Observations on some cardiopulmonary effects of midazolam, xylazine and a midazolam/ketamine combination in the goat

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ABSTRACT

Xylazine, midazolam and a midazolam/ketamine combination were administered to 6 goats in a randomised 3-way block design. All goats received all treatments with at least a 7-day interval between treatments. Statistically significant ($P < 0.05$) changes were observed in some of the measured cardiopulmonary variables for xylazine and midazolam/ketamine. Xylazine administration resulted in statistically significant decreases in minute volume, arterial partial pressure of oxygen, heart rate and mean arterial blood pressure. The increase in arterial partial pressure of carbon dioxide was not statistically significant. For the midazolam/ketamine combination, the decrease in tidal volume was statistically significant, but not the decrease in minute volume and increase in arterial partial pressure of carbon dioxide. The decrease in the arterial partial pressure of oxygen was also statistically significant. The mean arterial blood pressure for the combination was statistically significantly higher compared to xylazine. The changes in cardiopulmonary variables after midazolam administration were not statistically significant, such as tidal and minute volume, arterial partial pressure of oxygen and carbon dioxide. However, clinically significant effects such as hypoventilation and hypoxia were observed after its administration. The change in mean arterial blood pressure was minimal.

Key words: anaesthesia, caprine, ketamine, midazolam, xylazine.

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INTRODUCTION

Xylazine is commonly used in ruminants as a sedative or as an adjunct to ketamine anaesthesia[5,18]. For sheep and goats the use of xylazine represents an extra-label use of the drug. There are, however, unpublished observations from practising veterinarians that mortalities may be associated with the use of this drug in small stock. Published reports also indicate adverse effects such as hypoxaemia in the goat[9] and lung oedema in the sheep[20]. Alternatively, xylazine may be used as an anaesthetic adjunct in combination with ketamine to obtain anaesthesia[10]. The popularity of the benzodiazepines as anaesthetic adjuncts is increasing as a result of their mild cardiovascular effects, and its combined use with ketamine is recommended for old and debilitated animals[5]. Midazolam hydrochloride is a water-soluble benzodiazepine salt, the free base being highly lipid soluble, with low solubility in water. It exerts a dose-dependent sedative-hypnotic effect in the goat, and may be combined with ketamine for induction of anaesthesia[17]. The purpose of this investigation was to compare the effects of midazolam, xylazine and a midazolam/ketamine combination on cardiovascular and respiratory function in the goat.

MATERIALS AND METHODS

Six adult, castrated male goats of indigenous (nondescript) origin were used. The body mass varied between 28.5 and 47.5 kg. The mean body mass for the 6 goats was 41.5 kg. The right carotid arteries were previously surgically translocated[17] to a subcutaneous position in the jugular groove to facilitate arterial blood collection.

The doses to be used for midazolam hydrochloride (Dormicum, Roche) and ketamine hydrochloride (Anaket, Centaur) were first determined in a pilot trial. For the investigation, the anaesthetic agents were administered to the goats in a randomised 3-way block design. Each animal therefore received all treatments with at least a 7-day interval between treatments. The agents were injected intravenously (iv) into the jugular vein after venipuncture with a 20G teflon catheter (Jelco, Johnson & Johnson). Xylazine hydrochloride (Rompun, Bayer) was administered at a dose of 0.05 mg/kg, midazolam hydrochloride at 0.6 mg/kg and ketamine at 5 mg/kg.

