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Ketamine–Aminophylline-induced Decrease in Seizure Threshold

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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. This report briefly describes these cases. In addition, laboratory experiments in mice confirm a lowering of the seizure threshold with the concurrent use of both drugs.

REPORTS OF FOUR CASES

Patient 1. A 50-year-old, 50-kg woman was scheduled for a vocal cord stripping because of the development of hoarseness over a 3-month period. She had a history of alcohol abuse and chronic obstructive pulmonary disease with a marked bronchospastic component, for which she was being treated with 300 mg, qid, of a long-acting theophylline preparation. The patient denied a history of seizures. Four previous general anesthetics were uncomplicated. Physical examination was unremarkable. Preoperative laboratory tests were normal.

Ninety minutes prior to surgery, an iv infusion of aminophylline ($1 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$) was started and premedication of 5 mg diazepam was given im. Ketamine, 100 mg, was given iv over a 2-min period for induction of anesthesia. With the patient breathing spontaneously, 1.5 per cent halothane in oxygen was started. The patient developed random eye and limb movements. Approximately 2 to 3 minutes later, the patient became impossible to ventilate and developed a heart rate of 200 beats/min. Extensor spasm and opisthotonic posturing of the extremities, neck, and jaw ensued. Succinylcholine, 80 mg, was administered. Halothane was discontinued because of multifocal premature ventricular contractions (PVCs) and runs of ventricular tachycardia. The extensor seizures ceased. Ventilation via a mask became possible and intubation of the trachea was accomplished without difficulty. No wheezing was audible. Within minutes, ventilation again became impossible and the extensor spasms returned. Pancuronium 3 mg, iv, was given to facilitate controlled ventilation. Cardiac abnormalities continued despite 7.5 mg diazepam and 100 mg lidocaine. With continuous chest auscultation, 0.75 mg propranolol was given over a 5-min period, at which time heart rate decreased from 180 to 120 beats per minute and PVCs resolved. Blood gases were normal. Serum theophylline level was 19 μg/ml (therapeutic level 10–20 μg/ml). Surgery was cancelled. The patient was transferred to the recovery room and mechanically ventilated. The patient was alert and the trachea was extubated without problems two hours later.

Patient 2. A 56-year-old, 50-kg woman was scheduled for an emergency cholecystectomy for acute cholecystitis. She had a long history of asthma requiring 500 mg of a long-acting theophylline preparation bid and occasional im injection epinephrine. She received 500 mg theophylline, po, 6 hours before surgery. At the time of operation, she had mild expiratory rhonchi bilaterally. Induction of anesthesia was accomplished with 100 mg ketamine over a 2-min period. Lidocaine, 80 mg, iv, was given to prevent irritant-induced bronchospasm. With the patient breathing spontaneously, 2 per cent enflurane in oxygen was started. The patient became difficult to ventilate and developed extensor posturing of the upper extremities. Heart rate increased from 80 to 130 beats/min. Succinylcholine, 100 mg, was administered. Ventilation became possible. Intubation of the trachea was accomplished easily. No wheezing was audible. Diazepam 5 mg, iv, was given and enflurane and N_2O anesthesia proceeded without further incident.

Patient 3. A 23-year-old, 53-kg white woman was scheduled for an elective cholecystectomy. She had a history of asthma, which was exacerbated by aspirin administration. She was on no medication at the time of admission and was free of bronchospasm. The evening before surgery, a loading dose of aminophylline (5.9 mg/kg) and maintenance infusion ($1 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$) was started, which was continued up to the start of induction of anesthesia. Premedication consisted of 50 mg phenergan, im, and 0.4 mg atropine, im.

