

Clinical Pharmacology of ORG NC45 (NorcuronTM):

A New Nondepolarizing Muscle Relaxant

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To determine the neuromuscular effects of a new muscle relaxant, ORG NC45 (NorcuronTM), a monoquaternary homologue of pancuronium, 84 ASA Class I or II patients were studied under halothane and nitrous oxide anesthesia. The ED₅₀ (dose of muscle relaxant causing a 50 per cent depression of twitch tension) of pancuronium and ORG NC45 was 0.022 mg/kg ($r = 0.90$) and 0.015 mg/kg ($r = 0.80$), respectively, for a potency ratio of 1.5 (0.022/0.015). The duration of action (time from injection to 90 per cent recovery of control twitch tension) was 27 ± 5 min with ORG NC45, 0.02 mg/kg, and 65 ± 16 min with pancuronium in an equivalent dose of 0.03 mg/kg. The increase in duration of neuromuscular blockade from repetitive doses was greater with pancuronium than with ORG NC45. Reversal of an ORG NC45 neuromuscular blockade was accomplished with doses of neostigmine slightly less than those required for pancuronium. Under thiopental-nitrous oxide anesthesia, endotracheal intubation was easily performed using ORG NC45, 0.07–0.14 mg/kg. The duration of action of ORG NC45, 0.07 mg/kg, was about one-third that of pancuronium (0.1 mg/kg). It was concluded that ORG NC45 is more potent and has a shorter duration of action with both initial and repetitive doses than does pancuronium. With these characteristics and the reported lack of cardiovascular effects, the authors believe further clinical trials are warranted. (Key words: Antagonists, neuromuscular neostigmine. Neuromuscular relaxants: (ORG NC45, NorcuronTM); pancuronium. Potency, anesthetic: ED₅₀. Pharmacology: dose-response curves.)

ORG NC45 (NORCURONTM) is a monoquaternary homologue of pancuronium (fig. 1) which appears to have advantages over existing clinically used nondepolarizing muscle relaxants. In animals, ORG NC45 is a nondepolarizing muscle relaxant which has little or no cardiovascular effects^{1,2} and is more potent and shorter acting than pancuronium.^{2,3} These desirable characteristics led to the decision to proceed with clinical trials in humans. In this report we describe the neuromuscular blocking properties of ORG NC45 in anesthetized patients.

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Materials and Methods

Eighty-four adult surgical patients in ASA class I or II were studied. Their mean age was 48.6 ± 16 (SD) years, and body weight was 71.9 ± 13 kg. Informed patient consent was obtained. This study was approved by the University of California Human Research Committee. Premedication was with diazepam, 10 mg, orally. Anesthesia was induced with thiopental, 1–2 mg/kg, iv, and inhalation of halothane and nitrous oxide, 60 per cent. The trachea was intubated without the use of muscle relaxants, and ventilation was then controlled. Anesthesia was maintained with halothane, 0.4 and 1.0 per cent end-tidal, and nitrous oxide, 60 per cent, as measured continuously by mass spectrometry. PaCO₂ was maintained between 35–40 torr and esophageal temperature between 34.5–36.0° C. Neuromuscular function was assessed by using a Grass S-44[®] stimulator to administer supra-maximal square-wave bipolar pulses of 0.2-ms duration to the ulnar nerve at the wrist through thin-wall needle electrodes at 0.15 Hz. The resultant force of thumb adduction was quantitated with a force-displacement transducer (Grass FT-10[®]) and recorded on a polygraph.

Initially, the potency and time course of action of ORG NC45 were determined. Twenty patients were randomly given either 0.01, 0.014, or 0.02 mg/kg ORG NC45 after anesthesia had been maintained for at least 45 min. The maximal depression of control twitch tension, onset time (time from injection to maximal effect), duration of action (time from injection to 90 per cent recovery of control muscle twitch tension), and recovery time (time for twitch to recover from 25 to 75 per cent of control muscle twitch tension) were recorded. Nineteen additional patients were studied in an identical manner except that pancuronium was given instead of ORG NC45. Using a cumulative dose-response method,⁴ pancuronium was given in 0.005 mg/kg doses, iv, to nine patients until twitch tension was depressed to 5 per cent of control. The peak response from each dose was judged to be present when three consecutive twitches of equal height were recorded, after which the next dose of pancuronium was given. The remaining ten patients were given pan-

curonium, 0.03 mg/kg, iv. The onset, duration, and recovery times were measured.

