Midazolam and ketamine induction before halothane anaesthesia in ponies: cardiorespiratory, endocrine and metabolic changes

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Six Welsh gelding ponies were premedicated with 0.03 mg/kg of acepromazine intravenously (i.v.) prior to induction of anaesthesia with midazolam at 0.2 mg/kg and ketamine at 2 mg/kg i.v.. Anaesthesia was maintained for 2 h using 1.2 % halothane concentration in oxygen. Heart rate, electrocardiograph (ECG), arterial blood pressure, respiratory rate, blood gases, temperature, haematocrit, plasma arginine vasopressin (AVP), dynorphin, ß-endorphin, adrenocorticotropic hormone (ACTH), cortisol, dopamine, noradrenaline, adrenaline, glucose and lactate concentrations were measured before and after premedication, immediately after induction, every 20 min during anaesthesia, and at 20 and 120 min after disconnection. Induction was rapid, excitement-free and good muscle relaxation was observed. There were no changes in heart and respiratory rates. Decrease in temperature, hyperoxia and respiratory acidosis developed during anaesthesia and slight hypotension was observed (minimum value 76 $\pm$ 10 mm Hg at 40 mins). No changes were observed in dynorphin, ß-endorphin, ACTH, catecholamines and glucose. Plasma cortisol concentration increased from 220 $\pm$ 17 basal to 354 $\pm$ 22 nmol/L at 120 min during anaesthesia; plasma AVP concentration increased from 3 $\pm$ 1 basal to 346 $\pm$ 64 pmol/L at 100 min during anaesthesia and plasma lactate concentration increased from 1.22 $\pm$ 0.08 basal to 1.76 $\pm$ 0.13 mmol/L at 80 min during anaesthesia. Recovery was rapid and uneventful with ponies taking 46 $\pm$ 6 min to stand. When midazolam/ketamine was compared with thiopentone or detomidine/ketamine for induction before halothane anaesthesia using an otherwise similar protocol in the same ponies, it caused slightly more respiratory depression, but less hypotension. Additionally, midazolam reduced the hormonal stress response commonly observed during halothane anaesthesia and appears to have a good potential for use in horses.

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INTRODUCTION

Benzodiazepines have been used in horses combined with α-$_2$ agonists, tiletamine, ketamine and guaiphenesin (Rehm & Schatzmann, 1984; Hubbell *et al.*, 1989; Matthews *et al.*, 1991; Luna *et al.*, 1992). These combinations produced recumbency rapidly and smoothly, cardiorespiratory depression was mild, but in some studies recovery was long and unsatisfactory (Hubbell *et al.*, 1989). Luna *et al.* (1992) obtained a rapid and smooth induction and stable cardiorespiratory function during anaesthesia employing a combination of methotrimeprazine, guaiphenesin and midazolam for induction before halothane anaesthesia in horses. The addition of ketamine to this combination also resulted in quicker recovery from anaesthesia.

Midazolam, due its shorter duration of effect than most benzodiazepines, appears to have potential for use in horses. Also midazolam might be beneficial in reducing the endocrine stress response to anaesthesia observed in horses (Luna & Taylor, 1995). Benzodiazepines inhibited corticotropin-releasing factor (CRF) secretion from the hypothalamus *in vivo* and *in vitro* (Calgero *et al.*, 1988; Blasquez *et al.*, 1991) and prevented the CRF-induced release of pro-opiomelanocortin peptide, acting at the pituitary intermediate lobe of rats (Saland *et al.*, 1992). Midazolam prevented or reduced the increase in ß-endorphin, adrenocorticotropic hormone (ACTH), cortisol and adrenaline in response to anaesthesia and surgery in man (Crozier *et al.*, 1987; Desborough *et al.*, 1991).

The aim of this study was to evaluate the cardiorespiratory, metabolic and endocrine effects of midazolam and ketamine used for induction of anaesthesia before halothane anaesthesia in ponies. This would eliminate the need for α-$_2$ agonists which are widely used in this species, but which result in considerable cardiorespiratory depression, decreased cardiac output and a high incidence of atrioventricular block (Wagner *et al.*, 1991). Midazolam was chosen because of its potent hypnotic and muscle relaxant effects, which are essential for smooth induction of

anaesthesia. It was also chosen as an agent likely to attenuate the stress response commonly observed with halothane anaesthesia.

