The Effect of use of Pyridostigmine and Requirement of Vecuronium in Patients with Myasthenia Gravis

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Abstract:

CONTEXT: Patients with myasthenia gravis receive pyridostigmine, an anticholinesterase agent, as a part of therapy. These patients demonstrate a heightened sensitivity towards non-depolarising muscle relaxants. Continuing pyridostigmine till the day of the surgery or omitting it on the night before surgery could provide variable results with regards to the effect of vecuronium. AIMS: Myographic evaluation of a dose of vecuronium in patients with myasthenia gravis on pyridostigmine therapy. SETTING AND DESIGN: A randomised, double-blind, clinical study conducted in a teaching hospital. SUBJECTS AND METHODS: Medically (oral pyridostigmine) well-controlled adult patients with myasthenia gravis who were posted for thymectomy, were randomly divided into two groups. Patients in Group 1 received their last dose of pyridostigmine on the night before surgery while those in Group 2 received even the morning dose of the drug on the day of surgery. Neostigmine (1-2 mg) intravenously was used as rescue medication. Vecuronium (0.01mg/kg) was used for intubation and muscle relaxation during trans-sternal thymectomy and its effect was reversed using neostigmine and atropine. RESULTS: Fourteen patients (7 in each group) belonging to both sexes were enrolled in the study. The intubating dose of vecuronium showed quicker onset time (155 sec or 2.7min approx.) and peak effect (99% T₁ suppression) in patients belonging to Group 1, and 3/7 (43%) complained of respiratory discomfort while waiting for surgery. By giving the morning dose of pyridostigmine (Group 2), an identical intubating dose of vecuronium showed relative resistance (peak effect-97% T₁ suppression) and delayed onset time (198 sec approx.). However, the reversal was complete at the end of surgery in both the regimens. CONCLUSIONS: Omission of the pyridostigmine dose on the day of surgery predisposed patients with myasthenia gravis to the possibility of respiratory discomfort and sensitivity to vecuronium. Continued administration significantly prolonged the onset time of vecuronium and the patients required a higher dose of vecuronium. (J Postgrad Med 2003;49:311-5)

Key Words: Vecuronium, Myasthenia gravis, Pyridostigmine, Non-depolarising block.

Myasthenia gravis is an autoimmune disease, characterised by muscle weakness. It is related to the reduction in the functional acetylcholine (Ach) receptor population at the neuromuscular junction due to the presence of Ach-receptor antibodies. These patients have a variable response to muscle relaxants and are very sensitive towards non-depolarising muscle relaxants. It has been reported that vecuronium bromide in reduced doses is safe and effective and that larger the preoperative pyridostigmine dose, greater is the patient’s sensitivity to the non-depolarizing agents.1 It has also been suggested that the sensitivity to vecuronium in patients with myasthenia gravis may be influenced by the anti-cholinesterase therapy.2,3 The continued use of anti-cholinesterase therapy prior to thymectomy in patients with myasthenia gravis has been a matter of ongoing debate. The aim of this prospective clinical study was to compare the effect of two different regimens of pyridostigmine in patients with myasthenia gravis undergoing thymectomy under balanced general anaesthesia.