Dose-response curves were then constructed for each muscle relaxant. Doses were converted to log doses and, using simple linear regression, a regression line was calculated for each relaxant. Using analysis of covariance, a test was made for deviation from parallelism⁵ between the two regression lines for ORG NC45 and pancuronium. The ED₅₀ for each muscle relaxant (dose which resulted in 50 per cent depression of control muscle twitch tension) was then derived. Finally, onset, duration, and recovery times for the 0.02 mg/kg dose of ORG NC45 and the 0.03 mg/kg dose of pancuronium were compared by analysis of variance. Statistical differences were considered significant when $P < 0.05$.

To study the effect of repeated doses, 22 patients were randomly given 0.014, 0.02, or 0.04 mg/kg, iv, of ORG NC45. When the twitch tension recovered to 25 per cent of control, the same dose of ORG NC45 was then given again. To be included in this portion of the study, patients had to have received a dose of ORG NC45 in the above fashion at least three times in succession; 16 of the 22 patients met this requirement. The time from the injection of a dose of ORG NC45 to 25 per cent recovery of control muscle twitch tension was measured. Seven additional patients were studied in an identical manner except that pan-

TABLE 1. Endotracheal Intubation Conditions

Score	Endotracheal Intubation Conditions
0	Vocal cords abducted; good visualization; no patient movement.
1	Vocal cords abducted; good visualization; diaphragmatic movement with endotracheal intubation.
2	Vocal cords slightly adducted; fair visualization; coughing on intubation of trachea.
3	Vocal cords adducted; difficult visualization; gross movement of the extremities and coughing with endotracheal intubation.

curonium was used in a dose of 0.02 mg/kg repetitively. Differences in duration of neuromuscular blockade between ORG NC45 and pancuronium were analyzed by the Mann-Whitney test.⁵

To determine the ability of neostigmine to antagonize an ORG NC45 neuromuscular blockade, 16 of the above 22 patients were studied at the end of surgery when twitch tension was 5 per cent of control. Neostigmine, 3.5 µg/kg, and atropine, 0.1 mg, were then given iv every three min until muscle twitch tension was 100 per cent of control and a sustained response to a tetanic stimulus of 50 Hz was present. Antagonism from each 3.5 µg/kg dose of neostigmine was recorded as the twitch tension just before the next dose of neostigmine was given. The doses of neostigmine required for 20, 50, and 80 per cent recovery of control twitch tension were calculated and compared and analyzed by unpaired *t* test to similar data collected with an identical protocol using pancuronium already published by our group.⁶

To determine the dose of ORG NC45 required for endotracheal intubation, 21 unpremedicated surgical patients, ASA class I or II, were studied. Anesthesia was induced with thiopental, 1–2 mg/kg, iv, and 70 per cent nitrous oxide. Stimulation of the ulnar nerve was then initiated. Once a steady state twitch tension was obtained, 4 mg/kg thiopental and ORG NC45, in a randomly selected dose of 0.07, 0.14, or 0.28 mg/kg, were given as an iv bolus. Once the twitch had been completely abolished, the trachea was intubated and the intubating conditions were then scored according to the scale in table 1. Ventilation was controlled, and anesthesia was maintained with halothane and nitrous oxide as described above. To assess duration of neuromuscular blockade in the 0.14 and 0.28 mg/kg groups, additional patients were needed since all 5 patients in the 0.14 mg/kg group, and 3 of the 5 patients in the 0.28 mg/kg group, had their neuromuscular block reversed before the twitch tension had recovered to 90 per cent of control. Thus, an additional seven patients were given 0.14 or 0.28 mg/kg after intubation of the trachea under halothane anesthesia in the manner