Anesthesia was induced with 100 mg ketamine given over 2 minutes. Halothane 1.5 per cent in oxygen and 60 per cent nitrous oxide was inhaled with spontaneous ventilation. Within minutes, ventilation became impossible. The patient was rigid. The extremities were in marked extension. The jaw could not be opened. Heart rate increased from 100 to 140 beats/min. Succinylcholine, 20 mg, was given. The patient then relaxed and ventilation became possible. No wheezing was audible. Manual ventilation was continued with halothane, O_2, and 60 per cent N_2O. Within 3 min, ventilation became difficult, as rigidity resumed. Succinylcholine (80 mg) was given, and intubation of the trachea was accomplished without difficulty. No wheezing was audible and the halothane and N_2O anesthesia proceeded without further incident.

Patient 4. A 28-year-old, 85-kg woman was scheduled for an ileal bypass takedown and liver biopsy. She had asthma for the past ten years for which she was treated with 20 mg metaproterenol, po, bid. Laboratory values were normal except for alkaline phosphatase of 134 units.

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Surgery was delayed 24 hours because the patient developed expiratory rhonchi bilaterally during the night. Aminophylline, 5.9 mg/kg, was given followed by an infusion of 0.5 mg · kg^{-1} · h^{-1}. The patient arrived in the operating room free of bronchospasm after a premedication of 12 mg morphine sulfate im. Anesthesia was induced with 100 mg ketamine followed by 2 per cent halothane in oxygen. Within minutes, ventilation became impossible and upper extremities developed extensor posturing. Heart rate increased from 80 to 120 beats/min. Succinylcholine, 60 mg, iv, was given and patient became easy to ventilate via mask for about 2 to 3 min. An additional 60 mg succinylcholine was given to facilitate endotracheal intubation. No rhonchi were present. Halothane and N_2O anesthesia proceeded uneventfully.

Methods

The minimal electroshock seizure threshold is a sensitive test to evaluate convulsant and anticonvulsant effects of drugs.[1,2] The minimal electroshock seizure threshold test is performed by establishing for each experimental animal the current required to elicit forelimb or facial clonus (8–9.5 mA, 60 Hz sine waves, 0.2-s duration through Speigal corneal electrodes[3]).

The objective of our experiment was to determine whether aminophylline and ketamine, either alone or in combination significantly reduced the minimal electroshock seizure threshold in mice. A total of 240 male Swiss-Webster mice weighing 20 to 25 g were used. The mice were housed in groups of five and allowed free access to food and water for at least three days prior to experimentation. Each mouse was then shocked once every 48 hours until a given electrical current (±0.1 mA) consistently elicited clonic seizure activity. This established for each mouse the minimal electroshock seizure threshold. Most frequently, three or four test sessions were sufficient to accurately determine this threshold.

All injections of aminophylline and ketamine in distilled water were made intraperitoneally (0.1 ml/10 g body weight). In preliminary experiments, the hypnotic dose and the time to peak effect for intraperitoneal ketamine was determined in 100 mice by injecting doses of 25, 50, 100, and 200 mg/kg and noting both the time and minimal dose to produce maximal behavior impairment in 95 per cent of mice (loss of righting reflex and response to tail pinch). Ketamine, 100 mg/kg, produced maximal behavioral impairment 5 min after intraperitoneal injection. Lower doses of ketamine (25 mg/kg and 50 mg/kg) failed to produce anesthesia in these mice. An aminophylline dose, 100 mg/kg, was selected from the literature since this dose correlates well with the dose required to inhibit seizure-induced increases in cyclic AMP levels in mouse brain.[4] The time to peak effect of 15 min was chosen since this is the time to maximal levels of aminophylline in brain following intraperitoneal administration in mice.[4] Therefore, for all subsequent experiments, times to peak effects of 5 and 15 min were used for ketamine (100 mg/kg) and aminophylline (100 mg/kg), respectively.

