TITLE: INTRACEREBROVENTRICULAR POTASSIUM CHANNEL AGONISTS DO NOT DECREASE MAC IN RATS

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Introduction. Clonidine treatment has been reported to reduce anesthetic requirements in many situations. Studies with 4-amino-pyridine (4-AP) have suggested that the mechanism for action of clonidine might be via an agonist-like action on potassium channels in the CNS.[1] 4-AP has many actions, which include potassium channel antagonism. Two newly developed antihypertensive drugs, pinacidil (pin) and cromakalim (crom), are thought to have selective and specific agonist action on potassium channels.[2] Therefore, the effect on anesthetic requirement (MAC), of intracerebroventricular (icv) injections of pin, crom and 4-AP was undertaken to test the hypothesis that the mediation of general anesthesia might be via potassium channel agonism.

Methods. Healthy male rats were anesthetized with 5% isoflurane in oxygen. They were then placed in a specially constructed apparatus with an oxygen delivery system (3 L/min) and an isoflurane vaporizer in-line. The spontaneously breathing anesthetized rats were then exposed to 2.25% isoflurane concentration for 5 min. The concentration was then reduced in a stepwise fashion every 15 min until MAC was reached. Once baseline MAC had been determined, the isoflurane concentration was re-adjusted to 2.25% and icv drugs administered. MAC was then re-determined as before. Gas in the apparatus was assayed for isoflurane concentration by calibrated gas chromatography. Arterial samples were analyzed for blood gas values. Icv injection sites were later verified. Values in the different treatment groups were compared with values in their control groups by one way analysis of variance (ANOVA). Within each treatment group, the baseline and post-treatment MAC were compared with the paired t-test.

Results. Comparison by ANOVA of animals (n=72) in the various groups revealed no difference in their baseline MAC which was 1.60% (SEM = 0.02%) for isoflurane in oxygen. Control animals, injected icv with saline (or that had no injection), did not change their MAC with repeat measurement. Icv injections of 10 µg and 20 µg clonidine decreased MAC by 33% (ptt and ANOVA $p < 0.001$) and 53% (ptt $p < 0.005$; ANOVA $p < 0.001$) of baseline, when compared with saline controls, respectively. Neither crom 10 µg, crom 20 µg, pin 20 µg, nor 4--AP 20 µg had any effect on the value of the repeat MAC measurement. Compared with animals treated with only clonidine 10 µg, animals treated with icv clonidine 10 µg and additional icv crom 20 µg or additional pin 20 µg were no different. Substitution of 5 µg veratridrine (which mimics a high potassium medium in some models of neurotransmitter release) for crom or pin, attenuated the effect of clonidine ($F(1/11)=16.4$, $p<0.05$). However, 4/6 of these animals developed seizures. Additionally, all animals treated with 4-AP developed profound seizures, while none of the other treatment groups developed any observable behavioral changes.

Discussion. These data suggest that potassium channel agonism *per se* does not reduce anesthetic requirement for isoflurane. It does not rule out the possibility that site-specific potassium channel agonism might have an effect. Neither does it rule the possibility that the action of clonidine at selective sites within the CNS may be via potassium channel agonism at that site. Attempts to deliniate the mechanism of action of clonidine in the CNS that is responsible for its ability to dramatically reduce anesthetic requirement would therefore need to be highly localized.

References.
1. The FASEB J. 3:A1202, 1989
2. Br J Pharmacol. 98(4):1303-11, 1989

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TITLE: NEUROTOXICITY OF INTRATHECAL MIDAZOLAM IN RABBITS

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Drugs acting on spinal non-opoid receptors such as midazolam (M) are proposed for intrathecal use in humans.[1] A previous histological study about its neurotoxicity have shown many technical problems.[2] The aim of this study was to document the histological and the blood-brain barrier (BBB) effects of intrathecal M compared with saline solution 0,9% (S) and lidocaine (L) on the spinal cord in rabbits.

With approval of our Institutional Animal Investigation Committee, experiment was performed on 30 White New-Zealand rabbits randomly assigned to 3 groups of 10. A colorant, Blue Evans (5 ml.kg^{-1}) was iv injected 5 hrs before the intrathecal injection. A percutaneous puncture using a 24G needle was made in conscious animal in cervical zone. After the injection of 0.3 ml of 0.9% S, of 1% L or of 0.1% M the catheter was withdrawn. In killed animal by thiopental overdose on day 8, the spinal cord were removed and immersed in Karnovsky's fixative. Light and fluorescent microscopy were performed by a neuropathologist unaware of injected agent. On transverse spinal sections slides all animals were scored in 4 zones: upper and lower cervical, median thoracic and lumbar segments. For the histologic study a score 0 indicated no abnormalities; 1= constitued hemorrhage, glial cells reaction and diffusion of process on several zones; 2= extensive necrosis in the grey matter, hemorrhage or great intensity of the other lesions. For the BBB study a score 0 indicated no perivascular diffusion or spark around vessels; 1= slight diffusion; 2= wide diffusion. Then scores were averaged to obtain a level (A <3; B= 3-5 and C >6). Comparisons were carried out using a contingency table and a Mann-Whitney test when appropriate. $p<0.05$ was considered as significant.

Results (n animals) are summarized in the table. Animals with traumatic cord injuries (n=3) were excluded. BBB study revealed important vascular impairments in 8 out of 9 animals suggesting specific BBB lesions of M, while no specific lesion was found in the histological study. Because this toxic vascular action of M, its intrathecal use in man might be avoided.

	Histological level			BBB level			
Groups	A	B	C	A	B	C	
S	9	0	0	9	0	0	**
L	7	2	0	7	2	0	$
M	5	1	3	1	5	3	

Table: comparisons vs M: $ $p< 0.02$, ** $p< 0.001$.

References
1. Br. J. Clin. Pharmacol. 23:279-285, 1987.
2- Ann Fr Anesth Réanim 7:81-82, 1986.