Cardiovascular and respiratory effects of ketamine in the neonatal lamb

Frederick A. Burrows MD FRCPC, J.B. Norton MD, James Fewel PH D

To determine the cardiovascular and respiratory effects of intravenous ketamine in the neonatal lamb we studied six unpremedicated chronic neonatal lamb preparations. Each lamb was anaesthetized with ketamine 1 mg·kg^{-1}, allowed to recover and then anaesthetized with ketamine 2 mg·kg^{-1}. Mean arterial pressure, mean pulmonary artery pressure, mean left atrial pressure, pulmonary blood flow, heart rate, respiratory rate and arterial blood gases were measured before and at one, two, four, six, eight and ten minutes after the administration of each dose of ketamine. Pulmonary vascular resistance, systemic vascular resistance and the ratio of pulmonary to systemic vascular resistance were also determined. After the administration of either dose of ketamine, only respiratory rate changed significantly ($p \leq 0.05$), reaching a maximum after two minutes. This change was not associated with any arterial blood gas abnormalities. We conclude that in the presence of adequate ventilation, ketamine produces no significant cardiovascular effects in neonatal lambs.

Key words

ANAESTHETICS, INTRAVENOUS: ketamine: ANAESTHESIA: paediatric, neonatal.

From the Departments of Anesthesia and Pediatrics, University of Arkansas for Medical Sciences and the Arkansas Children's Hospital, Little Rock, Arkansas, U.S.A. and the Department of Anaesthesia, The Hospital for Sick Children and University of Toronto, Toronto, Ontario.

Address correspondence to: Dr. F.A. Burrows, Department of Anaesthesia, The Hospital for Sick Children, 555 University Avenue, Toronto, Ontario, M5G 1X8.

Ketamine hydrochloride is an agent frequently recommended for the induction of anaesthesia in children with congenital heart defects[1–4] and for sedation during cardiac catheterization.[5,6] It is also recommended for sedation of unco-operative neonates, infants and children for diagnostic procedures such as computerized tomography.[7,8] Although ketamine provides a stable level of anaesthesia, excellent analgesia, maintenance of respiratory reflexes and drive and maintenance of cardiovascular function,[9,10] it has been reported to produce hypoxaemia and elevations in pulmonary vascular resistance (Rp).[11–13]

The cardiovascular effects of intravenous ketamine have been studied in both animals and humans,[11–14] but its effects in infants are not clear. Ketamine is reported to have no significant influence on the circulation in children either before or after surgical repair of their congenital heart lesions.[15–17] Hickey *et al.*[17] suggested that the effects of ketamine in children apply to infants with similar defects. However, the myocardium and pulmonary circulation differ markedly between infants and children.

Futhermore, there is no study on the effect of the administration of ketamine on the cardiovascular system of the intact normal neonate or infant. Extrapolation of work done in children with congenital heart defects may not be relevant as their results may reflect the influence of the disease process on the myocardium and the pulmonary circulation. The purpose of our study, therefore, was to examine the effect of ketamine on the cardiovascular variables in the neonatal lamb model with a normal cardiovascular system.

Methods

We studied six chronically instrumented newborn lambs weighing <6 kg and less than eight days old. Each animal had undergone a lateral thoracotomy

one day after birth (Day 1). Left atrial (LA) and pulmonary arterial (PA) #5 French polyethylene catheters were inserted. The aortic catheter was inserted through the femoral artery and positioned in the abdominal aorta. Blood loss was less than 5 ml. Cardiac output (Qp) was monitored with a Gould Statham Flow meter SP2202 with Statham flow transducers from the Sp 7515 series. The transducers were 8, 9 or 10 mm in diameter depending on the size of the PA. Where present, patent ductus arteriosis was ligated. The lambs were allowed to recover for three days.

The electroencephalogram (EEG) was monitored by standard bipolar parietal leads. Heart rate (HR) was calculated from the peak-to-peak interval of the arterial pressure trace. The data were recorded simultaneously on an Electronics for Medicine® 12-channel recorder. Arterial blood gas analysis (pH, PCO_2, PO_2 and base excess) was performed (Corning 165®) Volume equivalent to blood withdrawn for analysis (approximately 10 ml) was transfused into the lamb immediately after sampling.

