Title: EFFECTS OF FLUMAZENIL ON CEREBRAL BLOOD FLOW AND INTRACRANIAL PRESSURE AFTER INCOMPLETE CEREBRAL ISCHEMIA IN GOATS.

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Introduction: In healthy subjects the specific benzodiazepine antagonist flumazenil (RO 15-1788) has no direct effect on cerebral blood flow (CBF) (1). In severely head injured patients rapid reversal of midazolam sedation by flumazenil may induce severe intracranial hypertension with a simultaneous decrease in cerebral perfusion pressure (CPP) (2). As it remains unknown whether flumazenil exerts deleterious effects on CBF and intracranial pressure (ICP) after incomplete cerebral ischemia this study was designed to evaluate the effects on CBF and ICP associated with antagonism of midazolam sedation by flumazenil in the reperfusion period after controlled incomplete global cerebral ischemia.

Methods: In 10 male mechanically ventilated goats weighing 17-31 kg anesthesia was achieved by etomidate (0.5 mg/kg/h) intravenously and nitrous oxide in oxygen (FIO_2=0.3). The endexpiratory carbon dioxide tensions ($P_{ET}CO_2$) were adjusted to 32-36 mmHg. CBF was measured by a magnetic flow probe placed around the internal maxillary artery (IM) after ligation of the contralateral IM as well as the infradental, temporal, occipital arteries. The buccinator, ophthalmic and ethmoidal arteries of both sides were artificially thrombosed by injection of 1500 I.E. thrombin into the IM cranial to the ligation. Thus virtually global CBF was supplied by one IM via the rete mirabile as the basilar artery in the goat provides only minimal flow to the circle of Willis (3). The femoral vein / artery and the sinus sagittalis were cannulated. Analog signals of heart rate (HR), arterial blood pressure (AP), central venous pressure (CVP) and intracranial pressure (ICP) were stored on magnetic tape (Racal, 7DS™). Arterial, central venous and sinus sagittalis blood samples were withdrawn every 15 min for measurement of blood gas tensions. After control recordings CBF was progressively reduced by 50 % every 30 min (occlusion of the external carotid artery) with a lower limit of 20 ml.min^{-1} which was also held constant for 30 min. Thereafter the ischemic period was terminated and the reperfusion period was studied for at least 120 min. 100-110 min after ischemia 10 mg midazolam (n=10) were given intravenously followed by application of 0.3-1.0 mg flumazenil (n=7) 3-5 min later. CPP was calculated as: CPP=AP-ICP . CBF was calculated per 100g tissue weigth post mortem. Data were subjected to analysis of variance (ANOVA) followed by Duncan's procedure for repeated measurements where appropriate ($p<0.05$).

Results: Arterial blood gases, HR and AP were maintained constant during progressive ischemia and were comparable interindividually. CBF-control values were: 59-85 ml.100g^{-1}.min^{-1}. Graded occlusion of the external carotid artery led to a concomitant decrease in ICP (-35-60 %) at a CBF of 20 to 30 ml.100g^{-1}.min^{-1}). Reperfusion led to a transient hyperemia (10-25 min) in 7 goats with a 10-210 % increase of CBF which was followed by lower perfusion (60-100 min: -10 % to - 25 %) compared to control. Injection of midazolam reduced AP, CBF and ICP still further in 3 animals. Flumazenil injected after midazolam led to an increase in HR, AP, CBF and ICP which was significant in 5 animals (cf. table, figure).

	HR	AP	CBF	ICP	CPP
	1/min	mmHg	ml/100g/min	mmHg	mmHg
Ischemia	85 ± 13	94 ± 11	18 ± 5	0± 3	?
Rep.1	131 ± 26*	119 ± 21*	151 ±34	25±11 *	94 ±19
Rep. 2	122 ± 25*	81 ± 17*	99 ±31 *	9± 5 *	72 ±14#
Mid.	109 ± 19*$	64 ± 13*#$	69 ±19 *#$	6± 4 *#$	58 ±13#$
Flum.	143 ± 35*§	132 ± 36*§	134 ±40 *§	22±13 *§	110 ±32#§

Table: HR, AP, CBF, ICP and CPP during and after incomplete cerebral ischemia (20 ml.100g^{-1}.min^{-1}). Rep. 1: 5-15 min during reperfusion period; Rep. 2: 30-60 min during reperfusion period. Significance: * vs. control; # vs Rep. 1; $ vs Rep. 2; § vs. Mid.; $p<0.05$

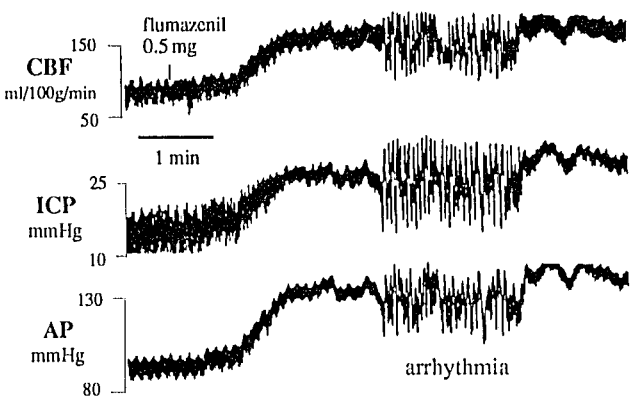

Figure: Effect of reversal of midazolam sedation by 0.5 mg flumazenil on AP, ICP and CBF in one goat during the reperfusion period 110-120 min after incomplete cerebral ischemia (20 ml.100g^{-1}.min^{-1})

CBF increased about 30-165% compared to the late reperfusion period.

Discussion: The data indicate that the increase in CBF and ICP following reversal of midazolam sedation with flumazenil is due to an impaired cerebral autoregulation after incomplete cerebral ischemia as CBF and ICP increased with a time lag of 1-5 sec after a rise in AP. In the 3 animals without preceeding injection of midazolam no changes in hemodynamic and cerebral dynamic parameters after flumazenil could be noted. Even though recovery was not evident flumazenil obviously led to a change in anesthetic depth which gave rise to an increased stress response resulting in possibly deleterious increases in CBF and ICP. CPP did not decrease as a consequence of a at this early time lacking brain edema.

References:

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