Effects of anaesthesia induction drugs on circulation in denervated intestinal loop preparation

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The effect of anaesthesia induction drugs on the intestinal circulation was evaluated in an isolated loop preparation in 28 dogs. Selected intestinal loops were perfused with aortic blood by a pump at a constant pressure of 100 mmHg. A mixture of ^{86}Rb and 9 μm spheres labeled with ^{141}Ce was injected into the arterial cannula supplying the intestinal segment while mesenteric venous blood was collected for activity counting. Diazepam in a dose of 3 mg·kg^{-1} was accompanied by a significantly lower clearance (Cl-Rb), and permeability-surface area product (PS) than pentobarbitone; there were no differences between diazepam and pentobarbitone in total blood flow (BF), vascular resistance (VR) and oxygen consumption in the intestinal segments. Circulatory variables observed after midazolam, 8 mg·kg^{-1} and an additional 16 mg·kg^{-1}, did not significantly differ from those seen during pentobarbitone. Ketamine in a dose of 8 mg·kg^{-1} was accompanied by a significantly lower BF, Cl-Rb, microsphere entrapment (Cl-Sph), PS, and higher VR and arterio-venous oxygen content difference. Sixteen mg·kg^{-1} of ketamine did not lead to any additional changes in determined variables of the intestinal circulation. Alpha-adrenoceptor blockade completely abolished vasoconstriction caused by ketamine, suggesting that the long-lasting vasoconstricting effect of ketamine on the intestinal circulation is mediated through catecholamines.

Key words

ANAESTHESIA INDUCTION DRUGS: ketamine, diazepam, midazolam, pentobarbitone, INTESTINAL BLOOD FLOW: isolated intestinal loop.

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Many reports are available on the haemodynamic effects of anaesthesia induction drugs such as barbiturates,[1,2] diazepam,[3–5] midazolam,[6–9] and ketamine.[10–16] However, relatively little is known about the effects of these drugs on haemodynamics in individual organs, particularly the splanchnic system.[17] Changes in regional blood flow during anaesthesia can be mediated through central mechanisms, related to a reduction in cardiac output and changes in vascular tone or to the release of various humoral substances such as catecholamines. These alterations may be induced by a direct influence of an anaesthetic on one or another area of the peripheral circulation. The splanchnic circulation may play an important role in alterations and maintenance of homeostasis during anaesthesia.[18–20]

This study was designed to evaluate the influence of anaesthesia induction drugs (pentobarbitone, diazepam, midazolam, and ketamine) in a dose-related fashion on the intestinal circulation in an isolated loop preparation. The preparation allowed us to determine the direct effects of these drugs on the peripheral circulation.

Methods

Experiments were performed on 28 dogs weighing 15 to 20 kg. The dogs were anaesthetized intravenously with pentobarbitone, 30 mg·kg^{-1}. Controlled ventilation, adjusted to maintain $PaCO_2$ at 35–40 mmHg, was provided with an Air Shield® ventilator through an endotracheal tube. Pancuron-

ium, 0.1 $mg \cdot kg^{-1}$, was given for muscle relaxation. Femoral arteries and veins were exposed and cannulated; 100 ml of blood were collected for future transfusion and replaced with 350 ml of Ringer's lactated solution. Ringer's lactated solution was also infused through the left femoral vein at a constant rate of 15 $ml \cdot kg^{-1} \cdot hr^{-1}$. A laparotomy was performed and a segment of the small intestine, supplied by a vascular arcade arise from a single mesenteric artery and vein, was selected. The isolated loop preparation[21,22] involved dissection of short segments of the mesentery artery and vein free of the mesentery. Heparin, 5 $mg \cdot kg^{-1}$ IV, was administered. The mesenteric vein was transsected and cannulated with polyethylene tubing. To achieve a 0 mmHg mesenteric venous pressure, blood from the mesenteric vein was collected in a reservoir placed at the level of the mesenteric vein and pumped back into the dog through a femoral vein. When the venous drainage was established, the mesenteric artery supplying the loop was transsected and cannulated, and arterial blood was pumped from the femoral artery through the intestinal segment (using a Holter precision roller pump) at a constant pressure of 100 mmHg by adjusting the flow rate. The completely isolated loop was placed between saline-soaked gauzes and plastic wrap, and temperature maintained at 37–38° C with a thermostatically controlled electric heating pad.

