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Title : CYCLIC AMP - AN EFFECTIVE ANTIDOTE AGAINST LETHAL AMOUNTS OF AMOBARBITAL IN THE RHESUS MONKEY

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Introduction. Drug abuse is a major social problem in contemporary America. The ready availability of sedative, hypnotic and tranquilizer drugs inevitably leads to abuses, the most extreme of which is suicide. Our initial discovery that the dibutyryl analog of adenosine 3':5' cyclic monophosphoric acid (dbcAMP) dose-dependently shortens narcosis induced by all anesthetic, hypnotic and sedative drugs tested (1, 2) led to our findings of the antidotal properties of dbcAMP. Rats (3) and rhesus monkeys (4) overdosed with a lethal dose of amobarbital survived when centrally treated with dbcAMP. We are reporting now data from a subchronic dbcAMP toxicity study in the rat and a delayed-response memory performance study (5) in the rhesus monkey. These investigations were conducted in order to evaluate the direct toxic effects of dbcAMP on the central nervous system (CNS). Our findings in both species strengthen our previous argument (3,4) that dbcAMP is the first true antidote to amobarbital overdosage and that it is devoid of toxicity. Extending our subacute studies to other species and adding chronic studies of all species involved will hopefully lead to the eventual use of dbcAMP in the treatment of drug overdose in man.

Methods. Male Sprague-Dawley rats were treated daily for 30 days with 10µl of dbcAMP (10µg) infused with a Sage syringe pump over a 60sec period into the lateral ventricle of the brain (ICV) through a stainless steel cannula stereotaxically implanted at least 10 days prior to experiment. Control group received vehicle saline (0.9%w/v/10µl). The rats' weight, body temperature and behavioral alterations were recorded daily. At end of experiment, rats were sacrificed, brains removed and fixed in Bowins solution. Brain sections through numerous structures were histologically examined under light microscope by our pathologist.

Male rhesus monkeys were subjected to delayed-response memory testing for 6 months prior to stereotaxic implantation of stainless steel cannulae ICV. Subsequently, training was resumed for 6 months. Each monkey was then overdosed with amobarbital (155mg/kg-IP). Control monkeys received saline (0.9%w/v ICV) while treated monkeys received dbcAMP (2-5mg ICV) after the mean arterial blood pressure fell below 50% of control values. One day post-treatment, the delayed-response memory test was resumed and continued for one year.

Results. Neither saline nor dbcAMP, administered to the rats over a 30 day period, altered body weight or temperature, locomotor activity, or diurnal-nocturnal sleep-wake patterns (as recorded on an electronic activity monitor). Histological examination of the sectioned brain areas revealed no evidence of tissue necrosis in either control or treatment groups.

Initially, all monkeys performed the delayed-response memory test slightly better than statistical chance on both the 20 and 40sec intervals. With increased familiarity with the procedure, they performed correctly at least 90% of the trials. The control amobarbital-overdosed monkeys treated ICV with saline died within 30min from cardiovascular collapse. In monkeys treated ICV with dbcAMP, the rapidly falling blood pressure stabilized and slowly returned to control values. Without supportive therapy, i.e. fluids or vasopressors, or removal of barbiturate by forced diuresis or dialysis, 100% of the treated monkeys survived. The treated monkeys displayed no apparent sequellae. No statistical difference in delayed-response memory testing was evident prior to and following the experiments.

Discussion. Our data suggest that amobarbital overdosage causes mortality primarily by CNS depression. This contention is borne out by the fact that recovery from overdosage occurs after administration of dbcAMP directly into the CNS. Protecting the CNS from irreversible brain damage is of major importance. Indeed, to have a patient survive but suffer brain damage is a poor therapeutic goal. That the delayed-response memory test is a very sensitive indicator of brain damage, particularly in the frontal lobe areas, in conjunction with our negative histological findings in rat brain, strongly support our postulate that dbcAMP reverses barbiturate overdosage without adding to the already present toxicity. Moreover, that our monkeys are thriving and showing no signs of sequellae years after their ordeal is our strongest argument for the eventual extrapolation of our findings from laboratory subjects to man.

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