For the investigation the goats were starved of food and water for a period of 12 hours. The goats were manually immobilised in lateral recumbency. A face mask was placed over the mouth and nostrils and an airtight seal obtained with the aid of cotton wool placed in the intermandibular space, and a glycerine lubricating jelly (KY Lubricating Jelly, Johnson & Johnson) around the edges of the mask. The face mask was connected to a physiological multi-parameter airway gas monitor with side-stream spirometry (Capnomac Ultima, Datex Instrumentarium Corporation, Helsinki) for the measurement of the tidal volume (V_T), minute volume, ventilation rate and end-tidal CO_2 concentration ($ETCO_2$). The apparatus was calibrated for the flow rate and analysis of gas. The V_T/kg was calculated as: mean body mass/mean V_T. The arterial blood pressure and electrocardiogram (ECG) were measured with a physiological multi-parameter monitor (Cardiocap II, Datex Instrumentarium Corporation, Helsinki). The arterial blood pressure was measured after percutaneous puncture of the carotid artery with a 20G intravenous cannula (Medican, Medical Specialities). The ECG was recorded with a 3-limb lead attached on the 2 front limbs and a hind limb using disposable electrodes. Arterial blood samples were collected anaerobically in 2.5 mℓ plastic, heparinised syringes, and stored in iced water. A pH/blood-gas analyser (ABL3, Radiometer, Copenhagen) was used to measure the blood-gas variables. The arterial partial pressure for oxygen (PaO_2) and carbon dioxide ($PaCO_2$) were corrected for body temperature. The analysis was performed within 2 h of collection. Arterial oxyhaemoglobin saturation was measured with an oximeter (OSM3, Radiometer, Copenhagen) with extinction coefficients for caprine blood. Observations on the cardiovascular and respiratory variables were made 5 min

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before administration of the drugs, and at 5 min intervals for 15 min after drug administration. The baseline measurements were only made once the animals relaxed after instrumentation, although minimal resistance or resentment to the physical immobilisation was encountered for the baseline measurements. It was observed that application of the face mask in conscious goats resulted in an increase in blood pressure, therefore the cardiovascular and arterial blood gas measurements were made before application of the face mask. Body temperature was measured before drug administration and after 15 min. The investigation was carried out in a temperature-controlled room that varied between 18 and 20 °C.

Data analysis

Variability of data was expressed by the standard deviation (±SD), and was recorded at each sample collection point. Data were analysed for statistically significant differences with a 1-way repeated measures analysis of variance. When significant differences were found, the Tukey all pairwise multiple comparison test was performed to identify significantly different samples for the ventilatory and cardiovascular variables. For ordinal data or when the values failed the normality or equal variance test, the Friedman repeated measures analysis of variance on ranks was used. Significantly different samples were further analysed with Dunnett's test. Significance was accepted at a confidence level of 95 %. A personal computer was used to analyse the data with SigmaStat for Windows, version 2 (Jandel Corporation).

RESULTS

The mean and standard deviation (±SD) recorded for ventilation, arterial blood-gas and cardiovascular variables are reported in Tables 1, 2 and 3, respectively. Changes in the following mean ventilatory variables were statistically significant ($P < 0.05$). For xylazine, the decrease in tidal volume at 10 and 15 min and the minute volume over the 15-min observation period, the mean $ETCO_2$ concentration for midazolam was significantly higher ($P < 0.05$) compared to xylazine over the 15 min treatment period (Table 1). For midazolam/ketamine the decrease in tidal volume at 10 and 15 min and the minute volume at 15 min were statistically significant. The $ETCO_2$ concentration for midazolam/ketamine was significantly higher compared to xylazine over the 15-min treatment period (Table 1). The mean V_T/kg for the conscious goats was 12 mℓ/kg. The minimum and maximum mean V_T/kg for midazolam was 7 and 9 mℓ/kg; for xylazine 7 and 8 mℓ/kg; and for midazolam/ketamine 4 and 10 mℓ/kg, respectively.

Table 1: **Mean and standard deviation** (SD) **of ventilatory variables in goats before and after intravenous midazolam, xyalazine and midazolam/ketamine administration.**

Variable[a]	Drug[b]	Time (min) –5	+5	+10	+15
V_T	mdz	528 (171)	292 (193)	293 (101)	373 (214)
	xyl	448 (102)	298 (98)	327 (158)*	339 (111)*
	m/k	573 (223)	413 (144)	164 (67)*	272 (120)*
f	mdz	18 (5)	20 (4)	23 (9)	16 (7)
	xyl	22 (6)	20 (6)	18 (8)	16 (9)
	m/k	17 (6)	23 (15)	18 (12)	19 (8)
V_E	mdz	10.5 (5.6)	7.8 (3.5)	7.2 (4.5)	6.3 (4)
	xyl	10.6 (4.2)	6.1 (2.3)*	5.3 (1.2)*	5.1 (2.2)*
	m/k	10.1 (5.2)	8.1 (6.0)	6.3 (3.1)	5.9 (2.9)*
$ETCO_2$	mdz[c]	5.8 (0.6)	5.1 (0.9)	4.7 (0.9)	5.4 (0.4)
	xyl	5.5 (0.5)	4.9 (2.6)	4.2 (1.8)	4.1 (1.3)
	m/k[d]	5.5 (0.6)	5.8 (1.0)	5.6 (1.0)	5.5 (0.7)