MATERIALS AND METHODS

Six Welsh pony geldings weighing between 218 and 330 kg (251 ± 17 kg) and 3–8 years (3.9 ± 0. 8 years) were used. These ponies had had their right carotid artery raised into a subcutaneous position at least one year previously. Food but not water was witheld for 12 h before anaesthesia. A 14 SWG catheter was introduced into the jugular vein under local anaesthesia and ponies were premedicated with 0.03 mg/kg of acepromazine intravenously (i.v.). An 18 SWG catheter was placed in the carotid artery under local anaesthesia. Induction of anaesthesia was performed by 10:00 h, 20 min after premedication, using 0.2 mg/kg of midazolam (Hypnoval, Roche, UK) and 2 mg/kg of ketamine (Vetalar, Parke Davis, UK) mixed in the same syringe and given i.v.. After tracheal intubation, anaesthesia was maintained with 1.2% end tidal (Kontron instruments, UK) halothane concentration (Halothane, RMB Animal Health, UK) in 100% of oxygen using a circle breathing system (JD Medical, USA). Ponies lay in left lateral recumbency during anaesthesia. After two hours of anaesthesia, the ponies were extubated and allowed to recover under observation.

Recovery was scored as follows: 5 (excellent – no struggling, standing at the first attempt); 4 (good – slight ataxia, but good stability); 3 (tolerable – some ataxia when standing, two or three unsuccessful attempts to stand); 2 (bad – excitement, paddling when in recumbency, marked ataxia with possible fall) and 1 (very bad – excitement during recumbency, many unsuccessful attempts to stand, ataxia and falls after standing, risk of trauma). Time from injection of midazolam/ketamine to recumbency, the quality of induction and time from the end of anaesthesia to standing were recorded.

All measurements were made before premedication, 20 min after premedication, immediately after induction, every 20 min during anaesthesia and at 20 and 120 min after the end of anaesthesia. Record was made of direct mean arterial blood pressure in the carotid artery (Minimon 7132 A, Roche-Kontron UK), heart rate and the electrocardiogram (Roche-Kontron system), respiratory rate, rectal temperature and arterial blood gases in blood withdrawn from the carotid artery (Corning 168 Blood Gas Analyser, USA). Venous blood samples were taken at the same time points for measurement of haematocrit, plasma glucose (YSI Model 23 A glucose analyser, UK), plasma lactate (Model 23 L lactate analyser), plasma arginine vasopressin (AVP), ACTH, ß-endorphin, dynorphin and cortisol concentrations measured by radio immunoassay assay and catecholamines measured by high performance liquid chromatography, according to Luna & Taylor (1995). Arterial blood pressure and blood gases were not measured before premedication.

Statistical analysis

Statistics were based on Morrison (1967) using Apple Macintosh Statview software. Analysis of variance (ANOVA) for repeated measures was used in order to assess changes with time, followed by Dunnett's test when a significant difference was observed. One way ANOVA, followed by Fisher's paired least square difference test when indicated, was used to compare midazolam/ketamine/halothane anaesthesia in this study with the data obtained at the same time points using a standard anaesthetic protocol (thiopentone/halothane anaesthesia), using the same ponies and identical conditions as reported previously (Luna & Taylor, 1995). Recovery score and time was compared with this previous study using unpaired Student's *t*-test. Differences were considered significant when $P < 0.05$. Results are expressed as mean ± standard error of the mean (SEM).

RESULTS

Induction was rapid, excitement-free and excellent muscle relaxation was observed. All ponies took 30 s from injection to recumbency and there were no limb movements after the ponies became recumbent. Intubation was easily performed in five ponies, but one pony needed an additional dose of 200 mg ketamine for intubation. Transition to halothane anaesthesia was smooth.

No changes in heart rate nor abnormalities in the ECG were observed during anaesthesia (Table 1). Hypotension developed from 20 min until the end of anaesthesia (Table 1). Blood pressure was higher during midazolam/ketamine/halothane than after thiopentone/halothane anaesthesia (Luna & Taylor, 1995) at 40 min anaesthesia and 20 min after disconnection.

