Effects of the neurokinin-1 antagonist maropitant on canine gastric emptying assessed by radioscintigraphy and breath test

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Keywords
Stomach, motility, dog, prokinetic, cisapride

Summary
Objective: Delayed gastric emptying is a well-recognised phenomenon in a number of canine disease conditions. Only a limited number of drugs have been reported to have some gastrokinetic effect in the dog. The aim of this study was to investigate prokinetic effects of maropitant. Material and methods: In a cross-over study 24 healthy adult Beagle dogs were randomised to receive either maropitant (2 mg/kg q24 h PO), cisapride (1 mg/kg q12 h PO) or placebo (vitamin-B12, 10 µg/dog q24 h PO) for 7 days with a 7-day washout period between treatments. Gastric emptying was measured simultaneously via 99mTc-Technetium radioscintigraphy and 13C-sodium acetate breath testing for 6 hours post-feeding. The decrease in radioactive counts in the stomach and the increase in 13CO2 concentration in exhaled breath (measured via gas chromatography) were plotted against time. The area under the curve was determined for each test and the time to 25%, 50% and 75% gastric emptying was calculated for each test and the time to 25%, 50% and 75% gastric emptying was calculated for each method. Friedman test was used to compare gastric emptying times. Results: With both methods, no difference for gastric emptying times was observed for any treatment. Conclusion and clinical relevance: Neither maropitant nor cisapride were shown to have an effect on gastric emptying in healthy beagles using radioscintigraphy or breath test when compared to placebo. Consequently, neither drug can be recommended as a gastric prokinetic in dogs.

Introduction
Gastric emptying is a complex part of the physiology of digestion. Reflex mechanisms ensure that the rate of gastric emptying is adapted to the amount of nutrients delivered to the duodenum; and gastric contractions, pyloric relaxation and duodenal motility are strictly coordinated (1). Delayed gastric emptying and disturbed antropyloroduodenal coordination have been described in the dog with mechanical (gastric neoplasia, foreign body, polyp) or functional obstruction (inflammation, ulceration, infection) (2) or

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Schlüsselwörter
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Zusammenfassung

secondary to pancreatitis, electrolyte disturbances, metabolic diseases, septicemia, drug administration (especially anticholinergics), and other conditions (2–6). Diagnosing and treating gastric emptying disorders is important, as gastric retention and excessive gastric distension can lead to vomiting/regurgitation and potentially aspiration pneumonia, which carries a guarded prognosis. In the authors’ experience, especially in dogs with significant systemic diseases (septicemia, peritonitis, severe metabolic derangements like diabetic ketoacidosis), prokinetics decrease the risk of aspiration pneumonia and hence morbidity and mortality. In addition, two recent studies documented delayed gastric emptying in dogs undergoing abdominal surgery (7) and the effect of anesethesia on gastrointestinal transit times (8).

Investigations into the effect of a variety of drugs on canine gastric emptying have given equivocal results (2). To date, no drug with sufficient prokinetic effect on the canine stomach to be of clinical benefit is available or tested sufficiently. Several classes of drugs have been investigated so far: There is only weak evidence that dopaminergic D2 antagonists (metoclopramide, domperidone) accelerate gastric emptying in dogs. Metoclopramide reversed gastric relaxation by dopamine infusion in dogs in an experimental setting (9) and accelerated emptying of liquids measured via gastric cannulation at high oral doses (10). Metoclopramide had no effect on gastric emptying of solids when measured by gastric cannulation or strain-gauge technique (10, 11), however, it improved antropyloroduodenal coordination in one study (11). Domperidone increased the pyloric diameter (assessed via ultrasound) in healthy dogs and humans, which was interpreted as improving antropyloroduodenal coordination (12).

