DOSE - RESPONSE RELATION OF PIPECURONIUM BROMIDE IN ADULT PATIENTS

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SUMMARY: Dose-response relation of pipecuronium bromide, a new non-depolarizing muscle relaxant, was investigated on adult patients undergoing elective surgery. ED₉₀ was found as 59.3 ± 12 µg/kg. Excellent intubation conditions were obtained in 14 patients. Maximal block was 98.7 ± 1.8 %.

As a result, it was concluded that excellent-good intubation conditions could be obtained with 59.3 ± 12 µg/kg of pipecuronium bromide.

Key Words: Neuromuscular Relaxants, Pipecuronium.

INTRODUCTION

Pipecuronium bromide is a new non-depolarizing neuromuscular blocking agent that is structurally similar to pancuronium and vecuronium (9). Both pipecuronium and pancuronium have biquaternary structures but differ in side chains attached to the steroid nucleus. Pipecuronium has piperazin rings attached at position 2 and 16 of the steroid nucleus, while pancuronium has piperidine rings. The structural modifications in pipecuronium are designed to improve its specificity leaving the neuromuscular effect intact while reducing the nicotinic side effects on the cardiac vagus nerve (9).

In vitro experiments have revealed that pipecuronium reversibly inhibits both human red blood cell acetylcholinesterase and human plasma cholinesterase, producing 50 % inhibition of enzyme activity (1).

In this study, the dose-response relation of pipecuronium bromide was investigated in adult man.

MATERIALS AND METHODS

20 adult patients (ASA class I-II) undergoing elective surgery were studied. The patients who had renal, metabolic or neuromuscular abnormalities were excluded. The patients were premedicated with 5 mg, diazepam and 0.5 mg, atropine sulfate intramuscularly.

In the operating room, venous cannulation, ECG monitoring and measurement of blood pressure were performed. Neuromuscular monitoring was carried out with a neuromuscular transmission monitor (Tatec Relaxograph TM). Anesthesia was induced with 5 mg/kg thiopental sodium and 50 mg meperidine intravenously. After induction of anesthesia the ulnar nerve was stimulated with train-of-four (TOF) supramaximal square wave stimuli of 0.1 msec. duration administered at 2 Hz. every 10 sec. After obtaining a control tracing with 20 µg/kg of pipecuronium followed by 5 to 10 µg/kg incre-
ments injected iv. until 90% block developed (Figure 1). Each dose was injected when the maximal effect of the previous dose had developed. When 90% block was obtained trachea was intubated.

The intubation conditions were graded according to a 4 point scale; 1=excellent (cords immobile, no cough, no diaphragmatic movement), 2=good (cords immobile, slight cough or slight diaphragmatic movement), 3=poor (cords moving, bucking), 4=impossible (6).

Anesthesia was continued with 0.5% halothan in a mixture of 33% O₂ + 66% N₂O. At the end of the surgical procedure, residual neuromuscular block was antagonised with 50 μg/kg neostigmin and 20 μg/kg atropine sulfate iv.

RESULTS

The demographic data of the patients were summarized in Table 1.

| Age (year) | 43.4 ± 15 |
| Weight (kg) | 61.7 ± 11.3 |
| Female | 6 |
| Male | 14 |

Table 1: Demographic data of patients.

Fade of responses to TOF stimulation was presented in Figure 1.

Neuromuscular properties of picecuronium bromide were shown in Table 2.

| ED₅₀ (μg/kg) | 41.4 ± 9.1 |
| ED₉₀ (μg/kg) | 59.3 ± 12 |
| Onset of 50% block (min.) | 3.4 ± 0.8 |
| Onset of 90% block (min.) | 4.6 ± 1.1 |
| Time to maximum block (min.) | 5.1 ± 0.7 |
| Time to 25% recovery (min.) | 75.4 ± 19 |

Table 2: Neuromuscular properties of picecuronium bromide.