*Statistically significant ($P < 0.05$) change from the baseline.
[a]V_T = tidal volume (mℓ); f = ventilation rate (breaths/min); V_E = minute volume (ℓ/min); $ETCO_2$ = end-tidal carbon dioxide concentration (%).
[b]mdz = midazolam; xyl = xylazine; m/k = midazolam/ketamine.
[c]Significantly ($P < 0.05$) higher for midazolam compared to xylazine over the treatment period.
[d]Significantly ($P < 0.05$) higher for midazolam/ketamine compared to xylazine over the treatment period.

The following changes in mean arterial blood-gas variables were statistically significant ($P < 0.05$): for xylazine the increase in $PaCO_2$ at 10 and 15 min, the decrease in PaO_2 and oxyhaemoglobin saturation over the 15-min observation period. The PaO_2, oxyhaemoglobin saturation and standard base excess for midazolam differed significantly ($P < 0.05$) from xylazine over the 15-min observation period (Table 2). For midazolam/ketamine the decrease in pH and PaO_2 was statistically significant over the 15 min observation period, and the arterial oxyhaemoglobin saturation at 5 min. The pH, PaO_2, oxyhaemoglobin saturation and standard base excess for midazolam/ketamine were significantly different ($P < 0.05$) from xylazine over the 15-min treatment period (Table 2).

The following changes in cardiovascular variables were statistically significant ($P < 0.05$) after drug administration: for xylazine the decrease in heart rate over the 15-min observation period, the decrease in diastolic and systolic arterial blood pressure at 10 and 15 min, and the decrease in mean arterial blood pressure over the 15-min observation period. The heart rate and diastolic blood pressure for midazolam were significantly different ($P < 0.05$) compared to xylazine over the 15-min treatment period. For midazolam/ketamine the increase in heart rate at 5 min, and the decrease in systolic arterial blood pressure at 10 and 15 min were statistically significant. Compared to xylazine, the heart rate and mean arterial blood pressure for midazolam/ketamine were significantly higher ($P < 0.05$) over the 15-min treatment period (Table 3). No ECG abnormalities were observed after the administration of midazolam or midazolam/ketamine over the 15-min observation period. Following xylazine administration, large increases in the arterial blood pressure were observed within 60 sec, and lasted for less than 5 min. During this hypertensive period 3rd-degree atrio-ventricular heart blocks were observed in some goats.

The mean body temperature remained unchanged at 38.6 ± 0.4 before and 38.6 ± 0.4 °C after midazolam; 38.4 ± 0.5 before and 38.4 ± 0.5 °C after midazolam/ketamine. With xylazine the temperature decreased from 38.8 ± 0.2 to 38.6 ± 0.3 °C.

DISCUSSION

Values obtained for ventilation variables in this investigation varied from the reference values recorded for conscious goats[6] and anaesthetised goats[16]. The mean baseline (conscious) tidal volume of 12.7 mℓ/kg or 527 mℓ/goat obtained in this investigation may indicate a considerably higher value compared to the resting reference value of 300–350 mℓ/goat[6], as no reference was made to the body mass of the goats. The mean ventilation rate of 18 breaths/min that was obtained is in agreement to the reference value of 20 breaths/min[6]. In the anaesthetised goats, the mean ventilation rate of 16 breaths/min for both midazolam and xylazine at 15 min was in accordance with the reference[16]. The minimum tidal volume of 4 mℓ/kg obtained with the midazolam/ketamine combination at

Table 2: **Mean and standard deviation** (SD) **of arterial blood gas variables in goats before and after intravenous midazolam, xyalazine and midazolam/ketamine administration.**

