The Clinical Pharmacology of Meptocurine: Dimethyltybocurarine Revisited

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The clinical pharmacology of meptocurine (formerly dimethyltybocurarine) was studied in 55 ASA class I–II patients. Evoked force of thumb adduction was measured at 0.15 Hz during nitrous oxide–morphine–thiopental anesthesia. The ED₉₀ and ED₅₀ for twitch inhibition were 0.13 and 0.28 mg/kg. The dose–response curve did not differ significantly from parallelism with curves for pancuronium and d-tubocurarine. Potency ratios were 0.25 and 1.8 versus pancuronium and d-tubocurarine. The speed of onset and the duration of meptocurine-induced block at high dosage employed for tracheal intubation did not differ significantly from the corresponding values obtained for approximately equipotent doses of pancuronium and d-tubocurarine. Meptocurine, 0.3 mg/kg, produced 96.1 per cent mean twitch depression within 4.8 ± 0.6 (SEM) minutes. Recovery to 25 per cent of the control twitch height took 82.4 ± 12.0 (SEM) minutes at this dose. Doses in the range 0.2–0.3 mg/kg are recommended for the production of abdominal relaxation during nitrous oxide–narcotic–thiopental anesthesia. Jaw relaxation was sufficient at 0.3 mg/kg for smooth tracheal intubation in 13 of 15 patients. Neostigmine antagonism of meptocurine-induced block required dosage and timing similar to those found by Katz in previous studies of d-tubocurarine and pancuronium.30,20

Meptocurine produced no significant change in heart rate or mean arterial pressure in doses as high as 0.3 mg/kg. At 0.4 mg/kg, heart rate increased 18 per cent and arterial pressure decreased 6.3 per cent. These changes were statistically significant, but generally not clinically important, and reflect a short-lasting (5–10 min) response suggestive of histamine release, which occurred in six of 18 subjects who received this dose. (Key words: Neuromuscular relaxants, meptocurine; Heart, cardiovascular effects; Sympathetic nervous system, ganglionic blockade; Histamine release; Antagonists, neuromuscular relaxants, reversal.)

Meptocurine, a nondepolarizing neuromuscular blocking agent formerly called dimethyltybocurarine, is a trimethylated derivative of d-tubocurarine.1,2 The neuromuscular blocking potency of meptocurine in animals is much greater than that of d-tubocurarine.3,4§ Meptocurine, on the other hand, is considerably less potent than its parent compound in its ability to inhibit autonomic responses and to release histamine.3–5,8,9 In fact, its only important side effect appears to be histamine release.8 Therefore, the difference in dosage necessary to produce neuromuscular versus autonomic inhibition, i.e., the “autonomic margin of safety,” is much greater for meptocurine than for d-tubocurarine.8 The clinical cardiovascular and hemodynamic effects of meptocurine, therefore, appear to be much less striking than those of d-tubocurarine.7–9

Meptocurine was introduced into clinical practice (as dimethyltybocurarine) in 1948, by V. Stoelting, Graf and Vieira10 and by Wilson, Gordon, and Raffan.11 Despite its relative lack of cardiovascular effects, the accumulation of data regarding the human neuromuscular pharmacology and the clinical use of meptocurine since that time has been scant, and the drug is probably not in widespread use by anesthesiologists at present. The lack of precise information defining the clinical neuromuscular pharmacology of meptocurine despite its apparent cardiovascular advantages has prompted the following investigation.

The study was specifically designed 1) to construct a dose–response curve at a low stimulus rate (0.15 Hz) for neuromuscular blockade by bolus doses of meptocurine in healthy subjects during nitrous oxide–narcotic–barbiturate anesthesia; 2) to correlate these data with clinical conditions of relaxation, particularly for tracheal intubation; 3) to measure the duration of neuromuscular block produced by meptocurine; 4) to define the neostigmine dosage requirement and timing for reversal of meptocurine block; 5) to define the cardiovascular dose–response to the drug; 6) to establish the dosage at which signs suggestive of histamine release occur in man.

