Modification of Pancuronium-induced Nondepolarizing Neuromuscular Block by Succinylcholine in Anesthetized Humans

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Abdominal surgery often requires a brief restoration of neuromuscular blockade to facilitate peritoneal and abdominal wall closure. This can be achieved with incremental administration of nondepolarizing muscle relaxants such as d-tubocurarine or pancuronium, but quite often at the price of undesired delayed recovery. Succinylcholine ideally is short-acting for this purpose, however, as a depolarizing agent, it carries the risk of either reversing or prolonging preexisting partial nondepolarizing neuromuscular blockade. Yet, Feldman had no objections to the administration of succinylcholine at the end of nondepolarizing blockade, providing that prompt recovery from the initial dose of succinylcholine has been demonstrated.

The conditions determining the degree of reversal or increase of partial nondepolarizing block by succinylcholine were studied by various authors. Katz and Young found that small doses of succinylcholine (0.1 mg/kg) reversed a partial nondepolarizing neuromuscular blockade, whereas an increase in the magnitude of blockade only occurred from higher doses of succinylcholine (0.3–2.0 mg/kg). The studies of Gray and Young demonstrate that the degree of preexisting nondepolarizing block also determines the response to succinylcholine. However, none of these authors studied the effect of succinylcholine at standardized levels of waning nondepolarizing neuromuscular blockade. It is the purpose of the present study to yield this information.

MATERIALS AND METHODS

Thirty-eight patients, ASA class II to III, undergoing peripheral or abdominal vascular surgery were divided randomly into five groups according to table 1. Informed consent had been obtained in all cases. Patients with disorders or medications known to affect neuromuscular transmission or blockade were excluded from the study.

Atropine 0.5–0.7 mg, droperidol 5 mg, and fentanyl 0.1 mg were given im as preanesthetic medication 45 min prior to the induction of anesthesia. Anesthesia was induced with thiopental 250–450 mg and fentanyl 0.2 mg, followed by orotracheal intubation under topical anesthesia without the aid of muscle relaxants. Anesthesia was maintained with 50% nitrous oxide and IV doses of fentanyl with controlled ventilation. After at least 20 min of anesthesia, pancuronium 0.075 mg/kg was administered iv. During the offset of pancuronium neuromuscular blockade, an IV bolus of succinylcholine 0.5 mg/kg was injected at different levels of recovery as indicated in table 1.

Neuromuscular transmission was monitored by means of the evoked isometric mechanomyogram of the left adductor pollicis muscle. The ulnar nerve was stimulated by 20-gauge needle electrodes at the wrist. Supramaximal trains of four stimuli (2 Hz for 2 s; pulse width 0.2 ms) were administered every 50 s. A 15-kg capacity force displacement transducer was attached to an arm board, securing the forearm in the supine position. The position of the transducer was adjusted individually to each patient’s thumb, providing a 200-g resting tension. After preamplification, the signals of the transducer were recorded on a polygraph.

The analysis of the tracings included single twitch tension (ST) in percentage of control as represented by the first twitch of each train-of-four in relation to the twitch tension before the administration of pancuronium, and train-of-four ratio (T4), i.e., the fractional size of the fourth twitch related to the first twitch of the same train. These variables were calculated as means and standard deviations according to the following time schedule (fig. 1): 10 min and immediately before succinylcholine administration, at maximum reversal of block, at maximum increase of block, immediately and 10 min after cessation of the succinylcholine effect. Statistical significance was assessed by Student’s † test. Correlations were calculated by the least-squares method.

RESULTS

In all groups of patients, the response to succinylcholine was biphasic, showing an initial antagonism followed by
TABLE 1. Protocol of Succinylcholine Administration (0.5 mg/kg) during Preexisting Partial Nondepolarizing Block Due to Pancuronium 0.075 mg/kg

<table>
<thead>
<tr>
<th>Group No.</th>
<th>Age (Years*)</th>
<th>Body Weight (kg*)</th>
<th>Succinylcholine 0.5 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6</td>
<td>48 ± 14</td>
<td>75 ± 12</td>
</tr>
<tr>
<td>2</td>
<td>7</td>
<td>62 ± 7</td>
<td>64 ± 12</td>
</tr>
<tr>
<td>3</td>
<td>7</td>
<td>48 ± 23</td>
<td>61 ± 5</td>
</tr>
<tr>
<td>4</td>
<td>11</td>
<td>48 ± 21</td>
<td>63 ± 9</td>
</tr>
<tr>
<td>5</td>
<td>7</td>
<td>52 ± 19</td>
<td>63 ± 9</td>
</tr>
</tbody>
</table>

ST = single twitch tension in per cent of control; T\(_4\) = fractional train of four ratio.