Variable[a]	Drug[b]	Time (min) –5	+5	+10	+15
pH	mdz	7.37 (0.03)	7.39 (0.09)	7.32 (0.08)	7.36 (0.02)
	xyl	7.43 (0.07)	7.39 (0.13)	7.39 (0.06)	7.43 (0.18)
	m/k[c]	7.42 (0.1)	7.23 (0.2)*	7.25 (0.2)*	7.32 (0.2)*
$PaCO_2$	mdz	4.7 (0.3)	5.1 (0.4)	5.1 (0.4)	4.7 (0.4)
	xyl	4.4 (0.7)	5.1 (0.3)	5.6 (0.4)*	5.5 (0.7)*
	m/k	5.4 (1.8)	6.1 (1.7)	5.9 (2.0)	5.7 (1.9)
PaO_2	mdz	9.5 (1.0)	7.0 (1.5)	7.1 (0.6)	7.7 (0.6)
	xyl[d]	8.5 (1.4)	4.2 (1.5)*	4.4 (1.5)*	4.5 (1.3)*
	m/k[e]	10.4 (1.5)	7.4 (1.6)*	7.9 (0.7)*	7.6 (1.4)*
HCO_3	mdz	19.5 (0.8)	20.0 (0.6)	19.0 (1.4)	18.8 (1.3)
	xyl	20.9 (0.6)	22.0 (1.1)	22.9 (2.6)	23.4 (1.7)
	m/k	20.7 (1.2)	19.1 (1.9)	20.3 (0.9)	18.2 (2.5)
SBE	mdz[f]	–4.7 (1)	–1.3 (7.4)	–6.2 (3.5)	–5.6 (1.3)
	xyl	–2.7 (1.2)	–0.3 (5.8)	0.5 (5.8)	3.0 (10.7)
	m/k[g]	1.0 (11.7)	–8.1 (5.9)	–7.8 (5.7)	–2.1 (9.7)
SAT	mdz	93.2 (0.9)	85.5 (9.5)	85.9 (4.1)	88.6 (1.9)
	xyl[h]	92.6 (1.6)	53.7 (19.8)*	57.1 (20.3)*	59.1 (18.4)*
	m/k[i]	94.3 (1.7	83.3 (9.2)*	87.4 (3.6)	85.6 (6.0)

*Statistically significant change from the baseline.
[a]PaO_2 = partial pressure of oxygen in arterial blood (kPa); $PaCO_2$ = partial pressure of carbon dioxide in arterial blood (kPa); SBE = standard base excess; SAT = arterial oxygen haemoglobin saturation; HCO_3 = bicarbonate.
[b]mdz = midazolam; xyl = xylazine; m/k = midazolam/ketamine.
[c]Midazolam/ketamine significantly ($P < 0.05$) different from xylazine over the treatment period.
[d]Xylazine significantly ($P < 0.05$) different from midazolam over the treatment period.
[e]Midazolam/ketamine significantly ($P < 0.05$) different from xylazine over the treatment period.
[f]Midazolam significantly ($P < 0.05$) different from xylazine over the treatment period.
[g]Midazolam/ketamine significantly ($P < 0.05$) different from xylazine over the treatment period.
[h]Xylazine significantly ($P < 0.05$) different from midazolam over the treatment period.
[i]Midazolam/ketamine significantly ($P < 0.05$) different from xylazine over the treatment period.

10 min was considerably less than the 7–8 mℓ/kg previously reported[16]. The maximal tidal volume of 14 mℓ/kg that was obtained with the midazolam/ketamine combination at 5 min is in excess of the reference value[16], and was probably measured before the full onset of anaesthesia. The variation between the minimum and maximum V_T/kg was also the greatest for this group. The large tidal volumes observed could be the result of apneustic breathing seen with ketamine[3].