Aortic pressure (via a femoral artery cannula) and perfusion pressure (pressure in the arterial limb between the pump and intestinal segment) were recorded with Statham transducers and a Grass polygraph. After 30 minutes of stable perfusion pressure, arterial and mesenteric venous blood samples were taken for pH and oxygen content determinations. A mixture of ^{86}Rb and 9 μm spheres labeled with ^{141}Ce was then injected within 15 seconds into the mesenteric artery (arterial cannula supplying the intestinal loop) while mesenteric venous blood was collected in test tubes for three minutes (15 seconds per tube) for activity counting. After three minutes of blood collection, pump perfusion was terminated. The intestinal segment was divided into four to six pieces and processed for activity counting. Then, another intestinal segment was prepared and processed in the same way. Blood drained from the mesenteric vein was replaced with blood that had been collected at the beginning of the experiment to maintain constant haematocrit values throughout the experiments. Two to four intestinal segments were used from each dog.

During each stage of measurements, PaO_2 was maintained above 100 mmHg, $PaCO_2$ between 35 and 40 mmHg, and haematocrit between 30 and 35 per cent. Observations with values not within these ranges were excluded from the study.

Group 1 (control group, four dogs) – all four intestinal segments in each dog were studied under intravenous pentobarbitone anaesthesia (30 $mg \cdot kg^{-1}$ plus 1–2 $ml \cdot kg^{-1} \cdot hr^{-1}$). The number of intestinal segments (n) studied under pentobarbitone was 73: in the control group there were four loops in four dogs (16 loops); the remaining 24 dogs had the first loop studied under pentobarbitone (24 loops); another 33 intestinal segments were used as the first loop of 33 dogs from another part of the study (published separately)[23] where the effects of narcotics on the intestinal circulation were studied.

Group 2 (six dogs) – the first intestinal segment was studied under pentobarbitone; the second intestinal loop was studied under intravenous diazepam, 3 $mg \cdot kg^{-1}$ (n = 6); the third segment was studied after an additional dose of diazepam, 6 $mg \cdot kg^{-1}$ (n = 6). Attempts were made to study the fourth intestinal segment after an additional 9 $mg \cdot kg^{-1}$ of diazepam.

Group 3 (six dogs) – the first intestinal segment was studied under pentobarbitone; the second loop was studied after intravenous midazolam, 8 $mg \cdot kg^{-1}$ (n = 6), was administered. The third segment was studied after an additional 16 $mg \cdot kg^{-1}$ (n = 6) and the fourth intestinal segment was studied after an additional 32 $mg \cdot kg^{-1}$ (n = 6) of midazolam was administered.

Group 4 (six dogs) – the first intestinal segment was studied under pentobarbitone; the second segment was studied after intravenous ketamine, 8 $mg \cdot kg^{-1}$ (n = 6), was administered. The third intestinal segment was studied after an additional 16 $mg \cdot kg^{-1}$ (n = 6) of ketamine was administered.

Group 5 (six dogs) – the first intestinal segment was studied also under pentobarbitone; the second loop was studied after ketamine, 8 $mg \cdot kg^{-1}$, and phentolamine, 1 $mg \cdot kg^{-1}$ (n = 6), which was administered approximately ten minutes before rubidium and microspheres injection. Phentolamine, 1 $mg \cdot kg^{-1}$, produces blockade of alpha-adrenoceptors.[24,25]

Ten to 15 minutes were required for the preparation of each isolated intestinal segment. The drug to be studied was injected immediately after the preparation was completed. A period of 10 to 15 minutes was needed to stabilize perfusion pressure. This period was followed by 30 minutes of stable perfusion and stable mean arterial pressures, and then another five minutes were required for blood sampling and injection of rubidium and microspheres. Thus, the action of a drug was studied 45 minutes after the drug was administered. In the last group, measurements were performed 45 minutes after ketamine and approximately ten minutes after phentolamine was injected, when the flow rate through the loop was adjusted to achieve perfusion pressure of 100 mmHg.

