# Postanaesthetic effects of ketamine–midazolam and ketamine–medetomidine on gastrointestinal transit time in rabbits anaesthetised with isoflurane

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## Abstract

**Background** Gastrointestinal stasis is a common perianaesthetic complication in rabbits. The objective of this study was to assess the impact on gastrointestinal transit time of ketamine–midazolam (KMZ) versus ketamine–medetomidine (later antagonised by atipamezole) (KMT-A) in rabbits anaesthetised with isoflurane.

**Methods** This was a cross-over, randomised, single-blinded, controlled, experimental trial. Seven healthy adult New Zealand White rabbits were used. Gastrointestinal transit time was assessed by contrast radiography in awake rabbits. Presence of contrast medium in the small intestine (gastric transit time), in the caecum (small intestinal transit time) and in faeces in the colon was assessed. One week later, 55 minutes isoflurane anaesthesia was induced with ketamine (15 mg/kg) and either midazolam (3 mg/kg) or medetomidine (0.25 mg/kg) by intramuscular injection. Thirty minutes after discontinuation of isoflurane, atipamezole (0.5 mg/kg) was administered only to rabbits in KMT-A treatment. Gastrointestinal transit time was then assessed in both treatment groups, beginning 30 minutes after cessation of isoflurane administration. Two weeks later, the treatment groups were interchanged.

**Results** Gastric and small intestinal transit times were significantly longer with KMT-A (92±109 minutes and 214±119 minutes, respectively) than with KMZ (1±0 minutes and 103±6 minutes, respectively) and in the awake state (7±7 minutes and 94±32 minutes, respectively).

**Conclusion** Clinicians should therefore be aware of the potential gastrointestinal side effects of KMT-A, particularly in rabbits at risk for gastrointestinal stasis.

## Introduction

Anaesthesia in healthy rabbits is associated with a risk of death of 0.73 per cent within 48 hours in comparison with 0.05 per cent in dogs and 0.11 per cent in cats.[1]

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Gastrointestinal stasis is a common perianaesthetic complication[2 3] that can lead to dehydration, gastrointestinal tympany, hepatic lipidosis, shock and death.[4] A very high incidence of gastrointestinal complications is reported, accounting 38 per cent of anaesthetic events in rabbits.[5]

Gastrointestinal effects of α2-agonists, ketamine, midazolam, isoflurane and antagonists such as atipamezole have been documented in other animal species. Alpha 2-agonists (medetomidine and dexmedetomidine) decreased the contractive motility of the caecum and colon in horses,[6] colon in dogs,[7] rumen in goats[8] and gastrointestinal transit in rats.[9] In dogs and rats, these effects were antagonised by the $\alpha_2$-antagonists atipamezole and yohimbine.[7 9] Ketamine did not affect gastrointestinal transit time in dogs[10]

and horses,[11] in contrast to pigs.[12] In mice, midazolam alone delayed gastrointestinal transit.[13] A prolongation of gastrointestinal transit time was also described after isoflurane anaesthesia in rats.[14] The effects of ketamine, α2-agonists, isoflurane, atipamezole and midazolam on gastrointestinal transit have not been studied in the rabbit.

The objective of the current study was to assess and compare the impact on gastrointestinal transit of two conventional anaesthetic protocols in the rabbit: induction with (1) ketamine–midazolam (KMZ) versus (2) ketamine–medetomidine (later reversed by atipamezole) (KMT-A), prior to isoflurane maintenance.

## Materials and methods

### Animals and husbandry

Seven adult females New Zealand White rabbits (*Oryctolagus cuniculus*) were used. They were aged six months with a mean±SD weight of 3.10±0.71 kg and with American Society of Anaesthesiologists grade 1. They were housed in 1 m × 2×1 cages (two animals per cage). The ambient temperature was 21°C, and light was turned on between 08:00 and 20:00. Throughout the study, rabbits received hay ad libitum, and vegetables (approximately 200 g celery leaves, endives, parsley) and pellets (approximately 15–20 g) at 20:00. Water was available ad libitum.