Subjects and Methods

The study was conducted in a hospital after obtaining clearance from the institution’s Ethics committee. The sample size was estimated as 14 patients in both the groups taking into consideration that a difference of 30 seconds (with standard deviation of 20) would be clinically significant. Thus, 14 adult patients of both the sexes suffering from generalised myasthenia gravis, undergoing trans-sternal thymectomy between January 1995 and April 1999 were included in the study after obtaining informed consent. All patients were examined preoperatively and their respiratory and cardiac status evaluated. Patients were randomly divided into two study groups. In patients belonging to Group 1, pyridostigmine was stopped on the night before the surgery. In patients of Group 2, pyridostigmine was continued and the morning dose was administered with sips of water. Rescue ne-
ostigmine (1 to 2 mg) intravenously was allowed in case the patient complained of excessive muscle weakness or breathing difficulty. Oral lorazepam (2 mg) was administered to all patients on the night before surgery. In addition to the routine monitoring of ECG, estimation of non-invasive arterial blood pressure, temperature, and urine output, pulse oximetry and capnography, and neuromuscular monitoring were also done. The ulnar nerve was stimulated at the wrist using surface electrodes and the Myotest (Biometer Ltd, Denmark). The adductor pollicis response on the thumb was recorded using Myograph-2000 (Biometer Ltd, Denmark). Mechanomyography was performed for the adductor pollicis response at 300 gm pre-tension. After the induction of anaesthesia with fentanyl (3 mcg/kg) and sodium thiopental (3-5mg/kg), the adductor response was stabilised at the titrated supra-maximal stimuli. Train-of-four (TOF) (4 stimuli at 2Hz) stimuli at 12-sec intervals were given at the ulnar nerve using surface electrodes by Myotest (Biometer Ltd, Denmark). Vecuronium (0.01mg/kg) was injected and its neuromuscular effect was monitored while assisting ventilation by facemask and maintaining anaesthesia by nitrous-oxide (65%) in oxygen with isoflurane (1%) on vaporiser setting with total fresh gas flow of 8l/min. Tracheal intubation was performed once T1 was suppressed up to 95% of control T1 height. Orotracheal intubation was graded clinically on a 1-4 scale: Grade 1–good jaw relaxation, vocal cords open, no response to intubation; Grade 2–good jaw relaxation, vocal cords open, minimal coughing on intubation; Grade 3–jaw relaxed, vocal cords moving, intubation requires firm pressure, marked coughing on endotracheal tube; Grade 4–intubation impossible due to poor jaw relaxation or closed vocal cords.

The effect of intubating dose of vecuronium was monitored to note the onset of intubation and the recovery time of intubation dose effect up to T1 amplitude 25% of its control. The incremental doses of vecuronium (one-fourth of the intubating dose) were repeated to maintain muscle relaxation at the level of with T1 just positive or maximum up to 10% of its control. Incremental dose intervals were also noted for each dose given during anaesthesia. At the end of surgery, the neuromuscular blockade was reversed with neostigmine (0.05mg/kg) and atropine (0.02mg/kg) prior to extubation. The extubation criteria were – adequate recovery of its control. Incremental dose intervals were also noted for each dose given during anaesthesia. At the end of surgery, the neuromuscular blockade was reversed with neostigmine (0.05mg/kg) and atropine (0.02mg/kg) prior to extubation. The extubation criteria were – adequate recovery of

After surgery, all the patients were observed for 24 hrs in the high dependency unit with standby facility for assisted respiration, if necessary. We recorded first dose response in terms of its peak effect (maximum block attained) and its onset time. Intubating dose effect (from the time of injection to recovery of T1 amplitude up to 25% of its control value) was also recorded. We also compared the duration of surgery, total dose of vecuronium used during total surgery (mg/kg), and success of extubation at the end of surgery. The occurrence of any side-effects peri-operatively and the need to use rescue neostigmine in both groups, were also recorded in the pre-designed proforma. The data were entered into the statistical package SPSS and the demographic data were compared using Student’s’ t test. All proportions were compared using x² test and the non-parametric method of statistical analysis, and the Mann Whitney U test was used to compare other parameters. Calculated p value of <0.05 was considered statistically significant at 90% confidence interval.

Results

The mean age of the studied patients was 33.7 years (range 20 to 40 years) and they weighed between 30 and 70 kg (mean 52.6 kg, SD 11.4 kg). The mean duration of illness was 15.1 months (range 6 to 27 months). None of the patients had any preoperative risk factors predicting the need for postoperative ventilator support. All patients were on pyridostigmine; 6 patients were also receiving prednisolone. The intubating dose in the form of one-tenth of the standard dose of vecuronium achieved 95% suppression of T1 in all patients giving excellent intubating conditions. The average (SD) duration of total anaesthesia time/surgery time was 180.3 min (55.5). Patient characteristics were similar in the two study groups (Table 1).

The median peak response of 97% T1 suppression in Group 2 patients was less than that in Group 1. The peak effect attained ‘0’ twitch response in 6 patients in Group 1 and only in 2 patients in Group 2. The onset time (mean ± SD) for peak neuromuscular block effect of the intubations dose was significantly (P<0.05) quicker in Group 1 patients (155±32 sec) than in Group 2 patients (198±32 sec). The total vecuronium dose (mean ± SD) required in Group 1 patients was significantly (P<0.05) lesser (0.02±0.02 mg/kg) than that needed