Oxygen tension and pH were measured with an Instrumentation Laboratories (IL) model 813 pH/blood-gas analyzer. Oxygen content was measured with an IL 282 Cooximeter adjusted for canine blood. Each shipment of microspheres (purchased from 3M Co., St Paul, MN) was checked for size of spheres (determined with a Coulter Counter used for determination of red cell size), fragmentation, and aggregation.[26] Microspheres were used only when size variations did not exceed standard deviations of 1 μm. Microspheres were labeled with ^{141}Ce and suspended in a ten per cent dextran solution with polysorbate (Tween 80). Microspheres were mixed in a special injector[26] with ^{86}Rb and diluted in 3 mL of normal saline. Each injection contained about 10^6 spheres and approximately 300 μCi of rubidium. Each of the isotopes generated approximately 0.5×10^6 counts/min. Radioactivity in the intestinal segment and mesenteric venous blood samples was analyzed with a Tracor 2250 gamma counting system (Tracor Northern, Middleton, WI).[21,27,28]

Total blood flow in each intestinal segment was measured directly by the amount of blood drained from the mesenteric vein. Each segment was weighed after the experiment and blood flow (BF) was calculated in $ml \cdot min^{-1} \cdot g^{-1}$.

Vascular resistance (VR) was calculated as follows:

$$VR\ (mmHg \cdot ml^{-1} \cdot min \cdot g) = \frac{\text{perfusion pressure (mmHg)}}{\text{blood flow } (ml \cdot min^{-1} \cdot g^{-1})}$$

Arteriovenous oxygen content difference ($AVDO_2$) was calculated and expressed in $mlO_2 \cdot dl^{-1}$ of blood. Oxygen uptake was calculated by multiplying intestinal blood flow by arteriovenous oxygen content difference. Rubidium, 9 μm sphere clearances and permeability-surface area product (PS) were calculated as described elsewhere.[23,29] The activity injected into the segment was compared with activity found in the blood and intestinal segment.

Data are presented as means ± standard errors of the mean. Differences between groups and control values (pentobarbitone) were tested by the use of a one-way analysis of variance.[30] Since the dogs within a particular treatment group were subjected to different doses of the same drug, differences between levels of the same drug were tested by use of a repeated measures analysis of variance. This allowed an adjustment for the between dog variability when comparing dosage levels for the same drug.[30] Individual comparisons between pairs of means were performed using Fisher's protected least significant difference test.[30] Pearson's correlation coefficient and the corresponding least squares regression equation were used as the measure of association when comparing two response measurements.[30] Differences were considered significant if $p < 0.05$. All computations were performed with the aid of the Statistical Analysis System.[31]

Results

The amounts of activity found in the intestinal segment and mesenteric venous blood did not differ from the injected activity by more than ten per cent. The difference in the activity of ^{141}Ce and ^{86}Rb (calculated per gram of tissue) between samples of one intestinal loop never exceeded ten per cent. There were no significant differences between variables observed during the first, second, third, and fourth segment preparations in the control group. A strong and significant correlation was found between rubidium and microsphere clearances, $r = 0.92$, $p < 0.0001$.

The main variables observed under the experimental conditions are presented in Tables I–III. Compared with pentobarbitone, diazepam in a dose of $3\ mg \cdot kg^{-1}$ was accompanied by a significantly lower rubidium clearance (Cl–Rb), and permeability–surface area product (PS); there were no significant differences between pentobarbitone and diazepam in total blood flow (BF), vascular

TABLE I Diazepam vs pentobarbitone in isolated intestinal segment (Mean ± SEM)

Groups	*BF*	*VR*	*$AVDO_2$*	*O_2up*	*Cl-Sph*	*Cl-Rb*	*PS*
1. Pent	0.56 ± 0.01	182 ± 5	3.6 ± 0.11	2.0 ± 0.1	0.52 ± 0.01	0.47 ± 0.01	1.07 ± 0.03
2. D3	0.52 ± 0.07	215 ± 27	3.91 ± 0.34	2.0 ± 0.3	0.47 ± 0.05	0.39 ± 0.04*	0.76 ± 0.09*
2. D6	0.60 ± 0.05	170 ± 13	2.91 ± 0.26†	1.7 ± 0.1	0.57 ± 0.05†	0.50 ± 0.03†	1.05 ± 0.08†