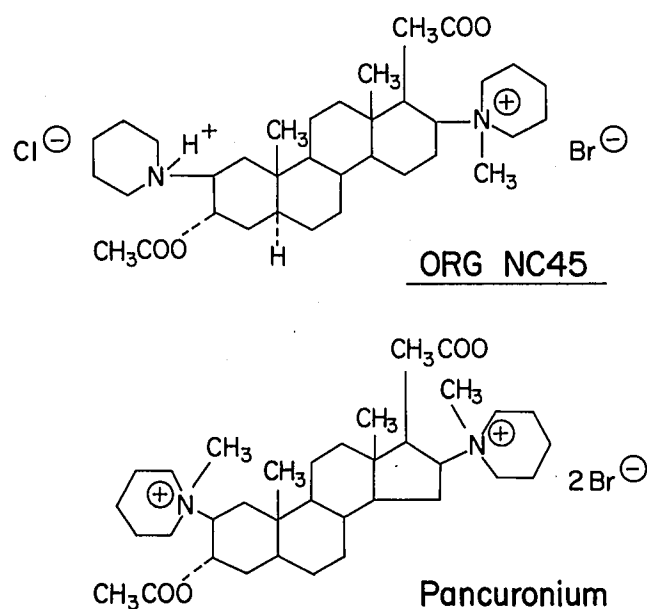


FIG. 1. Structures of ORG NC45 bromide and pancuronium bromide. Note the only difference in structure between the two drugs is that the nitrogen in the piperidine group to the left of the steroid nucleus is not quarternary and positively charged, whereas in pancuronium it is.

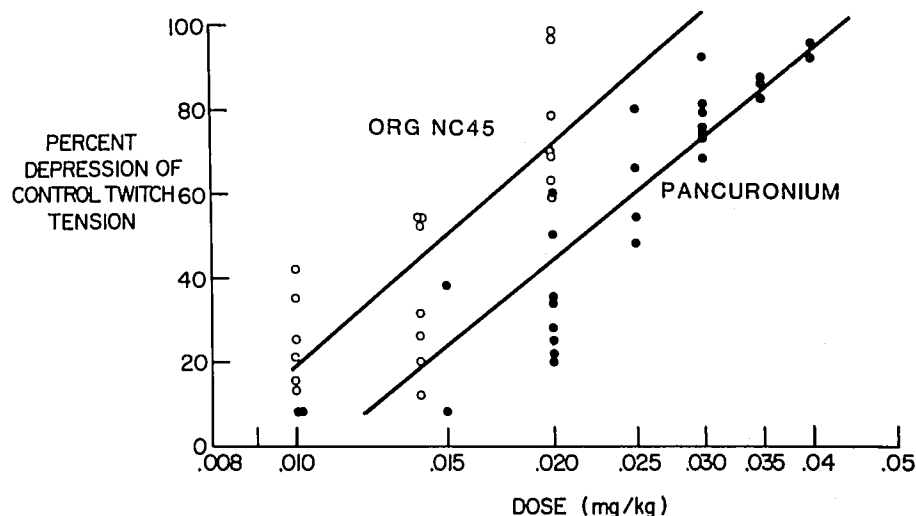


FIG. 2. Comparative dose-response curves obtained by simple linear regression of ORG NC45 and pancuronium data (plotted lotarithmically) under halothane anesthesia. Patient data points are shown for ORG NC45 (O) and pancuronium (●).

previously described. Five additional patients were studied in an identical manner except they received 0.1 mg/kg pancuronium, iv. These data were compared to the onset time and duration of action of 0.07 mg/kg ORG NC45, an equivalent dose.

Results

The ED_{50} of ORG NC45 was 0.015 mg/kg ($r = 0.80$) and 0.022 mg/kg ($r = 0.90$) for pancuronium, with a resultant potency ratio of 1.5 (0.022/0.015). The dose-response regression lines for ORG NC45 and pancuronium (Fig. 2) did not deviate from parallelism. Comparison of 0.02 mg/kg ORG NC45 and 0.03 mg/kg pancuronium, an equivalent dose, showed no significant difference in recovery times (table 2). The duration of action of ORG NC45 was shorter than that of pancuronium (table 2).

With repetitive doses, the duration of neuromuscular blockade with each subsequent dose of pancuronium increased (fig. 3). Although repetitive doses of ORG NC45 caused a slight increase in duration of neuromuscular blockade, the increases were signifi-

cantly less than those from pancuronium. Also, the absolute duration of neuromuscular blockade was significantly less with all doses of ORG NC45 when statistically compared to pancuronium ($P < 0.05$).

Neostigmine antagonized an ORG NC45 neuromuscular blockade. The interpolated values of neostigmine needed to reach 20, 50 and 80 per cent recovery of control twitch tension were slightly, but significantly, less than those doses of neostigmine previously reported to achieve the same levels of recovery after pancuronium blockade ($P < 0.01$) (fig. 4).⁶

Although endotracheal intubation was successful in all patients given 0.07 mg/kg ORG NC45, the conditions were not always optimal (table 3). We therefore conclude that the 'ideal endotracheal intubation dose of ORG NC45 is between 0.07 and 0.14 mg/kg. The doses of 0.07, 0.14, and 0.28 mg/kg ORG NC45 represent three, six, and nine times the ED_{90} , respectively (fig. 2). Though the onset times of an equivalent dose of ORG NC45, 0.07 mg/kg, tended to be shorter than that of pancuronium, 0.1 mg/kg, these differences were not statistically significant. The duration of