Serotonergic 5-hydroxytryptamine 4 (5-HT4) receptor agonists have potent prokinetic effects (13). Cisapride has been studied most extensively in dogs. It stimulates pyloric and duodenal motor activity, enhances antropyloroduodenal coordination and increases duodenal contractions (13). Unfortunately, since cisapride has been withdrawn from the European market due to cardiac side-effects in humans and dogs, there is a lack of an effective prokinetic drug alternative for dogs. Data on the prokinetic effect of novel 5-HT4 receptor agonists (i.e., velusetrag [14], mosapride [15, 16], prucalopride [17]) are limited. Motilin agonists (erythromycin and its derivatives) accelerate gastric emptying in the dog (18) by inducing phase III interdigestive contractions, which might not be ideal in a clinical setting and lead to “dumping” of poorly pre-digested gastric contents into the duodenum; whereas histamine H2-agonists (ranitidine, nizatidine), which stimulate intestinal motility by inhibiting acetylcholinesterase activity (19) only show a mild prokinetic effect on the canine stomach.

There has been speculation that the neurokinin (NK)-1 receptor antagonist maropitant might have prokinetic effects in dogs (20, 21). It is licensed as an anti-emetic for dogs and cats, and its effectiveness in treating and preventing vomiting due to a variety of causes has been shown in multiple studies (22–24). Both NK-1 receptors (25) and their natural ligand, the tachykinin substance P (SP) (26) have been identified in the canine stomach. There have been conflicting reports about the effects of tachykinins and their antagonists on gastric emptying in rodent models, with increased (27), decreased (28) and unchanged (29) gastric emptying rates documented. However, these studies are difficult to compare with each other, as SP was administered by different routes (aortic versus intra-peritoneal injection), at different dosages and different time-points in relation to feeding. To the authors’ knowledge, no study has assessed the effect of maropitant on postprandial patterns of canine gastric emptying.

Thus, the aim of this current study was to investigate the effect of maropitant on gastric emptying times in healthy dogs in an open label positive (cisapride) and placebo-controlled, randomised, cross-over design using the gold-standard of radioscintigraphy and the 13C-sodium acetate breath test, an indirect method that has been shown to correlate well with scintigraphic values (30).

Materials and methods

Study dogs

The study population consisted of 24 healthy Beagle dogs; eight female spayed and 16 male castrated. A power calculation had determined that 20 dogs would be sufficient to detect a change of 25% in gastric emptying times. The median age of the dogs was 4.5 years (range 1.4–6.6 years), mean weight was 12.8 kg (SD ± 3.6 kg) and body condition score of all dogs was in the range 3–4/5. Three dogs were privately owned and 21 dogs belonged to the research colony of the Small Animal Hospital in Giessen, Germany. Written informed owner consent was obtained for the three privately owned dogs before the start of the study. Ethical approval of the study protocol was obtained from the regional council board (approval number V54–19c20–15(1)GI 18/17).

Prior to the start of the study, dogs were deemed healthy based on physical examination and full haematology and biochemistry panels including normal results of a bile-acid stimulation test. In addition, all dogs were treated with fenbendazole at a dose of 50 mg/kg daily for 3 days within the 2 weeks before the start of the study. Daily clinical examinations were performed on each dog during the study period. Exclusion criteria were the presence of any clinical signs attributed to gastrointestinal disease (vomiting, diarrhoea, weight loss, and inappetence) in the 6 months before the study, a history of abdominal surgery or the administration of any drugs (except antiparasitics) within the last 14 days before the start of the study.

Study design

Two weeks before the study, a commercially available canned food was gradually introduced into the dogs’ diet. This was fed...
A baseline sample was obtained from each dog immediately before each test meal was ingested (± 10 minutes) after drug dosing, and gastric emptying was determined simultaneously by scintigraphy and $^{13}$C-sodium acetate breath test (see below).

**Test meal.** Half of the daily caloric requirements were calculated individually for each dog, based on the following formula: $70 \times \text{kg bodyweight}^{0.75} \times 1.6 = \text{kcal/day}$. Two-hundred MBq 99mTc-Technetium bound to albumin$^{2}$ (to avoid absorption) as well as 100 mg unbound $^{13}$C-sodium acetate$^{6}$ were added to each test meal, which was then mixed thoroughly using a household blender. A scintigraphic image of the food was visually inspected to confirm homogenous spread of the radioactive tracer within the test meal before feeding (data not shown). At least 75% (by weight) of the food had to be consumed within 15 minutes of it being offered to each dog, otherwise no measurement of gastric emptying was performed and that leg of the study for that dog was repeated at a later time (out of the assigned sequence). Drinking water was available ad libitum at all times, except when scintigraphic imaging and breath testing were being performed.