After midazolam administration, the minute volume continued to decrease over the 15-min observation period (Table 1). During the first 10 min a small increase in ventilation rate was associated with a decrease in the tidal volume, and was probably a reflex response to the decrease in the minute volume and tidal volume. The $ETCO_2$ continued to decrease for 10 min and could indicate ventilation/perfusion abnormalities, as the $PaCO_2$ changed very little from baseline during this period (Table 2). Hypoxaemia was observed as the PaO_2 decreased by 27 % to 7.0 kPa at 5 min. The arterial oxyhaemoglobin saturation followed a similar pattern as the PaO_2. The baseline arterial blood-gas values obtained in this investigation varied in some aspects from previously published studies, although references to conscious values in goats are limited[14]. Of interest was the reference PaO_2 of 6.2 kPa (43.25 mmHg), which agreed with the low baseline values recorded before midazolam (9.5 kPa) and xylazine (8.5 kPa) administration in this investigation. As hypoxia normally would serve as a powerful respiratory stimulant, it failed to do so after midazolam administration. In humans midazolam inhibits the central respiratory drive[4] and respiratory depression is the most significant adverse effect during conscious sedation[15]. The mean arterial blood pressure remained stable during this period, although a small decrease (7 %) occurred (Table 3). The systolic and diastolic arterial blood pressure reported for conscious goats are 16 and 11.2 kPa (120 and 84 mmHg), respectively[6], and are in agreement with the baseline measurements made in this investigation. The maximal increase in heart rate 5 min after midazolam administration did not coincide with the maximal decrease in arterial blood pressure at 15 min, and may therefore not be a reflex compensatory response to the decrease in arterial blood pressure. Alternatively, the decrease in heart rate may have been the result of hypnosis, although it is expected that the heart rate would also decrease immediately after its administration. The increase in heart rate following midazolam was in agreement with previous observations in the goat[17] and calf[12]. In the dog, midazolam resulted in a small increase in heart rate and mean arterial blood pressure. Cardiac output increased, while contractility and peripheral vascular resistance decreased[8]. In humans midazolam preserves the baroreceptor response to hypotension[11], which would enable the reflex increase in heart rate in response to a decrease in blood pressure.

Xylazine resulted in a decrease in minute volume, PaO_2 and arterial oxyhaemoglobin saturation, and an increase in $PaCO_2$, which indicated the magnitude of hypoventilation induced by this agent. Of significance was the simultaneous increase in $PaCO_2$ and the decrease in $ETCO_2$. The former was probably the result of hypoventilation, and the latter from a decrease in cardiac output, ventilation-perfusion mismatch, intrapulmonary shunts or a combination thereof. The statistically significant increase in the $PaCO_2$ is in contrast to previous studies where no increase was found with xylazine in sheep[2], or with a xylazine/ketamine combination[10]. No explanation for the low baseline mean PaO_2 of 8.5 ±1.4 kPa before xylazine administration could be found, and this may have influenced the values obtained after xylazine administration. Peripheral muscle relaxation induced by either xylazine or midazolam may in addition reduce ventilatory muscle function, and contribute towards the reduction in tidal volume as observed in this investigation. The hypoxia observed in this investigation is in agreement with previous investigations in the goat[9] and sheep[1]. In addition, xylazine may cause pulmonary oedema in sheep[20]. The hypoxaemia observed in this investigation after the administration of xylazine could therefore indicate that a combination of hypoventilation and intrapulmonary mechanisms was possibly responsible for the hypoxaemia. Xylazine is an α_1 and α_2 adrenoceptor agonist that also acts extrasynaptically on α_2 receptors in vascular smooth muscle to cause vasoconstriction[19]. In sheep an increase in airway pressure is reported, which is an indication of altered pulmonary mechanics, *i.e.* dynamic lung compliance or an increase in airway resistance[2,13]. In addition, it may possibly increase pulmonary vascular resistance. The former will result in reduced alveolar ventilation, and the latter in increased pulmonary arterial pressure. In either case it will result in hypoxaemia and an

Table 3: **Mean and standard deviation** (SD) **of cardiovascular variables in goats before and after intravenous midazolam, xyalazine and midazolam/ketamine administration.**

Variable[a]	Drug[b]	Time (min)			
		–5	+5	+10	+15
HR	mdz	75 (20)	82 (18)	72 (18)	70 (24)
	xyl[c]	73 (15)	67 (22)*	61 (16)*	57 (9)*
	m/k[d]	72 (12)	91 (16)*	88 (15)	86 (15)
SAP	mdz	16.2 (2.1)	17.2 (2.7)	15.8 (1.6)	15.1 (1.9)
	xyl	17.2 (1.4)	15.3 (1.5)	14.9 (2.3)*	14.4 (2.0)*
	m/k	17.0 (1.6)	15.1 (3.0)	15.0 (2.8)*	14.8 (3.1)*
DAP	mdz	11.1 (2.3)	11.7 (0.7)	11.7 (1.4)	11.0 (2.7)
	xyl[e]	12.0 (1.2)	8.9 (1.0)*	8.2 (1.6)*	8.6 (1.1)*
	m/k	10.9 (1.9)	11.1 (2.4)	10.8 (3.0)	10.4 (3.4.)
MAP	mdz	13.8 (1.4)	13.4 (1.1)	13.1 (1.2)	12.8 (2.1)
	xyl	14.3 (1.3)	11.8 (1.2)*	11.0 (1.4)*	10.9 (1.6)*
	m/k[f]	14.2 (2.0)	13.8 (2.8)	12.6 (3.3)	12.2 (3.1)

