Pyridostigmin (Mestinon) as an Antagonist of 
\(d\)-Tubocurarine

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The effects of pyridostigmin were compared with those of edrophonium and neostigmine in anesthetized patients. Pyridostigmin was superior to edrophonium and equal to neostigmine as an antagonist of \(d\)-tubocurarine. Pyridostigmin produced fewer oropharyngeal secretions and decreased the heart rate less than did neostigmine. Further clinical studies of pyridostigmin should be carried out to confirm or deny this initial favorable experience. It is recommended that adequate recovery from neuromuscular block be defined as return of twitch height to the control level and, more important, the restoration of well sustained tetanus (30 cps.) to the level seen prior to the administration of any neuromuscular blocking agents.

At this institution pyridostigmin (Mestinon) is the anticholinesterase of choice in the treatment of myasthenia gravis. According to Osserman and Grob its main advantages over neostigmine (Prostigmin) include greater effectiveness, a longer duration of action and fewer muscarinic side effects. Because of the fewer muscarinic side effects, patients receiving atropine and neostigmine, upon changing to pyridostigmin, are often able to discontinue atropine. It is also easier to avoid overdose with pyridostigmin than with neostigmine because of the wider margin between the therapeutic and toxic doses.

Pyridostigmin, an analogue of neostigmine, is chemically the dimethyl carbamic ester of 3-hydroxy-1-methylpyridinium, while neostigmine is the dimethyl carbamic ester of 3-hy-

\[ \text{Pyridostigmin} \]
\[ \text{Neostigmine} \]

The decreased side effects, greater duration of action, and lesser toxicity of pyridostigmin raised the possibility that this agent might be of value as an antagonist of \(d\)-tubocurarine (dTC). The following study was therefore undertaken.

Methods

Patients were studied during anesthesia and operation. Most of the patients received atropine or scopolamine (0.4–0.8 mg.), secobarbital or pentobarbital (50–100 mg.) and/or meperidine (50–100 mg.) for preanesthetic medication. Anesthesia was usually induced with thiamylal sodium and maintained with nitrous oxide-thiamylal, nitrous oxide-meperidine, or nitrous oxide-trichlorethylene. Tracheal intubation, when necessary, was accomplished with the aid of 50–100 mg. of succinylcholine given intravenously. A Wright ventilometer was used to measure tidal volume. The electrocardiogram was monitored on an ORM-1 cardioscope and in some cases recorded on a polygraph. Ventilation was spontaneous or, when necessary, controlled manually or with a Frumin respirator.
Neuromuscular transmission was studied in 78 patients in a manner previously described. Briefly, the ulnar nerve was stimulated at the elbow or wrist and the adduction of the thumb measured with a force displacement transducer and recorded on a polygraph. In another 80 patients the ulnar nerve was stimulated with a Grass stimulator (Model S4) or with a Block-Aid Monitor and the magnitude of block was estimated by observing the adduction of the thumb. The response to tetanic stimulation (30 cps.) was also determined.

The following drugs were used: d-Tubocurarine chloride (Tubarine); edrophonium chloride (Tension); neostigmine methyl sulfate (Prostigmin); pyridostigmin bromide (Mestinon). All drugs were injected intravenously. dTC was given to 158 patients in the following manner. In 50 patients (Group A) dTC was given in a fashion similar to that in our prior study of edrophonium and neostigmine. Ten patients received a single dose of 0.6 mg./kg. over 1–3 minutes. Forty patients received a test dose of 0.1 mg./kg. rapidly (1–3 seconds) followed in 5–10 minutes by 0.2–0.4 mg./kg. of dTC. No additional dTC was given for one hour. Then 0.15–0.2 mg./kg./hour was injected in divided doses. In 100 patients (Group B) smaller amounts of dTC were given. The effect of a test dose of 0.1 mg./kg. of dTC on twitch height was determined. Five to 10 minutes later, 0.1–0.3 mg./kg. of dTC was injected. No additional dTC was given for 30–60 minutes. Then 0.1–0.15 mg./kg./hour was injected in divided doses. In 8 additional patients studied on 2 or more occasions a single dose of 0.2–0.4 mg./kg. of dTC was given. Except where otherwise indicated, 1 mg. of atropine sulfate was injected intravenously 30–60 seconds prior to the injection of each 2.5-mg. dose of neostigmine or 10-mg. dose of pyridostigmin. One dose of neostigmine was given to 47 patients and two doses to 7 patients. With pyridostigmin, 96 patients received one dose and 12 patients two doses.