TABLE 2. Time Course of Action of ORG NC45 and Pancuronium

Drug	Dose (mg/kg)	Number of Patients	Per Cent Twitch Depression*	Onset Time* (Min)	Duration of Action* (Min)	Recovery Time* (Min)
ORG NC45	0.01	6	25 ± 5	6.7 ± 1.0	14 ± 5	N/A†
ORG NC45	0.014	7	36 ± 7	6.3 ± 0.6	16 ± 2	N/A
ORG NC45	0.02	7	76 ± 6	6.0 ± 0.31	27 ± 5‡	14.1 ± 2.9§
Pancuronium	0.03	10	89 ± 8	4.5 ± 0.4	65 ± 16	26 ± 8

* Values are means ± SEM.

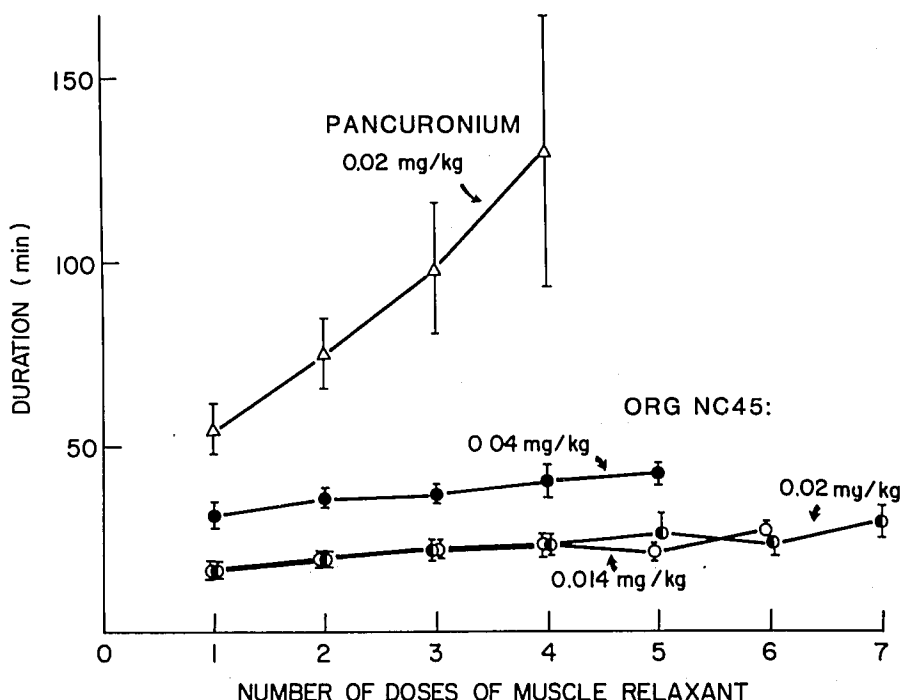
† N/A = Not applicable since neuromuscular block did not exceed 75 per cent depression of control muscle twitch.

‡ Duration significantly less ($P < 0.05$) for ORG NC45 than

that for pancuronium.

§ Mean value determined from three patients in whom neuromuscular block did not exceed 75 per cent depression of control muscle twitch.

FIG. 3. Effect of repetitive doses on duration of neuromuscular blockade seen with ORG NC45 and pancuronium. Each symbol and vertical bracket represents the mean \pm SEM, respectively, for that muscle relaxant dose number. Lines are drawn to enhance the visual interpretation.



action of ORG NC45 was at least one-third shorter than that of pancuronium (table 3).

The duration and recovery times in those patients who received halothane before ORG NC45 were combined with those of patients who received the same dose of ORG NC45 for endotracheal intubation before halothane was initiated because of the lack of a significant difference between them.

Although we state that 84 patients were studied, a total of 101 studies are listed. This apparent discrepancy is because 17 patients were used for two

studies. Those patients who received one dose of ORG NC45 for the dose response studies (fig. 2) were then used for the repetitive dose study (fig. 3).