$^{99m}$Tc-Technetium radioscintigraphy. As previously described$^{3}$, dogs were kept in sternal position above the gamma camera with minimal restraint. Image acquisition time was 60 seconds. Ventral images were taken immediately after intake of the test meal, every 15 minutes for the first 2 hours, every 30 minutes for the following 2 hours, and finally every 60 minutes for another 2 hours. These time points have been shown to be sufficient for optimal calculation of gastric emptying in an earlier study$^{31}$. The area of the stomach (region of interest, ROI) was defined manually based on the morphological features of the stomach visible, and all pixels within this region were counted automatically. Subsequently, decay-corrected radioactivity counts were plotted against time. Total area-under-the-curve (AUC) was calculated and, using the percentiles of the AUC, gastric emptying times at different stages (25%, 50% and 75% of emptying) were determined as described previously$^{30}$.

$^{13}$C-sodium acetate breath test. A baseline sample was obtained from each dog immediately before each test meal was ingested. Subsequent breath samples were taken at the same time points as used for the scintigraphic measurements. These time points have been validated in earlier studies$^{7,30,32}$. Samples were collected via a commercially available anaesthetic face mask$^{7}$ for small animals that fitted tightly around the dogs’ muzzles. The mask was connected to a three-way valve (allowing the dogs to breathe normally throughout the process) and attached to a commercially available glass vial$^{8}$. Filling of each vial was ascertained by the build-up of condensation; they were then sealed immediately, labelled and analysed within 14 days. A pilot study conducted before the start of sampling had shown that breath samples were stable at room temperature for up to 3 weeks after collection (data not shown). The $^{13}$CO$_2$ content of breath samples from each time point was assessed in duplicates using gas chromatography with Isotope Ratio Mass Spectrometry. Ion currents consistent with the mass of $^{12}$C [44] and $^{13}$C [45] were measured against a certified International Atomic Energy Agency (IAEA) reference material. To allow Craig correction for $^{13}$O, $^{18}$O (mass 46) was also determined [33]. The $^{13}$CO$_2$/$^{12}$CO ratio ($\Delta^{13}$C) was calculated using the integrated software$^9$ and Excel 2007-SP1$^{10}$. Delta $^{13}$C was expressed in permille, where $\Delta^{13}$C is the $^{12}$C/$^{13}$C isotope ratio in relation to a primary reference isotope ratio (PDBe standard) [33]. The AUC and thus quartiles of gastric emptying (25%, 50% and 75%) were determined similarly to the scintigraphic measurements.

**Statistical analysis**

Statistical analysis was performed using SPSS statistical software$^{11}$. Data were assessed for normal distribution by inspection of histograms and found to be normally distributed. Median values of 25%, 50% and 75% gastric emptying times between the three

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2. Cerenia®, Zoetis Germany, Berlin, Germany
3. PropulsidTM, Pharmacia & Upjohn Co., a division of Zoetis (Pfizer), New York, USA
4. Vitamin B12-ratiopharm, Ratiopharm GmbH, Ulm, Germany
5. Solco-Nanocoll, Sorin-Biomedica, Munich, Germany
6. $^{13}$C-sodium acetate, cat. # 298042, Sigma Aldrich, Munich, Germany
7. Anaesthetic mask for small animals, Heiland Vet (today: Henry Schein Vet), Hamburg, Germany
8. Non-evacuated Exetainer, Labco, Wycombe, United Kingdom
9. IonVantage 1.1., GV Instruments, Wittenhawe, United Kingdom
10. Excel 2007-SP1, Microsoft, Unterschleissheim, Germany
11. IBM SPSS Statistics 19.0, IBM Corp., Armonk, New York, USA