The 8 patients who had two or more operations, we compared the effects of pyridostigmin with those of neostigmine (4 patients), edrophonium (3 patients) or with spontaneous recovery (3 patients). The anesthetic manage-

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<th>Time Required for Return of Twitch Height to Control Level (min.)</th>
<th>Pyridostigmin Group A</th>
<th>Pyridostigmin Group B</th>
<th>Neostigmine Group B</th>
<th>Neostigmine Previous Study*</th>
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<tr>
<td>Percentage Spontaneous Recovery</td>
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<td>40–44</td>
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* Patients from previous study (Reference 4).

Results

The neuromuscular effects of pyridostigmin were determined in 108 patients. The 50 patients in Group A received an average dose of dTC of 0.29 mg./kg./hour (range of 0.1–0.6 mg./kg./hour). In every patient one or two injections of 10 mg. of pyridostigmin restored twitch height to the control level. This includes 10 patients in whom no twitch could be seen or recorded at the time of reversal. The speed of recovery was more rapid the greater the degree of spontaneous recovery from dTC. Where spontaneous recovery of twitch height was 0–25 per cent of control, pyridostigmin restored twitch height to the control level in 5–31 minutes. Where spontaneous recovery was greater than 25 per cent, pyridostigmin produced full recovery in 3–15 minutes (table 1).

Since our use of relaxants was somewhat modified as a result of our prior study with neostigmine, we also compared the effects of pyridostigmin and neostigmine in an additional 100 patients (Group B) whose management was similar. The choice of antagonist was randomly determined (using a table of random numbers). The average dose of dTC in patients receiving pyridostigmin was 0.22 mg./kg./hour and in patients receiving neostigmine 0.23 mg./kg./hour. The results obtained with
Fig. 1. Action of pyridostigmin as an antagonist of dTC. \( \uparrow P = 10 \text{ mg. of pyridostigmin.} \)

**Panel A.** Total dose of dTC was 0.2 mg./kg. Pyridostigmin injected 20 minutes after initial dose of dTC.

**Panel B.** Total dose of dTC was 0.45 mg./kg. Pyridostigmin injected 105 minutes after initial dose of dTC.

**Panel C.** Total dose of dTC was 0.5 mg./kg. Pyridostigmin injected 158 minutes after initial dose of dTC.

**Panel D.** Total dose of dTC was 0.4 mg./kg. Initial injection of pyridostigmin 70 minutes after initial dose of dTC.

**Panel E.** Total dose of dTC was 0.8 mg./kg. Initial injection of pyridostigmin 200 minutes after initial dose of dTC.

Pyridostigmin and neostigmine were similar. In every patient, one or two intravenous injections of 2.5 mg. of neostigmine or 10 mg. of pyridostigmin (fig. 1) restored twitch height to the control level. The time required for pyridostigmin or neostigmine to restore the twitch height to the control level varied from 3–12 minutes where twitch height had spontaneously recovered to greater than 25 per cent of control. Where a lesser degree of spontaneous recovery was present, the antagonists required 5–21 minutes to produce full recovery of twitch height (table 1).