Discussion

Our data from anesthetized patients are very similar to those found by others¹⁻³ in animals. Booij *et al.*² found ORG NC45 to be 1.6, 4.5, and 9.3 times more potent than pancuronium, metocurine and *d*-tubocurarine, respectively, in dogs. Krieg *et al.*³ found ORG

FIG. 4. Dose of neostigmine needed for 20, 50 and 80 per cent recovery of control muscle twitch tension for ORG NC45 and pancuronium (mean \pm SEM). The data for pancuronium are from Miller *et al.*⁶

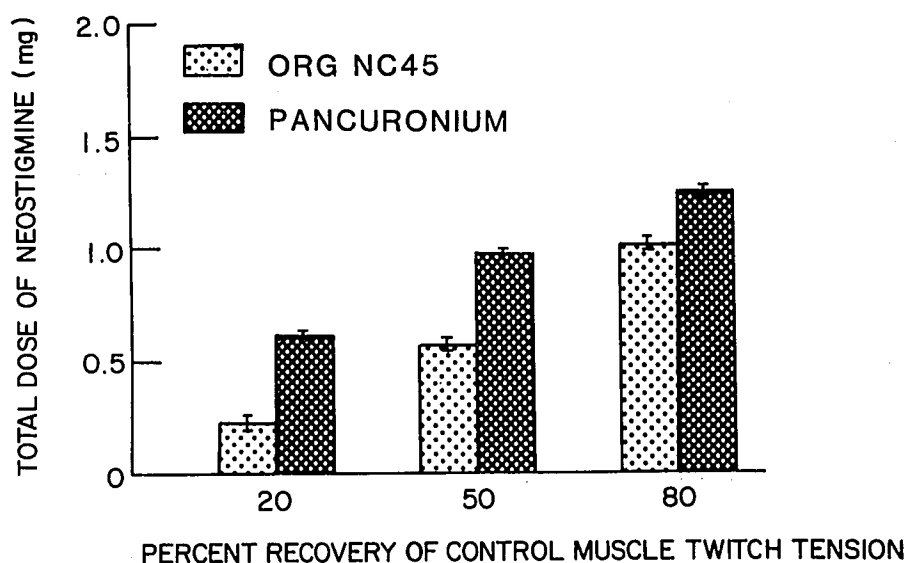


TABLE 3. Time Course of Action and Endotracheal Intubation Conditions with ORG NC45 and Pancuronium

Drug	Dose* (mg/kg)	Number of Patients	Onset Time† (min)	Duration of Action† (min)	Recovery Time† (min)	Endotracheal Intubation Score†
ORG NC45	0.07	11	3.8 ± 0.9	34 ± 8‡	8.0 ± 0.4‡	1.3 ± 0.4
ORG NC45	0.14	9	2.8 ± 0.1	104 ± 6	21 ± 1	0.4 ± 0.2§
ORG NC45	0.28	8	2.1 ± 0.4	174 ± 12	38 ± 5	0.0§
Pancuronium	0.10	5	5.3 ± 1	114 ± 21	35 ± 5	1.0 ± 0.3

* All doses caused a 100 per cent depression of twitch tension.

† Values are means ± SEM.

‡ Of the 11 patients studied, only 7 had the neuromuscular block terminate spontaneously long enough for recovery and duration

times to be obtained.

§ The intubation conditions were assessed in only 5 of these patients. The remaining patients received ORG NC45 after endotracheal intubation.

NC45 to be 1.74 times more potent than pancuronium in humans. We found ORG NC45 to be 1.5 times more potent than pancuronium. The duration of neuromuscular blockade with ORG NC45 was also significantly shorter than the other three muscle relaxants at a dose three times the ED₉₀.² We also found that ORG NC45 has a shorter duration of action than that of pancuronium when equivalent doses were compared (table 2). Of the four muscle relaxants that Booij *et al.*² studied ORG NC45 was the only one which did not have any significant cardiovascular effects. Although our study was not designed to evaluate the cardiovascular effects of ORG NC45, we, too, did not observe any change in blood pressure or heart rate.

In further work, Booij *et al.*⁷ showed the neuromuscular blockade of ORG NC45 to be reversible with neostigmine at doses similar to those required for reversal of pancuronium neuromuscular blockade. We found that ORG NC45 required similar or even slightly less neostigmine for reversal than pancuronium (fig. 4). Further study is required to determine if this difference in neostigmine requirements is significant.

