The Muscle Relaxants and Renal Excretion

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Neuromuscular transmission was observed in 11 patients undergoing operation while in terminal renal failure. In 6 patients d-tubocurarine was used to produce abdominal relaxation and prolonged paresis was not encountered. In 5 patients in whom gallamine was used, there was evidence of persistent paresis in three instances. Possible differences between the metabolism of d-tubocurarine and gallamine are discussed. The recommendation is made that gallamine is contraindicated in the presence of poor renal function. There does not appear to be any evidence that d-tubocurarine is contraindicated in such cases.

In the past few years, a variety of reports have appeared suggesting an association between poor renal function and prolonged action of muscle relaxants.¹⁻⁶ In most of these cases gallamine triethiodide has been implicated.

The duration of paresis in some of these reports was very long. In one instance, the paresis lasted 36 hours and in another the patient was unable to breathe for five days after gallamine, 120 mg. All these patients had one thing in common—anuria or poor renal function. However, apart from observing muscle weakness, no attempt was made to determine the extent of neuromuscular block in these patients.

The concept that renal excretion per se can influence the duration of action of muscle relaxants in man is an interesting and exciting one; surprisingly enough, very few studies have been made along these lines even in the experimental animal. Goodman and Gilman and Foldes imply that the renal route is the main pathway of excretion of gallamine, but conclusive demonstration of this occurrence in man has not been provided.

Recently, we were presented with the opportunity of studying drug action in a group of patients undergoing bilateral nephrectomy in preparation for renal transplantation at a later date. These patients had nonfunctioning kidneys. At our institution, both kidneys are removed some days prior to the insertion of a renal homograft. It has been our practice to use a light plane of general anesthesia together with a muscle relaxant for this type of operation. In the absence of functioning renal tissue (i.e., bilateral nephrectomy) it follows that the relaxant drug cannot be renally excreted. We postulated, therefore, that if renal excretion does play any part in determining the duration of action of these relaxant drugs, it should be clearly evident in these cases.

Method

Eleven patients undergoing bilateral nephrectomy (and splenectomy) or exploration of renal tissue in the presence of anuria were studied. In each instance there was absence of renal function both before and after operation. As far as possible preoperative drugs and antibiotics were reduced to the minimum (table 1). Induction of anesthesia was achieved with thiopentone, cyclopropane, or nitrous oxide and oxygen. Complete muscle paralysis for intubation was obtained with succinylcholine chloride (40–60 mg.). Anesthesia was maintained with a nitrous oxide–oxygen mixture (6:2 liters/minute); ventilation was controlled. Neuromuscular transmission was monitored before, during and after the operation either with a peripheral nerve
stimulator, or an electromyograph. In each case, the presence of normal neuromuscular transmission was established before the administration of the non-depolarizing relaxant. The signs used to define the presence of a non-depolarization block were: (1) Fade of successive muscle responses at both twitch (1/second) and tetanic (50/second) rates of nerve stimulation. (2) Post-tetanic facilitation, after a five-second burst of tetanic stimulation. (3) Improvement of neuromuscular transmission following the administration of an anti-cholinesterase drug. All patients were observed for several days postoperatively in the Intensive Care Unit.

Results

A summary of the results obtained in 11 patients without renal function is given in table 2. Certain aspects, however, need further elaboration.

*d-Tubocurarine Series* (Cases 1–6). In 6 patients (5 male, 1 female) who received *d*-tubocurarine, the paralysis was easily reversed with neostigmine (Prostigmine) at the end of the operation. No subsequent signs of paresis (i.e., recurarization) were observed during the postoperative period. For example, in case 3, though the patient was anuric both before operation and for two days afterwards (finally requiring hemodialysis), there was evidence of some spontaneous recovery from the drug; following reversal with neostigmine there were no further signs of recurarization.

*Gallamine Series* (Cases 7–11). Of 5 patients (1 male, 4 female) who received gallamine, three showed evidence of persistent neuromuscular block, viz:

Case 8. This 13 year old girl underwent the operation of bilateral nephrectomy and splenectomy. She received a total dose of gallamine of 110 mg. in 1½ hours. By the end of the operation spontaneous respiration had returned. The last dose of gallamine had been given 40 minutes previously and the respiratory minute volume (measured by a Wright respirometer) was 9 liters/minute, although the hypothenar muscles still showed evidence of a non-depolarizing block. In view of the adequate respiratory exchange we decided to allow the neuromuscular block to wear off naturally, without anticholinesterase therapy. One hour later, however, there was no obvious recovery from the block, and the patient developed an episode of respiratory obstruction owing to a combination of copious secretions and relaxed jaw muscles. Upon the administration of neostigmine (2.5 mg.), there was a dramatic improvement in muscle tone and no further paresis was observed. The course in this patient illustrates that, despite an interval of one hour and forty minutes after the last dose of gallamine, there was little evidence of spontaneous recovery of neuromuscular transmission.