Methods

Fifty-five adult ASA class I–II patients of either sex scheduled to undergo various elective surgical procedures were studied. Their ages ranged from 19 to 67 years (mean 42.3 ± 2.1, SEM). They weighed 43 to

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100 kg (mean 64.3 ± 1.8, SEM). All subjects were informed of the purpose of the study and gave consent. All were free of known neuromuscular, cardiovascular, and renal disease.

Each subject received morphine sulfate (0.15 mg/kg) and scopolamine hydrobromide (0.003 mg/kg) intramuscularly as premedication approximately an hour prior to being transported to the operating room. This type of premedication was used to promote slow baseline heart rates, i.e., a relatively vagotonic state. Any effect of metocurine resulting in a heart rate increase might thereby be accentuated.

Anesthesia was induced with thiopental, 3–5 mg/kg, given intravenously (iv). Each patient then received nitrous oxide and oxygen (4 liter:2 liter mixture) by mask in a semiclosed system. Ventilation was assisted or controlled manually to maintain end-tidal P\textsubscript{CO\textsubscript{2}} in the range 35–45 torr (checked by end-tidal gas analysis in a Beckman LB-1 analyzer and/or arterial blood-gas determination). Supplemental morphine, 0.1–0.2 mg/kg, or thiopental, 2–4 mg/kg, was given iv to maintain a stable level of light anesthesia in the absence of surgical stimulation, as indicated by pupillary constriction, tolerance of an oral airway, regular respirations at 10–12/min, and stable heart rate and arterial pressure in the normal range. Rectal temperatures, measured by a Yellow Springs thermoprobe, ranged from 34.5 to 37 C.

The electrocardiogram (lead I) was monitored continuously on an oscilloscope. Arterial pressure was determined once per minute by cuff or, when indicated by the surgical procedure, it was recorded continuously through a Statham P23DI transducer from an indwelling 18-gauge cannula placed percutaneously in a radial artery. Heart rate was recorded continuously by a Grass model 7P44 tachograph triggered either by the R wave of the electrocardiogram or by the arterial pulse wave.

The ulnar nerve was stimulated at the wrist through 22-gauge steel needle electrodes at 0.15 Hz with square-wave pulses 0.2 msec in duration. The stimuli were delivered at supramaximal voltage by a Grass S88 stimulator through an S1U5 isolation unit. Train-of-four stimulation (2.0 Hz for two seconds) was applied at random during metocurine block to evaluate fade, indicating the mechanism of block. Both train-of-four and tetanic (50 Hz for five seconds) stimulation were used to evaluate adequacy of recovery from block, after reversal. Evoked force of thumb adduction was measured via a Grass FT10 force-displacement transducer.

After a five- to ten-minute stable control period, metocurine was administered iv as a single rapid bolus. Only a single dose of metocurine was studied in each patient. Surgical stimulation began and tracheal intubation was accomplished only after the maximum neuromuscular and cardiovascular responses of the dose under study had been attained.

Neostigmine, 0.03–0.075 mg/kg, and atropine, 0.02–0.04 mg/kg, were given iv as a mixture to antagonize residual metocurine block at the termination of the surgical procedure. The high dosages (0.075 mg/kg neostigmine and 0.04 mg/kg atropine)
were used only when 95 per cent or more twitch depression was present at the time of reversal.

To permit comparative evaluation of metocurine with pancuronium and \( d \)-tubocurarine, dose–response curves for the latter drugs were constructed from 53 (pancuronium) and 52 (\( d \)-tubocurarine) ASA class I–II patients in whom neuromuscular transmission was studied under the same conditions described above for metocurine.\(^4\)

Dose–response curves for neuromuscular blockade were plotted on log-probit coordinates. Best-fit straight lines were determined by probit regression by computer. Goodness of fit of the data to a straight line on log-probit scales was evaluated by the chi-square test. Testing of the dose–response curves for parallelism was done by the method of Litchfield and Wilcoxon.\(^2\) Statistical comparison of the durations of action of approximately equipotent doses of metocurine, \( d \)-tubocurarine and pancuronium used to provide profound relaxation for tracheal intubation was done by analysis of variance. Statistical differences were considered significant when \( P < 0.05 \).