The increase in duration of neuromuscular blockade from repetitive doses was greater with pancuronium than with ORG NC45 (fig. 3). This part of our study was designed to mimic and perhaps exaggerate the way muscle relaxants are sometimes administered clinically. Because the duration of neuromuscular blockade is minimally prolonged with repeated administration of ORG NC45, we believe that the likelihood of having a prolonged and possibly difficult to reverse neuromuscular blockade after repeated doses of a muscle relaxant will be attenuated with ORG NC45. The most likely explanation for this difference between pancuronium and ORG NC45 may be a difference in the pharmacokinetics of the two muscle relaxants. In rats, about 60 to 70 per cent of an injected dose of ORG NC45 and only 10–15 per cent of pancuronium appear in the bile within an hour after administration (personal observation).

Whether this is the route of elimination in humans and accounts for the shorter duration of action and the lesser increase in duration of repetitive doses of ORG NC45 remains to be determined.

Because of a duration of action which is at least one-third shorter than that of equivalent doses of pancuronium, ORG NC45 may be preferred for intubation of the trachea when a long duration of neuromuscular blockade is not desired. Although the onset times with these larger doses of ORG NC45 tended to be shorter (table 3), the differences were not statistically significant. Perhaps our experimental design did not accurately assess the time needed to reach satisfactory intubation conditions once the drug had been given. Agoston *et al.* (personal communication) found that satisfactory intubation conditions were present before complete abolition of the muscle twitch. If so, the onset time for satisfactory intubating conditions as defined by our study could be reduced by one or even two min for both ORG NC45 and pancuronium. However, because of a shorter duration of action than pancuronium and little or no cardiovascular effect, ORG NC45 may be considered for use in the rapid intravenous sequence technique of induction of anesthesia and endotracheal intubation as an alternative to succinylcholine or pancuronium.

In summary, ORG NC45 is a nondepolarizing muscle relaxant 1.5 times more potent than pancuronium. Although its onset time is similar to that of pancuronium, the duration of action is shorter. The prolongation of neuromuscular blockade after repeated doses is less with ORG NC45 than pancuronium, and neostigmine easily reverses an ORG NC45 neuromuscular blockade. The endotracheal intubation dose of ORG NC45 is between 0.07–0.14 mg/kg. No cardiovascular side effects were noted, even at the high doses of ORG NC45 used for endotracheal intubation. As Savarese and Kitz⁸ suggested, a lack of cardiovascular side effects or a shorter duration of action would make a new muscle relaxant having either property clinically

important, and with ORG NC45, both of these properties exist. From the results of this initial clinical study, we believe more intense clinical trials are indicated.

References

1. Durant NN, Marshall IG, Savage DS, et al: The neuromuscular and autonomic blocking activities of pancuronium, ORG NC45 and other pancuronium analogues in the cat. *J Pharm Pharmacol* 31:832-836, 1979
2. Booij LHDJ, Edwards RP, Sohn YJ, et al: Cardiovascular and neuromuscular effects of ORG NC45, pancuronium, metocurine and *d*-tubocurarine in dogs. *Anesth Analg (Cleve)* 59:26-30, 1980
3. Krieg N, Crul JF, Booij LHDJ: Relative potency of ORG NC45, pancuronium, alcuronium and tubocurarine in anaesthetized man. *Br J Anaesth* 52:783-788, 1980
4. Donlon JV, Ali HH, Savarese JJ: A new approach to the study of four nondepolarizing relaxants in man. *Anesth Analg (Cleve)* 53:934-939, 1974
5. Zar JH: *Biostatistical Analysis*. Englewood Cliffs, Prentice-Hall, 1974, pp 109-114, 133-139, 230-232
6. Miller RD, Larson CP, Way WL: Comparative antagonism of *d*-tubocurarine-, gallamine-, and pancuronium-induced neuromuscular blockades by neostigmine. *ANESTHESIOLOGY* 37: 503-509, 1972
7. Booij LHDJ, van der Pol F, Crul JF, et al: Antagonism of ORG NC45 neuromuscular blockade by neostigmine, pyridostigmine and 4-aminopyridine. *Anesth Analg (Cleve)* 59:31-34, 1980
8. Savarese JJ, Kitz RJ: The quest for a short-acting nondepolarizing neuromuscular blocking agent. *Acta Anaesth Scand (Suppl)* 53:43-58, 1973

Errata

The article, "The Dynamic Responses of Liquid-filled Catheter Systems for Direct Measurements of Blood Pressure" (*ANESTHESIOLOGY* 53:498-504, 1980), contained several errors. Trantec® is spelled incorrectly (Tranek®) on pages 499 and 501. In the footnotes on page 499, Jelco is spelled Telco, and Tygon® is a product of Norton Health Care Products, Akron, Ohio 44309, not North American Instrument Company.