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Title CHLORBUTANOL IS RESPONSIBLE FOR KETAMINE NEUROTOXICITY IN RABBITS

Authors J.M. Malinovsky, M.D., J.Y. Lepage, M.D., J.M. Mussini*, M.D., A. Cozian, M.D., M. Pinaud, M.D., Ph.D.

Affiliation Lab. Anesth. et *Lab. Ana-Path., Fac. Méd., Univ. Nantes , 44035, France

Ketamine (K) has been used intrathecally in humans without causing neurological lesions,[1] but neurotoxicity studies are required to determine whether it should be used as a spinal analgesic agent. We performed histological and blood-brain barrier (BBB) studies in rabbits to check the neurotoxicity of K, free ketamine (f-K), d-enantiomer (d-K) or its preservative chlorbutanol (C) as compared to lidocaine (L), which has a long safety record.

With approval of our institution Animal Investigation Committee, experiments were carried out on 50 White New-Zealand rabbits randomly assigned to 5 groups of 10. Intrathecal injection of 0.3 ml of 1% K, 1% d-K, 1% f-K, 0.05% C or 1% L, in the conscious animal, was performed using a technique previously described.[2] On day 8, the dye was i.v. injected 2 hours before death, and spinal cord was then carefully removed. Light and fluorescent microscopy were performed by a neuropathologist unaware of the injected agent. On transverse sections, all animals were scored in 4 zones (from upper cervical to lumbar segments) using a previously described classification.[2] Only homogeneous scores higher than the worst induced following intrathecal lidocaine (L) were considered as pathological. Statistics were performed using the Chi-square test, and $p<0.05$ being considered as significant.

Results (n animals) are summarized in Table. Animals with traumatic cord injuries (n=5) were excluded. Only the BBB study showed evidence of neurotoxicity for ketamine in comparison with lidocaine. Significant pathological scores in both studies for the C group suggest that the preservative is implicated in ketamine neurotoxicity.

As free ketamine (f-K) or its d-enantiomer (d-K) intrathecally administered did not caused significant lesions, these drugs could be included among those available for intrathecal analgesia in humans.

	H study			BBB study		
group	normal	pathological	p	normal	pathological	p
L	9	0	¶¶	9	0	¶¶¶
K	8	2		7	3	†
d-K	7	0	¶	6	1	¶
f-K	9	0	¶¶	8	1	¶
C	4	6		3	7	

Table 1: Comparisons vs C: ¶p<0.04, ¶¶p<0.02,¶¶¶p<0.01; and vs K: †p<0.04

References
1- Anaesthesia 39:1023-1028, 1984
2- ANESTHESIOLOGY 72, 3A:A677 , 1990

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TITLE: SUBARACHNOID DISODIUM EDTA INDUCES CONCENTRATION-DEPENDENT TETANIC CONTRACTION IN RATS: PREVENTION BY $CaCl_2$ PRETREATMENT.

Authors: BC Wang, MD, D Li, MB MA, JM Hiller, PhD, EJ Simon, PhD, G Budzilovich, MD

Affiliation: Depts of Anesthesiology, Pharmacology, Psychiatry and Pathology, New York Univ Medical Center, New York, NY 10016

Introduction: Severe back pain after epidural injection (inj) of chloroprocaine-MPF, which contained EDTA and relief with $CaCl_2$ have been reported[1,2,3,4]. Subarachnoid (SAS) Disodium EDTA induces tetanic contractions (TC) in rats[5]. The effect of concentration variation of Na_2 EDTA on the induction of TC and prevention by $CaCl_2$ pretreatment was examined in this study.

Method: With institutional approval, SAS catheters with an intraluminal volume of 0.02 ml were implanted through lumbar laminectomy in 3 groups of 0.5-0.6 kg male Sprague Dawley rats anesthetized with 0.5 ml/kg intramuscular inj of a mixture which contained per ml: 42.85 mg Ketamine, 8.57 mg Xylazine and 1.42 mg Acepromazine. One week post surgery, animals received different hourly SAS inj as follows: G1 (n=6) normal saline (NS) 0.05 ml pH 5 for 7 hrs; G2 (n=6) 5 hourly doses of 0.05 ml Na_2 EDTA of 0.3 mM, 0.75 mM, 1.5 mM and 3 mM, on different days (pH 4.5). G3 (n=6) 1 mM $CaCl_2$ 148 μl + 3 mM Na_2 EDTA 148μl.

Results: TC of the extremities (more on the lower), 100+/minute for 2-7 minutes, were seen in 5 of 6 rats after 3 mM Na_2 EDTA inj: 4 after the 1st, and 1 after the 2nd. Three after 1.5 mM Na_2 EDTA: one each after the 1st, 2nd and 3rd inj. TC were not observed after NS or $CaCl_2$ + 3 mM Na_2 EDTA (G3).

Following euthanasia, histological examination of one spinal cord after SAS Na_2 EDTA revealed moderate to severe degeneration of spinal roots.

Discussion: The effect of Na_2 EDTA appears to be concentration dependent. Prevention of TC by $CaCl_2$ pretreatment suggests that hypocalcemia may be the cause. It is known that EDTA chelates calcium and that hypocalcemia causes tetany. This mechanism may be operant in the development of TC following SAS EDTA. Soza et al[6] have reported that immersion of rat hemidiaphragm in Ca^{++}-free Krebs solution containing Ca^{++} chelator in vitro leads to separation of basal lamina from the plasma membrane as well as transient contracture and rapid loss of twitch response (calcium paradox (CP) phase 1).

Speculatively, excitatory amino acid and NMDA receptors[7] may play a role. EDTA contained in radiographic contrast medium also causes hypocalcemia, increase of parathyroid hormone[8] and ventricular fibrillation[9]. Therefore, further study is warranted before incorporating EDTA in any agent which may enter SAS either intentionally or accidentally (e.g. through inadvertent dura puncture).

Conclusion: SAS inj of 1.5 mM - 3 mM Na_2 EDTA can cause TC which may be prevented by prior inj of $CaCl_2$.

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