Respiratory rate decreased immediately after induction only (Table 1). One pony had one minute's apnoea immediately after induction followed by 3 min of irregular breathing. Arterial partial pressure of CO_2 and O_2 increased during anaesthesia and pHa decreased (Table 1).

Body temperature decreased significantly from 80 min during anaesthesia until 20 min after disconnection (Table 1).

Plasma glucose concentration increased only at 120 min after disconnection (Table 1). Plasma lactate concentration increased from 60 min during anaesthesia, remaining higher than control until 20 min after disconnection (Table 1). Haematocrit decreased after premedication, remaining low thereafter (Table 1).

Plasma AVP concentration increased only at 100 min during anaesthesia, similar to thiopentone/halothane anaesthesia (Luna & Taylor, 1995) (Fig. 1). Plasma dynorphin, ß-endorphin and ACTH concentrations did not change with time. Plasma dynorphin concentrations were lower than during thiopentone/halothane anaesthesia at 2 ($P = 0.018$), 40 ($P = 0.031$), 60 ($P = 0.035$) and 120 min ($P = 0.007$) of anaesthesia. Plasma ß-endorphin concentrations were lower than during thiopentone/halothane anaesthesia at 20 ($P = 0.048$), 60 ($P = 0.004$) and 120 min ($P = 0.020$) of anaesthesia. Plasma ACTH concentrations were lower than during thiopentone/halothane anaesthesia at 60 ($P = 0.016$), 80 ($P = 0.049$) and 100 min ($P = 0.036$) of anaesthesia (Luna & Taylor, 1995) (Figs 1 and 2).

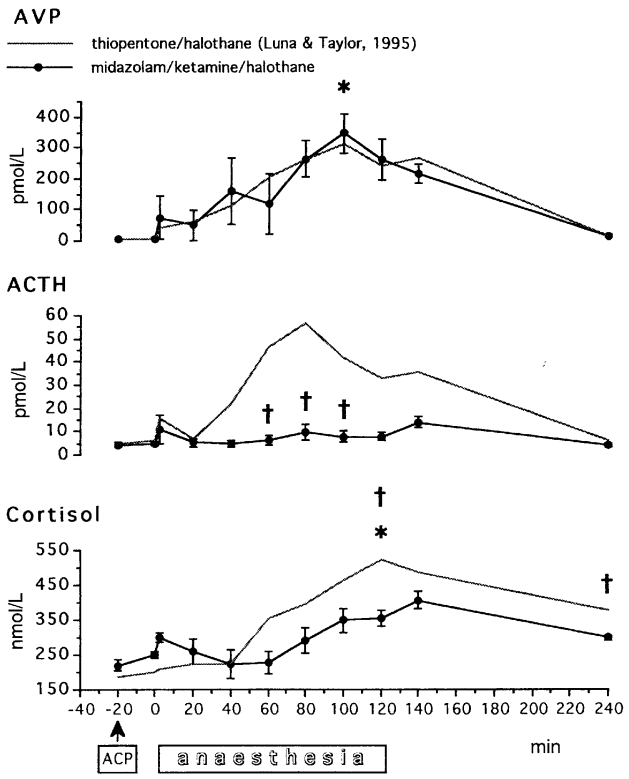

Fig. 1. Mean (SEM) plasma AVP, ACTH and cortisol concentrations in six ponies anaesthetized with midazolam, ketamine and halothane. *Significant change from pre-anaesthetic value. †Significant difference from thiopentone/halothane anaesthesia (Luna & Taylor, 1995).