<table>
<thead>
<tr>
<th>Group of dogs</th>
<th>Treatment 1</th>
<th>Treatment 2</th>
<th>Treatment 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Maropitant</td>
<td>Cisapride</td>
<td>Placebo</td>
</tr>
<tr>
<td>B</td>
<td>Maropitant</td>
<td>Placebo</td>
<td>Cisapride</td>
</tr>
<tr>
<td>C</td>
<td>Cisapride</td>
<td>Placebo</td>
<td>Maropitant</td>
</tr>
<tr>
<td>D</td>
<td>Cisapride</td>
<td>Maropitant</td>
<td>Placebo</td>
</tr>
<tr>
<td>E</td>
<td>Placebo</td>
<td>Maropitant</td>
<td>Cisapride</td>
</tr>
<tr>
<td>F</td>
<td>Placebo</td>
<td>Cisapride</td>
<td>Maropitant</td>
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treatments were compared using Friedman test (as data were not normally distributed). In addition, the effect of any treatment throughout the open label placebo-controlled cross-over study was investigated separately for each stage of gastric emptying (25%, 50% and 75%) using a linear mixed effect model. To accomplish this, three dummy variables were created for each treatment sequence (compare to ▶ Table 1) in each individual dog (0 = no treatment, 1 = treatment). Setting the dog ID as random effect, these “treatment” dummy variables were – together with the current treatment effect – included into the model as fixed main effects. Significance was set at p < 0.05.

Results

Study dogs and test meal. All dogs accepted the test meals voluntarily at the first time of offering. One dog vomited approximately 1 hour after feeding. A subsequent clinical examination of the dog did not reveal any possible cause nor any sign of ill health. The test was aborted for this animal and this leg of the analysis repeated 2 weeks later. This dog exhibited no further vomiting during the second test.

Technetium radioscintigraphy. Gastric emptying showed a sigmoidal pattern in all dogs. Lag phases varied in duration and were absent in six dogs. Gastric emptying times are summarized in ▶ Table 2. No significant difference could be detected between treatments at any stage: p = 0.607 at 25%, p = 0.214 at 50% and p = 0.167 at 75% gastric emptying (▶ Fig. 1). Treatment had no significant effect across all groups for all time points (▶ Table 3).

Table 2  Median (range) of gastric emptying times (minutes) at different stages (25%, 50%, 75%) in 24 dogs with different treatments, measured via radioscintigraphy (sc) and 13C-sodium acetate breath test (b).

<table>
<thead>
<tr>
<th>Method</th>
<th>Gastric emptying</th>
<th>Gastric emptying time (minutes)</th>
<th>Placebo</th>
<th>Maropitant</th>
<th>Cisapride</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radioscintigraphy</td>
<td>25%</td>
<td>37.4 (26.6–45.7)</td>
<td>36.3 (28.1–49.2)</td>
<td>35.99 (27.8–45.6)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>50%</td>
<td>80.2 (56.9–98.8)</td>
<td>78.5 (58.7–105.8)</td>
<td>76.2 (62.3–97.9)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>75%</td>
<td>140.6 (97.4–173.8)</td>
<td>137.6 (99.3–182.5)</td>
<td>132.6 (107.4–169.8)</td>
<td></td>
</tr>
<tr>
<td>13C-sodium acetate breath test</td>
<td>25%</td>
<td>88.7 (79.1–117.0)</td>
<td>91.6 (66.8–115.9)</td>
<td>92.6 (72.3–119.0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>50%</td>
<td>155.7 (125.2–191.9)</td>
<td>156.3 (110.1–190.6)</td>
<td>157.1 (117.7–180.8)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>75%</td>
<td>231.7 (179.9–265.4)</td>
<td>231.1 (164.2–268.8)</td>
<td>222.5 (171.1–257.0)</td>
<td></td>
</tr>
</tbody>
</table>

Table 3  Effect of pre-treatment with different drugs (maropitant, cisapride or placebo) on gastric emptying times (minutes) at different emptying stages (25%, 50%, 75%) measured via radioscintigraphy (sc) and 13C-sodium acetate breath test (b) in a mixed linear model.