### Study design

A single-blinded, randomised, cross-over controlled study was conducted to compare the two protocols. Rabbits were assigned randomly to KMZ or KMT-A, using a random number generator (Microsoft Office Excel 2010). Two weeks (wash-out) after anaesthesia with one drug combination, rabbits were anaesthetised with the other.

### Anaesthesia

Rabbits were not fasted. Anaesthesia was induced between 08:30 and 08:45. For the KMZ treatment, midazolam (Midazolam Mylan; Mylan bvba/sprl, Belgium) 3 mg/kg and ketamine (Nimatek; Eurovet Animal Health, Netherlands) 15 mg/kg were injected in the lumbar epaxial muscles (intramuscular). Ketamine 15 mg/kg and medetomidine (Domitor; Orion Corporation, Finland) 0.25 mg/kg were administered intramuscularly in the lumbar epaxial muscles in the KMT-A treatment.[15] To keep the observer blinded, syringes were prepared by a technician and topped up with 0.9 per cent saline to obtain identical volumes between the two treatments.

Once sufficiently relaxed, a supraglottic airway device (V-gel Rabbits R3; Docsinnovent, UK) was inserted, and the rabbit was positioned in dorsal recumbence on an insulated mattress. Isoflurane (Vetflurane; Virbac SA, France) was administered in oxygen (500 ml/kg/minute) via a non-rebreathing Bain system with rabbits breathing spontaneously. The isoflurane vaporiser calibration was checked before and after the study. An infrared light was used to maintain body temperature in the physiological range (37.7°C–40.2°C). Eye ointment (Ocry-gel; TMV, France) was applied to avoid corneal drying.

After 15 minutes of stabilisation, anaesthesia was maintained during 40 minutes (administration of isoflurane during a total duration of 55 minutes). The percentage of delivered isoflurane to achieve an appropriate depth of anaesthesia for surgery (absence of palpebral reflex, absence of response to pinching the toe but persistence of the corneal reflex) was recorded. Isoflurane administration was then stopped and rabbits received 100 per cent oxygen until removal of the supraglottic airway device, in sternal recumbency. Atipamezole 0.5 mg/kg (Antisedan; Orion Corporation, Finland) was injected intramuscularly in rabbits in the KTM-A treatment, 30 minutes after isoflurane administration ceased. The same volume of NaCl 0.9 per cent, prepared by a technician, was injected intramusculary in rabbits of the KMZ treatment.

### Monitoring

Heart rate (HR), indirect arterial blood pressure (ABP), respiratory rate (*f*R), end-expired carbon dioxide tension (ET CO2), arterial oxygen saturation of haemoglobin (SpO2), rectal temperature (T) and heart rhythm were monitored one week before anaesthesia (awake state), immediately before anaesthesia, during anaesthesia, during the immediate postanaesthetic period and two days after anaesthesia. HR and rhythm were recorded with an ECG (Mindray; PM-9000vet, China), ABP with a Doppler blood flow probe (Doppler Vet BP; Mano Medical, France), SpO2 with a pulse oximeter (Mindray; PM-9000vet, China), *f*R and ET CO2 with a capnograph (Mindray; PM-9000vet, China). An electronic temperature probe (Mindray; PM-9000vet, China) was inserted into the rectum to measure the body temperature.

### Gastrointestinal contrast study

A gastrointestinal tract contrast study was conducted at three time points: (1) in the awake state, one week before the first anaesthesia, and (2) and (3) at the time for each modality of anaesthesia at two-week interval.

At each time points, a 30 per cent suspension of barium sulphate (12 ml/kg) (Micropaque Suspension; Guerbet, France)[16] was administered via nasogastric tube between 10:00 and 10:30 hours in the morning. After application of topical anaesthetic spray (xylocaine 10 per cent), a nasogastric tube (5 Fr × 37 cm) was passed, and its position in the stomach was confirmed with right latero-lateral radiograph. To assess the transit time of the contrast agent, a ventro-dorsal radiograph was performed one minute after the administration of barium sulphate, then after 15, 30, 60, 120, 240, 360

and 420 minutes.[17] The contrast study ended when barium sulphate was present in the hard faeces in the colon. The time points at which barium was detected for the first time (1) in the small intestine, (2) in the caecum and (3) in hard faeces in colon, were called, respectively (1) gastric transit time, (2) small intestinal transit time and (3) time to formation of hard faeces (figure 1). Times to the first food intake and faecal output were recorded.