**Results**

Metocurine produced a typical nondepolarizing block, evidenced by absence of muscular fasciculation during onset, marked fade on tetanic and train-of-four stimulation during block, and marked post-tetanic twitch facilitation. Metocurine is approxi-

\( ^4 \text{Drugs used were metocurine iodide (Lilly), \( d \)-tubocurarine chloride (Abbott), pancuronium bromide (Organon), and neostigmine methylsulfate (Roche).} \)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (mg/kg)</th>
<th>Number of Subjects</th>
<th>Per Cent Twitch Inhibition Mean ± SEM (Range)</th>
<th>Time to Maximum Effect, Min Mean ± SEM (Range)</th>
<th>Time for Twitch Recovery to 25 Per Cent of Control, Min Mean ± SEM (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metocurine</td>
<td>0.1</td>
<td>11</td>
<td>32.0 ± 9.7 (2–96)</td>
<td>5.4 ± 0.4 (3.5–8.0)</td>
<td>—</td>
</tr>
<tr>
<td>Metocurine</td>
<td>0.2</td>
<td>11</td>
<td>79.5 ± 7.4 (17–99)</td>
<td>6.8 ± 0.3 (5.0–7.5)</td>
<td>—</td>
</tr>
<tr>
<td>Metocurine(^+)</td>
<td>0.3</td>
<td>15</td>
<td>96.1 ± 2.0 (70–100)</td>
<td>4.8 ± 0.6 (1.5–8.0)</td>
<td>82.4 ± 12.0 (42–167)</td>
</tr>
<tr>
<td>Metocurine(^+)</td>
<td>0.4</td>
<td>18</td>
<td>98.8 ± 0.5 (92–100)</td>
<td>4.1 ± 0.5 (1.5–10.0)</td>
<td>106.9 ± 10.5(^+) (50–162)</td>
</tr>
<tr>
<td>( d )-Tubocurarine(^+)</td>
<td>0.6</td>
<td>12</td>
<td>97.3 ± 0.6 (85–100)</td>
<td>5.7 ± 1.1 (1.5–15.0)</td>
<td>80.5 ± 6.9 (48–108)</td>
</tr>
<tr>
<td>Pancuronium(^+)</td>
<td>0.1</td>
<td>13</td>
<td>99.3 ± 0.4 (97–100)</td>
<td>4.0 ± 0.6 (1.5–7.5)</td>
<td>99.3 ± 15.0 (48–174)</td>
</tr>
</tbody>
</table>

\(^*\) Times listed are from the moment of injection.

\(^+\) Doses commonly used for tracheal intubation. There was no significant difference among times to maximum effect at these doses.

\(^+\) Significantly longer than with \( d \)-tubocurarine, 0.6 mg/kg, and metocurine, 0.3 mg/kg (\( P < 0.05 \)), but not pancuronium, 0.1 mg/kg.
Table 2. Rate of Antagonism of Metocurine Block by Neostigmine

<table>
<thead>
<tr>
<th>Depth of Block</th>
<th>Number of Subjects</th>
<th>Per Cent Twitch Inhibition Mean ± SEM (Range)</th>
<th>Dose Neostigmine mg/kg</th>
<th>Reversal Time, Min Mean ± SEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate</td>
<td>7</td>
<td>48.6 ± 1.8 (45–55)</td>
<td>0.05</td>
<td>5.5 ± 0.5</td>
</tr>
<tr>
<td>Deep</td>
<td>6</td>
<td>79.0 ± 1.8 (75–85)</td>
<td>0.05</td>
<td>7.6 ± 0.4†</td>
</tr>
<tr>
<td>Very deep</td>
<td>4</td>
<td>98.0 ± 2.3 (95–100)</td>
<td>0.075</td>
<td>17.5 ± 2.0</td>
</tr>
</tbody>
</table>

* Each subject received a single intravenous bolus of neostigmine together with atropine, 0.02–0.04 mg/kg. Times were measured from the point of injection of neostigmine to the return of twitch to 98 per cent of the control height.
† Significantly longer (*P < 0.05*) than the corresponding time at moderate depth of block.