<table>
<thead>
<tr>
<th>Table 1: Characteristics of patients in the two study groups</th>
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<tr>
<td>Number of patients (n)</td>
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<tr>
<td>Male: Female</td>
</tr>
<tr>
<td>Weight (Kg) [mean (SD)]</td>
</tr>
<tr>
<td>Height (cm) [mean (SD)]</td>
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<tr>
<td>Duration of Surgery (min) [mean (SD)]</td>
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<tr>
<td>Osserman grade II b</td>
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<tr>
<td>Dose of Pyridostigmine (mg/day) [mean (SD) (range)]</td>
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<tr>
<td>Duration of Pyridostigmine therapy (days) [mean (SD)]</td>
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in patients belonging to Group 2 (0.035±0.02 mg/kg). Breathing difficulty was the most common side-effect in the patients of Group 1. Two patients required rescue neostigmine (2.5 mg) intravenously in the preoperative ward 3 hours before shifting to the operation-theatre. The neuromuscular blockade was reversed with the standard dosage of neostigmine (2.5 mg) and atropine (1.2 mg). None of the patients required postoperative ventilator support. All patients remained haemodynamically stable (Table 2).

### Discussion

Patients of myasthenia gravis are known to be extremely sensitive to the effects of non-depolarising muscle relaxants. The degree of sensitivity is variable even among patients who are in complete remission, although patients who have severe disease and require higher dose of pyridostigmine tend to be more sensitive than others. Hence, caution is required while using non-depolarising agents in patients with myasthenia gravis. The use of Atracurium infusion has been recommended during video-assisted thoracoscopic thymectomy. However, due to its exclusive cardiovascular stability vecuronium is still very commonly used in India. We used balanced anaesthesia with isoflurane (1%) in all our patients and one-tenth of the standard vecuronium dose was found to be safe and effective in producing optimum intubations and surgical conditions, with satisfactory reversal of the blockade postoperatively.

The total dose of vecuronium required in our study was almost half of that described by Baraka and Tabboush. Isoflurane has been reported to induce a significant depressant effect on neuromuscular transmission in myasthenic patients, and it has also been reported to augment the effect of vecuronium. This is why we could get 95% twitch suppression with one-tenth of the vecuronium dose used for intubations in normal patients and could intubate all patients. Pyridostigmine acts by inhibiting synaptic acetylcholinesterase, thus overcoming the deficit in receptor density in patients with myasthenia gravis. The high pyridostigmine concentration seemingly reduces the sensitivity of these patients to non-depolarisers. The variability in disease severity and in the response to non-depolarisers makes comparisons difficult. Eisenkraft et al compared the effects in 4 patients who were given pyridostigmine on the morning of surgery with those in whom it was withheld and failed to demonstrate any difference in sensitivity to vecuronium. Nilsson and Meretoja have reported that a higher daily dose of pyridostigmine was associated with increased sensitivity to vecuronium. Paterson et al compared vecuronium response in two patients. They reported a higher vecuronium response in myasthenic patients getting no anticholinergic therapy when compared to the effects noted in a patient who was on therapy. Paterson et al however, failed to demonstrate any differences in sensitivity to mivacurium in two patients receiving pyridostigmine as compared to two who were not.

In the present randomised, controlled, prospective study with a larger number of patients, we could reconfirm that the withdrawal of pyridostigmine prior to surgery clinically did not make a significant difference in terms of intubating condition at 95% twitch suppression. The omission of pyridostigmine on the night before surgery, however, did show greater sensitivity towards vecuronium during isoflurane anaesthesia and these patients required a lesser dose of vecuronium throughout surgery than the patients in whom pyridostigmine was continued. The patients were more prone to develop respiratory distress and even required rescue neostigmine. Contrary to a single case report of hypersensitivity to neostigmine and