Case 9. This 19 year old girl, weighing 50 kg., underwent the operation of bilateral nephrectomy and splenectomy prior to renal transplantation. She received gallamine, 110 mg., over a period of 1½ hours. At the end of the operation, a severe degree of neuromuscular block was present. Neostigmine 3.0 mg., with atropine 1.0 mg., were given in divided doses. Five minutes later the respiratory minute volume was 6.0 liters/minute and the amplitude of the electromyogram had returned to 95 per cent of the preoperative value. Following return of consciousness, the minute volume was maintained and the patient was able to talk and to move her legs and arms freely. Her condition was considered very satisfactory.

In the intensive care unit the vital signs remained stable for the next few hours. The patient was able to talk but remained relatively immobile with long periods of drowsiness. No evidence of increasing neuromuscular block was obtained up to three hours postoperatively.

On waking next morning, she complained of blurred vision and generalized weakness. On examination there was marked ptosis of both eyelids and severe generalized weakness in all the limbs and an inability to raise the head. Electromyography revealed the recurrence of the signs of a non-depolarization block (fade and posttetanic facilitation). Following the intravenous injection of edrophonium (Tensilon) 10 mg. there was a dramatic improvement in vision and muscle power. The electromyographic pattern returned to normal with complete absence of the signs of a non-depolarization block. After a few minutes, as was to be expected, the effect of this anticholinesterase therapy started to wane, and an intramuscular injection of neostigmine 1.25 mg. with atropine 0.5 mg. was given. The spectacular improvement returned and, whereas before therapy she had lain relatively immobile, the patient was now able to raise her legs and lift her arms above her head, even to read the newspaper. Recovery was maintained for about six to eight hours, after which the signs of minimal muscle weakness insidiously became apparent.

Thirty hours after operation generalized weakness and diplopia had again returned, and the electromyogram showed the characteristic signs of a non-depolarization block. A further intramuscular dose of neostigmine 1.25 mg. with atro-
<table>
<thead>
<tr>
<th>Case</th>
<th>Preop. Drugs</th>
<th>Hematocrit (%)</th>
<th>B.U.N. (mg. %)</th>
<th>W.B.C.</th>
<th>Na⁺ (mEq./L)</th>
<th>K⁺ (mEq./L)</th>
<th>Cl⁻ (mEq./L)</th>
<th>HCO₃⁻ (mEq./L)</th>
<th>Creatinine (mg./L)</th>
<th>Premedication Drugs (mg.)</th>
<th>Anesthesia (mg., or L/min.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Erythromycin Staphecillin</td>
<td>33</td>
<td>60</td>
<td>7,500</td>
<td>142</td>
<td>4.2</td>
<td>102</td>
<td>28</td>
<td>16</td>
<td>Meperidine 75, Hyoscine 0.4</td>
<td>Thiopeptol 275, Succinylcholine 120, Nitrous oxide/oxygen (6:2)</td>
</tr>
<tr>
<td>2.</td>
<td>Digoxin Aldomet Apressoline</td>
<td>34</td>
<td>51</td>
<td>6,200</td>
<td>136</td>
<td>6.6</td>
<td>102</td>
<td>18.8</td>
<td>10.8</td>
<td>Atropine 0.4</td>
<td>Halothane 0.5%, Succinylcholine 40, Nitrous oxide/oxygen (6:2)</td>
</tr>
<tr>
<td>3.</td>
<td>Immuran Digoxin Aldomet Methicillin</td>
<td>38</td>
<td>55</td>
<td>21,000</td>
<td>131</td>
<td>5.0</td>
<td>—</td>
<td>23.8</td>
<td>5.6</td>
<td>Meperidine 100, Hyoscine 0.4</td>
<td>Thiopeptol 250, Succinylcholine 50, Nitrous oxide/oxygen (6:2)</td>
</tr>
<tr>
<td>4.</td>
<td>Aldomet Thorazine</td>
<td>36</td>
<td>56</td>
<td>8,500</td>
<td>141</td>
<td>4.9</td>
<td>101</td>
<td>26.0</td>
<td>9.8</td>
<td>Nembutal 100, Morphine 8.0, Atropine 0.4</td>
<td>Thiopeptol 200, Succinylcholine 60, Meperidine 100, Nitrous oxide/oxygen (6:2)</td>
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<tr>
<td>5.</td>
<td>Nil</td>
<td>34</td>
<td>62</td>
<td>12,100</td>
<td>143</td>
<td>5.4</td>
<td>—</td>
<td>21.4</td>
<td>12.0</td>
<td>Morphine 10</td>
<td>Thiopeptol 150, Succinylcholine 60, Nitrous oxide/oxygen (6:2)</td>
</tr>
<tr>
<td>6.</td>
<td>Nil</td>
<td>33</td>
<td>65</td>
<td>7,300</td>
<td>142</td>
<td>4.7</td>
<td>98</td>
<td>23.5</td>
<td>16.0</td>
<td>Pentobarbital 100, Atropine 0.4</td>
<td>Cyclopropane, Succinylcholine 50, Meperidine 50, Nitrous oxide/oxygen (6:2)</td>
</tr>
<tr>
<td>7.</td>
<td>Digoxin Amphogel</td>
<td>31</td>
<td>61</td>
<td>9,500</td>
<td>140</td>
<td>4.8</td>
<td>100</td>
<td>—</td>
<td>—</td>
<td>Pentobarbital 50, Atropine 0.2</td>
<td>Thiopeptol 200, Succinylcholine 40, Nitrous oxide/oxygen (6:2), Halothane 0.5%</td>
</tr>
<tr>
<td>8.</td>
<td>Apressoline Aldomet Penicillin</td>
<td>35</td>
<td>60</td>
<td>8,400</td>
<td>135</td>
<td>4.3</td>
<td>99</td>
<td>28</td>
<td>5.8</td>
<td>Morphine 8, Atropine 0.4</td>
<td>Halothane, Succinylcholine 40, Nitrous oxide/oxygen (6:2)</td>
</tr>
</tbody>
</table>
pne 0.5 mg. was given and full muscle power was, once more, restored. Thirty-six hours after operation vision again became blurred and there was some loss of grip-strength. A further intramuscular dose of neostigmine 1.25 mg. with atropine 0.5 mg. was given.