TABLE 1. Incidence of Seizure Activity

Drug	Number of Mice Tested	Seizure Threshold Reduction	Number of Mice Exhibiting Seizure Activity
Ketamine	25	20%	0
Ketamine	25	10%	0
Aminophylline	25	20%	0
Aminophylline	25	10%	0
Ketamine and aminophylline	20	20%	5*
Ketamine and aminophylline	20	10%	18†

* $P < 0.05$.
† $P < 0.001$.

In the remaining 140 mice in which the minimal electroshock seizure threshold had already been established for each mouse, either ketamine (50 mice) or aminophylline (50 mice) alone was administered. Half the mice receiving each drug were then shocked with a current 20 per cent below the previously determined threshold, and half the mice 10 per cent below the threshold during which observations were made of seizure activity.

Aminophylline and ketamine were then administered sequentially to the 40 remaining mice to determine whether the two drugs together would decrease the seizure threshold. Twenty of the mice were shocked at currents 20 per cent below threshold and 20 were shocked with current 10 per cent below threshold.

A reduction of seizure threshold was determined by the observation of forelimb or facial clonus or by the production of a major motor (Grand mal) seizure.

The data were analyzed using chi-square tests.[5] The level of statistical significance used was $P < 0.05$.

Results

Neither ketamine (100 mg/kg) nor aminophylline (100 mg/kg) administered alone decreased the seizure threshold, as all animals tested at both 10 per cent and 20 per cent 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 per cent below threshold current, five of 20 animals demonstrated forelimb or facial clonus and none exhibited major motor seizure activity ($P < 0.05$). At a current 10 per cent below threshold, only two of 20 animals failed to exhibit seizure activity. Fourteen of 20 exhibited forelimb or facial clonus and four exhibited major motor seizure activity, as evidenced by tonic hindlimb extension ($P < 0.001$).

Discussion

The minimal electroshock seizure threshold test is a classic method for evaluating the ability of drugs to either raise or lower the seizure threshold in experimental animals.[1,2] Failure to exhibit seizure activity following the administration of a current 20 per cent above a previously determined seizure threshold is taken as evidence of an anticonvulsant effect of a drug. Conversely, the occurrence of seizure activity at currents 20 per cent below the previously determined seizure threshold is evidence that the seizure threshold has been lowered. The present experiment was designed to determine whether ketamine or aminophylline, either alone or in combination, lowered the minimal electroshock seizure threshold in mice. This experiment offers a possible explanation for the clinical phenomena observed in our cases.

The experiments in mice demonstrate that neither ketamine nor aminophylline at doses of 100 mg/kg lower the minimal electroshock seizure threshold. However, when administered together, a clinically apparent reduction in seizure threshold is observed. This appears to be verified by our clinical cases. The first case clearly demonstrated sustained seizure activity. Although the other cases demonstrated less obvious signs of seizure activity, we believe that the generalized extensor rigidity accompanied by total inability to ventilate the patient was indeed the result of central nervous system hyperexcitability.

Reports attempting to delineate the effects of ketamine on brain excitability are controversial. Ketamine can produce seizure-like activity, primarily electroencephalographic but rarely accompanied by behavioral convulsions.[6] Radney and Badola reported generalized extensor spasm in two infants following iv ketamine in doses 7 to 9.5 times higher than used in any of our patients.[7] Conversely, Reder *et al.*[8] demonstrated the antiepileptic properties of ketamine with drug-induced suppression of pentylenetetrazol-induced convulsions in two-day-old chicks. Finally, Celsia *et al.*[9] demonstrated that ketamine neither raises nor lowers seizure thresholds and that sleep may be a more potent stimulator of convulsions than ketamine in the epileptic patient. While the present study did not test for an antiepileptic action of ketamine (*i.e.*, an increase in seizure threshold), it demonstrated that ketamine at anesthetic doses did not significantly lower seizure threshold in the Swiss-Webster mouse.