Table 3. Effect of Neostigmine Dose on Rate of Antagonism of Metocurine Block

<table>
<thead>
<tr>
<th>Number of</th>
<th>Per Cent Twitch Inhibition Mean ± SEM</th>
<th>Dose of Neostigmine mg/kg</th>
<th>Reversal Time, Min Mean ± SEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>52.0 ± 3.3</td>
<td>0.03</td>
<td>9.1 ± 1.1</td>
</tr>
<tr>
<td>5</td>
<td>51.6 ± 3.3</td>
<td>0.06</td>
<td>6.1 ± 0.5†</td>
</tr>
</tbody>
</table>

* Each subject received a single intravenous bolus of neostigmine together with atropine, 0.02–0.04 mg/kg. Times were measured from the point of injection of neostigmine to the return of twitch to 98 per cent of the control height.
† Significantly shorter than the corresponding time using 0.03 mg/kg neostigmine (*P < 0.05*) (statistical comparisons by unpaired *t* test).

arterial pressure 6.3 per cent and increased heart rate 18 per cent (fig. 2, table 4). These changes were statistically significant (*P < 0.01* and *P < 0.001*, respectively). Twelve of the 18 subjects who received metocurine, 0.4 mg/kg, however, manifested stable cardiovascular responses, mean arterial pressure and heart rate not being significantly altered in this subgroup.

The statistically significant changes found with 0.4 mg/kg metocurine were probably due to a response suggestive of systemic histamine release that occurred in the remaining six of 18 patients who received this dose. This response was defined as the development of at least two of the following criteria within 1–2 minutes after metocurine administration: 1) an erythematous rash on the face and upper trunk; 2) tachycardia, with increase of heart rate to more than 125 per cent of the control value; 3) hypotension, with decrease of mean arterial pressure to less than 80 per cent of control. These apparent signs of histamine release were always brief, spontaneous dissipation occurring within five to ten minutes. Heart rates after this time generally were somewhat slower than during the control period. For example, 45 minutes after metocurine administration in all patients, heart rates averaged 67.7 ± 2.2 (SEM) beats/min, versus 74.3 ± 1.6 during the control period. Bronchospasm did not occur in any patient.

In a few patients, erythema, hypotension and tachycardia occurred during continuous radial arterial pressure recording, thus permitting the timing and pattern of this response to be measured. The syndrome occurred 1–2 minutes after injection of metocurine, consistent with the "delayed depressor response" described by Paton.13

Discussion

Metocurine was synthesized as a derivative of *d*-tubocurarine by King14 in 1935. Early studies15–18 disclosed that the agent was 0.5 to 10 times as potent a neuromuscular blocking agent as *d*-tubocurarine in several mammalian species, but probably not more active than the parent compound in blocking autonomic ganglia or releasing histamine.19–21 Carefully quantitated comparisons of the autonomic effects of the two agents, however, were not carried out.

Initial reports of the clinical use of metocurine estimated its potency at two to ten times that of *d*-tubocurarine; its duration of action was thought to be a little shorter.10,22,23 Less histamine release was found,11 and no decrease in blood pressure could be attributed to the drug.10

These investigations appear to have generated little interest in metocurine, and its clinical use has since been probably much less widespread than that of *d*-tubocurarine. Perhaps an important reason for this is the oft-quoted remarks of Moge and Trenvan23 regarding the complexity of the metocurine molecule, the difficulty in synthesis of the drug, and the possible problem of the batch-to-batch consistency of potency. This is no longer troublesome, since improved understanding of the chemistry of the curare alkaloids now permits accurate standardization of production samples.††

