In cats with cardiogenic thromboembolism, is treating with aspirin associated with a better outcome?

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BOTTOM LINE

- Based upon current evidence, aspirin appears to be well tolerated, particularly at lower doses. However, there is no evidence that aspirin is effective in preventing recurrent cardiogenic thromboembolism or cardiac-associated death in cats with cardiac disease.
- Aspirin appears to be inferior to clopidogrel for the prevention of subsequent thromboembolic events and in promoting survival in cats with a history of arterial thromboembolism.

Clinical scenario

You are presented with a mature feline patient with a peracute onset of tachypnoea and non-ambulatory paraparesis. The cat is hypothermic, with a sternal systolic murmur and cold, stiff hindlimbs with pale cyanotic nail beds and poorly palpable hindlimb pulses. You provide oxygen therapy, diuretics and analgesia and perform a cardiac ultrasound, which identifies ventricular myocardial thickening and left atrial enlargement consistent with hypertrophic cardiomyopathy (HCM). You diagnose the cat with a cardiogenic feline arterial thromboembolism (FATE).

Your clients are keen to explore treatment for the patient and, as part of this, you plan to instigate antiplatelet therapy to reduce the likelihood of a second event. However, there is no licensed antiplatelet therapy for cats. A colleague has always used aspirin, but you are uncertain if there is any evidence to support its use.

The question

In [cats with cardiogenic thromboembolism], is treating with [aspirin] associated with a better outcome [reduced risk of arterial thromboembolism or death] compared with [alternative treatments, no treatment or placebo]?

Search parameters

The search strategy is available as a supplement to this article on *Vet Record*'s website at http://veterinaryrecord.bmj.com/content/185/12/376

Search outcome

- Forty-eight papers found in Medline search
- Twenty-five were excluded as they did not answer the question
- Thirteen were excluded as they related to species other than cats
- Seven were excluded as they were not primary research papers or systematic reviews
- Three relevant papers from Medline

- Twenty-eight papers found in CAB Abstracts search
- Ten were excluded as they did not answer the question
- Three were excluded as they related to species other than cats
- Twelve were excluded as they were not primary research papers or systematic reviews
- Three relevant papers from CAB Abstracts

- Three relevant papers found in total

Search last performed: 11 January 2019

Summary of evidence

Paper 1: Arterial thromboembolism in cats: acute crisis in 127 cases (1992–2001) and long-term management with low-dose aspirin in 24 cases[1]

Patient group: Forty-four cats who were discharged following presentation with arterial thromboembolism at a university teaching hospital in North America between 1992 and 2001. Eighteen were treated with a high dose of aspirin (HDA: at least 40 mg taken orally every 24 to 72 hours), 24 were treated with a low dose of aspirin (LDA: 5 mg taken orally every 72 hours) and two did not receive anticoagulants.

Study type: Retrospective cross-sectional study

Outcomes: The primary endpoints relevant to this clinical scenario were recurrence of FATE and death in cats that survived to discharge. Other outcomes for which data were collected included frequency of side effects attributed to aspirin treatment.

Key results: There was no significant difference in survival curves between cats receiving HDA and LDA (P=0.882). Although aspirin-attributed gastrointestinal side effects appeared to be more frequent for HDA-treated cats (22 per cent) than for LDA-treated cats (4 per cent), no statistically significant difference was proven.

Study weaknesses: The number of cats discharged without aspirin treatment was very small, so the difference in survival or FATE recurrence between aspirin-treated and untreated groups was not statistically analysed (or the results were not reported). There was variability in the concurrent medication administration before and after discharge from the presenting FATE episode, including six cats that were treated with aspirin before their first episode (three in the HDA group and three in the LDA group) and two cats that received heparin as well as aspirin after discharge from hospital post-FATE, which may affect the results.

The rationale for why each cat was assigned each dose is not clear, but is likely to have been affected by clinical bias at the time of prescription. Whether or not a significant difference was found between FATE recurrence in the LDA and HDA groups was not reported, although it appeared that cats treated with LDA were more likely to survive a subsequent FATE than cats treated with HDA.

Paper 2: Arterial thromboembolism in 250 cats in general practice: 2004-2012[2]

Patient group: Ninety-seven cats, under the care of three general practices in the UK, in which treatment had been attempted for FATE. Twenty-five cats received aspirin, 10 cats received aspirin and clopidogrel and two cats received clopidogrel alone.

Study type: Retrospective cross-sectional study

Outcomes: Mortality less than one day after presentation, between one and seven days after presentation and more than seven days after presentation was recorded. The circumstances of death – confirmed or suspected FATE-related, dyspnoea-related or neither FATE- nor dyspnoea-related – were also recorded.

Key results: Absence of antiplatelet therapy (aspirin, clopidogrel or both) was a negative predictor of mortality up to seven days after presentation (hazard ratio 8.26, P=0.001), but it was not correlated with survival beyond seven days after presentation.