## Statistics

Data were collected in Microsoft Excel and analysed with Stat direct (Medical Statistics Software, Cheshire, UK). The gastrointestinal transit was quantified in two ways: first by the mean±SD (range) times (minutes) of the time points (1, 15, 30, 60, 120, 240, 360 or 420 minutes) reached by each rabbit for each of the three stages of filling (presence of contrast in the small intestine, in the caecum and formation of hard faeces), and secondly, by counting the number of rabbits that had reached each of the three stages at each radiographic time point. Shapiro-Wilk test was used to examine the normality of data. Because of normality, the paired Student's *t* test was used to compare data between two drug combinations protocols and the repeated measures analysis of variance to compare more than two drug combinations protocols except for small intestinal transit time and time to the first food intake that were non-parametric data and were compared by using the Wilcoxon signed rank test and Friedman test. A p value <0.05 was considered as significant.

## Results

Anaesthesia induced by KMZ required significantly higher isoflurane vaporiser settings (1.8 per cent±0.3 per cent) to reach a surgical depth of anaesthesia, than by KMT-A (1.0 per cent±0.4 per cent).

Mean (±SD) HR, *f*R, ET CO2, SpO2, ABP and T in the seven rabbits in the awake state were all within normal ranges and did not significantly differ from those immediately before anaesthesia, and two days later, indicating that animals were all healthy and in a similar physiological status throughout the study.

### Gastrointestinal transit study

Results of transit studies in the awake state and after anaesthesia are summarised in table 1 and figure 2. Gastric transit time and small intestinal transit time were significantly longer in KMT-A treatment than in KMZ treatment and after anaesthesia than in the awake state. Time to formation of hard faeces did not differ between KMT-A, KMZ and the awake state. At T 1 minute, a significantly higher number of rabbits presented barium in the small intestine in the KMZ treatment compared with the KMT-A treatment. At T 120 and 240 minutes, a significantly higher number of rabbits had barium present in the hard faeces in the awake state than after anaesthesia with KMT-A and KMZ. The times to first food intake and faecal output did not differ between KMT-A (121±86 and 378±166 minutes, respectively) and KMZ (93±24 and 304±189, respectively).

## Discussion

Slowing gastrointestinal transit might lead to gastrointestinal stasis, a common self-aggravating and multifactorial syndrome associated with a significant mortality in pet rabbits.[18] It is characterised by a reduction/absence of stool production, anorexia, dehydration and abdominal pain.[19] Prolonged ileus can lead to alteration of the gastrointestinal microflora (dysbiosis) leading to proliferation of pathogens such as *Clostridia* subspecies and enterotoxaemia.

Although the current study demonstrated a statistically significant slowing of transit times in the KMT-A treatment, it is unclear to what extent this could cause clinical digestive stasis, because the degree of transit inhibition required to cause stasis is not known. Obviously, the clinical status of rabbits in this study was not adversely affected. They were healthy, of calm disposition and they did not receive any medications that could affect gut transit. Time to formation of hard faecal pellets and faecal output did not differ between KMZ and KMT, indicating that they did not develop intestinal stasis. Furthermore, no painful procedure was performed. It has been reported that rabbit patients are frequently stressed, anorexic, painful or receiving other medications, and all these factors can have adverse effects on a rabbit's gastrointestinal motility.[2] Additionally, gastrointestinal stasis can occur secondarily to any other clinical disease,[20] which produces alterations in fluid balance and/or in gastrointestinal motility.[19] It cannot be excluded that the delay due to the use of KMT-A for induction of anaesthesia might not have an impact on diseased animals.

Various methods of transit measurement have been used in rabbits, including contrast radiography after oro-gastric administration of radiopaque markers or liquid contrast medium, such as iodixanol or barium sulphate solutions. The transit times in awake animals in the current study were in relative accordance with those observed in other studies,[16 17 21] with gastric transit time between 8 and 30 minutes, small intestinal transit time between 40 and 60 minutes and presence of barium in hard faeces after 240 minutes. However, in the other studies, no information was available about diet and feeding regimen, which are known to influence transit times.