<table>
<thead>
<tr>
<th>Method</th>
<th>Gastric emptying</th>
<th>Effect of pre-treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Maropitant</td>
<td>Cisapride</td>
</tr>
<tr>
<td>Radioscintigraphy</td>
<td>25%</td>
<td>0.067</td>
</tr>
<tr>
<td></td>
<td>50%</td>
<td>0.057</td>
</tr>
<tr>
<td></td>
<td>75%</td>
<td>0.060</td>
</tr>
<tr>
<td>13C-sodium acetate breath test</td>
<td>25%</td>
<td>0.508</td>
</tr>
<tr>
<td></td>
<td>50%</td>
<td>0.290</td>
</tr>
<tr>
<td></td>
<td>75%</td>
<td>0.199</td>
</tr>
</tbody>
</table>

Fig. 1  Gastric emptying times for different treatments assessed via radioscintigraphy in 24 dogs. C = cisapride, M = maropitant, P = placebo.

Abb. 1  Szintigraphisch ermittelter Effekt verschiedener Medikamente auf die Magenentleerungszeit bei 24 Hunden. C = Cisaprid, M = Maropitant, P = Plazebo.
Discussion

In the present study, both a direct (radioscintigraphy) and an indirect method (breath testing) were used to evaluate the solid phase gastric prokinetic effects of orally administered maropitant and cisapride compared to placebo in healthy Beagle dogs. Neither method was able to detect a significant difference in gastric emptying times between the three treatments. These findings are similar to two preliminary studies investigating the effect of maropitant on gastric motility by wireless motility capsule (20) or ultrasound (21). In both of these studies, maropitant and other prokinetic agents did not accelerate gastric emptying time when compared to placebo (20) and only metoclopramide (and not maropitant) had an effect on antral motility (21).

The fact that maropitant has no effect on gastric emptying in the dog is interesting since tachykinins in general, and SP in particular, have been reported to both stimulate and inhibit motility of the stomach and the pyloric sphincter via NK receptors in different studies (34–36). For example, although SP was shown to cause a dose-dependent contraction of the canine stomach in vivo, this response declined with subsequent SP injections and could be fully blocked by atropine (36). In other studies, SP was found to stimulate only circular contractions of the antrum and fundus, with no effect on the gastric corpus or pylorus when measured using strain-gauge techniques (34), and thus possibly no effect on overall gastric emptying either. Another study described a potential dual role for SP in the canine stomach, where it was found to increase basal tone of the gastric smooth muscles in vivo, but to inhibit peristaltic contractions (mainly spike potentials) (35). In this study it was concluded that SP was a modulator of gastric motility rather than a main driver of contractions (35). Thus antagonising SP with an NK-1 receptor antagonist could in theory have the opposite effect; decreasing basal tone and promoting contractions.

The overall effect of NK-1 receptor inhibition on gastric contractions may be too small to measure in an in vivo situation compared to the effect exhibited by other naturally occurring neurotransmitters (especially acetylcholine) or intestinal peptides (for example pentagastrin or gastrin-releasing peptide) (37, 38), which might “overrule” modulation by SP or other tachykinins. Other reasons why we were not able to demonstrate an effect of maropitant on gastric emptying may lie with the complicated mechanism of NK receptor regulation and signalling: There is some evidence that NK-1 receptor signalling is differentially regulated by binding of its ligands – SP-binding and binding of other tachykinins can cause different effects (39). The presence of different NK-1 receptor subtypes with different affinities to antagonists has also been proposed (39). Alternatively, as neurokinin receptors are located on smooth muscle cells, neurons and epithelial cells, their regulation might elicit different responses depending on the site of activation or blockage. It is also possible that the main tachykinin receptor in the intestine of the dog is not NK1, but NK2, as there is some evidence for this in other species (40), but this has not been investigated in the dog to date. A recent study documented a 12% variation coefficient of gastric emptying times measured using scintigraphy (41). Hence, even though an effort was made to ensure adequate power of the present study to detect a difference (estimate of gastric emptying variation was based on the available literature at the time and the experience of the authors), it cannot be ruled out that the number of dogs was too small, especially in the light of moderate individual variations.

