Dose Response of Succinylcholine at the Adductor Pollicis of Children with Cerebral Palsy During Propofol and Nitrous Oxide Anesthesia

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Children with cerebral palsy may be resistant to paralysis induced by nondepolarizing neuromuscular blocking drugs. Potency of a bolus of succinylcholine in children with cerebral palsy has not been studied previously. Therefore, we measured the response of the adductor pollicis to succinylcholine in children with cerebral palsy anesthetized with propofol and nitrous oxide. Forty children between the ages of 2 and 10.2 yr with spastic quadriplegic cerebral palsy were randomly assigned to receive 100, 175, 250, or 375 μg/kg of succinylcholine during anesthesia with propofol and nitrous oxide. The ulnar nerve was stimulated with a train-of-four supramaximal stimulus every 10 s and the compound electromyogram of the adductor pollicis recorded by a Datex NMT monitor. Plasma cholinesterase activity was measured in all patients with three different substrates (propionylthiocholine, benzoylcholine, and succinylcholine). Dibucaine number was also determined using inhibition of benzoylcholine degradation. ED₉₀ of succinylcholine was 146.8 μg/kg with 95% confidence intervals of 111.4-193.7 μg/kg. ED₉₀ of succinylcholine was 360.5 μg with 95% confidence intervals of 273.3-475.5 μg/kg. We conclude that children with cerebral palsy are slightly sensitive to succinylcholine, but probably not sufficiently to be clinically important.

(Anesth Analg 1994;79:761-5)

Cerebral palsy is a group of disorders of movement and posture caused by a nonprogressive lesion of the developing brain (1). This is the most commonly occurring nervous system disorder in children. Etiology varies, but the characteristic feature remains the motor disorder. Spastic quadriplegia is the most common variety of cerebral palsy. The severity of motor dysfunction was classified into four groups by Evans and Alberman (2).

Children with cerebral palsy have a higher incidence of gastroesophageal reflux and slower gastric emptying than normal children have (3). They also frequently drool as a result of decreased ability to clear pharyngeal secretions. Many anesthesiologists respond to the presence of these medical conditions by using a rapid sequence technique for induction of anesthesia and intubation of the trachea in these patients.

Children with cerebral palsy are resistant to neuromuscular blockade induced by vecuronium (4). Resistance to nondepolarizing muscle relaxants in paretic upper extremities of patients with residual hemiplegia has been demonstrated (5,6). Although cerebral palsy in children often has been compared to adult onset upper motor neuron syndrome (7), there are many differences between the characteristics and distribution of signs. In cerebral palsy, instead of disuse, there is constant and repeated spasm of the extremities with dysfunctional motion. This reflects the differing responses of the maturing nervous system to insult (8).

Muscular denervation leads to extrajunctional proliferation of acetylcholine receptors which produces an increased response to succinylcholine and resistance to the effects of nondepolarizing relaxants (9,10). This phenomenon is observed regularly in individuals who have suffered a stroke, have spinal cord injuries, or have an immobilized limb in a cast (9–17). If resistance to vecuronium in children with cerebral palsy (4) is due to a change in function of the neuromuscular
junction, such as proliferation of extrajunctional receptors, sensitivity to the paralytic effects of succinylcholine might be altered in these patients. However, children with cerebral palsy do not experience significant increase in plasma potassium after administration of succinylcholine as has been observed in adults with upper motor neuron disease (18). Potency of succinylcholine has not been documented in children with cerebral palsy. Therefore, we conducted a dose-response study of succinylcholine using a single-dose technique in 40 children with spastic cerebral palsy.

Methods

After obtaining clinical research review committee approval and written informed consent from all patients or their parents, 40 ASA class I or II patients aged 2-10 yr were studied. All patients had spastic quadriplegic cerebral palsy with motor involvement of Class 3 or 4 (2). No patient was receiving anticonvulsants. Other exclusion criteria included a history of gastroesophageal reflux, aminoglycoside therapy, hepatic or renal insufficiency, or known electrolyte abnormalities. All patients were scheduled to undergo muscle or tendon releases or osteotomies.

Patients received either oral or intranasal midazolam (oral, 500 µg/kg; intranasal, 200 µg/kg). The intranasal route was used when patients were uncooperative or otherwise unable to swallow oral medication. An intravenous (IV) catheter was placed when the patient was sedate and a blood sample was obtained for assay of plasma cholinesterase. Patients received 10-20 µg/kg of atropine IV prior to induction of anesthesia and after blood was drawn for plasma cholinesterase assay.

