Title : DUAL EFFECT OF KETAMINE ON THE PERIPHERAL VASCULATURE

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Introduction. Zimmerman and Liao (1) demonstrated that sympathetic cardiovascular reflexes were preserved during Ketamine administration. Ivankovich, et al. (2) showed a central stimulant effect on the cardiovascular system (CVS) by Ketamine. Miletich, et al. (3) reported that Ketamine has a cocaine-like effect. Flocke, et al. showed the peripheral cocaine-like chronotropic effect of Ketamine. However, others have shown a direct depressant effect of Ketamine on the CVS. Therefore, in the current study we tried to visualize these two effects on the hind limb and paw vasculature of the dog.

Methods. Twenty-six mongrel dogs, weighing between 19 and 24 kg, were anesthetized with Ketamine supplemented with thiopental and nitrous oxide (Part I) or pentobarbital (Part II). The blood pressure and perfusion pressure (PP) were monitored. In Part I the technique utilized was Beck's model of the isolated hind limb vasculature. The hind limb was autoperfused via a constant flow pump (Sigmamotor) from the abdominal aorta through a femoral arterial catheter. Since perfusion flow was constant, changes in PP would be proportional to changes in resistance. Furthermore, the perfusion circuit delay permitted the separate observation of sympathetic vasoconstriction and Ketamine vasodilator effect on hind limb vasculature. The sympathetic outflow was studied during Ketamine administered rapidly intravenously or via the carotid artery (the carotid sinus was denervated). In Part II the peripheral cocaine-like effect of Ketamine was studied in the isolated paw vasculature with constant blood flow. In Part III the uptake of tritiated norepinephrine into the dog's isolated paw artery was studied with arterial segments incubated with tritiated norepinephrine at 5 µg/ml, 50 µg/ml and 500 µg/ml of Ketamine (calculated to be achieved by paw infusion rate of 0.1 mg/min, 1 mg/min and 10 mg/min of Ketamine respectively). The incubated sample was counted in a liquid scintillation spectrometer. Statistical significance ($p<0.05$) was determined by a paried t test.

Results. After 5 mg/kg IV Ketamine the perfusion pressure rose significantly (38.57±4.5 mm Hg) below control level. After lumbar sympathectomy the rise of PP was abolished completely after Ketamine IV, but fall of PP remained. Femoral arterial injection of Ketamine (1 mg, 2.5 mg, 5 mg and 10 mg) showed significant fall in PP due to its direct vasodilation effect. Carotid arterial injection of Ketamine (5 mg, 10 mg and 25 mg) resulted in a significant rise in PP (15±4.4, 27±6.8 and 31.2±6.6 mm Hg respectively), as well as rise in arterial pressure.

In the paw perfusion study, the cocaine-like effect will potentiate vascular responses to sympathetic nerve stimulation as well as to exogenous norepinephrine. Ketamine 0.1 mg/min and 1 mg/min infused into the paw arterial vasculature failed to show potentiation of response to 2 cps and 10 cps sympathetic stimulation. Rather, we observed some depression of the responses to norepinephrine 0.5 µg and norepinephrine 1 µg at 1 mg/min infusion rate ($p<0.1$). At 10 mg/min infusion of Ketamine all vascular responses were significantly depressed. Response to 2 cps, 10 cps, 0.5 µg norepinephrine and 1 µg norepinephrine were 13%, 18%, 29% and 29% of control respectively. On the other hand the measured uptake of tritiated norepinephrine incubated with Ketamine 5 µg/ml, 50 µg/ml and 500 µg/ml was 104%, 76.6% ($p<0.05$) and 44.4% ($p<0.05$) of control respectively.

Conclusions and Discussion.

1. 5 mg/kg Ketamine caused sympathetic mediated vasoconstriction and direct vasodilation in the hind limb vasculature immediately after injection.
2. The carotid arterial injection of Ketamine caused transient vasoconstriction of hind limb vasculature.
3. Ketamine at low concentrations (5 µg/ml) did not show the uptake blockade of tritiated norepinephrine, but high concentrations (50 µg/ml and 500 µg/ml) exhibited a cocaine-like effect. At blood levels of Ketamine showing marked inhibition of norepinephrine uptake the direct depressant effect of Ketamine predominates.

References.

1. Zimmerman, BG and Liao, JC: Reflex vasodilation in the cat and dog anesthetized with Ketamine. Pro. Soc. Exp. Biol. Med. 144:268-272, 1973.
2. Ivankovich, AD, Miletich, DJ, Reimann, C, et al.: Cardiovascular effect of centrally administered Ketamine in goats. Anesth. Analg. (Cleve) 53:924-931, 1974.
3. Miletich, DJ, Ivankovich, AD, Albrecht, RF, et al.: The effect of Ketamine on catecholamine metabolism in the isolated perfused rat heart. Anesthesiology 39:271-277, 1973.