In the current study, it was interesting that cisapride, which was chosen as the “positive control”, did not have a prokinetic effect when compared to placebo. This might appear puzzling, as 5-HT₄ agonists have been shown to consistently accelerate gastric emptying in rodents and humans (42, 43). This might be due to the dosing regimen used here or the formulation of the drug used.
There are only few studies documenting the effects of cisapride on gastric emptying times using non-invasive techniques. It was shown to accelerate total gastroduodenal emptying and improve antropyloroduodenal coordination in one study (18). However, no effect of cisapride on gastric motility was observed via tracking of orally ingested barium sulphate spheroids (6) or scintigraphy (44) in healthy dogs. In addition, some recent studies assessing antral contraction amplitude, frequency and motility index showed that the effect of cisapride on these parameters was inferior to that of metoclopramide (21, 45). Some synthetic 5-HT4 agonists have been shown to be more effective in promoting both liquid and solid phase gastric emptying in the dog (43). It might be concluded then that cisapride is not as effective as other 5-HT4 agonists in stimulating canine gastric emptying in healthy dogs, thus it may not be ideal as a positive control in experimental studies or even in a clinical setting. However, at the time this study was conducted, no other 5-HT4 agonist was commercially available, and cisapride was considered the best option for a positive control.

We consider it unlikely that the failure to detect any prokinetic effects of maropitant or cisapride in the present study was due to the techniques used to measure gastric emptying. In general, non-invasive direct techniques are considered superior to invasive or indirect methods, as gastric emptying can be observed in real time, the test meal resembles “normal” food, there is no need for general anaesthesia/permanent restraint and preferential monitoring of either liquid or solid phase gastric emptying can be observed; which is why radioscintigraphy is considered the gold-standard against which other methods should be compared (31). Invasive methods such as those using strain-gauges (intragastric balloons and fixed intragastric volumes of saline) are for obvious reasons not a feasible option in a clinical setting. Indirect methods (plasma tracers, breath test) assume that the rate-limiting step to detection of the tracer substance is gastric emptying (i.e. normal absorption and metabolism of the substrate is assumed), if this requirement is fulfilled, these techniques are usually much easier to perform (with a test meal resembling normal food) and do not require specialist equipment or handling of radioactive material (31). Here we used the 13C-sodium acetate breath test as an indirect alternative to radioscintigraphy, as this method has been described as useful in measuring gastric emptying in the dog (32), and it correlates well with measurements obtained by scintigraphy (30). Both techniques give different average gastric emptying times, as one (scintigraphy) is a direct method and another a direct one (breath test) relying on metabolism of a marker substance before it can be detected non-invasively. Hence, reference values for normal versus abnormal gastric emptying times always also depend on the method used. In the present study, the absence of significant differences in gastric emptying times between treatments demonstrated with either technique, strengthen the validity of these observations. In addition, there was a good correlation between both methods in the present study (data not shown).

Overall, it seems necessary to draw a careful distinction between drug effects in an experimental setting (in vivo or in vitro), where effects on single muscle layers or gastric contraction patterns may be observed, especially when other mediators of gastriointestinal motility are artificially blocked, and clinical settings. In addition, it is likely that the induction of muscle contractions in the stomach alone is not enough to significantly increase gastric emptying, but that sequential contractions and antropyloroduodenal coordination are more important (46). Even though some improvement in this coordination has been observed in the dog with 5-HT4 agonists (18), it is possible that it is mediated by other mediators entirely. In rats, this coordination has been found to be mediated via ghrelin (46). This gastrointestinal peptide has also been used successfully to accelerate gastrointestinal motility in dogs with post-operative gastric ileus (47). While the goal of the present study was not to elucidate if and how maropitant or cisapride influence antropyloroduodenal coordination, this may be an interesting topic for further research.

In conclusion, neither maropitant nor cisapride demonstrated clinically relevant effects on different stages of gastric emptying in healthy dogs in this study. As this study did not include dogs with gastric dysmotility, recommendations regarding their use in naturally occurring gastric emptying disorders is difficult. It is worth noting, however, that the lack of a prokinetic effect of maropitant may be beneficial in individual cases where the cause of vomiting is unclear and gastric obstruction cannot be entirely ruled out. Studies assessing the effect of maropitant in dogs with abnormal gastric motility are necessary to further elucidate its effects in these situations.

**Conflict of interest**
The authors declare not to have any conflict of interest. All consumables used in this study were sponsored and supplied by Zoetis (Paris, France).

**References**