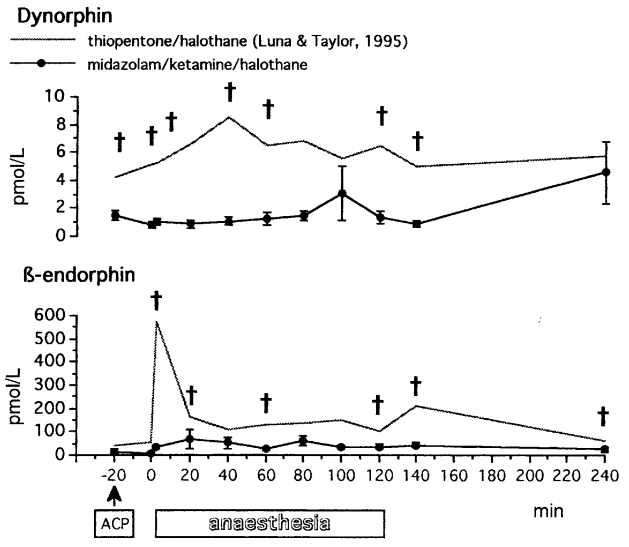

Fig. 2. Mean (SEM) plasma dynorphin and β-endorphin concentrations in six ponies anaesthetized with midazolam, ketamine and halothane. †Significant difference from thiopentone/halothane anaesthesia (Luna & Taylor, 1995).

Plasma cortisol concentration increased at the end of anaesthesia only (Fig. 1), but this change was smaller than during thiopentone/halothane anaesthesia at 120 min during anaesthesia (P = 0.0007) and at 120 min after disconnection (P = 0.028) (Luna & Taylor, 1995).

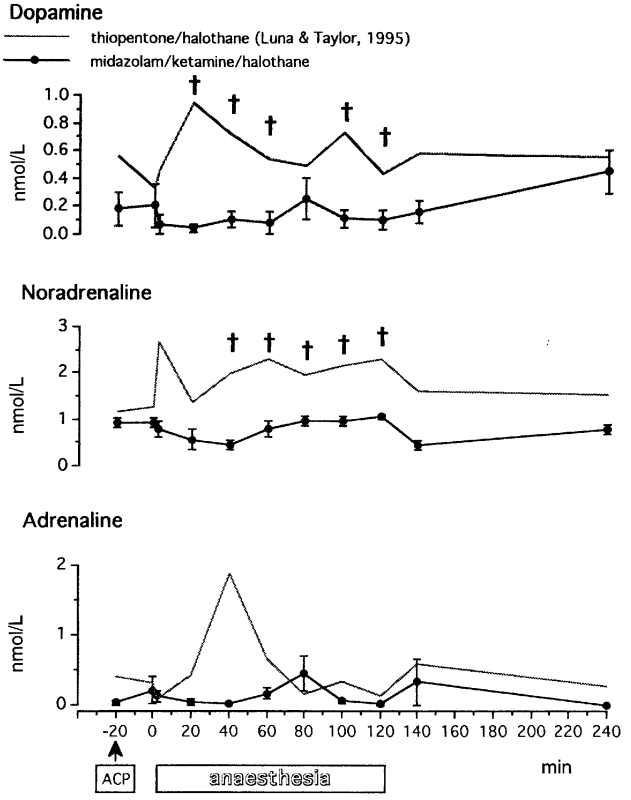

Fig. 3. Mean (SEM) plasma dopamine, noradrenaline and adrenaline concentrations in six ponies anaesthetized with midazolam, ketamine and halothane. †Significant difference from thiopentone/halothane anaesthesia (Luna & Taylor, 1995).

Plasma dopamine, noradrenaline and adrenaline concentrations did not change with time (Fig. 3). Plasma dopamine concentrations were lower than during thiopentone/halothane anaesthesia at 20 (P = 0.011), 40 (P = 0.031), 60 (P = 0.015), 100 (P = 0.035) and 120 min (P = 0.022) of anaesthesia (Luna & Taylor, 1995). Plasma noradrenaline concentrations were lower than during thiopentone/halothane anaesthesia at 40 (P = 0.015), 60 (P = 0.025), 80 (P = 0.007), 100 (P = 0.032) and 120 min (P = 0.031) of anaesthesia (Luna & Taylor, 1995).

Recovery was smooth and uneventful. Time from disconnection of halothane/O_2 to standing was 46 $\pm$ 6 min and the median recovery score was 4. No difference was observed between the midazolam/ketamine/halothane and thiopentone/halothane anaesthesia groups in recovery score nor recovery time, which were 3. 2 and 73 $\pm$ 17 min, respectively, in this last anaesthetic protocol (Luna & Taylor, 1995).