* Figures indicate level of recovery when succinylcholine (0.5 mg/kg) was administrated.

a transient increase of the partial pancuronium block. One representative tracing from each group is depicted in figure 2. Figure 1 summarizes the results of all patients in terms of both single twitch tension and train-of-four ratio. Succinylcholine (0.5 mg/kg) given at 25% recovery of single twitch tension (group 1) exerted an acute partial antagonism of the pancuronium block (P < 0.0005), followed by a moderate depression of twitch tension if compared with the presuccinylcholine level. With train-of-four ratio back to 0.25 (group 2), the quantitative relation between reversal and increase of block due to succinylcholine was unpredictable. No correlation could be verified between the level of single twitch recovery and the reversal or increase of block secondary to succinylcholine. Succinylcholine given at 75% recovery (group 3) caused little antagonism, followed by a more pronounced increase in the depth of block, all changes being statistically significant (P < 0.05). However, in two cases from groups 2 and 3, only consistent partial antagonism following succinylcholine administration without subsequent depression of twitch tension was observed. If given at 100% twitch recovery (group 4) or when train-of-four fade was no longer present (group 5), succinylcholine produced subtotal or total neuromuscular blockade (P < 0.0005).

The biphasic response of partial nondepolarizing block to succinylcholine also was reflected by the train-of-four ratio with the same statistical significance (figure 1). In fact, like single twitch depression, train-of-four fade decreased immediately after succinylcholine administration and increased during its second phase of action. However, during its first phase of action, succinylcholine given at 75% recovery (group 3) was more effective in reversing train-of-four fade than in increasing single twitch tension. The most consistent increase of train-of-four fade during the second phase of the succinylcholine effect was shown by patients having received this drug at 100% recovery (group 4). Very little fade occurred in group 5, where succinylcholine was injected after complete restoration of train-of-four response, and in six of these patients the train-of-four response resembled that of a plain depolarizing block. Additionally, the tracings of group 4 and 5 in figure 2 show an elevation of the base line immediately after succinylcholine administration, reflecting some degree of muscle fasciculation. This did not occur in groups 1, 2, and 3. Gross muscle contractions such as are often seen after succinylcholine alone never were observed. The overall duration of the succinylcholine effect was 10–20 min (fig. 1).

DISCUSSION

The biphasic response of partial nondepolarizing neuromuscular blockade to succinylcholine 0.5 mg/kg is in line with the results of previous authors. \(^\text{2,3,6}\) Furthermore, this study demonstrates that with a constant dose of succinylcholine, the proportional relation between reversal

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**Fig. 1.** Modification of pancuronium (PC) induced neuromuscular blockade by succinylcholine (Sch) 0.5 mg/kg. Single twitch tension (ST) and train-of-four ratio (T\(_4\)) are given as means and standard deviations. Zero in time scales refers to the time of succinylcholine administration.
Fig. 2. Representative original tracings showing the changing pattern of biphasic response of pancuronium- (PC) induced partial nondepolarizing neuromuscular blockade to succinylcholine (SCh). Advanced recovery from pancuronium blockade favors the increase of block by succinylcholine 0.5 mg/kg.

and subsequent increase of block depends on the stage of recovery from nondepolarizing neuromuscular blockade at the time of succinylcholine administration. If, as in group 3 and 4, the reversing effect of succinylcholine is relatively weak, it may be detected more readily by the train-of-four rather than by single twitch stimulation. These results support similar findings of Lee.8,9