Forty-eight hours after operation patient again complained of diplopia, difficulty in raising her head and weakness in her arms and legs. This weakness had been steadily increasing over the previous few hours. A further intramuscular dose of neostigmine 1.25 mg. with atropine 0.5 mg. was given with return to full muscle power. From this time on, no further dose of anti-cholinesterase was required and both vision and muscle power were still maintained. The patient made an uneventful recovery from the operation, and later underwent a homograft transplant operation. One year later she was alive and well with no recurrence of muscle weakness symptoms. Since there was no evidence either preoperatively or at any time subsequently that this patient had any pathological condition affecting neuromuscular transmission (e.g., myasthenia gravis), we assume that the postoperative muscle weakness was due to the continued presence of gallamine at the motor end-plate.

Case 11. This 17 year old male patient with chronic renal failure and uremia was, by mistake, given an overdose of gallamine 380 mg. during the course of an operation for exploration of a transplanted kidney in the iliac fossa. At the end of the anesthesia, an unsuccessful attempt was made to reverse the neuromuscular block with neostigmine 2.5 mg. and atropine 0.5 mg. Repeated similar attempts were made with little or no change in the block during the next three days. At this point, hemodialysis was instituted with some improvement but it was not until the second dialysis that all signs of the residual neuromuscular block disappeared.

### Table 1. (Continued)

<table>
<thead>
<tr>
<th>Preop. Drugs</th>
<th>Case</th>
<th>Prop. Drugs</th>
<th>Hematocrit (%)</th>
<th>B.U. N. (mg. %)</th>
<th>W.B.C.</th>
<th>R.B.C.</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>Nil</td>
<td>43</td>
<td>35</td>
<td>10,000</td>
<td>10,000</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>Diamox</td>
<td>33</td>
<td>38</td>
<td>8,900</td>
<td>8,900</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>Nil</td>
<td>34</td>
<td>38</td>
<td>7,900</td>
<td>7,900</td>
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</tbody>
</table>

### Discussion

Abdominal relaxation in 11 patients undergoing operation for chronic renal failure was achieved with either d-tubocurarine or gallamine. In all patients there was complete absence of renal function at the time of operation and for many hours afterwards. Hemodialysis was performed on the third and fifth days. Of the 6 patients who received d-tubocurarine, all showed evidence of a normal recovery pattern and, following reversal of the block with an anti-cholinesterase, no further paresis was observed. On the other hand, of 5 patients who received gallamine, 3 showed

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*This case is described in detail elsewhere (Way and Singer 1966).*
evidence of paresis in the postoperative period. One patient who received only 110 mg. of gallamine showed signs of recurring paresis, despite anticholinesterase therapy, for up to 48 hours after the operation. In another patient who received 360 mg. hemodialysis was required three days later before normal neuromuscular transmission was restored.