DISCUSSION

Although administration of midazolam and ketamine induced recumbency rapidly, making good control of the pony's head

essential in order to prevent trauma, some aspects of the induction were good. A standard response was observed, as all ponies lay down 30 s after midazolam/ketamine injection. In addition, the transition to recumbency was intermediate between the slow, smooth, variable and sometimes ataxic α-$_2$ adrenoceptor agonist/ketamine effect and the very rapid, sometimes violent effect of thiopentone. In the present study, the good muscle relaxation compared with detomidine/ketamine induction (Luna *et al.*, 1996) was presumably caused by midazolam enhancing GABA in neural transmission (Costa *et al.*, 1975). The hypnotic effect of midazolam is manifest through depression of the limbic system and the muscle relaxant effect through inhibition of the internuncial neurones at spinal levels (Costa *et al.*, 1975). Midazolam also successfully inhibited the muscle twitching and excitement usually caused by ketamine (White, 1982).

Midazolam also appeared to counteract the sympathomimetic effects of ketamine, stabilising heart rate throughout anaesthesia (White, 1982; Cartwright & Pingel, 1984). The hypotension observed during anaesthesia is a typical effect of halothane (Steffey & Howland, 1980), and the absence of compensatory tachycardia reflects halothane-induced depression of baroreflex sensitivity (Hellyer *et al.*, 1989). However, blood pressure was 18–25 mmHg higher in this study compared with thiopentone/halothane anaesthesia (Luna & Taylor, 1995), indicating that midazolam/ketamine induction provided relatively good cardiovascular stability and avoided the severe hypotension commonly observed during halothane anaesthesia with other induction techniques (Luna & Taylor, 1995; Luna *et al.*, 1996).

Ventilatory depression leading to respiratory acidosis is common during halothane anaesthesia (Steffey & Howland, 1980). Midazolam/ketamine induced bradypnoea immediately after induction leading to hypercapnia which was more marked than during thiopentone/halothane anaesthesia at the same time point (Luna & Taylor, 1995). Respiratory acidosis was greater throughout midazolam/ketamine/halothane than during thiopentone/halothane anaesthesia (minimum $P = 0.014$ at 60 min) (Luna & Taylor, 1995). Ketamine increases the respiratory response in both normocapnic and hypercapnic dogs by elevating minute ventilation (Kelly *et al.*, 1971) and diazepam alone did not change the respiratory rate or blood gas values in horses (Muir *et al.*, 1982). Also in man the ventilatory response to CO_2 was unaffected in midazolam or diazepam sedated volunteers (Forster *et al.*, 1980). In the light of these reports, the greater respiratory depression seen during midazolam/ketamine/halothane in the present paper compared with thiopentone/halothane anaesthesia (Luna & Taylor, 1995) is surprising. It may be a feature of the combination of midazolam and halothane in the equine species.

Arginine vasopressin increased during midazolam/ketamine/halothane in a similar manner to that during thiopentone/halothane anaesthesia (Luna & Taylor, 1995), probably in response to hypotension and/or a specific effect of halothane (Simpson & Forsling, 1977; Share, 1988). Intracerebroventricular administration of GABA in rats produced a time-and dose-dependent reduction in plasma AVP (Otake *et al.*, 1991). Agents which reduced GABA catabolism decreased AVP release in response to hypovolemia and, furthermore, GABA antagonists or substances that inhibit GABA synthesis increased AVP secretion (Skalar & Schrier, 1983). This GABA-inhibition of AVP release was demonstrated under both nonosmotic and hyperosmotic conditions (Skalar & Schrier, 1983; Otake *et al.*, 1991) and midazolam would be expected at least to reduce halothane-induced AVP secretion. Use of thiopentone, which is known to facilitate transmission of GABA (Harvey, 1980), also did not attenuate AVP release during halothane anaesthesia in ponies (Luna & Taylor, 1995). This suggests that halothane, with or without hypotension, appeared to be a stronger stimulus to AVP release than any midazolam or thiopentone-induced inhibition.