It was possible in 8 patients who underwent multiple operations to compare in the same patient the effects of pyridostigmin with: (1) spontaneous recovery from dTC, (2) edrophonium, or (3) neostigmine. Representative results are shown in figures 2, 3, and 4. The patient represented in figure 2 required 75 minutes to recover spontaneously from 0.3 mg./kg. of dTC, while on another occasion the injection of 10 mg. of pyridostigmin (30 minutes after the same dose of dTC) restored twitch height to the control level in 3 minutes. Figure 3 is a comparison of the effects of
edrophonium and pyridostigmin. In this patient 40 mg. of edrophonium antagonized the effects of 0.4 mg./kg. of dTC in 22 minutes. However, pyridostigmin (10 mg.) injected under comparable conditions restored twitch height to the control level in 8 minutes. In figure 4 it can be seen that the effects of neostigmine and pyridostigmin in antagonizing dTC were similar.

Adequacy of Reversal. It became obvious during our studies that the adequacy of reversal by pyridostigmin or neostigmine could not always be satisfactorily determined by measuring the respiratory rate and tidal volume. As previously reported apparently adequate spontaneous ventilation could be present despite marked depression of the twitch response. It was also obvious that the adequacy of reversal could not always be satisfactorily determined by observation of the twitch response. During prolonged surgery it was frequently difficult to remember the magnitude of the control twitch. In addition, it appeared that recovery of the twitch height to the control level does not always signify full recovery of neuromuscular transmission. It was observed that some patients did not clinically appear to be fully recovered from the effects of dTC, despite the return of the twitch height (recorded on the polygraph) to the control

Fig. 3. Comparison of effects of pyridostigmin and edrophonium. Panel A. Forty-five minutes prior to first ↑E, 0.4 mg./kg. of dTC injected intravenously. At each ↑E, 10 mg. of edrophonium injected. Panel B. The same patient on another occasion received 0.4 mg./kg. of dTC. Forty-five minutes later at ↑P, 10 mg. of pyridostigmin given. Note more prompt recovery with pyridostigmin than with edrophonium.

Fig. 4. Comparison of effects of pyridostigmin and neostigmine. On two separate occasions patient received 0.3 mg./kg. of dTC. Thirty minutes later, either 10 mg. of pyridostigmin injected at ↑P (Panel A) or 10 mg. of neostigmine injected at ↑N (Panel B). Note similar effects.
level. Using a rate of stimulation of 30 cps, we noted that tetanus was not as well sustained as it was prior to the injection of dTC. After waiting 5 to 15 minutes or injecting additional pyridostigmin or neostigmine, we observed well sustained tetanus. The patient now appeared to have recovered from the effects of dTC and was able to take deep breaths, cough vigorously, and raise and hold his head off the bed for 10 seconds. As a result of these observations, our current practice is to consider the patient adequately recovered from dTC only if the twitch has returned to the control level and tetanus at 30 cps. is well sustained.

Other Observations. In a preliminary study of 6 patients, 10 mg. of pyridostigmin was injected without the prior injection of atropine. Our impression, based upon observing the patient for 10 to 20 minutes after the injection of pyridostigmin, was that this agent did not produce oropharyngeal secretions and that prior treatment with atropine was not necessary. Therefore atropine was not injected prior to pyridostigmin in the first 14 patients studied. However, it was subsequently observed in 2 patients that approximately 20 to 30 minutes after the pyridostigmin, there was a marked outpouring of secretions. Although we did not observe oropharyngeal secretions in the operating room during the first 10 to 20 minutes after pyridostigmin, we learned upon inquiry that secretions were observed in the recovery room. They caused no alarm since the amount of secretions was felt to be approximately equal to that observed with 1 mg. of atropine and 2.5 mg. of neostigmine. Thereafter, 1 mg. of atropine was injected intravenously 30 to 60 seconds prior to 10 mg. of pyridostigmin. It appeared that the amount of secretions with the atropine-pyridostigmin combination was less than with atropine-neostigmine.