The study was performed on Day 5. Recovery from surgery was assessed solely by observation of the animal. The animal was considered suitable for further study if there were no signs of infection or obvious restriction of movement due to the site of surgery.

The lambs were suspended in a sling in the upright position and were nursed from a bottle. The transducers were mounted on a rack next to the animal at mid-thoracic level. To provide a quiet environment for the lambs all equipment was positioned outside the room and the animal was visualized with a remote camera.

Each lamb was studied twice: first, 1 $mg \cdot kg^{-1}$ ketamine was administered and then, after return of the EEG and cardiovascular variables to control levels (at least one hour), 2 $mg \cdot kg^{-1}$ ketamine was administered. The ketamine was administered into the LA line over 30 seconds. During each study, control measurements were made immediately before ketamine administration.

Systemic vascular resistance (Rs) was calculated from the formula:

$$Rs(mmHg \cdot ml^{-1} \cdot kg^{-1}) = \frac{\text{mean arterial pressure } (\overline{MAP})}{\text{cardiac output (Qp)}}$$

and pulmonary vascular resistance from the formula:

$$Rp(mmHg \cdot ml^{-1} \cdot min^{-1} \cdot kg^{-1}) = \frac{\text{mean pulmonary artery pressure } (\overline{PAP}) - \text{mean left atrial pressure } (\overline{LAP})}{Qp}$$

Statistical significance ($p \leq 0.05$) was determined using the Bonferonni t test, analysis of variance and the Student-Newman-Keuls multiple range test.

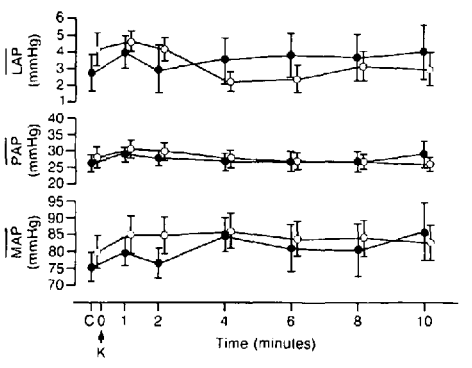

FIGURE 1 $\overline{MAP}$, $\overline{PAP}$ and $\overline{LAP}$ control values (C) and after administration of ketamine (K) 1 $mg \cdot kg^{-1}$ (●—●) and 2 $mg \cdot kg^{-1}$ (○—○). The bars represent the standard error of the mean (SEM).

Results

The control values for $\overline{MAP}$, $\overline{PAP}$, $\overline{LAP}$, HR, RR, Qp, Rp, Rs and $Rp \cdot Rs^{-1}$ did not differ significantly between the two doses of ketamine (Figures 1–3). Only RR changed significantly during the study periods. Control RR was 48.17 ± 4.98 breaths per minute (BPM) before ketamine 1 $mg \cdot kg^{-1}$ and 52.2 ± 3.47 BPM before ketamine 2 $mg \cdot kg^{-1}$. RR increased significantly reaching a maximum two minutes after administration of either dose of ketamine (80 ± 7.96 BPM for ketamine 1 $mg \cdot kg^{-1}$ and 95.4 ± 8.17 BPM after ketamine 2 $mg \cdot kg^{-1}$). RR no longer differed significantly from control six minutes after the administration of ketamine 1 $mg \cdot kg^{-1}$ but still significantly increased (68.2 ± 11.61 BPM) above control ten minutes after the administration of ketamine 2 $mg \cdot kg^{-1}$. Arterial pH,