*Statistically significant ($P < 0.05$) change from baseline.
[a]HR = heart rate (beats/min); SAP = systolic blood pressure (kPa); DAP = diastolic blood pressure (kPa); MAP = mean arterial blood pressure (kPa).
[b]mdz = midazolam; xyl = xylazine; m/k = midazolam/ketamine.
[c]Xylazine significantly ($P < 0.05$) different from midazolam over the treatment period.
[d]Midazolam/ketamine significantly ($P < 0.05$) different from xylazine over the treatment period.
[e]Xylazine significantly ($P < 0.05$) different from midazolam over the treatment period.
[f]Midazolam/ketamine significantly ($P < 0.05$) different from xylazine over the treatment period.

increase in the alveolar-arterial oxygen partial pressure difference. Arterial hypoxaemia and pulmonary oedema (as observed in sheep[20]) may possibly be the result of pulmonary hypertension. In sheep minimal changes in pulmonary vascular resistance and pulmonary arterial pressure occurred after the administration of a xylazine/ketamine combination[3]. The effect of xylazine on its own on the latter 2 variables in the goat is not known. With xylazine the decrease in mean arterial blood pressure and diastolic blood pressure was statistically significant and corresponded with decreases in blood pressure observed in sheep[1]. The decrease in arterial blood pressure is probably the result of the decrease in heart rate and the presynaptic activation of α_2-adrenoceptors resulting in peripheral vasodilatation. The effect of heart rate and peripheral vascular resistance was reflected in the magnitude of the decrease in blood pressure, 32 % for the diastolic blood pressure and 24 % for the mean arterial blood pressure. Both the minimum systolic and diastolic blood pressure values recorded for xylazine in this investigation were within the reported limits for anaesthetised goats[16]. The combined effect of hypoventilation, hypoxia and hypotension would strongly suggest that the supplementation of oxygen after the administration of xylazine to goats is advisable, and that the use of this agent in compromised goats is not recommended.

Midazolam/ketamine resulted in hypoventilation characterised by a decrease in minute volume and tidal volume. The mean tidal volume of 164 mℓ was the lowest value obtained during this investigation for all 3 agents and probably coincided with the time of maximal anaesthetic depth. The changes in the $ETCO_2$ followed a similar pattern to the changes in the $PaCO_2$ during this period, but in contrast to the direction of changes with xylazine, that may indicate improved pulmonary gas exchange. The increase in heart rate was probably the action of the ketamine. Ketamine is known to support arterial blood pressure and increase heart rate by sympathetic stimulation[7]. The only statistically significant change in the acid-base balance was observed after midazolam/ketamine administration (Table 2) and was associated with a small increase in the $PaCO_2$, indicating a metabolic acidosis. It is possible that the hypoxic ventilatory drive may have increased ventilation and therefore only resulted in the relatively small increases in the $PaCO_2$ and $ETCO_2$. The decrease in standard base excess to –7.8 confirmed the existence of metabolic acidosis. The baseline pH for the goats observed in this study is much lower compared to a previous study[10], but the magnitude of the decrease in pH is similar after a atropine/diazepam/ketamine combination. The reported decrease in the standard base excess was also small in comparison to the decrease observed in this study.

The administration of xylazine to the goats resulted in statistically significant changes in the ventilatory and cardiovascular variables. For midazolam the changes in the cardiovascular and ventilatory variables were not statistically significant. The mean arterial blood pressure was maintained. However, hypoventilation was sufficient to result in hypoxia and oxyhaemoglobin desaturation. For the midazolam/ ketamine combination, statistically significant changes occurred in pulmonary variables. The changes in the cardiovascular variables were not statistically significant, and maintained within acceptable clinical limits.

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