Assessment of gastrointestinal transit in rabbits is complex because of production of two types of faeces: hard faeces and caecotrophs (soft faeces).[22] Rabbits are hindgut-fermenting herbivores, and the caecal microflora alters the digesta and makes it available to be reingested by caecotrophy. This nycthemeral process (and so the transit time) is influenced by

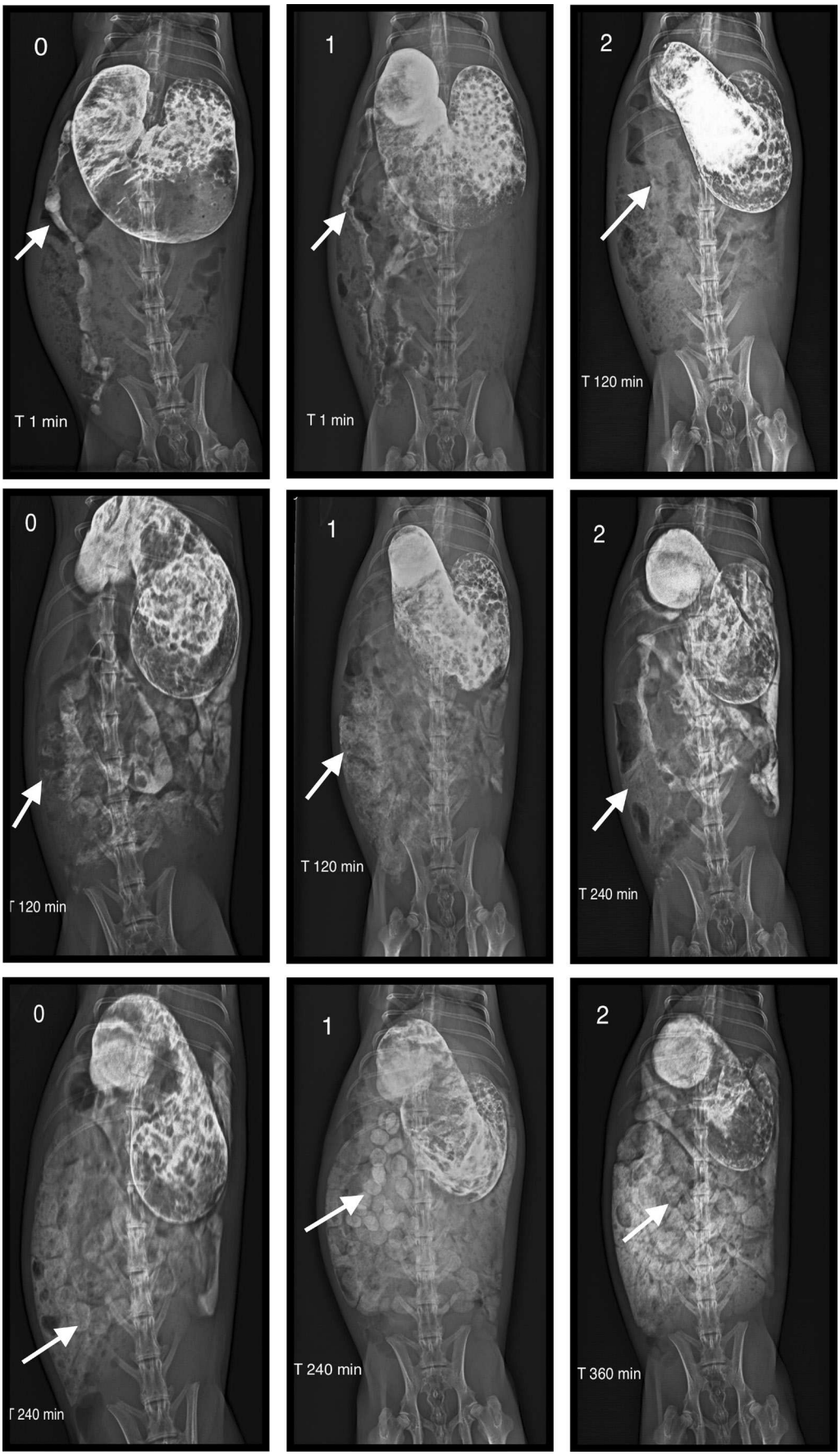


**Figure 1** Gastric emptying (presence of contrast in the small intestine), caecal filling (presence of contrast in the caecum) and formation of hard faeces in the awake state (0) and in the postanaesthetic period in the same rabbit in which anaesthesia was induced with KMZ (1) and KMT-A (2) prior to isoflurane anaesthesia. In this rabbit, gastric emptying (presence of barium in the small intestine is indicated by the arrow) had started at T 1 minute in the awake state and with KMZ and at T 120 minutes with KMT-A. Filling of the caecum (presence of barium in the caecum is indicated by the arrow) had started at T 120 minutes in the awake state and with KMZ and at T 240 minutes with KMT-A. Barium was present in the hard faeces (as indicated by the arrow) at T 240 minutes in the awake state and with KMZ and at T 360 minutes with KMT-A. It is of note that when gastric emptying started, barium frequently appeared as small inconspicuous 'traces' in group KMT-A. In contrast, barium formed long uninterrupted 'traces' in all the rabbits in the awake state and in the group KMZ. The entire transit study of this rabbit is shown in appendix. KMT-A, ketamine-–medetomidine (later reversed by atipamezole); KMZ, ketamine-midazolam.

**Table 1** Mean±SD (range) gastrointestinal transit variables in seven rabbits in the awake state and in the postanaesthetic period of isoflurane anaesthesia after induction with KMT-A or KMZ

| | Awake state | KMZ | KMT-A |