General anesthesia was induced with 2-4 mg/kg of propofol preceded by 1 mg/kg of lidocaine IV. Propofol infusion, 200-400 µg·kg⁻¹·min⁻¹, with 60%-70% nitrous oxide and oxygen maintained anesthesia. No volatile drugs were administered during the course of the study. Ventilation was controlled via mask and the patients’ tracheas were intubated after administration of the second dose of succinylcholine when paralysis was complete. End-tidal carbon dioxide was maintained between 30 and 40 mm Hg. After induction of anesthesia, the palmar surface of the arm without the IV line was cleansed with alcohol and surface electrodes were placed over the ulnar nerve near the wrist and over the adductor pollicis muscle in the thenar eminence (19). Prior to administering succinylcholine, the ulnar nerve was stimulated supra-maximally using a train-of-four stimulus at 10-s intervals. Two to three minutes of stable electromyogram (Datex, Helsinki, Finland) was obtained prior to administration of succinylcholine. Palmar temperature of the monitored hand and esophageal temperature were recorded.

The first 30 patients received by random assignment either 175, 250, or 375 µg/kg of succinylcholine. A fourth dosage group, 100 µg/kg, was added after the results from the first 15 patients showed the estimated ED₅₀ to be lower than 175 µg/kg. Succinylcholine was given at the hub of a “T” connector of a rapidly running IV infusion after a stable baseline was obtained 5-7 min after induction of anesthesia. When maximum response was obtained from the first dose, a second dose of 500 µg/kg was given to facilitate intubation. All patients achieved 100% depression of neuromuscular function after this dose.

Plasma cholinesterase was determined using three different substrates. Propionylthiocholine is the substrate most commonly used (20), while benzoylcholine is preferred for genotyping (21). Since the drug of interest in our study was succinylcholine, we also examined the activity of plasma cholinesterase using succinylcholine as a substrate (22). Dibucaine number was also determined using inhibition of benzoylcholine degradation (23).

Log transformation of the dose and probit transformation of the percent depression of neuromuscular function were performed. The dose-response data were examined for deviation from a linear relationship according to Finney (24). Because the data satisfied the assumption of linearity, linear regression of transformed data was performed by the method of least squares. Point estimates of ED₅₀ and ED₉₅ were derived by inverse prediction and 95% confidence intervals were calculated for the potency estimates (25). Demographic and anesthetic variables of the four dosage groups were compared using analysis of variance. A P < 0.05 was considered statistically significant. The mean and SEM are presented.

Results

ED₅₀ of succinylcholine was 146.8 µg/kg with 95% confidence intervals of 111.4-193.7 µg/kg. ED₉₅ of succinylcholine was 360.5 µg/kg with 95% confidence intervals of 273.3-475.5 µg/kg. The slope and intercept of the dose-response linear regression were 4.2153 (SE 0.77) and -4.1134 (SE 1.78), respectively (Fig. 1). Median and range values for maximum twitch depression and times to maximum block are shown in Table 1.

The groups were comparable for age, weight, initial to final baseline difference in the electromyogram, and amount of propofol administered during induction and maintenance. No patient had a palmar temperature less than 33°C. All patients had plasma cholinesterase levels and dibucaine number within normal range. The plasma cholinesterase activity ranged from
Figure 1. Simple linear regression of log of the dose versus probit of the response (percent neuromuscular block).

Table 1. Onset Times and Neuromuscular Block (NMB) in the Four Dosage Groups

<table>
<thead>
<tr>
<th>Dosage groups (µg/kg)</th>
<th>100</th>
<th>175</th>
<th>250</th>
<th>375</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time (s) to maximum NMB</td>
<td>45 (30–60)</td>
<td>55 (40–70)</td>
<td>55 (30–70)</td>
<td>60 (20–70)</td>
</tr>
<tr>
<td>Maximum NMB (%)</td>
<td>18.3 (10–58)</td>
<td>54 (31.5–100)</td>
<td>67 (17.5–100)</td>
<td>93.8 (87–100)</td>
</tr>
</tbody>
</table>

Values are median (range).

14 to 21 µmol·L⁻¹·min⁻¹ with benzoylcholine as substrate, from 3063 to 6374 µmol·L⁻¹·min⁻¹ using propionylthiocholine as substrate, and from 24 to 139 µmol·L⁻¹·min⁻¹ using succinylcholine as substrate. No cardiovascular instability or suggestion of hypokalemia was evident during the study.