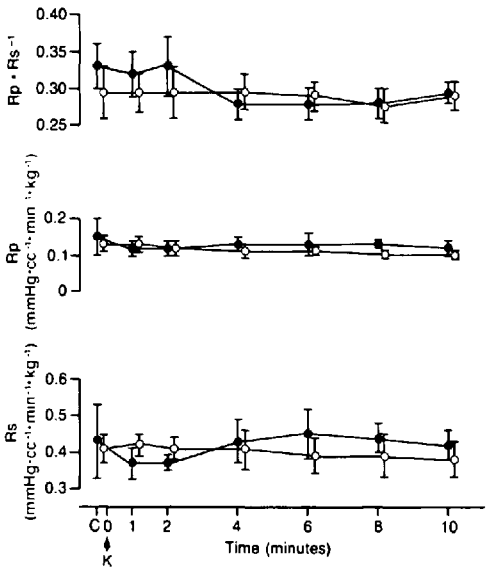

FIGURE 2 Rs, Rp and the Rp-to-Rs ratio control values (C) and after administration of ketamine (K) 1 mg·kg^{-1} (●—●) and 2 mg·kg^{-1} (○—○). The bars represent SEM.

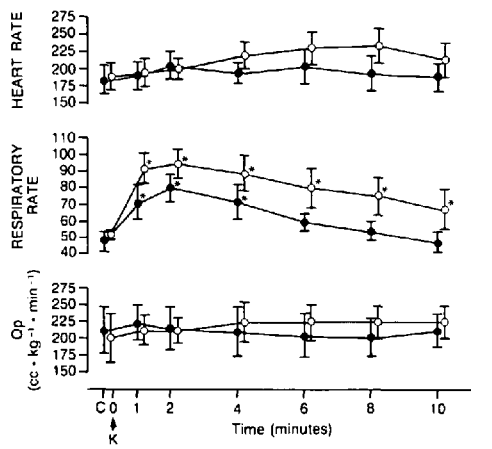

FIGURE 3 Qp, RR and HR control values (C) and after administration of ketamine (K) 1 mg·kg^{-1} (●—●) or 2 mg·kg^{-1} (○—○). The bars represent the SEM.

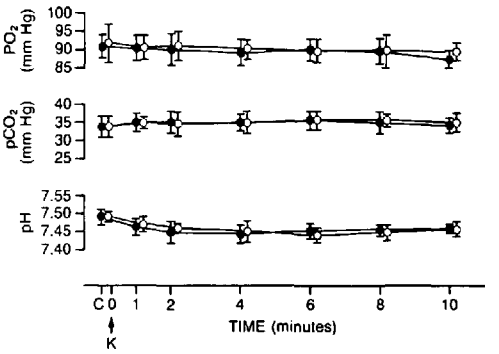

FIGURE 4 Arterial pH, pCO_2 and pO_2 control values (C) and after administration of ketamine (K) 1 mg·kg^{-1} (●—●) and 2 mg·kg^{-1} (○—○). The bars represent the SEM.

PCO_2 and PO_2 (Figure 4) did not change significantly during the study period.

There was no statistical difference in any variable between the two doses of ketamine.

Discussion

Ketamine (1 mg·kg^{-1} or 2 mg·kg^{-1}) produced no significant cardiovascular changes when administered to neonatal lambs with normal, intact cardiovascular anatomy. However, it did increase the respiratory rate without significant changes in the arterial blood gases.

The effect of ketamine on the cardiovascular system varies with age. In adults, ketamine stimulates the cardiovascular system.[18–22] In the absence of autonomic control, however, ketamine directly depresses the myocardium.[23,24] The effect of ketamine on the cardiovascular system in children is not clear. In children undergoing cardiac catheterization, previous studies reported increases in blood pressure[15] and heart rate[16] while others reported no change in blood pressure, heart rate or cardiac index.[17] Our data suggest the lack of significant effect of ketamine on the cardiovascular system in neonatal lambs.