Recent studies have quantitated major differences

** Called "delayed" because the histamine-releasing agent must first reach vascular mast cells, from which histamine and other vasoactive substances are displaced. The vascular response to histamine becomes apparent within several circulation times after the initial intravenous injection of the histamine-releasing agent. It is not immediate (one circulation time) as after a direct-acting agent.
†† Personal communication. James C. Boylan, Ph.D., Head, Parenteral Products Development Division; Lowell Lowary, Ph.D., Department Head, Pharmacological Testing; John Woodside, Ph.D., Director of Control Laboratories, Eli Lilly and Company, Indianapolis, Indiana.
in the autonomic and histamine-releasing properties of metocurine and \(d\)-tubocurarine. Hughes and Chapple\(^3\) have shown that metocurine has no inhibitory effect upon sympathetic responses (nictitating membrane contraction) in the cat in doses as high as 1.0 mg/kg, or approximately 30 times the amount required for nearly complete neuromuscular blockade in their study. McCullough et al.\(^6\) found no significant effect of metocurine, 0.4 mg/kg, upon spontaneous postganglionic sympathetic activity or plasma histamine levels in the cat. These results were in marked contrast to data obtained in a prior similar study of \(d\)-tubocurarine.\(^5\) We have shown\(^\#\#\) that metocurine is 14 times more potent than \(d\)-tubocurarine as a neuromuscular blocking agent in the cat but three times less potent in its ability to block ganglia or release histamine.

The 1.8 to 1 ratio of neuromuscular blocking potency of metocurine to \(d\)-tubocurarine in man determined in this study is somewhat lower than that suggested in the literature,\(^10\) and very similar to the ratio of 1.7 to 1 obtained by us in another study.\(^37\) Although the potency ratios for the two drugs are similar in the two studies, the absolute values for \(ED_{50}\) obtained in the present study are about 50 per cent higher than those found in our earlier investigation.\(^27\) The difference exists because the faster stimulus rate used in the earlier study (0.25 versus 0.15 Hz) increases the apparent potency of nondepolarizing relaxants, shifting the dose–response curve to the left and lowering the \(ED_{50}\) derived from the curve.\(^\$\$\) Stimulation at slow rates (0.15–0.10 Hz) does necessitate a higher dosage of neuromuscular blocking agent in order to produce a given inhibition of twitch. Greater clinical relaxation, because of the

\[\text{Fig. 2. Neuromuscular and cardiovascular effects of metocurine in ASA class I–II patients during nitrous oxide–morphine–thiopental anesthesia. Indirectly elicted thumb twitch (0.15 Hz) was recorded simultaneously with heart rate (by tachograph) and arterial pressure (by cuff or directly via radial cannula). Data points represent maximum changes from control values. Metocurine was administered as a rapid bolus intravenously to four groups of subjects. Only one dose of metocurine was studied in each individual. ** } P < 0.01; *** P < 0.001.\]

higher dosage, will result when relaxant administration is guided by peripheral nerve stimulation at these rates. The present study indicates that the most profound clinical relaxation usually necessary (i.e., for smooth tracheal intubation) corresponds to 95–98 per cent twitch inhibition at 0.15 Hz. This amount of relaxation probably cannot routinely be achieved with-

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### Table 4. Cardiovascular Effects of Metocurine