Discussion

The dose-response relationship of succinylcholine in normal children has been studied by several investigators (26,27). One study (26) reported ED₅₀ values of 228 µg/kg and 216 µg/kg and ED₉₀ values of 445 µg/kg and 454 µg/kg for 1- to 4-yr and 5- to 10-yr age groups, respectively. Slopes of the dose-response linear regression reported in these studies were 5.7 and 5.1 for the two age groups mentioned. Another study (27), which examined neonates, infants, and children, reported ED₅₀ of 184 µg/kg and ED₉₀ of 352 µg/kg for the children (1.4–7.3 yr), with significantly different ED values for neonates and infants. However, the weighted or common slope for the regression including all three age groups was 1.97 probits log⁻¹. This slope is excessively shallow in comparison to other dose-response studies. Stimulus frequencies were the same for both studies mentioned above.

Confidence intervals around point estimates of ED₅₀ and ED₉₀ were not reported in the previous studies. In comparing estimates of ED₅₀ and ED₉₀ from one study to another, variation in the data should be considered. Therefore, we produced 95% confidence intervals for our estimates of potency (28–31). Point estimates of the ED₅₀ of succinylcholine reported in normal children in the above studies are higher than the upper limit of 95% confidence interval for the ED₅₀ estimated from our study. Point estimates of the ED₉₀ of succinylcholine in normal children, however, fall within the 95% confidence intervals of ED₉₀ estimated from our study. Because the ED₅₀ is estimated from dose-response studies with narrower confidence intervals than is the ED₉₀, differences in relative potency will be more apparent if ED₅₀ values are compared rather than ED₉₀ values. Thus, we conclude that there is a statistically significant, but relatively small difference in the effects of succinylcholine on neuromuscular transmission between previously studied normal children and those with cerebral palsy in the present study. ED₉₀ estimated from this study overlaps with ED₉₀ estimated from normal children (26,27). Clinically, several times ED₉₀ of succinylcholine is administered as a bolus for paralysis. Hence the difference in ED₉₀ which we noted in comparison to previous studies of normal children is probably not clinically significant.

In contrast to the relatively similar potency of succinylcholine in this study in children with cerebral palsy compared to children without cerebral palsy, vecuronium was significantly less potent (<50%) in children with cerebral palsy than in children without cerebral palsy (4). However, children with cerebral palsy in that study were also receiving anticonvulsant medications. The known interaction between anticonvulsants and muscle relaxants may have contributed to the resistance to vecuronium shown by the children with cerebral palsy in that study (32–35). Long-term phenytoin therapy causes significant change in acetylcholine receptor function and/or receptor number (32). Increased protein binding of nondepolarizing...
muscle relaxants is also documented under similar conditions (36). If changes in receptor properties resulting from cerebral palsy rather than from anticonvulsant medications caused resistance to vecuronium in the above-mentioned study, then it would be expected that patients with cerebral palsy would demonstrate sensitivity to succinylcholine. However, a previous study of children with cerebral palsy did not find evidence for greatly increased sensitivity to succinylcholine such as that which is present after denervation injury (18). The lower ED50 we observed in patients with cerebral palsy relative to historic controls was small and could have been due to methodologic differences between studies rather than physiologic differences between patients. Comparison with historic controls rather than concurrent controls is always problematic. Small differences in anesthetic or monitoring methods or unidentifiable differences between one population and another may produce small differences in estimates of potency. In this study, lidocaine may have enhanced the effects of succinylcholine. Unfortunately, it is unlikely that a normal concurrent control could be studied, owing to the recent contraindications placed on the use of succinylcholine during nonemergent anesthetics in normal children by the Food and Drug Administration.

The constant state of spasticity in the skeletal muscles of children with cerebral palsy suggests that response to neuromuscular blockers might be different from normal children. The state of constant spasticity keeps the muscles and neuromuscular junctions in an exercised state. Exercise itself can change receptor properties causing sensitivity to nondepolarizing muscle relaxants (37). The children with cerebral palsy tend to be very thin morphologically because of difficulty in handling and swallowing food and higher energy expenditure due to spasticity. Dietary and exercise-related differences could contribute to differences in neuromuscular function (37,38). An increase in cholesterol content and change in sarcosomal membrane composition may contribute to changes in receptor properties as well (38).

We conclude that the ED50 of succinylcholine determined in this study of children with Grades 3 and 4 cerebral palsy was less than reported previously for similarly aged normal children. However, ED50 values reported previously were within 95% confidence intervals determined in this study. Although there is a difference in the ED50 determined in our study, this is probably clinically insignificant when comparing clinical pharmacology of succinylcholine between normal children and those with cerebral palsy.

References


36. Kim CS, Arnold FJ, Itani MS, Martyn AJ. Decreased sensitivity to metocurine during long-term phenytoin therapy may be attributable to protein binding and acetylcholine receptor changes. Anesthesiology 1992;77:500–6.
