The Influence of Bambuterol (Carbamylated Terbutaline) on the Duration of Action of Succinylcholine-induced Paralysis in Humans

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Bambuterol (bis-dimethylcarbamylated terbutaline) is being investigated as an orally administered prolonged-acting treatment for bronchospasm. Adding two carbamate groups to terbutaline results in bambuterol, an inert prodrug compound that is broken enzymatically to yield the active compound, terbutaline.‡ Because bambuterol is slowly biocorverted, it has a high affinity for lung tissue, and is bioconverted in the lung.** It can be administered once daily for the treatment of asthma. However, as the carbamate groups are cleaved from bambuterol, they selectively inhibit the activity of pseudocholinesterase,¹ the enzyme responsible for the degradation of succinylcholine. Therefore, we determined the interaction of bambuterol-induced decreases in pseudocholinesterase activity and succinylcholine-induced neuromuscular blockade.

MATERIALS AND METHODS

After obtaining approval from our committee on human research and informed consent, we studied 24 adults aged 28-57 yr, ASA physical status I or II, undergoing elective surgery. Patients were taking no drugs and had no diseases known to alter neuromuscular function. At 10:00 PM the evening before surgery, patients took either bambuterol, 30 mg, or placebo. On the morning of surgery, anesthesia was induced with thiopental, nitrous oxide, and isoflurane. Laryngoscopy and tracheal intubation were performed without the aid of muscle relaxants: lidocaine, 160 mg, was sprayed into the trachea during laryngoscopy. Anesthesia was then maintained with nitrous oxide, 60-70%, and isoflurane, 0.9-1.2% end-tidal, as measured by mass spectroscopy. Ventilation was controlled to maintain end-tidal PCO₂ at 30-40 mmHg. The ulnar nerve was stimulated with supramaximal train-of-four pulses (4 square-wave pulses, 0.2 ms duration, at 2 Hz) every 15 s via 27-gauge needle electrodes placed at the wrist. Twitch tension of the adductor pollicis was measured using a Gould Statham® UTC3 strain gauge. After obtaining stable values for twitch tension and end-tidal concentrations of nitrous oxide and isoflurane, we administered succinylcholine, 1 mg/kg, as a rapid intravenous bolus. We recorded the time to onset of neuromuscular blockade (100% depression of the first component of the train-of-four [T1]); the time to initial recovery, 25%, 50%, and 50% recovery of T1; and the value of the train-of-four ratio (tension of the fourth component of the train-of-four divided by T1) at the time that T1 was 50% of control.

One day prior to surgery (before bambuterol or placebo was administered) and, again, approximately 30 min prior to the administration of succinylcholine, we obtained 10 ml of heparinized blood. This blood was centrifuged at 2000 rpm for 10 min and plasma was analyzed for pseudocholinesterase (acetylcholine acetylhydrolase, International Enzyme Commission number 3.1.1.8) using a modified radioisotope method.³ Enzyme activity was expressed as μmoles of ³H-acetylcholine hydrolyzed per minute per ml plasma. Normal values for our laboratory range from 0.4-1.3 μmoles acetylcholine·min⁻¹·ml plasma⁻¹ at pH 7.4 and 20° C. A urine sample was obtained from each subject on the morning of surgery. This urine was frozen and subsequently analyzed for terbutaline by liquid chromatography. Neither the patient nor the investigators were aware whether the patient had been given bambuterol or placebo.

Mean values for time from administration of succinylcholine to 100% depression of T1, initial recovery of T1, and recovery of T1 to 90% of control, and time for twitch

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tension to recovery from 25% to 75% of control for the two groups were compared using the Mann-Whitney U-test. Analysis of linear regression was used to compare pseudocholinesterase activity to the initial recovery of T1 and to the recovery of T1 to 90% of control. \( P < 0.05 \) was considered statistically significant.

**RESULTS**

Thirteen subjects received bamberterol and 11 received placebo; terbutaline was detected in the urine of all subjects given bamberterol and none of those given placebo. The interval between administration of bamberterol and sampling of pseudocholinesterase activity ranged from 10 to 12.5 h. The groups were comparable in age, weight, gender distribution, total dose of thiopental, and end-tidal concentrations of nitrous oxide and isoflurane (table 1).

Onset of neuromuscular blockade was similar for subjects given bamberterol and placebo (table 2). Time to first recovery of T1, time for T1 to recover to 90% of control, and time for T1 to recover from 25% to 75% of control were longer in subjects given bamberterol. Train-of-four ratio at the time that T1 was 50% of control ranged from 46% to 93% in subjects given bamberterol; train-of-four ratio exceeded 79% in all subjects given placebo.