|---|---|---|---|
| Gastric transit time (minutes) | 7±7 (1–15) | 1±0* (1) | 92±109*† (1–240) |
| Small intestine transit time (minutes) | 94±32 (60–120) | 103±67 (60–240) | 214±119*† (60–360) |
| Time to formation of hard faeces (minutes) | 206±91 (120–360) | 291±64 (240–360) | 300±77 (240–420) |

*Value significantly different from that measured in awake animals ($p<0.05$).
†Value significantly different from the corresponding value measured in animals from KMZ treatment.
KMT-A, ketamine–medetomidine (later reversed by atipamezole); KMZ, ketamine–midazolam.

feeding regimen. In rabbits fed ad libitum, food intake peaks between 19:00 and 01:00, which corresponds to the excretion of hard faeces. Food intake is minimal approximately six hours after the peak, which corresponds to the ingestion of caecotrophs (mainly in the morning).[23] In rabbits fed ad libitum, food ingested in the morning persists for three to four hours longer in the gastrointestinal tract than food ingested in the afternoon.[24] In contrast, the retention time is greater for food consumed in the afternoon in rabbits fed only during the diurnal period.[25] For this reason, all the rabbits in this study were fed at the same time. The contrast was also given at the same time for every rabbit.

Interindividual variations in caecotrophy periods exist, but faecal output and food ingestion rhythms appear to be particularly stable over time within individuals.[23 24] For this reason, a cross-over design was interesting to compare KMT-A and KMZ, so that