<table>
<thead>
<tr>
<th>Dose (mg/kg)</th>
<th>Number of Subjects</th>
<th>Heart Rate* Per Cent of Control Mean ± SEM (Range)</th>
<th>Mean Arterial Pressure* Per Cent of Control Mean ± SEM (Range)</th>
<th>Response Suggestive of Histamine Release Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1</td>
<td>11</td>
<td>98.4 ± 2.5   (86–117)</td>
<td>96.6 ± 2.1   (85–105)</td>
<td>0</td>
</tr>
<tr>
<td>0.2</td>
<td>11</td>
<td>98.2 ± 2.5   (89–111)</td>
<td>97.7 ± 1.2   (92–104)</td>
<td>0</td>
</tr>
<tr>
<td>0.3</td>
<td>15</td>
<td>103.5 ± 3.0  (91–136)</td>
<td>99.3 ± 3.1   (60–111)</td>
<td>1/15 (6.6 per cent)</td>
</tr>
<tr>
<td>0.4</td>
<td>18</td>
<td>118.0 ± 4.4* (92–150)</td>
<td>99.7 ± 2.0*  (77–105)</td>
<td>6/18 (33.3 per cent)</td>
</tr>
</tbody>
</table>

Data represent maximum changes from control values, in the absence of stimulation. Response suggestive of histamine release was defined as the occurrence in any individual of two or more of the following: erythematous rash; heart rate increase to more than 125 per cent of control; decrease in mean arterial pressure to less than 80 per cent of control. See text for further details.

\*Mean control heart rate = 74.3 ± 1.6 beats/min.

\**Mean control mean arterial pressure = 83.0 ± 1.9 torr.

\# P < 0.01.

\#\$ P < 0.001.
out abolishing twitch during nitrous oxide–narcotic–barbiturate anesthesia when stimulus rates of 0.25 Hz or more are used. Monitoring at 0.15–0.1 Hz therefore has the advantage of permitting correlation of twitch depression with the entire range of clinical relaxation, without abolition of the observed evoked response. We consequently prefer monitoring at these rates of stimulation.

The ED₉₀ for twitch inhibition of 0.28 mg/kg reported in this study agrees closely with a dose (0.3 mg/kg) recently found by Hughes, Ingram and Payne⁹ to produce 82 to 100 per cent twitch inhibition at 0.1 Hz in six patients during nitrous oxide–pentazocine–thiopental anesthesia. This is three times the dosage (as high as approximately 0.1 mg/kg) recommended for use with nitrous oxide anesthesia by the manufacturer. The latter figure is probably derived from earlier studies⁸,¹¹ and should be updated.

The marked dissimilarity in the relative neuromuscular blocking potencies of metocurine versus d-tubocurarine in the cat and man (14.0 in the cat vs 1.8 in man) is one of the more extreme examples of species differences among neuromuscular blocking drugs known to the authors. Earlier clinical investigators, expecting roughly similar potencies of metocurine in the cat and man (since this is true of d-tubocurarine)²⁸ may have overestimated the potency of metocurine in man.

At equipotent high bolus dosages used for intubation, the respective durations of action of metocurine, d-tubocurarine, and pancuronium in man appear similar (table 1). The same conclusion was reached by us in a different comparison of the three agents⁵⁷ at lower dosages.

In man, the response to metocurine, like responses to other nondepolarizing relaxants,²⁹,³⁰ shows marked individual variation (table 1). For this reason, it seems appropriate to administer a small dose (0.05–0.1 mg/kg) initially and to evaluate the response, preferably with a nerve stimulator, before giving larger amounts for full relaxation. The use of such test doses of nondepolarizing relaxants has been advocated by others.²⁹,³² This practice may prevent overdosage, prolonged block, and difficulty with reversal. This is particularly important when metocurine or a similarly long-acting nondepolarizing relaxant is to be employed during a procedure expected to take 45 to 60 minutes.