Pseudocholinesterase activity decreased in all subjects given bamberterol; post-bamberterol pseudocholinesterase activity varied from 9% to 73% of control values. Time to initial recovery of T1 (fig. 1) and time for T1 to recover to 90% of control both varied as a function of pseudocholinesterase activity \( (P < 0.05) \). The subject whose pseudocholinesterase activity was most depressed \( (9\% \) of control) developed the most prolonged neuromuscular blockade \( (60.25 \text{ min to } 77\% \text{ recovery of control}) \).

For three subjects given bamberterol, T1 recovered to between 90% and 95% of control, then did not recover further spontaneously; train-of-four ratio was approximately 60–73% at that time. For a fourth subject given bamberterol, T1 plateaued at 77% of control, at which time train-of-four ratio was approximately 75%. For these four subjects, when T1 had not increased further during 10 min, each was given edrophonium, 0.5 mg/kg; within 4 min, T1 recovered to the control value and train-of-four ratio exceeded 92%.

**DISCUSSION**

Rapid recovery of neuromuscular function following administration of succinylcholine depends on succinylcholine being metabolized by pseudocholinesterase. Although the more than two-fold variability in pseudocholinesterase activity in subjects who are genotypically normal is not associated with changes in the duration of action of succinylcholine, genotypically normal subjects whose pseudocholinesterase activity is below the normal range develop prolonged succinylcholine-induced neuromuscular blockade. In the present study, we found that subjects whose pseudocholinesterase activity was depressed at the time that succinylcholine was administered developed prolonged neuromuscular blockade. We also observed that the subject whose pseudocholinesterase activity was most depressed developed the most prolonged neuromuscular blockade. Thus, our findings are consistent with those of Viby-Mogensen, and suggest that subjects whose pseudocholinesterase activity is below the normal range will have prolonged succinylcholine-induced neuromuscular blockade, regardless of whether the decreased pseudocholinesterase activity occurs genetically or is drug-induced.

We observed that those subjects whose pseudocholinesterase activity was most depressed and who developed prolonged neuromuscular blockade also developed train-of-four fade (phase II block). This contrasts to Viby-Mo-
gensen’s finding that phase II block did not occur in genotypically normal subjects whose pseudocholinesterase activity was markedly depressed. However, he found phase II block in some subjects heterozygous for an abnormal cholinesterase and in all subjects homozygous for atypical cholinesterase. In addition, all subjects receiving a prolonged infusion of succinylcholine eventually develop phase II block. The results of these studies suggest that phase II block occurs as a result of the neuromuscular junction being exposed to succinylcholine either at high concentrations, or for prolonged periods, or both. Thus, the neuromuscular junctions of our subjects whose pseudocholinesterase activity was most depressed would have been exposed to higher concentrations of succinylcholine for longer periods, and, as expected, developed phase II block.

We observed that full neuromuscular function did not recover spontaneously in four subjects given bambuterol, all of whom showed signs of phase II block. These subjects all demonstrated significant improvement in neuromuscular function when given edrophonium. Edrophonium is known to antagonize phase II block induced by prolonged infusions of succinylcholine. Our observations suggest that phase II block induced by a single dose of succinylcholine in subjects with drug-induced depression of cholinesterase activity can also be antagonized with edrophonium.

If the prolongation of succinylcholine-induced neuromuscular blockade following bambuterol depends on the degree of inhibition of pseudocholinesterase, patients who would experience the longest neuromuscular blockade are those who receive succinylcholine when their pseudocholinesterase activity is maximally depressed. Although we did not follow the time course of bambuterol-induced depression of pseudocholinesterase activity, data from the manufacturer (AB Draco, Lund, Sweden) suggest that maximal depression of pseudocholinesterase activity following this dose of bambuterol occurs approximately 2–6 h following administration; pseudocholinesterase activity is still markedly depressed 10 h after administration. Thus, subjects who take bambuterol at bedtime are likely to have prolongation of succinylcholine-induced neuromuscular blockade if they receive succinylcholine at approximately 8:00 AM. For this reason, we selected subjects who would receive succinylcholine at approximately that hour; despite this, neuromuscular blockade exceeded 1 h in duration in only one patient; in addition, neuromuscular blockade in that patient could be antagonized with edrophonium. However, all our patients had normal pseudocholinesterase activity prior to administration of bambuterol, and we do not know whether succinylcholine-induced neuromuscular blockade would have been greatly prolonged had we studied subjects whose baseline pseudocholinesterase activity was depressed. Of note, the manufacturer expects that the dose of bambuterol used in this study, 30 mg, will not be used clinically. The maximal dose to be used clinically, 20 mg, may prolong succinylcholine-induced neuromuscular blockade less.

In summary, we found that bambuterol prolonged the duration of a single dose of succinylcholine and produced phase II block in some subjects. The effect of bambuterol on succinylcholine-induced neuromuscular blockade emphasizes the need to monitor neuromuscular function whenever a muscle relaxant is administered.

**REFERENCES**