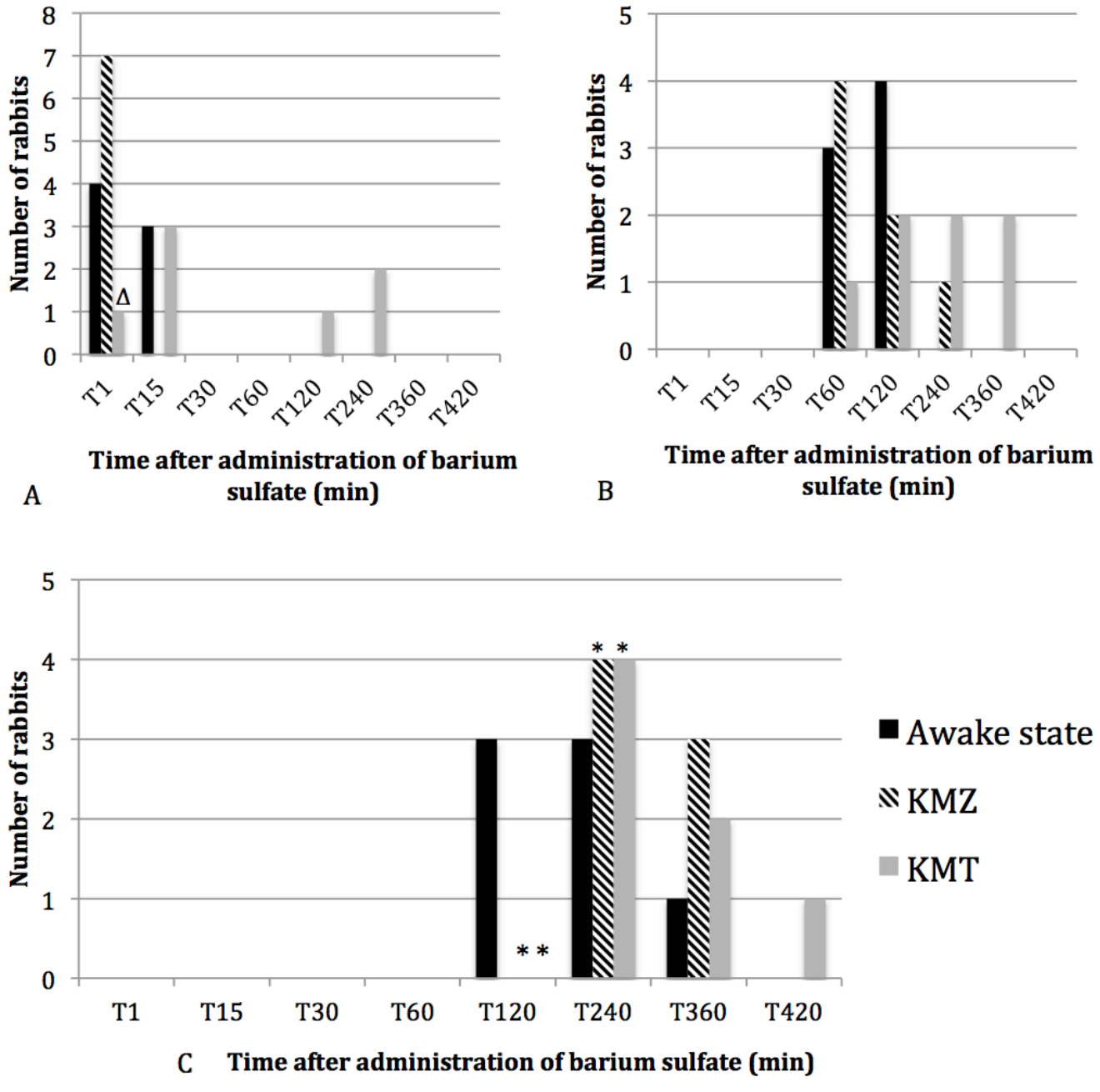


**Figure 2** Number of rabbits whose (A) gastric emptying (contrast in the small intestine), (B) filling of the caecum (contrast in the caecum) and (C) formation of hard faeces had begun at each radiographic time (minutes), during the gastrointestinal contrast study performed in the awake state and under anaesthesia with isoflurane, induced with KMT-A or KMZ in seven rabbits. Δ: value significantly different from the corresponding value measured in animals from KMZ group. *Value significantly different from that measured in awake animals ($p<0.05$). KMT, ketamine–medetomidine; KMZ, ketamine-midazolam.

each rabbit acted as its own control. As photoperiod also affects the caecotrophy period of rabbits,[25] the same light–dark cycle was maintained throughout the experiment. In addition, the diet composition (more than 70 per cent hay, 20–28 per cent vegetables (celery, endives and parsley) and 2–3 per cent of pellets) was the same throughout the experimental period, as it can influence the transit time.[17]