Metocurine produced 90 to 100 per cent twitch inhibition in half (8 of 16) the individuals who received 0.2 mg/kg. This degree of block was found to correlate well with good clinical relaxation. Katz,²⁹,³¹ in studies of pancuronium and d-tubocurarine during nitrous oxide–narcotic–barbiturate anesthesia, also concluded that 90 per cent twitch depression corresponded to good relaxation during this type of anesthesia. Nearly all subjects (13 of 15) had 95–100 per cent twitch depression after 0.3 mg/kg metocurine; jaw relaxation was sufficient in this subgroup to allow easy laryngoscopy and tracheal intubation. We therefore recommend 0.2 mg/kg as an appropriate dose of metocurine for good abdominal relaxation during nitrous oxide–narcotic–barbiturate anesthesia. This dose may be increased to 0.3 mg/kg to include individuals not sufficiently relaxed at the lower dose. Similarly, we recommend 0.3 mg/kg for tracheal intubation in most patients. In the small proportion of individuals in whom this amount is not sufficient, the dose may be increased to 0.4 mg/kg. The latter dose produced profound jaw relaxation and absence of reflex laryngeal closure within four minutes, such that intubating conditions were excellent in all cases. Recovery of the twitch to 25 per cent of control takes about 24 minutes longer with 0.4 mg/kg metocurine than with 0.3 mg/kg (table 1). The larger dose should therefore be used for operative procedures expected to take longer than 150 minutes.

Dosages and times listed in table 1 refer only to the use of metocurine during nitrous oxide–narcotic–barbiturate anesthesia. No data regarding the neuromuscular blocking action of metocurine in the presence of potent anesthetic vapors are available. We may speculate, however, that reduced dosage may be necessary, perhaps proportional to ratios summarized by us for d-tubocurarine.³³

Comparison of our data (table 3) for reversal of the action of metocurine with the studies of Katz²⁹,³⁰ suggests that the neostigmine requirements for reversal of metocurine, d-tubocurarine, and pancuronium are approximately equal. The speeds of reversal by neostigmine of comparable depths of block produced by the three drugs also appear similar.

The neuromuscular blocking action of metocurine does not seem to differ importantly from those of other nondepolarizing agents. Its cardiovascular effects in man, however, are distinctly different and clinically advantageous. Metocurine does not block cardiac muscarinic receptors,³⁴ and therefore does not produce tachycardia in the absence of histamine release. Its lack of hypotensive action in man is due to significantly weaker ganglionic-blocking and histamine-releasing potencies than those of d-tubocurarine.³,⁵,⁶,⁴⁴

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Although we were able to demonstrate a modest response suggestive of histamine release by metocurine in 33 per cent of the individuals who received 0.4 mg/kg, this very large dose was given as a single rapid bolus, since our study was designed to accentuate any side effects of metocurine. The intensity of the histamine-release response depends upon the rapidity of administration of a histamine-release substance. Slower administration of metocurine, as is customary with d-tubocurarine, might minimize this effect and facilitate the achievement of relaxation without significant cardiovascular change. This might be important in patients who have poorly compensated circulatory states. Some indication of this is apparent in the recent work of Zaidan et al., who administered metocurine, 0.35 mg/kg, over a three-minute period to patients with coronary-artery disease. The latter were receiving a beta-adrenergic blocking drug and were to undergo coronary-artery bypass grafting during nitrous oxide-morphine (0.5 mg/kg) anesthesia. Metocurine produced no significant change in heart rate or mean arterial pressure. Cardiac output increased 26 per cent due to increased stroke volume in the face of slightly lowered peripheral resistance. These hemodynamic changes might be viewed as beneficial, since they imply improved myocardial efficiency and emphasize the potentially most important area of clinical utility of metocurine.

Since metocurine does not cause important cardiovascular changes, the drug may be the relaxant of choice in the administration of anesthesia to patients who have cardiac disease. For example, in coronary-artery disease, aortic stenosis, or hypertensive cardiovascular disease, rate-pressure product increases or hypotensive episodes might precipitate myocardial ischemia. The lack of a vagolytic (cardiac m miscarpirine) blocking action of metocurine and its weak ganglionic-blocking and histamine-releasing actions may be more desirable in these patients than the vagolytic effects of gallamine and pancuronium and the more powerful ganglionic-blocking and histamine-releasing properties of d-tubocurarine.

In mitral stenosis, heart rate increases may seriously decrease left ventricular filling, decreasing stroke volume and cardiac output. The lack of a vagolytic action of metocurine may also be advantageous in this situation.

References