BF = blood flow in $ml \cdot min^{-1} \cdot g^{-1}$, VR = vascular resistance in the intestinal segment in $mmHg \cdot ml^{-1} \cdot min \cdot g$, $AVDO_2$ = arteriovenous oxygen content difference in ml of oxygen in 100 ml of blood, O_2up = oxygen uptake in $mlO_2 \cdot min^{-1} \cdot 100\,g^{-1}$, Cl-Sph = microsphere clearance (entrapment) in $ml \cdot min^{-1} \cdot g^{-1}$, Cl-Rb = rubidium clearance in $ml \cdot min^{-1} \cdot g^{-1}$, PS = permeability surface area product. Pent = pentobarbitone $30\,mg \cdot kg^{-1}$; D3 = diazepam $3\,mg \cdot kg^{-1}$; D6 = diazepam $6\,mg \cdot kg^{-1}$.
*$p < 0.05$ vs group 1, Pent; †$p < 0.05$ vs group 2, D3.

TABLE II Midazolam vs pentobarbitone in isolated intestinal segment (Mean ± SEM)

Groups	*BF*	*VR*	*$AVDO_2$*	*O_2up*	*Cl-Sph*	*Cl-Rb*	*PS*
1. Pent	0.56 ± 0.01	182 ± 5	3.6 ± 0.11	2.0 ± 0.1	0.52 ± 0.01	0.47 ± 0.01	1.07 ± 0.03
3. M8	0.49 ± 0.03	207 ± 14	2.75 ± 0.50*	1.3 ± 0.2*	0.46 ± 0.03	0.42 ± 0.02	0.93 ± 0.04
3. M16	0.49 ± 0.02	206 ± 8	3.60 ± 0.53	1.8 ± 0.3	0.46 ± 0.02	0.42 ± 0.01	1.97 ± 0.04
3. M32	0.60 ± 0.04†‡	170 ± 11†‡	2.00 ± 0.35*‡	1.2 ± 0.2*‡	0.56 ± 0.03†‡	0.53 ± 0.03†‡	1.26 ± 0.10*†‡

See Table 1 for abbreviations of variables. Pent = pentobarbitone $30\,mg \cdot kg^{-1}$; M8 = midazolam $8\,mg \cdot kg^{-1}$; M16 = midazolam $16\,mg \cdot kg^{-1}$; M32 = midazolam $32\,mg \cdot kg^{-1}$.
*$p < 0.05$ vs group 1, Pent; †$p < 0.05$ vs group 3, M8; ‡$p < 0.05$ vs group 3, M16.

TABLE III Ketamine vs pentobarbitone in isolated intestinal segment (Mean ± SEM)

Groups	*BF*	*VR*	*$AVDO_2$*	*O_2up*	*Cl-Sph*	*Cl-Rb*	*PS*
1. Pent	0.56 ± 0.01	182 ± 5	3.6 ± 0.11	2.0 ± 0.1	0.52 ± 0.01	0.47 ± 0.01	1.07 ± 0.03
4. K8	0.24 ± 0.03*	451 ± 52*	5.73 ± 0.49*	1.3 ± 0.1*	0.23 ± 0.02*	0.22 ± 0.02*	0. 59± 0.05*
4. K16	0.33 ± 0.02*†	307 ± 19*†	5.31 ± 0.60*	1.7 ± 0.2	0.32 ± 0.02*†	0.27 ± 0.02*†	0.56 ± 0.07*
4. K8α	0.70 ± 0.05*†	145 ± 11†	1.93 ± 0.45*†	1.3 ± 0.3*	0.64 ± 0.04*†	0.55 ± 0.02*†	1.11 ± 0.05†

See Table 1 for abbreviations of variables. Pent = pentobarbitone $30\,mg \cdot kg^{-1}$; K8 = ketamine $8\,mg \cdot kg^{-1}$; K16 = ketamine $16\,mg \cdot kg^{-1}$; K8α = ketamine $8\,mg \cdot kg^{-1}$ plus phentolamine $1\,mg \cdot kg^{-1}$ (to block alpha-adrenoceptors).
*$p < 0.05$ vs group 1, Pent; †$p < 0.05$ vs group 4, K8.

resistance (VR), and oxygen consumption in the intestinal segments (Table I). A doubled dose of diazepam did not lead to additional changes in BF, VR and oxygen consumption while Cl-Rb, microsphere entrapment/clearance (Cl-Sph), and PS increased and did not differ from corresponding values observed during pentobarbitone anaesthesia. Experiments with further increasing doses of diazepam could not be performed. Animals that received an additional $9\,mg \cdot kg^{-1}$ of diazepam died or developed serious arterial hypotension and could not be studied.

