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. ED_{90} was found as 59.3 ± 12 µgr/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 µgr/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 sulfat intramuscularly.

In the operating room, venous canulation, ECG monitoring and measurement of blood pressure were performed. Neuromuscular monitoring was carried out with a neuromuscular transmission monitor (Tatex Relaxograph TM). Anesthesia was induced with 5 mg/kg thiopenthal 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 µgr/kg of pipecuronium followed by 5 to 10 µgr/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 % O_2 + 66 % N_2O. At he end of the surgical procedure, residual neuromuscular block was antagonised with 50 µgr/kg neostigmin and 20 µgr/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 : Demografic data of patients.

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

Neuromuscular properties of pipecuronium bromide were shown in Table 2.

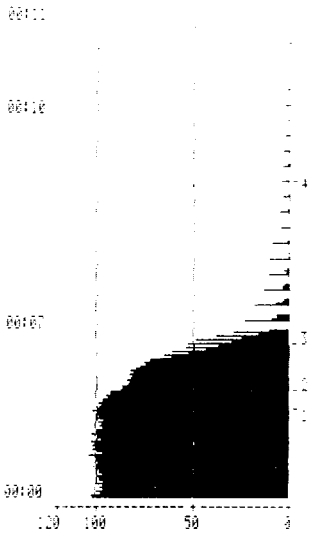

Fig - 1 : Fade of responses to TOF stimulation.

ED_{50} (µgr/kg)	41.4 ± 9.1
ED_{90} (µgr/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 pipecuronium bromide.

The mean dose of pipecuronium for obtaining 90 % neuromuscular block (ED_{90}) was 59.3 ± 12 µgr/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 cholinoceptors at the motor endplate, rapid onset time, absence of cardiovascular side-effects and lack of histamine-releasing properties (1).

Pipecuronium bromide has been introduced into clinical practice in eastern Europe recently. Our study was performed to determine the human dose-response relation of pipecuronium 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 supression produces sufficient jaw and laryngeal paralysis for laryngoscopy and tracheal intubation (6).

85 to 95 percent twitch supression 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 pipecuronium bromide. We determined ED_{90} of pipecuronium bromide as 59.3 ± 12 µgr/kg. This dose was similar with which of Newton (50 µgr/kg) and Tassonyi (59 µgr/kg) (10, 13). Wierda reported an ED_{95} of 44.6 to 48.7 µgr/kg with three different anesthetic methods (14). In another study, it was reported that ED_{95} of pipecuronium was 44.96 µgr/kg and it was claimed that

muscle relaxation could be obtained with 40 to 50 µgr/kg pipecuronium for 40 to 50 minutes (11).

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

After intubation, a non-depolarizing agent, usually 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-depolarizing neuromuscular blockade after 30-60 minutes. When a non-depolarizing agent is used for intubation, 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 sufficient to perform endotracheal intubation smoothly.

In this study, 90 percent twitch supression was reached within 4.6 ± 1.1 min. in spite of increments. This period was 5.4 ± 1.1 min. with 44.6 µgr/kg µgr/kg in Wierda's study, 5.5 ± 0.8 min with 50 µgr/kg pipecuronium in Tassonyi's study and 5 ± 0.4 min. with 59 µgr/kg pipecuronium in Boros's study (3, 13, 14). Larijani reported the onset time of 2.6 ± 0.8 min. with 70 µgr/kg pipecuronium (9).

Higher doses (80-100 µgr/kg) were reported to shorten the onset time of neuromuscular block as 2 to 2.5 minutes (4, 5, 6).

As a result, we concluded that good-excellent intubating conditions could be obtained with 59.3 ± 12 µgr/kg pipecuronium bromide within 4.6 ± 1.1 minutes.

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