One limitation of this study was the difficulty in expressing, and statistically comparing, the gut transit times between the different treatments. Results reported in previous studies are usually expressed in mean times±SD. In our opinion, it is difficult to express transit in mean times because the transit evaluation is performed only at times defined by the technique (T 1, T 15, T 30, T 60, T 120, T 240, T 360 and T 420). For this reason, we used also numbers of rabbits reaching the different stages at the different time-points to compare the techniques. Another limitation is the decreased accuracy of the measurements over time due to the increasing time intervals between radiographs, which could have obscured any difference of time to formation of opacified hard faeces. Gastrointestinal transit times could also be affected dose dependently. Our protocols followed the doses of a previous published comparison between KMT and KMZ in rabbits.[15] The doses chosen should however be put into perspective as protocols using lower doses of medetomidine and ketamine are reported (10 mg/kg ketamine, 0.15 mg/kg medetomidine).[2]

Contrast agents might also not progress along the gastrointestinal tract as the natural content. For example, barium sulphate is hypo-osmolar and inert compared with food and therefore does not initiate events induced by the biochemical components of food.[26] The impact of barium on gastrointestinal transit in rabbits is not known. Furthermore, administration of a liquid contrast medium evaluates only the transit time of a liquid phase. The use of solid spheres of barium in conjunction with liquid contrast could have enabled further and more accurate information to be gathered, as the solid contrast medium does not dilute in the digestive content. However, the objective of the current study was not to measure an absolute value of transit time but to compare transit times between states (awake and anaesthesia) and protocols (KMZ and KMT-A). Finally, despite the crossover design, the number of rabbits used in this study remains a limitation for performing statistical analyses.

The current study showed significant differences in the proximal part of the gastro-intestinal tract, with delayed gastric transit time and small intestinal transit time in the KMT-A treatment compared with both the KMZ treatment and the awake state. This might be explained by either the effect of medetomidine or the absence of antagonism of its gastrointestinal effects by atipamezole. Though the injection of atipamezole may bias the comparison of KMT-A and KMZ, its inclusion reflects common clinical practice in rabbit medicine, posing a more relevant clinical question. As illustrated by the higher requirement of isoflurane vaporiser settings in the KMZ treatment, the anaesthetic depth produced by the two different protocols was different, and this could also have contributed to the difference of gastrointestinal transit times observed in the two treatments. However, to date, no study has evaluated the effect of isoflurane on gastrointestinal transit time in rabbits.

The direct inhibitory effect of α2-agonists on gut transit, reported in other species,[6–9] is due to activation of presynaptic α2-adrenoceptors located on parasympathetic (cholinergic) nerve terminals, which decreases the release of acetylcholine and, consequently, inhibits gastrointestinal motility.[27] Activation of central α2-adrenoreceptors could also be involved.[28]

The gastrointestinal effects of α2-agonists have been successfully countered by $\alpha_2$-antagonists in rats following clonidine[29] and dexmedetomidine,[9] and in dogs following medetomidine.[7] However, atipamezole, which is highly selective for α2-adrenoceptors, but not especially selective for any particular subtype of α2-adrenoceptor,[30] did not antagonise the inhibitory effects of medetomidine on spontaneous and electrically evoked phasic contractions of small intestine in horses in an in vitro study.[31]

In other studies, the gastrointestinal effects of an $\alpha_2$-agonist (oxymetazoline) selective for the α2A-adrenoceptor subtype were also not antagonised by either yohimbine (non-selective a2-adrenoceptor antagonist) or a selective α2A-adrenoceptor antagonist.[27 29] Authors suggested therefore that, besides stimulation of presynaptic α2-adrenoceptors, other mechanisms could contribute to the inhibitory effect of oxymetazoline on gut motility: for example, it could have an inhibitory action on gastrointestinal transit through receptors that are not antagonised by $\alpha_2$-antagonists.[27 29]

## Conclusion

A prolonged gastrointestinal transit time in the proximal digestive tract was identified in healthy rabbits anaesthetised with the KMT-A protocol in comparison with those anaesthetised with the KMZ protocol. It would be interesting to assess both techniques in diseased animals. In the meantime, considering the cardiac and gastrointestinal side effects of KMT-A, it may be advisable to avoid this protocol when rabbits at risk for gastrointestinal stasis require anaesthesia.

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**Competing interests** None declared.

**Patient consent for publication** Not required.

**Ethics approval** The ethical committee for animal welfare of Namur approved the experimental protocol (17288 VA).

**Data availability statement** All data relevant to the study are included in the article.



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