Circulatory variables observed after midazolam, $8\,mg \cdot kg^{-1}$ and an additional $16\,mg \cdot kg^{-1}$, did not significantly differ from those seen during pentobarbitone anaesthesia (Table II). An additional $32\,mg \cdot kg^{-1}$ of midazolam was associated with a significant increase in PS without concomitant changes in Cl-Rb and Cl-Sph.

Compared with pentobarbitone, ketamine in a dose of $8\,mg \cdot kg^{-1}$ was accompanied by a significantly lower BF, Cl-Rb, Cl-Sph, PS, and higher VR and $AVDO_2$ (Table III). Supplemented $16\,mg \cdot kg^{-1}$ of ketamine did not lead to any additional changes in determined variables of the intestinal circulation; however, values of BF, Cl-Rb, Cl-Sph, and PS were lower, and values of VR and $AVDO_2$ were higher than those observed during pentobarbitone anaesthesia.

Additional experiments were performed to eluc-

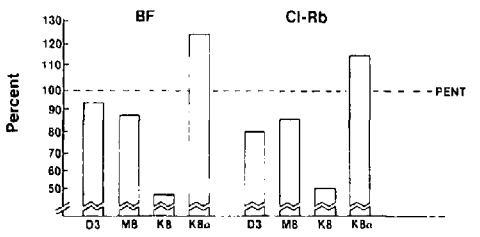

FIGURE Effect (per cent change) of intravenous anesthetics on intestinal blood flow (BF) and rubidium clearance (Cl-Rb). Pent = pentobarbitone anaesthesia (100%); D3 = diazepam, $3 \cdot kg^{-1}$; M8 = $8\ mg \cdot kg^{-1}$; K8 = ketamine $8\ mg \cdot kg^{-1}$; K8α = ketamine $8\ mg \cdot kg^{-1}$ plus alpha-adrenoceptor blockade. Absolute values and levels of significance are presented in Tables I, II, and III.

idate the mechanisms of the increase in VR caused by ketamine (Table III). Alpha-adrenoceptor blockade abolished completely vasoconstriction cause by ketamine. Ketamine, $8\ mg \cdot kg^{-1}$, in conditions of alpha-adrenoceptor blockade (phentolamine, $1\ mg \cdot kg^{-1}$) was accompanied by a substantially and significantly higher BF, Cl-Rb, Cl-Sph and PS, and a significantly lower VR and $AVDO_2$ (Table III, Figure) compared with the same dose of ketamine alone.

Discussion

Rubidium is highly diffusable across exchange vessels, which means that most of the substance presented in the exchange vessels is absorbed by tissues. Consequently, the ratio of absorbed to non-absorbed rubidium would represent the ratio of the blood flow through nutritive vessels to flow through non-nutritive vessels. The results of the present study (a strong correlation between microsphere entrapment and rubidium clearance) demonstrate that 9 μm spheres and rubidium behave in the vascular bed in a similar way, i.e., spheres are trapped and rubidium is absorbed in the nutritive exchange vessels and shunted through non-nutritive vessels where exchange does not occur, or occurs to a limited extent. The results show that anaesthesia induction drugs do not upset the association between 9 μm spheres entrapment and rubidium clearance observed under other conditions.[21-23,32]

The injection of spheres and rubidium in 3 ml of saline probably decreased the haematocrit of the blood perfusing the intestinal segment. The use of Tween 80 during the injection probably also affected circulation.[33] However, these influences were apparently short-lasting and similar in all groups, and therefore allowed certain differences between groups to be observed. Similar activities found in different pieces of each intestinal loop showed adequate mixing of spheres and rubidium in the blood stream. The perfusion of the intestinal segment by a pump with constant pressure assured independence of the intestinal circulation from the systemic circulation, while complete isolation of the segment (including transsection of the vessels supplying the loop) assured independence of the intestinal circulation from the neural regulatory mechanisms. Thus, this preparation allowed us to study the direct influence of anaesthetics on the intestinal circulation. Indirect effects related to various hormonal factors (e.g., epinephrine, histamine, etc.) could not be excluded.