Pyridostigmin decreased the heart rate less than did neostigmine. With atropine (1 mg.) and neostigmine (2.5 mg.) the heart rate was usually the same as or less than that seen prior to the injection of these agents. However, the heart rate after atropine (1 mg.) and pyridostigmin (10 mg.) was usually 10 to 20 per cent greater than before these agents. We are currently studying the use of 0.5 to 1 mg. of scopolamine prior to 10 mg. of pyridostigmin.

Recirculation was not observed in any of the patients receiving pyridostigmin. In all of the patients who received pyridostigmin, adequate reversal as described above was seen. Although in our previous study, the effects of dTC could not be completely antagonized by neostigmine in 2 patients, this does not represent a true difference in effectiveness of neostigmine and pyridostigmin since: (1) we modified the use of dTC on the basis of our prior study (less dTC on a mg./kg./hour basis was used in the present study), and (2) twice as many patients received neostigmine in our previous study as received pyridostigmin in the present study.

Discussion

Following the synthesis of pyridostigmin in 1945, there were several animal studies comparing it with neostigmine in terms of anticholinergic activity, cholinesterase inhibiting activity, and toxicity. It was variously reported that pyridostigmin had 1/2, 1/4, 1/5, or 1/10 the anticholinereaction of neostigmine. Using optimal doses of these agents, they were equally effective in antagonizing the action of dTC. Smith et al., measuring the time interval between the injection of anticholinesterase and the moment at which the head drop dose of dTC was antagonized sufficiently to permit a rabbit to raise its head, found that neostigmine produced this effect in 20 seconds, and pyridostigmin in 28 seconds, as compared with the control recovery of 382 seconds. The duration of anticholinergic action in this study was 60 minutes for neostigmine and over 80 minutes for pyridostigmin. In another study, the speed of reversal of dTC by neostigmine and pyridostigmin were not significantly different.

In addition to antagonizing the neuromuscular blocking action of dTC, neostigmine and pyridostigmin if given in sufficient dosage can themselves produce a neuromuscular block. The dose of neostigmine which produced a neuromuscular block was 0.1 or 0.122 mg./kg. and that for pyridostigmin was 1.3 or 1.6 mg./kg. The effective anticholinergic dose of neostigmine was 0.05 mg./kg. and that for
pyridostigmin 0.20 or 0.25 mg./kg.\(^5\),\(^7\).\(^8\) The margin between anticholinesterase and neuromuscular blocking doses of pyridostigmin is greater than that of neostigmine. Thus the likelihood of an excessive dose of anticholinesterase producing a neuromuscular block of its own is less with pyridostigmin. In general, the toxicity of pyridostigmin has been reported as less than that of neostigmine, both on an absolute basis\(^5\),\(^6\),\(^9\) and comparing equieffective anticholinesterase doses.\(^8\)

The anticholinesterase activity of pyridostigmin has variously been reported as 1/5,\(^8\) 1/8,\(^7\) 1/10,\(^10\) or 1/20,\(^5\) that of neostigmine. In all of these studies but one,\(^8\) the anticholinesterase activity of pyridostigmin correlated well with its anticholinesterase activity. Further support for cholinesterase inhibition as the mechanism of anticholinesterase pyridostigmin activity and neostigmine was the demonstration that prior inactivation of cholinesterase by tetraethylpyrophosphate eliminated the anticholinesterase activity of pyridostigmin and neostigmine.\(^8\) Although the anticholinesterase activity of neostigmine has been attributed in part to a direct stimulant acetylcholine-like action on the motor endplate,\(^11\) this effect cannot account for the anticholinesterase action of pyridostigmin, which does not have a direct stimulant action.\(^8\)

