveal that simple ligation of the distal portion of the feline aorta does not result in reduced blood flow to the hind limbs or the classical clinical signs of paresis or paralysis associated with SATE. Under such conditions, blood flow is maintained through extensive vertebral collateral circulation and epaxial muscle collateral circulation. However, when a thrombus is created within the isolated aortic segment, there is loss of this collateral circulation and clinical signs of SATE are evident.[6,7,31] This same effect can also be seen when serotonin is injected into the isolated aortic segment in the absence of thrombus formation, suggesting a primary role for serotonin in the pathogenesis of SATE.[7] The role of serotonin is further supported by results of a study[8] that revealed the maintenance of collateral circulation and absence of clinical signs of SATE with a thrombus within an isolated aortic segment when preadministration of the serotonin antagonist cyproheptadine was used. More than 98% of circulating serotonin is located in platelets and released when platelets are activated. Ticlopidine reduces serotonin release from activated platelets in rabbits, rats, humans, and dogs.[32-35] Ticlopidine also reduces the contractile response of pulmonary and femoral arterial ring preparations to multiple vasoconstrictive agents, including serotonin.[36] Our serotonin secretion data gave somewhat conflicting results. There was a significant reduction in serotonin release in response to collagen as an agonist at 10 days in the 250-mg administration period, although there was no significant reduction in collagen-induced platelet aggregation. Conversely, despite significant reductions in ADP-induced platelet aggregation during this treatment period, the reduction in serotonin release in response to ADP was not significant. The small sample size of this study likely played a large role in this finding (post hoc study power estimate, 27%). One cat had an increase in serotonin and 1 cat had a

negligible decrease, whereas the remaining 4 cats had a mean of > 70% reduction in serotonin release in response to ADP on day 10 of administration. Another possible factor is that we stored the plasma from the aggregation studies at –80°C for 2 months. The manufacturer of the serotonin assay suggests using either fresh plasma or plasma that has been stored at –20°C for no longer than 2 weeks. The secretion studies were not done on any other treatment period because of the lack of substantial altered platelet function. Serotonin was only measured on day 10 of the 250-mg dosage period because this most likely represented the maximal drug effect on platelet secretion.

Various adverse reactions to ticlopidine develop in 10% to 15% of human patients, which is not significantly different than placebo, although the incidence of severe hematologic adverse reactions is higher with ticlopidine, compared with placebo.[16] Gastrointestinal disturbances including nausea and diarrhea are most common, with a prevalence of approximately 10%, and can generally be reduced if the drug is given with food. The second most common adverse reactions are dermatologic, including maculopapular or urticarial rashes.[16] Hematologic adverse reactions include bleeding, although this is usually infrequent and rarely important even during or after surgery.[16] Prevalence of agranulocytosis is < 1%, and it promptly resolves with discontinuation of administration of the drug.[17] The most severe potential adverse reaction is thrombotic thrombocytopenic purpura, which occurs in 1 of 5,000 human patients.[37] There is an unusual to rare hepatic adverse reaction with cholestatic jaundice, increased total and conjugated serum bilirubin concentrations, and increased serum activities of ALP and transaminases.[16]

The cats in our study did have dose-dependent gastrointestinal adverse effects. Anorexia and vomiting began to be seen sporadically during the 100-mg administration period and progressed in severity and frequency during the 200-mg and 250-mg administration periods. There was also a significant reduction in body weight, similar in degree, during all treatment periods. The vomiting was usually seen immediately after drug administration and abated as soon as administration was discontinued (first day of the washout period). Ticlopidine is severely bitter and could be irritating to oral mucous membranes and the gastric mucosa. Similar adverse effects to ticlopidine have been seen in dogs.[34] It is interesting that the anorexia and vomiting decreased during the administration periods, suggesting that cats developed some degree of tolerance, which has also been seen in humans. The cats did not have any bleeding abnormalities such as petechiae, ecchymoses, hematochezia, or hematuria during any treatment period.

There were significant increases in Hct and concentrations of WBCs, neutrophils, and platelets in treatment groups, but these values were within reference ranges and not considered clinically important. However, the changes in Hct were consistently seen and could represent a drug effect. Shifts in water between intravascular and extravascular spaces appear to be the most probable explanation. None of the cats appeared clinically dehydrated, and plasma protein concentrations were not increased beyond reference range, although there were mild increases from baseline values. Measurement of SUN and creatinine concentrations along with urine specific gravity could have supported the diagnosis of water shifts, but these were not performed. These parameters were not measured because the cats never appeared clinically dehydrated and adverse renal effects of ticlopidine have not been reported. The increases in WBC and neutrophil concentrations could represent a drug effect, but because these were inconsistently identified, they most likely represented a stress response or a change secondary to release of epinephrine. Objective platelet concentrations were limited because the platelets were too clumped to be counted in many of the samples. There was a significant increase in total bilirubin concentration at the end of the 250-mg administration period, in which 4 cats had minimally increased values (0.5 to 0.7 mg/dL; reference range, 0.0 to 0.4 mg/dL). Unfortunately, individual fractions of bilirubin (conjugated, unconjugated, and Δ) were not measured, so it was unclear what was responsible for the increase. Possibilities included mild cholestatic disease, increased RBC turnover, and altered binding of the Δ fraction. Cholestasis appeared unlikely because there was a reduction in mean activities of ALP and ALT over the same treatment period. Likewise, the increase in Hct did not support increased RBC turnover.

Two cats were removed from the study because of stenotic choanae or sudden death. The stenotic choanae were felt to be congenital in nature, and the clinical signs were most likely exacerbated because of daily drug administration. There was no identifiable cause of death in the cat that died suddenly, although there was mild chronic myocardial fibrosis. However, there was no evidence of hemorrhage or hepatic injury that could be consistent with adverse effects associated with administration of ticlopidine. In addition, the cat died during the resting period between the 100-mg and 200-mg administration periods after platelet aggregation values had returned to reference range. It did not appear that ticlopidine was responsible for this death, but this could not be completely ruled out.

Ticlopidine had consistent antiplatelet effects in cats when administered at 250 mg every 12 hours. Significant reduction in platelet aggregation in response to ADP was reached within 3 days of treatment, whereas significant prolongation in OMBT was not detected until after 10 days of treatment. These antiplatelet effects resolved within 3 days after discontinuation of the drug. However, there was a dose-dependent gastrointestinal adverse effect that we conclude precludes the clinical usefulness of this drug in the prevention of SATE in cats.

[a]Ticlid, generously provided by Ticlid, Hoffmann-La Roche Inc, Nutley, NJ.
[b]KetaFlo, Abott Laboratories, North Chicago, Ill.
[c]Acepromazine maleate injectable, Phoenix Pharmaceutical, St Joseph, Mo.
[d]Atropine sulfate, Phoenix Pharmaceutical, St Joseph, Mo.
[e]Surgicutt adult, International Technidyne Corp, Edison, NJ.
[f]Chrono-Log Corp, Havertown, Pa.

[g]IBL Immuno-Biological Laboratories, Hamburg, Germany.
[h]SPSS 11.0 for Windows, SPSS Inc, Chicago, Ill.
[i]Statistix 7.0 for Windows, Analytical Software, Tallahassee, Fla.

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