It is important to realize that the effects of diazepam, midazolam, and ketamine on the intestinal circulation were studied in the presence of pentobarbitone, laparotomy, and controlled ventilation. Therefore, the observed changes reflect intestinal circulatory responses to the complex of pentobarbitone, controlled ventilation, laparotomy, and the drug in question rather than the drug per se. However, since the only changed component in this complex was the drug in question, it is reasonable to assume that the differences between groups were mainly related to each drug studied.

During this study, pentobarbitone was used in a dose of $30\ mg \cdot kg^{-1}$ which is routinely used in dogs.[17] The first dose of midazolam ($8\ mg \cdot kg^{-1}$) and the first dose of ketamine ($8\ mg \cdot kg^{-1}$) were used since we had previously used these doses successfully in dogs to keep them unconscious or at least highly sedated.[19,34] The first dose of diazepam ($3\ mg \cdot kg^{-1}$) probably produced a strong sedative effect only.[35] The ratio of LD_{50} of midazolam to LD_{50} of diazepam equals 3.4.[36] For the first dose we used a slightly smaller ratio or, in others words, the first dose of diazepam ($3\ mg \cdot kg^{-1}$) was probably somewhat higher than the first dose of midazolam ($8\ mg \cdot kg^{-1}$) in terms of toxicity, but probably lower in terms of hypnotic/sedative effects. However, later during the experiments the doses of the drugs were doubled and then tripled to observe the dose-related response within a wide spectrum of the

effects of the anaesthesia induction drugs. The animals tolerated very well the tripled increase of the dose of midazolam but could not tolerate a similar increase in diazepam. The underlying mechanisms are not clear and the present study did not address this question. However, it is reasonable to assume that the higher tolerance to midazolam can be related to certain pharmacokinetic differences, namely a much shorter half-life of midazolam compared with diazepam[37–40] and the stronger metabolite activity of diazepam than midazolam.[41,42] Therefore, the third dose of diazepam was given when the previous doses (in conjunction with diazepam metabolites) still had a substantial pharmacologic influence, while subsequent doses of midazolam (16 and 32 $mg \cdot kg^{-1}$) were administered when the pharmacologic effect of the first 8 $mg \cdot kg^{-1}$ was very minimal.

The effects of diazepam and midazolam on the intestinal circulation were similar when compared with the effects of pentobarbitone (Tables I, II). Midazolam decreased intestinal oxygen consumption in a dose independent manner: there were no statistically significant differences between values of oxygen uptake observed during three different doses of midazolam (Table II). Oxygen uptake observed during the second dose of midazolam did not differ significantly from values seen during pentobarbitone. It seems that one point on the dose-response curve (midazolam dose vs oxygen uptake) did not reach a level of statistical significance. A slightly higher PS without concomitant changes in rubidium clearance and microspheres entrapment, as well as a lower oxygen consumption, was observed during midazolam administered in a dose of 32 $mg \cdot kg^{-1}$ compared with pentobarbitone and midazolam in a dose of 16 $mg \cdot kg^{-1}$. A decrease in oxygen consumption with preserved total flow suggests that high doses of midazolam affected tissue metabolism. An increase in PS without concomitant increases in rubidium clearance and microsphere entrapment suggests an increase in the number of functioning capillaries and/or an increase in membrane permeability.

Ketamine in both doses studied (8 and 16 $mg \cdot kg^{-1}$) was accompanied by a substantial vasoconstriction and a decrease in total blood flow (nutritive and non-nutritive) measured directly, and nutritive blood flow, determined with rubidium and microspheres (Table III). Apparently this vasoconstriction was not related to the direct effect of ketamine on the vasculature for the following reasons. Firstly, alpha-adrenoceptor blockade abolished the vasoconstricting effect of ketamine (Table III, Figure); and secondly, the direct effect of ketamine on isolated vessels is relaxation.[43,44]

Vasoconstriction was completely abolished by alpha-adrenoceptor blockade (Table III, Figure). Thus, it appears that ketamine affected the intestinal circulation through catecholamines or by directly stimulating nerve endings and/or alpha-adrenergic receptors. It was been shown that ketamine releases epinephrine and norepinephrine.[45–48] It is interesting to note that a substantial vasoconstriction in the intestines was observed for at least 45 minutes after ketamine injection. It has been shown that an increase in blood pressure, cardiac output, and heart rate with a concomitant increase in epinephrine and norepinephrine plasma concentrations usually do not last more than 10 to 20 minutes after ketamine injection.[46,49,50] The present study shows that vasoconstriction in the splanchnic system is maintained after ketamine injection for a much longer time than would be expected from previous data available in the literature.