A review of the laboratory and clinical studies comparing pyridostigmin and neostigmine suggested that pyridostigmin, because of its lesser toxicity, equal effectiveness and longer action, might be a clinically valuable antagonist of dTC. Textbooks of anesthesiology, however, indicate that pyridostigmin has been considered unreliable as an antagonist of dTC. This opinion was usually based upon the 1954 report of Brown\(^12\) who studied the effects of 5–10 mg. of pyridostigmin in 50 patients. Using clinical criteria, he felt the onset of action of pyridostigmin to be slower than that of neostigmine. Further, there was satisfactory antagonism of dTC in only 36 of 50 patients studied. There were, however, reports in the European and Canadian literature in which it was mentioned, usually in passing, that pyridostigmin did antagonize the effects of dTC and other neuromuscular blocking agents. The present study was therefore undertaken to determine the effectiveness of pyridostigmin as an antagonist of dTC. The results demonstrate that in terms of anticholinesterase effect pyridostigmin is superior to edrophonium and equal to neostigmine, while producing fewer side effects than neostigmine. We do not believe it is possible to state after only 108 cases that pyridostigmin is superior to neostigmine and should replace it. But, as a result of this study, the author is now routinely using pyridostigmin rather than neostigmine to antagonize the effects of dTC. It is hoped that others will use pyridostigmin and compare it with neostigmine, so that the clinical value of these agents may be determined under a wide variety of conditions.

As a result of studies of neuromuscular blocking agents and their antagonists, the author has modified the manner in which the residual effects of dTC are antagonized. Since reversal may require as much as 30 or 40 minutes, rather than waiting until the operation has been completed, atropine (1 mg.) and pyridostigmin (10 mg.) are given approximately 10 minutes before the end of the operation. The course of reversal is watched and if necessary a second dose of 10 mg. of pyridostigmin, preceded by 1 mg. of atropine, is given. Adequate reversal is defined as recovery of twitch height to the control level and, even more important, the restoration of well-sustained tetanus (30 cps.) to the level seen prior to the administration of any neuromuscular blocking agents. In some patients, the rapidity of antagonism of dTC is such that it may be necessary to inject additional small amounts of thiobarbiturates to permit the conclusion of surgery, particularly the placement of the skin sutures. We believe that early reversal, which permits observation of the patient in the operating room until well-sustained tetanus is present, is of sufficient importance to outweigh possible objections to the occasional administration of thiobarbiturates at the end of the operation.

**Summary**

The efficacy of pyridostigmin as an antagonist of dTC was determined. It was found to be superior to edrophonium and equal to neostigmine as an antagonist of dTC. Pyridostig-
min produced fewer oropharyngeal secretions and decreased the heart rate less than did neostigmine.

It is recommended that adequate recovery from neuromuscular block be defined as return of the twitch height to the control level and, more important, the restoration of well-sustained tetanus (30 cps.) to the level seen prior to the administration of any neuromuscular blocking agents.

References


Respiration

PULMONARY MECHANICS

Dead space, lung compliance, cervical tracheal volume change and total lung resistance were measured simultaneously in anesthetized dogs, paralyzed or open-chest, and the responses to nerve section and stimulation and ventilation with different gas mixtures were studied. Bilateral cervical vagotomy changed all four parameters in a way consistent with airway dilatation, and bilateral vagal stimulation had the opposite effect. A weak airway dilator role was indicated by the sympathetic nerves. Ventilation with 4 per cent CO₂ or 8 per cent CO₂ or 10 per cent O₂ caused opposite, but weaker responses. The responses to the three airway constricting gas mixtures were present, but reduced in intensity after bilateral cervical vagotomy and some even weaker responses were present after additional bilateral sympathectomy. During restoration of airway smooth muscle tone by electrical stimulation of the distal ends of the cut vagon nerves, administration of CO₂-rich or hypoxic gas mixtures had no greater effect than during controls with the vagon cut but without stimulation. No dilator responses to hypercapnia or hypoxia were seen, either in innervated or denervated trachea and airways. (Green, M., and Widdicombe, J. C.: The Effects of Ventilation of Dogs with Different Gas Mixtures on Airway Calibre and Lung Mechanics, J. Physiol. 186: 363 (Oct.) 1966.)