Title: BAMBUTEROL (CARBAMYLATED TERBUTALINE) PROLONGS THE DURATION OF ACTION OF SUCCINYLCHOLINE

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Introduction. Bambuterol is an orally-administered prolonged-acting treatment for bronchospasm. Adding two carbamate groups to terbutaline results in bambuterol, an inert prodrug compound which is broken enzymatically to yield the active compound, terbutaline. Because bambuterol is bioconverted slowly and has high affinity for lung tissue, it can be taken once daily. However, as carbamate groups are cleaved, they selectively inhibit pseudocholinesterase activity. Therefore, we determined the interaction of bambuterol-induced decreases in pseudocholinesterase activity and succinylcholine-induced neuromuscular blockade.

Methods. After obtaining approval from our committee on human research and informed consent, we performed a double-blinded study in 24 adults aged 28-57 years, ASA PS I or II, undergoing elective surgery. At 10 PM the evening before surgery, patients took either bambuterol, 30 mg, or placebo. On the morning of surgery, anesthesia was induced with thiopental, N_2O, and isoflurane and the trachea was intubated without the aid of muscle relaxants. Anesthesia was maintained with N_2O (60-70%) and isoflurane (0.9-1.2% end-tidal); PCO_2 was maintained normal. The ulnar nerve was stimulated with supramaximal train-of-four (TOF) pulses every 15 s. Adductor pollicis twitch tension was measured using a strain gauge. After obtaining stable values for twitch tension and anesthetic concentrations, we gave succinylcholine, 1 mg/kg, iv. We recorded time to initial recovery, 25%, 75%, and 90% recovery of the first component of the TOF (T1) and the value of the TOF ratio when T1 was 50% of control. One day prior to surgery (before bambuterol or placebo was administered) and, again, 30 min prior to administration of succinylcholine, we obtained heparinized blood to determine pseudocholinesterase activity.[1] Values for the two groups were compared using the Mann-Whitney *U*-test. Linear regression was used to compare pseudocholinesterase activity to time to initial recovery of T1 and to recovery of T1 to 90% of control. $P<0.05$ was considered statistically significant.

Results. Recovery of neuromuscular function was prolonged in subjects given bambuterol (table). In subjects given bambuterol, TOF ratio ranged from 46-93%; TOF ratio exceeded 79% in all subjects given placebo. Post-bambuterol pseudocholinesterase activity varied from 9-73% of control values. Time to initial recovery of T1 and time for T1 to recover to 90% of control varied as a function of pseudocholinesterase activity (fig.). For four subjects given bambuterol, T1 recovered to 77-95% of control, then did not recover further spontaneously; TOF ratio was approximately 60-75% at that time. 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 TOF ratio exceeded 92%.

Table. Values (mean±SD) for recovery of neuromuscular function following succinylcholine in subjects given bambuterol or placebo.

	Bambuterol (n = 13)	Placebo (n = 11)
Time to initial recovery of T1 (min)	15.1 ± 4.2*	5.6 ± 1.8
Time to 90% recovery of T1 (min)	24.9 ± 12.2*†	11.2 ± 3.7
Time for T1 to recover from 25% to 75% of control (min)	3.2 ± 1.7*	2.4 ± 1.8

*Different from placebo ($P<0.05$) by the Mann-Whitney *U* test.

† One patient received edrophonium when T1 plateaued at 77% of control at 60.25 min. This value was used as the time to 90% recovery for this patient.

Discussion. Genotypically-normal subjects with pseudocholinesterase activity below the normal range develop prolonged succinylcholine-induced neuromuscular blockade;[2] similarly, subjects whose pseudocholinesterase activity was depressed at the time that succinylcholine was administered developed prolonged blockade. Subjects whose pseudocholinesterase activity was most depressed also developed TOF fade (phase II block). This contrasts to the finding that phase II block did not occur in genotypically-normal subjects whose pseudocholinesterase activity was markedly depressed[2]; however, similar to our subjects, phase II block occurs in some subjects heterozygous for abnormal cholinesterase[2] and in all subjects homozygous for atypical cholinesterase.[2]

Data from the manufacturer (AB Draco) suggest that bambuterol maximally depresses pseudocholinesterase activity 2-6 h following administration; pseudocholinesterase activity is still markedly depressed 10 h after administration, the time at which we administered succinylcholine. Thus, subjects who take bambuterol at bedtime are likely to have prolonged neuromuscular blockade if they receive succinylcholine at approximately 8 AM. However, neuromuscular blockade exceeded 1 h in only one patient; in addition, that patient's neuromuscular blockade could be antagonized. Draco expects that the maximal bambuterol dose used clinically will be 20 mg; this smaller dose may prolong succinylcholine-induced neuromuscular blockade less.

In summary, bambuterol prolonged the duration of a single dose of succinylcholine and produced phase II block in some subjects.

References.

1. Calvey TN, Williams NE, Muir KT, Barber HE: Plasma concentration of edrophonium in man. Clin Pharmacol Ther 19:813-820, 1976
2. Viby Mogensen J: Cholinesterase and succinylcholine. Dan Med J 30:129-150, 1983

Figure. Effect of bambuterol or placebo on succinylcholine, 1 mg/kg. X-axis is pseudocholinesterase activity 30 min prior to succinylcholine; y-axis is time to initial recovery of T1.