Our concept of the mechanism of action of aminophylline has recently become controversial.[10,11] If aminophylline exerts its effects through inhibition of the monophosphate enzyme phosphodiesterase with a resultant increase in 3′5′ cyclic adenosine (cAMP), the increase in adrenergic activity should be accompanied by a reduction in seizure frequency. However, if the drug acts through inhibition of adenosine via adenosine receptors,[12] an epileptic rather than an antiepileptic effect might be expected. Although we, did not evaluate a potential antiepileptic effect of aminophylline, when aminophylline is administered in doses of 100 mg/kg, the seizure threshold in mice was not lowered.

Of interest in the animal experiments (and in support of the clinical studies) was the observation that when the two drugs were administered sequentially to the same mice, there was a significant decrease in seizure threshold as evidenced by the observation that at a current 10 per cent below threshold, 18 of 20 mice exhibited either facial or forelimb clonus (14 mice) or a major motor seizure (four mice). Therefore, although the mechanism of this interaction effect is unknown, the studies in mice support the clinical observation that neither drug used alone significantly lowers seizure threshold but that the concurrent use of the two agents may result in a reduced seizure threshold.

There are numerous reports of aminophylline-induced seizures.[10] Zwillich *et al.* found that patients with seizures had serum theophylline levels in excess of 25 μg/ml.[13] The mean theophylline levels in his eight patients was 53 ± 5 μg/ml. The theophylline serum concentration in Case 1 was 19 μg/ml (therapeutic level 10–20 μg/ml). Serum theophylline determinations were not available in the other three cases.

Aminophylline-induced cardiac arrhythmias have been reported in anesthetized humans.[14] The tachycardia in Case 1 may have been exacerbated by the ketamine. It is possible that the new calcium channel blocking drugs might have been a better choice than beta-adrenergic antagonists in treating the tachycardia in our asthmatic patient, but these drugs were not then available.[15]

The use of these two drugs in combination during anesthesia is not uncommon. Asthmatic patients are often receiving aminophylline at the time of surgery; ketamine has been advocated as a good drug for use in asthma in humans[16] and ketamine has been shown to prevent increases in pulmonary resistance induced by antigen in an animal model of asthma.[17]

These case reports and the accompanying study should serve to alert the anesthesiologist to the possible occurrence of seizures during concomitant use of ketamine and aminophylline. Perhaps ketamine should be avoided in some patients currently taking aminophylline, or antiseizure premedication be instituted in patients at risk.

References

1. Swinyard EA, Brown WC, Goodman LS: Comparative assays of antiepileptic drugs in mice and rats. J Pharmacol Exp Ther 106:319–330, 1952

2. Swinyard EA: Laboratory assay of clinically effective antiepileptic drugs. J Am Pharm Assoc 38:201–204, 1949
3. Swinyard EA: Laboratory evaluation of antiepileptic drugs. Epilepsia 10:107–119, 1969
4. Sattin A: Increase in the content of adenosine 3′,5′-monophosphate in mouse forebraine during seizures and prevention of the increase by methylxanthines. J Neurochem 18:1087–1096, 1971
5. Swinscow TDV. Statistics at Square One, 7th ed. London, British Medical Assocation, 1980, pp 43–53
6. Steen PA, Michenfelder JD: Neurotoxicity of anesthetics. ANESTHESIOLOGY 50:437–453, 1979
7. Radney PA, Badola RP: Generalized extensor spasm in infants following ketamine anesthesia. ANESTHESIOLOGY 39:459–460, 1973
8. Reder BS, Trapp LD, Troutman KC: Ketamine suppression of chemically induced convulsions in the two-day-old white leghorn cockerel. Anesth Analg (Cleve) 59:406–409, 1980
9. Celesia GG, Chen R-C, Bamforth BJ: Effects of ketamine in epilepsy. Neurology 25:169–172, 1975
10. Stirt JA, Sullivan SF: Aminophylline. Anesth Analg (Cleve) 60:587–602, 1981
11. Bergstrand H: Phosphodiesterase inhibition and theophylline. Eur J Respir Dis (Suppl 109):37–44, 1980
12. Fredholm BB: Theophylline actions on adenosine receptors. Eur J Respir Dis (Suppl 109):29–36, 1980
13. Zwillich CW, Sutton FD, Neff TA: Theophylline-induced seizures in adults: correlation with serum concentrations. Ann Intern Med 82:784–787, 1975
14. Roizen MF, Stevens WC: Multiform ventricular tachycardia due to the interaction of aminophylline and halothane. Anesth Analg (Cleve) 57:738–741, 1978
15. Kapur PA, Flacke WE: Epinephrine-induced arrhythmias and cardiovascular function after verapamil during halothane anesthesia in the dog. ANESTHESIOLOGY 55:218–225, 1981
16. Corssen G, Gutierrez J, Reves JC, Huber FC: Ketamine in the anesthetic management of asthmatic patients. Anesth Analg (Cleve) 51:588–596, 1972
17. Hirshman CA, Downes H, Farbood A, Bergman NA: Ketamine block of bronchospasm in experimental canine asthma. Br J Anaesth 51:713–718, 1979