Observations made during another study had revealed that there was no evidence of "revascularization"—as measured electromyographically in the hypothenar muscles—after either d-tubocurarine or gallamine in a group of 22 patients with normal renal function. The period of study varied from 7–24 hours. 10

In the past, a few isolated case-histories have been reported suggesting a relation between poor renal function and a prolonged response to the muscle relaxants—particularly gallamine triethiodide. Unfortunately, there have been only a few studies made on the role of the kidney in the excretion of relaxant drugs. It is generally believed that both gallamine and decamethonium are excreted unchanged in the urine while, originally, it was thought that only about one-third of the injected dose of d-tubocurarine was eliminated by this pathway. 11–13, 14, 15 Recently, however, some doubt on the low renal excretion of d-tubocurarine has been cast by the work of Fleischli and Cohen. 16 These workers extended the period of study up to 24 hours and found that they were able to recover 60–70 per cent of the drug unchanged in the urine. Furthermore, additional studies showed that small quantities were eliminated unchanged in

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex</th>
<th>Age</th>
<th>Wt. (kg.)</th>
<th>Operation Proposed</th>
<th>Relaxant</th>
<th>Dose (mg.)</th>
<th>Duration of Operation (hr.)</th>
<th>Reversal (Neostigmine) (mg.)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>35</td>
<td>63</td>
<td>Nephrectomy transplant failure (anuria)</td>
<td>dte</td>
<td>27</td>
<td>2</td>
<td>2.5</td>
<td>Reversal satisfactory and maintained.</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>16</td>
<td>47</td>
<td>Bilateral nephrectomy &amp; splenectomy</td>
<td>dte</td>
<td>30</td>
<td>2</td>
<td>NIL</td>
<td>Spontaneous recovery. Respiratory minute volume 6.0 liters/minute at end of anesthesia. Neuromuscular transmission normal within 40 minutes.</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>35</td>
<td>66</td>
<td>Exploration of transplant failure (anuria)</td>
<td>dte</td>
<td>30</td>
<td>1½</td>
<td>1.5</td>
<td>Reversal satisfactory and maintained.</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>20</td>
<td>65</td>
<td>Bilateral nephrectomy &amp; splenectomy</td>
<td>dte</td>
<td>27</td>
<td>2</td>
<td>3.0</td>
<td>Reversal satisfactory and maintained.</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>59</td>
<td>57</td>
<td>Bilateral nephrectomy &amp; splenectomy</td>
<td>dte</td>
<td>54</td>
<td>2½</td>
<td>2.5</td>
<td>Reversal satisfactory and maintained.</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>28</td>
<td>59</td>
<td>Bilateral nephrectomy</td>
<td>dte</td>
<td>24</td>
<td>2</td>
<td>1.5</td>
<td>Reversal satisfactory and maintained.</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>41</td>
<td>44</td>
<td>Bilateral nephrectomy &amp; splenectomy</td>
<td>Gallamine</td>
<td>80</td>
<td>2</td>
<td>2.5</td>
<td>Reversal satisfactory and maintained.</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>13</td>
<td>33.4</td>
<td>Bilateral nephrectomy</td>
<td>Gallamine</td>
<td>110</td>
<td>1½</td>
<td>2.5</td>
<td>Partial recovery without reversal. Respiratory obstruction due to paresis one hour after operation. Reversal satisfactory.</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>19</td>
<td>50</td>
<td>Bilateral nephrectomy</td>
<td>Gallamine</td>
<td>110</td>
<td>1½</td>
<td>3.0</td>
<td>Initial reversal satisfactory but recurrarisation requiring additional reversal recurred up to 48 hours after operation.</td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>27</td>
<td>46</td>
<td>Bilateral nephrectomy</td>
<td>Gallamine</td>
<td>80</td>
<td>1½</td>
<td>2.5</td>
<td>Reversal satisfactory and maintained.</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>17</td>
<td>60</td>
<td>Exploration of kidney</td>
<td>Gallamine</td>
<td>380</td>
<td>2</td>
<td>2.5</td>
<td>Reversal never satisfactory. Paresis persisted for three days despite repeated attempts at reversal. Only relieved by hemodialysis.</td>
</tr>
</tbody>
</table>
the bile. They concluded, therefore, that there was no significant metabolism of \(d\)-tubocurarine in vivo.