Ketamine increases the pulmonary artery pressure and pulmonary vascular resistance in adults[12,14,25] and in children.[16] In infants and neonates, however, our results and other recent findings suggest ketamine 1 or 2 mg·kg^{-1} has no significant effect on either

the pulmonary artery pressure or the pulmonary vascular resistance ($Rp \cdot Rs^{-1}$).[17] This age-related difference in responses to ketamine is not fully understood. Abdalla *et al.* suggested the responses in infants may reflect an immaturity of innervation of the pulmonary vasculature and the myocardium.[26] The enhanced responses with increasing age may reflect an increasing maturity of innervation in the pulmonary vasculature.[16] We believe this explanation is unlikely since both infants and neonates have demonstrated increased pulmonary vascular reactivity to a variety of stimuli.[27] Because ketamine has a dual effect on vascular smooth muscle (a direct effect causing vasodilatation and an indirect effect causing vasoconstriction), demonstrated in older animals, the net effect on the systemic vascular resistance is minimal.[13,28] This result is demonstrated as well in the studies on children,[16] infants[17] and our own study in neonatal lambs.

Hickey *et al.*[17] postulated that discrepancies in the effect of ketamine on the pulmonary vasculature were indirect effects of ketamine on the airway and ventilation. They demonstrated minimal haemodynamic response to ketamine in subjects whose airway and ventilation were maintained. This postulate is supported by studies in which haemodynamic changes were demonstrated only in association with significant changes in pH and PO_2.[12,23,25]

The increase in RR after ketamine in this study occurred although there was no evidence of hypoxia, hypercapnia or acidosis. The stability of the arterial blood gases leads us to speculate the increased RR was coincident with a decreased tidal volume, with the minute ventilation remaining unchanged. Adults breathing spontaneously in room air demonstrate significant reductions in arterial oxygenation and minute ventilation after the administration of ketamine $2\ mg \cdot kg^{-1}$ intravenously as a rapid bolus.[14,29] In contrast, patients premedicated with diazepam 10–15 mg intramuscularly and spontaneously breathing room air who received ketamine $2\ mg \cdot kg^{-1}$ intravenously over 60 seconds showed no significant change in arterial oxygenation or shunt fraction.[30] Furthermore, the administration of an infusion of ketamine $1\ mg \cdot kg^{-1}$ intravenously during vaginal deliveries produced no significant changes in maternal or infant arterial blood gases.[31] The respiratory response to carbon dioxide is maintained during ketamine anaesthesia and ketamine does not produce significant respiratory depression except when it is given as a rapid intravenous bolus. Increased RR has not been demonstrated previously and may represent an effect on an immature respiratory center or a reflex response to the injection of the drug into the left atrium, although such a reflex has not been described.

Care should be exercised when using ketamine in the critically ill newborn. Although we demonstrated no statistically significantly increase from control levels of HR or MAP, there is a trend towards an increase and the potential for increased cerebral perfusion pressure and consequently, cerebral blood flow is present. Because of the possible relationship between increased cerebral blood flow and intraventricular haemorrhage, blood pressure and heart rate must be monitored carefully during administration of ketamine.[32–34] Ketamine has no significant effect on the cardiovascular system in healthy neonatal lambs, but it does increase the respiratory rate although pulmonary gas exchange is unaffected. This confirms our clinical impression of the safety and stability of utilizing ketamine as a sedative/anaesthetic agent in healthy neonates.

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Résumé

Afin de déterminer les effets respiratoires et cardiovasculaires de l'injection intra-veineuse de kétamine chez l'agnelet ont a étudié six préparations non prémédiquées. Chaque agnelet a été anesthésié avec la kétamine 1 $mg \cdot kg^{-1}$ puis après le réveil ré-anesthésié avec 2 $mg \cdot kg^{-1}$. La tension artérielle moyenne, la pression moyenne de l'artère pulmonaire, la pression moyenne de l'oreillette gauche, le flot pulmonaire sanguin, la fréquence cardiaque, la fréquence respiratoire, les gaz sanguins, ont été mesuré avant et après une, deux, quatre, six, huit et dis minutes de l'administration de chaque dose de kétamine. La résistance vasculaire pulmonaire, la résistance vasculaire systémique et leur rapport ont été déterminées. Après l'administration de la dose de kétamine, seule la fréquence respiratoire a changé significativement ($p < 0.05$) atteignant un maximun après deux minutes. Ce changement n'était pas associé avec des anomalies des gaz sanguins. On conclut qu'en présence d'une ventilation adéquate, la kétamine ne produit pas d'effets cardiovasculaires significatifs chez les agnelets.