No changes were seen in plasma dynorphin, and although it was lower at some time points than during thiopentone/halothane anaesthesia (Luna & Taylor, 1995), this could be related to the relatively higher basal values observed before midazolam/ketamine/halothane anaesthesia. Again, as observed during thiopentone/halothane anaesthesia (Luna & Taylor, 1995) and detomidine/ketamine/halothane anaesthesia (Luna *et al.*, 1996), dynorphin secretion did not appear to be influenced by midazolam/ketamine/halothane anaesthesia, suggesting that dynorphin does not play an important role during anaesthesia in the equine species.

Pro-opiomelanocortin-derived peptides (ß-endorphin and ACTH) did not increase during midazolam/ketamine/halothane anaesthesia, in contrast to the elevation during thiopentone/halothane anaesthesia (Luna & Taylor, 1995). Nor was any increase observed immediately after induction, in contrast to a marked increase in the thiopentone/halothane study (Luna & Taylor, 1995). Although cortisol increased at the end of anaesthesia, this response was blunted and significantly less pronounced than during thiopentone/halothane anaesthesia (Luna & Taylor, 1995). In contrast to the effect on AVP, midazolam and ketamine induction successfully prevented the pituitary-adrenocortical activation commonly observed during thiopentone/halothane anaesthesia. Ketamine is unlikely to be implicated in this pituitary-adrenocortical suppression as it actually increases ACTH and cortisol secretion during anaesthesia, before surgery, in man (Lacoumenta *et al.*, 1984), so it appears that midazolam was the most likely agent to have blunted the pituitary-adrenocortical activation. Benzodiazepines inhibited secretion of pro-opiomelanocortin-derived peptides from rat hypothalamus and pituitary both *in vivo* and *in vitro* (Blasquez *et al.*, 1991) and suppressed CRF-induced ß-endorphin secretion from the pituitary intermediate lobe of rats (Saland *et al.*, 1992).

Most studies reported midazolam-induced inhibition of ß-endorphin, ACTH and cortisol release during anaesthesia and surgery in man (Crozier *et al.* 1987; Desborough *et al.*, 1991) and this effect appears to be centrally mediated rather than a depression in adrenal function (Crozier *et al.*, 1987).

Plasma dopamine and noradrenaline concentrations were lower than during thiopentone/halothane anaesthesia (Luna & Taylor, 1995). Midazolam reduced basal plasma concentrations of catecholamines by 50% (Aantaa *et al.*, 1991) and also attenuated the anaesthesia-induced adrenaline release in man (Crozier *et al.*, 1987). It was also reported that midazolam

counterbalanced the cardiovascular stimulatory effects of ketamine (White, 1982; Cartwright & Pingel, 1984) and in the present study probably prevented the increase in catecholamine levels which would be expected with the use of this dissociative anaesthetic (Baraka *et al*., 1973).

During anaesthesia the ponies appeared to be deeply anaesthetized, as assessed by eye position and absence of reflexes. It is likely that the depth of anaesthesia was greater than necessary for surgery. The MAC value of halothane in horses is 0.88% and surgical anaesthesia is usually obtained using 1.2 – 1.4 MAC (Steffey, 1991). In this anaesthetic protocol 1.36 MAC of halothane was used. Diazepam (0.044 mg/kg i.v.) reduced MAC by 30% in horses (Matthews *et al*., 1990) and considering that midazolam appears to be twice as potent as diazepam (Vree *et al*., 1981), adequate anaesthesia using a lower halothane concentration might have been expected, which would minimize the cardiorespiratory effects.

The time taken for induction from injection to recumbency, was between that for thiopentone (Luna & Taylor, 1995) and detomidine/ketamine induction (Luna *et al*., 1996) and is a benefit of midazolam/ketamine induction; it combined the favourable aspects of the other two induction techniques; induction was neither so fast as to cause injury, nor was it slow with consequent ataxia and resistance from the animal. Recovery quality and post-anaesthetic ataxia was similar to that seen after thiopentone-halothane anaesthesia (Luna & Taylor, 1995). Although not significantly different, recovery tended to be shorter with this technique (47 $\pm$ 6 min) compared with thiopentone/halothane anaesthesia (73 $\pm$ 17 min) (Luna & Taylor, 1995).