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Upper Airway Edema—An Anaphylactoid Reaction to Succinylcholine?

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Succinylcholine (SCh) was reported to cause histamine release in 1957 when skin reactions were observed in four patients.[1] Since then, at least 12 additional cases of hypersensitivity to the drug have been described.[2–11] This report presents a case of probable SCh-induced upper airway edema in a patient with bronchial asthma and known penicillin allergy.

REPORT OF A CASE

A 30-year-old term-pregnant woman with history of bronchial asthma and of urticarial rash following penicillin administration required emergency cesarean section because of fetal distress. She had received no previous anesthesia. Physical examination and laboratory data were within normal limits. After preoxygenation, application of monitoring devices, and intravenous injection of 0.4 mg atropine and 3 mg *d*-tubocurarine, anesthesia was induced with ketamine (50 mg) and thiopental (100 mg), iv. Following administration of 100 mg SCh, a 7-mm single-use low-pressure cuff endotracheal tube was inserted with ease. Anesthesia was maintained with nitrous oxide–oxygen–halothane 0.5 per cent, until delivery of the infant. After clamping of the umbilical cord, halothane administration was discontinued and respiration controlled by a volume-limited ventilator. Meperidine, 50 mg, 10 mg diazepam, and 50 mg thiopental were injected iv in divided doses, and a total dose of 250 mg SCh was infused in a 0.1 per cent solution during the 70 min of surgery. Fluctuations in heart rate and blood pressure were unremarkable throughout.

At the end of the procedure, the patient was awake and responsive and the endotracheal tube was removed. Immediately thereafter, she began to show signs of respiratory distress and deepening cyanosis of the mucous membranes. Attempts to ventilate her by face mask were unsatisfactory despite insertion of oro- and nasopharyngeal airways. Laryngoscopy revealed marked edema of palate, pharynx, and larynx; the cords could no longer be visualized but it was possible, with difficulty, to insert a 6-mm endotracheal tube. Oxygen 100 per cent was administered to the spontaneously breathing patient, and 40 mg dexamethasone was injected iv. Moderate swelling of lips and eyelids was also evident, but no wheezing or skin rash was detected. The heart rate which had increased during the period of respiratory difficulty returned to normal within 5 min. Chest radiogram revealed no abnormalities, but a neck soft tissue radiogram suggested tissue swelling. An otolaryngology consultant confirmed the diagnosis of angioedema. Three hours later, the endotracheal tube was removed without problems. Steroid treatment was continued for one additional day.

Two days postpartum, skin tests were performed with 0.1 ml of all drugs used intravenously during anesthesia and with saline as control. The tests were negative for atropine, *d*-tubocurarine, thiopental, meperidine, and diazepam. There was a strongly positive reaction to SCh, both with and without preservative: wheals approximately 10 mm in

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