Title: CONCURRENT USE OF KETAMINE AND AMINOPHYLLINE DECREASE SEIZURE THRESHOLDS

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Introduction. During the past nine years, we have observed the occurrence of extensor-type seizures in four asthmatic patients receiving theophylline within minutes following induction of anesthesia with ketamine. The minimal electroshock seizure threshold is a sensitive test to evaluate convulsant and anticonvulsant effects of drugs.[1,2] It is a classic method for evaluating the ability of drugs to either raise or lower seizure thresholds in experimental animals. It is performed by establishing for each experimental animal the current required to elicit forelimb or facial clonus. Failure to exhibit seizure activity following administration of a current 20% above the previously determined threshold is taken as evidence of an anticonvulsant effect of a drug. Conversely, the occurrence of seizure activity at currents 20% below the previously determined seizure threshold is evidence that the seizure threshold has been lowered. To understand and offer a reasonable explanation for the clinical phenomena observed, a study was designed to determine whether ketamine or aminophylline, either alone or in combination lowered the minimal electroshock seizure threshold in mice.

Methods. Studies were performed in 140 male Swiss-Webster mice weighing 20 to 25 grams. The minimal electroshock seizure threshold test was performed by establishing for each mouse the current required to elicit forelimb or facial clonus (8-9.5 mA, 60 Hz sine waves, 0.2 sec. duration through Speigal Corneal electrodes[3]). Each mouse was shocked once every 48 hours until a given current (± 0.1 mA) consistently elicited clonic seizure activity. This established for each mouse the minimal electroshock seizure threshold. All injections of aminophylline and ketamine in distilled water were made intraperitoneally (0.1 ml per 10 grams body weight). In preliminary experiments, the hypnotic dose and time to peak effect for ketamine was determined. Ketamine 100 mg/kg produced maximal behavioral impairment 5 minutes after intraperitoneal injection. An aminophylline dose, 100 mg/kg, was selected from the literature since this dose correlated well with the dose required to inhibit seizure-induced increases in cyclic cAMP levels in mouse brain.[4] The time of 15 minutes was chosen since this was the time to maximal levels of aminophylline in brain following intraperitoneal administration in mice.[4] Fifteen minutes after intraperitoneal injection of aminophylline (100 mg/kg), 25 mice were shocked at a current 20% below and 25 mice, 10% below the minimal electroshock seizure threshold. Five min. after intraperitoneal injection of ketamine (100 mg/kg), 25 mice were shocked similarly. The same doses of ketamine and aminophylline were administered sequentially to the remaining 40 mice, 20 of which were shocked at 20% and 20 shocked at 10% below the minimal electroshock seizure threshold. A reduction of seizure threshold was determined by the observation of forelimb or facial clonus or by the production of a major motor seizure. Data were analyzed by Chi Square tests. The level of statistical significance used was $p < .05$.

Results. Neither ketamine nor aminophylline administered alone decreased the seizure threshold, as all animals tested at both 10% and 20% below their previously determined seizure threshold current failed to demonstrate forelimb or facial clonus (Table 1). However, when ketamine and aminophylline were administered sequentially to 40 mice at 5 and 15 min. prior to electroshock challenge, a decrease in seizure threshold was noted (Table 1). When tested at 20% below threshold current, 5 of 20 animals demonstrated forelimb or facial clonus ($p < .05$). At a current 10% below threshold, 14 of 20 mice exhibited forelimb or facial clonus and 4 exhibited major motor seizure ($p < .001$).

Discussion. These experiments in mice demonstrate that neither ketamine nor aminophylline, at doses of 100 mg/kg, lowers the minimal electroshock seizure theshold in mice. However, when administered together, a clinically apparent reduction in seizure threshold is observed. The concurrent use of aminophylline and ketamine is not uncommon in patients with asthma requiring anesthesia. These studies support our clinical observations and suggest that ketamine be avoided in patients taking aminophylline, or anti-seizure premedication be instituted in patients at risk.

Table 1:

Drug	Total Number of Mice	Seizure Threshold Reduction	Number of Mice Seizing
Ketamine	25	20%	0
Ketamine	25	10%	0
Aminophylline	25	20%	0
Aminophylline	25	10%	0
Ketamine-Aminophylline	20	20%	5*
Ketamine-Aminophylline	20	10%	18**

*$p < .05$ **$p < .001$

References

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