The use of midazolam/ketamine for induction prior to halothane anaesthesia in horses appears promising. Midazolam does not suppress steroidogenesis and the adrenal cortex is able to respond when stimulated by ACTH (Crozier *et al*., 1987). It remains open to question whether reduction of the endocrine stress response directly at the pituitary or hypothalamic level is a positive attribute or not. In the present study, midazolam attenuated, rather than totally suppressed, pituitary secretion, apparently maintaining the pituitary capable of responding if stimulated. It may be better to use an anaesthetic protocol that does not itself cause a stress response, but does not block it at such point that the pituitary is incapable of working under life threatening conditions. This effect should be further investigated by assessment of the stress response during surgery under midazolam anaesthesia to test whether it blocks a response to standard stressor.

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Table 1. Arterial blood gas values, respiratory rate, heart rate, mean arterial blood pressure (MABP), temperature, haematocrit, glucose and lactate during midazolam/ketamine/halothane anaesthesia (mean ± SEM)

Mins	- 20	0	2	20	40	60	80	100	120	140	240
PaO_2 (kPa)		14.6 ± 1.2	29.5 ± 4.1*	53.9 ± 2.3*	57.5 ± 1.9*	58.1 ± 2.4*	55.9 ± 3.3*	54.9 ± 3.8*	54.6 ± 2.7*	10.8 ± 0.7	13.9 ± 0.3
$PaCO_2$(kPa)		5.9 ± 0.2	8.1 ± 0.2*	7.7 ± 0.3*	8.2 ± 0.4*	8.9 ± 0.2*	9.2 ± 0.3*	9.6 ± 0.3*	9.9 ± 0.3*	7.1 ± 0.5	6.3 ± 0.1
pH		7.42 ± 0.02	7.29 ± 0.02*	7.30 ± 0.02*	7.27 ± 0.02*	7.22 ± 0.02*	7.21 ± 0.02*	7.18 ± 0.02*	7.17 ± 0.03*	7.31 ± 0.03*	7.37 ± 0.01
Resp. Rate	14 ± 1	13 ± 2	6 ± 1*	11 ± 1	12 ± 1	12 ± 1	12 ± 1	11 ± 1	12 ± 1	9 ± 2	16 ± 2
Heart Rate	47 ± 2	42 ± 2	46 ± 2	43 ± 2	42 ± 1	41 ± 2	41 ± 1	41 ± 2	41 ± 2	35 ± 2*	51 ± 2
MABP (mmHg)		115 ± 6	98 ± 12	74 ± 10*	76 ± 10*	83 ± 9*	85 ± 8*	89 ± 10*	91 ± 9*	133 ± 9	
Temperature (°C)	37.9 ± 0.2	37.8 ± 0.1	37.7 ± 0.1	37.4 ± 0.1	37.2 ± 0.1	37.0 ± 0.2	36.9 ± 0.2*	36.7 ± 0.3*	36.5 ± 0.3*	36.4 ± 0.3*	38.0 ± 0.2
Haematocrit (L/L)	0.35 ± 0.01	0.29 ± 0.01*	0.29 ± 0.01*	0.28 ± 0.018	0.30 ± 0.01*	0.30 ± 0.01*	0.30 ± 0.01*	0.31 ± 0.01*	0.30 ± 0.01*	0.29 ± 0.01*	0.30 ± 0.01*
Glucose (mmol/L)	4.71 ± 0.07	4.69 ± 0.10	4.84 ± 0.09	4.63 ± 0.15	4.62 ± 0.20	4.47 ± 0.26	4.41 ± 0.34	4.35 ± 0.43	4.34 ± 0.45	4.42 ± 0.37	6.37 ± 0.28*
Lactate (mmol/L)	1.22 ± 0.08	1.26 ± 0.09	1.20 ± 0.18	1.43 ± 0.16	1.59 ± 0.16	1.69 ± 0.14*	1.76 ± 0.13*	1.74 ± 0.12*	1.74 ± 0.11*	1.82 ± 0.12*	1.49 ± 0.04

*denotes significant change from pre-anaesthetic value ($P < 0.05$).

- 20 mins = before premedication; 0 mins = after acepromazine administration, before midazolam/ketamine induction; 2 – 120 mins = after midazolam/ketamine administration, during anaesthesia; 120 mins = end of anaesthesia.