Ketamine in a dose of 8 $mg \cdot kg^{-1}$ was accompanied by lower oxygen uptake than pentobarbitone. This reduction in oxygen uptake was associated with an increase in $AVDO_2$ and therefore was due, at least partially, to severe vasoconstriction with a subsequent decrease in blood and oxygen delivery to the intestinal segment. Another, or rather an additional cause for this reduction in oxygen uptake could be related to a decrease in oxygen requirement due to the effect of ketamine on tissue metabolism. A doubled dose of ketamine diminished vasoconstriction and improved oxygen delivery. Oxygen uptake had a tendency towards restoration, but the difference did not reach a level of statistical significance. A combination of ketamine, 8 $mg \cdot kg^{-1}$, with alpha-adrenoceptor blockade was accompanied by lower oxygen uptake and better oxygen delivery (higher BF and Cl-Rb) than pentobarbitone. This could be related to a decrease in oxygen requirement due to ketamine and possible phentolamine. The effect of phentolamine on intestinal oxygen uptake has not been studied to our knowledge; however, some vasodilators can decrease intestinal oxygen uptake.[51–53] It is conceivable that the anti-adrenergic effect of phentolamine

is accompanied by a decrease in metabolic rate and oxygen requirement.

In summary, ketamine has a profound and long-lasting vasoconstricting effect on the splanchnic vasculature. Compared with pentobarbitone and diazepam, midazolam and ketamine influence tissue metabolism and decrease oxygen requirement and consumption in the intestines, probably to a lesser extent and not in a dose-related manner as inhalational agents do.[22] A substantial decrease in oxygen requirement and consumption in the intestines observed during inhalation anaesthesia[22] might provide a relative increase in oxygen supply to the liver, resulting from a higher oxygen content in the portal blood. If anaesthesia induction drugs are accompanied by decreases in cardiac output (and therefore splanchnic blood flow) similar to those developing during inhalation anaesthesia, the oxygen supply to the liver could be relatively worse during intravenous than during inhalation anaesthesia. Higher values of cardiac output during anaesthesia induction drugs would be needed to maintain oxygen supply to the liver similar to that observed during inhalation anaesthesia. Thus, regarding the preservation of liver function, anaesthesia induction drugs might not have advantages over inhalational agents. Clinical implications of these speculations are not clear, however, considering that hepatic oxygen deprivation plays a very important role in the development of liver damage during anaesthesia,[54,55] the point seems to be worth noting.

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Résumé

Les effets des agents anesthésiques utilisés lors de l'induction sur la circulation intestinale ont été évalués chez 28 chiens utilisant une préparation où un circuit intestinal est isolé. Les circuits d'intestin choisis ont été perfusés avec du sang aortique utilisant une pompe à pression constante de 100 mmHg. Un mélange de Rb86 et des microsphères de 9 μm marqués avec du Ce 141 ont été injectés dans la canule artérielle nourissant le segment intestinal alors que le sang veineux mésentérique a été recueilli afin de mesurer la radioactivité résiduelle. Le diazepam à des doses de 3 mg·kg^{-1} a démontré une clairance de rubidium (Cl-Rb) et un produit surface-perméabilité (PS) significativement plus bas que le pentobarbitone. Il n'y avait aucune différence entre le diazepam et le pentobarbitone quant au flot sanguin total (BF), résistance vasculaire (VR) et consommation d'oxygène des segments d'intestin. Les perturbations de la circulation observées après midazolam, 8 mg·kg^{-1} et une dose additionnelle de 16 mg·kg^{-1} n'étaient pas significativement différentes de celles observées lors de l'induction avec le pentobarbitone. La ketamine à des doses de 8 mg·kg^{-1} était accompagnée par un Cl-Rb, un BF, une capture de microsphères (Cl-Sph), un PS, significativement plus bas. La VR et la différence artério-veineuse du contenu en oxygène étaient plus hautes. 16 mg·kg^{-1} de ketamine n'ont pas amené des changements additionnels dans les variables étudiées. Un blocage des récepteurs alpha-adrénergiques a complètement aboli la vasoconstriction causée par la ketamine suggérant que l'effet vasoconstricteur de la ketamine est dû aux catécholamines.