### Table 2: Comparison of the vecuronium dose effect in the two study groups

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n=7)</th>
<th>Group 2 (n=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intubation interval (sec) [mean (SD)]</td>
<td>89 (27)</td>
<td>138 (36)*</td>
</tr>
<tr>
<td>Grades of Laryngoscopy and intubations (median and range)</td>
<td>1.0 (1-3)</td>
<td>2.0 (2-3)</td>
</tr>
<tr>
<td>Peak Effect of intubating dose (median and range)</td>
<td>0.99 and 0.96-1.0</td>
<td>0.97 and 0.95-1.0*</td>
</tr>
<tr>
<td>Peak effect onset time (sec) [mean (SD)]</td>
<td>155 (32)</td>
<td>188 (32)*</td>
</tr>
<tr>
<td>Duration of intubating dose effect (min) [mean (SD)]</td>
<td>38.4 (20)</td>
<td>29.8 (25)</td>
</tr>
<tr>
<td>Total vecuronium dose (mg/kg) [mean (SD)]</td>
<td>0.02 (0.02)</td>
<td>0.035 (0.02)*</td>
</tr>
<tr>
<td>Repeat dose intervals (min) [mean (SD) and range]</td>
<td>27 (18); 18-47</td>
<td>18 (20); 12-33</td>
</tr>
<tr>
<td>Side-effects encountered (No of patients)</td>
<td></td>
<td></td>
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<tr>
<td>Breathing difficulty preoperatively</td>
<td>3 (43%)</td>
<td>0</td>
</tr>
<tr>
<td>Incidence of neostigmine use pre-operatively</td>
<td>2 (28%)</td>
<td>0</td>
</tr>
<tr>
<td>Breathing difficulty postoperatively</td>
<td>1 (14%)</td>
<td>1 (14)</td>
</tr>
<tr>
<td>Postoperative failed extubation</td>
<td>0</td>
<td>0</td>
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* Statistically significant (P<0.05) difference from Group 1.
vecuronium in a sero-negative patient by Kim and Mangold⁵, we could safely use neostigmine reversal at the end of surgery and successfully extubated all the patients.

Our study suggested that the optimisation of the medical condition with pyridostigmine until the morning of surgery followed by anaesthesia using isoflurane with one-tenth the standard intubating dose of vecuronium in patients with myasthenia gravis is safe. The omission of pyridostigmine on the night before surgery makes patients more susceptible to develop muscle weakness while waiting for the surgery and the patients show significant sensitivity towards vecuronium although neostigmine reversal is safe in all patients with myasthenia gravis.

References

Expert Comments

Anaesthetic management of patients with myasthenia gravis

This article presents an answer to an interesting question in the field of anaesthetic management of patients with myasthenia gravis (MG). Whether the use of a morning dose of pyridostigmine prior to surgery is appropriate or not for MG patients treated with pyridostigmine has long been a matter of debate. Although some similar studies have been carried out for small numbers of patients,¹ ³ this article confirmed the results for a larger number of patients with a randomised prospective study, and the results are clear and agree with our expectations.

When investigating neuromuscular responses to muscle relaxants only, even in MG patients, drugs which might affect neuromuscular transmission such as pyridostigmine should be avoided. However, this constitutes a clinical problem. In this study, 2 of 7 patients in a group not administered pyridostigmine required a rescue dose of neostigmine before transfer to the operating theatre because of breathing difficulty. On the other hand, no such problems were observed among the patients in the group where pyridostigmine administration was continued. This suggests the advisability of continuing the clinical use of the anti-cholinesterase for MG patients on the morning of surgery.

As for sensitivity to vecuronium, the peak effects of the initial dose of vecuronium (0.01mg/kg) were higher and the onset time was quicker for the group without pyridostigmine than for patients who continued to receive the drug. In addition, total doses of vecuronium necessary to maintain muscle relaxation during surgery were larger for the group with pyridostigmine, although the grades of laryngoscopy and intubations indicated no significant differences between the two groups. In previous studies regarding the sensitivity to muscle relaxants in MG patients, the use of morning doses of anticholinesterase was not consistent. In some studies, the morning dose of the drugs was continued,⁴ ⁶ but in others, the drugs were omitted.⁷ ¹⁰ The results of this study indicate that the methods of previous studies in which the morning dose of the drugs was continued were clinically suitable, while the sensitivity to muscle relaxants in MG patients where neuromuscular responses only were examined (morning dose of anti-cholinesterase omitted) might be higher than that seen in the
other studies. This study indicates such a possibility.

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References


Announcement

New Website for the journal

The Journal of Postgraduate Medicine is pleased to announce the launch of a new version of its website from August 2003. The site address would remain same [www.jpgmonline.com]. The features of the new site include:

- Free full text availability of articles form 1980
- Direct link to abstracts and full text from the cited references
- Link from text of articles to various databases and search engines
- Facility to submit comments on articles
- Email notifications on new issue release
- Statistics of articles download and visits
- Better user interface
- New structure based on OpenURL, DC Metadata and other international standards