The biphasic response of partial pancuronium neuromuscular blockade may be explained by both prejunctional and postjunctional effects of succinylcholine. When combining with prejunctional cholinophores, succinylcholine may promote the availability of acetylcholine in the motor nerve endings.10 At the postjunctional level, succinylcholine during its first phase of action may add to the depolarizing effect of acetylcholine, both of them antagonizing preexisting nondepolarizing blockade. However, during its second phase of action, succinylcholine then should not cause train-of-four fade. In fact, the absence of train-of-four fade after succinylcholine administration was only observed in group 5, where no signs of residual nondepolarizing blockade were detectable prior to its injection. In groups 1 and 2, where considerable residual neuromuscular blockade interfered with the action of succinylcholine, the train-of-four ratio paralleled the decreasing twitch tension. Under these conditions, during its first phase of action, succinylcholine may combine with free postjunctional cholinicersors and thereby open a certain proportion of postjunctional ionic channels. The latter then may be plugged immediately by pancuronium molecules. In addition, those cholinizers, where pancuronium has been replaced by succinylcholine might undergo phase II block.11 Both of these proposed mechanisms are compatible with an increasing train-of-four fade during the second phase of the effect of succinylcholine (groups 1 to 4). However, an exhaustive explanation of all the succinylcholine effects cannot be provided on the basis of a clinically oriented study alone.

From the clinical point of view, our data confirm the traditional concept that nondepolarizing and depolarizing drugs are mutual antagonists,12 although under certain conditions succinylcholine may augment a partial nondepolarizing block. Consequently, succinylcholine given for transient increase of partial nondepolarizing block carries the risk to act as a partial reversal agent, and it is certainly not a suitable drug to transiently augment any amount of partial nondepolarizing neuromuscular blockade. Its administration may be considered only if nearly complete recovery of neuromuscular transmission has been demonstrated with the aid of a nerve stimulator.4 However, in this case the dose of succinylcholine then should be at least 0.5 mg/kg. It remains to be investigated whether the problem of short-term increase of waning nondepolarizing neuromuscular blockade will be solved more satisfactorily by the administration of the newly developed intermediate or short-acting nondepolarizing muscle relaxants, such as vecuronium13,14 or atracurium.15

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Pulmonary Edema Following Naloxone Administration in a Patient Without Heart Disease

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Naloxone, an opiate antagonist with little or no intrinsic agonist activity, often is used to reverse the effects of narcotics. There have been several reports of adverse effects following naloxone administration. These include hypertension,1 pulmonary edema,2 ventricular arrhythmias,3 and cardiac arrest.4 With the exception of one patient who received 0.1 mg iv of naloxone, the usual single dose mentioned in these reports varied between 0.2–0.4 mg iv.

To minimize any adverse reactions, I commonly administer naloxone in incremental doses of 0.04–0.08 mg iv over several minutes. In one healthy man, this practice lead to pulmonary edema.

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Key words: Antagonists, narcotic: naloxone. Complications: pulmonary edema.

REPORT OF A CASE

A 26-year-old, 85-kg male was scheduled for an operative arthroscopy on an outpatient basis. There was no significant medical history. The patient was not taking any medications and was allergic to tetanus toxoid. Laboratory tests, which included chest roentgenogram, CBC, and urinalysis, were all within normal limits. An EKG was not done. The patient’s only prior anesthetic was for a tonsillectomy as a child. An iv was started in the operating room. Monitoring included an EKG, a blood pressure cuff, a precordial stethoscope, a neuromuscular blockade monitor, and an oxygen analyzer. The patient was not premedicated. A combination of thiopental 775 mg, fentanyl 300 mcg, pancuronium 1.5 mg, metocurine 6 mg iv, and 70% nitrous oxide was used for the anesthetic. The surgery lasted 77 min. The last 50 mcg of fentanyl was given iv 26 min before the surgery was finished. The total anesthesia time was 110 min. Ventilation was controlled with a tidal volume of 0.85 l at a rate of 8 breaths·min⁻¹. Blood pressure varied between 90/60 and 120/80 mm Hg during surgery. Muscle relaxants were reversed with a combination of edrophonium 30 mg and atropine 0.8 mg iv. Nitrous oxide was discontinued, and the trachea was extubated after 100% oxygen had been given for several minutes.

The patient was quite sleepy with small pupils and slow, shallow respirations. The neuromuscular blockade monitor showed a sustained response to a tetanic stimulus with no fade. Incremental doses of naloxone 0.04–0.08 mg iv were given over 5–10 min. The total dose used was 0.3 mg. The patient became more awake, and respirations increased in rate and depth. He then was transferred to the recovery room. A total of 1,100 ml of lactated Ringer’s solution was given iv.

In the recovery room, the initial blood pressure was 140/90 mm Hg,