Only a single leg being affected (P=0.001), being non-dyspnoeic at presentation (P=0.045), absence of congestive heart failure (CHF) (P=0.02) and not being treated with heparin (P=0.023) were all indicators of survival between one and seven days after presentation.

Study weaknesses: Due to the retrospective nature of this study, some records are incomplete and lacking information relevant to the investigation. For example, only 63 of the 97 cats that underwent treatment for their thromboemboli had sufficient clinical history available to enable the presence or absence of CHF at presentation to be identified. Also, it is not noted whether any of the cats with previously diagnosed cardiomyopathy were on medication to manage their condition before their first thromboembolism.

The authors identify that the protective value of antiplatelet therapy between one and seven days after presentation may be spurious, and no prolonged benefit was recorded after seven days. Additionally, the aspirin dosage used was not reported. As with the study by Smith and colleagues,[1] the fact that this is a retrospective study means that the prescription in each case is likely to have been affected by some level of clinical bias. In addition, approximately half of the cats surviving for more than 24 hours also received heparin, which may have affected the results.

Paper 3: Secondary prevention of cardiogenic arterial thromboembolism in the cat: the double-blind, randomised, positive-controlled feline arterial thromboembolism; clopidogrel vs aspirin trial (FAT CAT)[3]

Patient group: Seventy-five cats with underlying cardiac disease, under the care of 52 practices throughout North America, New Zealand and Europe, who had survived a FATE one to three months before enrolment in the study. Thirty-nine of the cats (52 per cent) were treated with clopidogrel (18.75 mg taken orally every 24 hours), and 36 (48 per cent) were treated with aspirin (81 mg taken orally every 72 hours).

Study type: Multicenter, double blind, randomised, positive-controlled study

Outcomes: The primary outcome measured was recurrence of FATE, and the secondary outcome measured was death. A combined endpoint of recurrence and cardiac-associated death (or euthanasia) was also evaluated. Other relevant outcomes included whether aspirin or clopidogrel administration was associated with any adverse reactions.

Key results: Compared with aspirin, clopidogrel administration significantly reduced the likelihood of recurrent FATE (75 per cent versus 49 per cent, P=0.024) and prolonged the median time to secondary FATE (192 days versus 443 days). Clopidogrel administration significantly reduced the likelihood of the combined endpoint of secondary FATE and/or cardiac-associated death (P=0.033) and increased the median time to the combined endpoint (346 days for clopidogrel versus 128 days for aspirin).

Both drugs were well tolerated – one cat in each group experienced adverse effects. No clinically relevant changes to biochemical and haematological parameters were observed between treatment groups.

Study weaknesses: The primary weakness of this study is the absence of a negative control group. So, although clopidogrel appears superior to aspirin, we cannot deduce with certainty whether there is an overall benefit of clopidogrel compared with a lack of treatment or placebo. Other weaknesses of the study are that two cats had received aspirin (one assigned to each group) and one received clopidogrel (assigned to the aspirin group) before the trial period and that two cats from each of these groups were lost to follow-up. Given the limited sample size, these points may or may not be of significance.

Comments

Difficulties in appraising the evidence included comparison of aspirin in combination with another treatment to no treatment, or a lack of control when comparing aspirin alone to another treatment or another dose. The doses of aspirin used varied between studies, and none of the studies followed the British Small Animal Veterinary Association dose recommendations.[4]

The strength of evidence is markedly strongest for Hogan and colleagues[3] due to it being a prospective, double-blinded, randomised, more markedly multicentre clinical trial with an increased cohort size following repeat power calculations. Of the retrospective papers, Borgeat and colleagues[2] was strongest – being a multicentre study with a larger patient population than the study by Smith and colleagues.[1]

The frequency of gastrointestinal side effects with aspirin appears to be low, especially with conservative doses of less than 40 mg every 24 to 72 hours. However, the overall weight of evidence in favour of prescribing aspirin is poor, and there is strong evidence that clopidogrel is a superior antiplatelet choice. Given the increased frequency of side effects in HDA-treated cats,[1] conservative dosing may be prudent if aspirin is to be prescribed.

References

1 Smith S, Tobias A, Jacob K, *et al*. Arterial thromboembolism in cats: acute crisis in 127 cases (1992–2001) and long-term management with low-dose aspirin in 24 cases. *J Vet Intern Med* 2003;17:73–83

2 Borgeat K, Wright J, Garrod O, *et al*. Arterial thromboembolism in 250 cats in general practice: 2004-2012. *J Vet Intern Med* 2013;28:102–8

3 Hogan D, Fox P, Jacob K, *et al*. Secondary prevention of cardiogenic arterial thromboembolism in the cat: the double-blind, randomised, positive-controlled feline arterial thromboembolism; clopidogrel vs aspirin trial (FAT CAT). *J Vet Cardiol* 2015;17(Suppl 1):306–17

4 Ramsey IK. BSAVA Small Animal Formulary: Part A, Canine and Feline. 9th edn. Gloucester: British Small Animal Veterinary Association, 2017

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doi: 10.1136/vr.l5690

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