The mean dose of picecuronium for obtaining 90% neuromuscular block (ED₉₀) was 59.3 ± 12 μg/kg (Table 2). Neuromuscular blockade was 100% in 12 patients and 95 ± 2.5% in the others. Intubation conditions were excellent in 6 patients and were good in the others. The mean time necessary to obtain 90% neuromuscular block was 4.6 ± 1.1 minutes.

DISCUSSION

The clinical need for new neuromuscular blocking drugs still persists today. Generally the desirable properties of a new muscle relaxant include a non-depolarizing mode of action, high affinity for cholinoreceptors at the motor endplate, rapid onset time, absence of cardiovascular side-effects and lack of histamine-releasing properties (1).

Picecuronium bromide has been introduced into clinical practice in eastern Europe recently. Our study was performed to determine the human dose-response relation of picecuronium bromide under general anesthesia.

The second twitch in the train-of-four becomes undetectable at about 90 percent block of the first response. A 95 percent twitch suppression produces sufficient jaw and laryngeal paralysis for laryngoscopy and tracheal intubation (6).

85 to 95 percent twitch suppression was reported to be sufficient for endotracheal intubation in various studies (2, 5, 8, 10, 12). So, we preferred obtaining 90 percent neuromuscular block with increments of picecuronium bromide. We determined ED₉₀ of picecuronium bromide as 59.3 ± 12 μg/kg. This dose was similar with which of Newton (50 μg/kg) and Tassonyi (59 μg/kg) (10, 13). Wierda reported an ED₅₀ of 44.6 to 48.7 μg/kg with three different anesthetic methods (14). In another study, it was reported that ED₉₀ of picecuronium was 44.96 μg/kg and it was claimed that
muscle relaxation could be obtained with 40 to 50 
\( \mu \text{g/kg} \) pipecuronium for 40 to 50 minutes (11).

Some authors reported more lower ED\(_{90}\) and
ED\(_{95}\) using cumulative dose-response logarithmic
curves. The ED\(_{90}\) and ED\(_{95}\) of pipecuronium were
reported as 31.5 \( \mu \text{g/kg} \) and 34.9 \( \mu \text{g/kg} \) by Azad,
33 \( \pm 1.6 \mu \text{g/kg} \) and 35.1 \( \pm 1.7 \mu \text{g/kg} \) by Chae,
22.1 \( \pm 1 \) and 23.6 \( \pm 1.1 \mu \text{g/kg} \) by Foldes (2, 5, 7). Our
results were not comparable with these results.

After intubation, a non-depolarizing agent, usu-
ally in a low dose (ED\(_{90-95}\)), is given to produce
surgical relaxation. This procedure enables the
anesthesiologist to perform a rapid intubation and
yet be able to reverse the subsequent non-depolar-
izing neuromuscular blockade after 30-60 minutes.
When a non-depolarizing agent is used for intub-
ation, higher doses (usually twice the ED\(_{90-95}\)) are
needed in order to produce satisfactory conditions
for intubation within a reasonable period of time
(12). According to these data, our ED\(_{90}\) was suf-
ficient to perform endotracheal intubation smoo-
thly.

In this study, 90 percent twitch suppression was
reached within 4.6 \( \pm 1.1 \) min, in spite of incremen-
ted. This period was 5.4 \( \pm 1.1 \) min. with 44.6 \( \mu \text{g/kg} \)
\( \mu \text{g/kg} \) in Wierda’s study, 5.5 \( \pm 0.8 \) min with 50
\( \mu \text{g/kg} \) pipecuronium in Tassonyi’s study and 5
\( \pm 0.4 \) min. with 59 \( \mu \text{g/kg} \) pipecuronium in Boros’s
study (3, 13, 14). Larijani reported the onset time of
2.5 \( \pm 0.8 \) min. with 70 \( \mu \text{g/kg} \) pipecuronium (9).

Higher doses (80-100 \( \mu \text{g/kg} \)) were reported to
shorten the onset time of neuromuscular block as 2
\( \pm 2.5 \) minutes (4, 5, 6).

As a result, we concluded that good-excellent
intubating conditions could be obtained with 59.3 \( \pm 
12 \mu \text{g/kg} \) pipecuronium bromide within 4.6 \( \pm 1.1 
minutes.

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