At one time it was also generally held that \(d\)-tubocurarine was metabolized in the liver, but Stead and Andrews \(^\text{17}\) in a study on dogs concluded emphatically that the liver played no part in the process. Kalow \(^\text{14}\) supported the contention that the liver may accumulate a small, but never substantial, amount of \(d\)-tubocurarine. On the evidence available, therefore, it would appear that both \(d\)-tubocurarine and gallamine are primarily excreted unchanged in the urine, but a small amount of \(d\)-tubocurarine may accumulate in the liver and finally pass unchanged into the biliary system.

The results of this clinical study suggest that, in the case of gallamine, there is a relationship between duration of action of the drug and renal excretion. This does not appear to be the case with \(d\)-tubocurarine. In fact, Vourc'h \(^\text{19}\) reported on 6 patients undergoing operation for terminal renal failure who received \(d\)-tubocurarine without any abnormal response. Since that time he has used \(d\)-tubocurarine in a total of 33 patients with renal failure and not one has shown a prolonged reaction. In many cases, spontaneous recovery occurred in the absence of anti-cholinesterase therapy. \(^\text{19}\) Our study is in accord with his findings with \(d\)-tubocurarine, but 3 out of the 15 patients in renal failure who received gallamine showed some evidence of a prolonged response.

The question, therefore, must be asked, if both these relaxant drugs are primarily excreted unchanged in the urine, why is it that only gallamine shows evidence of persistent muscular weakness? Certainly it would appear, in normal subjects, that gallamine is more rapidly eliminated in the urine than \(d\)-tubocurarine. Time, however, cannot be an important factor as a urine flow was not established in some of the patients who received \(d\)-tubocurarine until 10–15 days after operation. \(^\text{19}\) The answer to this paradox must lie in some difference in the distribution of the two drugs within the body.

Kalow \(^\text{14, 20}\) postulated three overlapping phases in the metabolism of \(d\)-tubocurarine. In the first, immediately after injection, the plasma concentration is very high; as this “slug” reaches the end-plates, muscle paralysis takes place. With each circulation as mixing occurs, so the plasma concentration falls, though some of the drug remains bound to the plasma proteins. \(^\text{21}\) Equilibrium is established between the concentration of the drug at the end-plate and that in the plasma.

The second phase comes about more slowly and now the plasma concentration falls gradually for two reasons. First, there is a redistribution of the relaxant molecules to nonspecific or inactive receptors \(^\text{22}\) in various organs of the body. Cavillito \(^\text{23}\) termed this area the “acceptor tissue depot” to denote that the drug is temporarily stored yet brings about no pharmacological response. Secondly, the concentration of the drug in renal tissue is very high and, consequently, starts to pass into the urine. Clinical recovery takes place during this phase. In fact, with \(d\)-tubocurarine, neuromuscular activity returns when the plasma level has fallen to about two-thirds of the original paralysis level. \(^\text{23}\) The same holds true for gallamine. \(^\text{24}\) The third and final phase is prolonged (taking many hours) and is mainly concerned with destruction or transformation of the drug.

The main interest, therefore, lies in the second phase. In the absence of renal excretion, the redistribution of the drug to other parts of the body becomes increasingly important. In this context Kalow \(^\text{14}\) in emphasizing the importance of total body water, states: “Until the contrary is proved, the possibility should not be dismissed that the extra-cellular concentration of \(d\)-tubocurarine is lowered by a process of dilution in the total water of skeletal muscle and/or some other organ.” Fleischli and Cohen \(^\text{19}\) support this concept and suggest that, apart from the acceptor tissue depot, the principal area of redistribution lies in the extra- and intracellular fluid of muscle.

Unfortunately, there are no studies available on the distribution of gallamine within the body. The most acceptable explanation, therefore, of the persistent high plasma concentration of gallamine in patients with poor renal function would appear to be that gallamine
does not easily enter those compartments which are readily available to d-tubocurarine.

From a clinical point of view, the importance of renal excretion in determining the duration of action of the muscle relaxants (particularly gallamine) appears to have been largely overlooked. If such a relation were firmly established then the creation of an artificial diuresis might prove valuable in the treatment of a prolonged apnea or paresis.

Conclusions

The results of this study suggest that there is a relation between the duration of action of gallamine and renal excretion. The use of gallamine in the presence of poor renal function would, therefore, appear clinically contraindicated. There is no evidence to suggest that d-tubocurarine is harmful in such cases.

We would like to thank Drs. J. Najarian and W. Silen for permission to publish details of cases under their care, and Dr. Stuart C. Cullen for his helpful advice in the preparation of this manuscript.

References