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A CLINICAL STUDY ON VECURONIUM IN CHILDREN:
A Comparison with Fazadinium and Pancuronium

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One of the most important drawbacks of non-depolarizing muscle relaxants is that they have a longer time to the onset of action and longer duration of action. Vecuronium (Org NC 45) (Vm) which is a steroidal agent similar to pancuronium (Pm) but with only one quaternary nitrogen group was found in both experimental and clinical studies to be more rapid in onset and shorter in duration of action than Pm[1-4]. This study was designed to evaluate the use of Vm in children and compare its effects to those of Pm, a chemically related compound whose use in children has been well established and fazadinium (Fm), a non-depolarizing muscle relaxant with a faster onset of action, in doses reported to be sufficient to provide satisfactory intubating conditions[5-7].

Material and Methods

Ninety children between the ages of six months to twelve years who underwent elective surgery which required tracheal intubation and/or muscle relaxation were studied. The patients were randomly assigned to one of three groups: The first group received Vm 0.1 mg/kg (n: 30), the second group Fm 1 mg/kg (n: 30) and the third group Pm 0.1 mg/kg (n: 30). These doses are considered approximately equipotent providing satisfactory intubating conditions[5-7]. Each patient was given a single dose of relaxant as an i.v. bolus. Distribution according to age, sex, weight and duration of anesthesia in all groups are shown in Table I.

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TABLE I: Physical Characteristics of the Patients and Duration of Anesthesia

Relaxant	n	Sex F	Sex M	Age (yrs)	Weight (kg)	Duration of Anesthesia (min)
Vecuronium	30	11	19	6.4 ± 0.6	18.5 ± 1.2	63.4 ± 4.8
Fazadinium	30	11	19	5.6 ± 0.6	18.1 ± 1.4	73.2 ± 3.4
Pancuronium	30	10	20	6.5 ± 0.6	20.0 ± 1.0	81.1 ± 5.0

Premedication consisted only of atropine 0.015 mg/kg in the younger and atropine 0.015 mg/kg plus diazepam 0.15 mg/kg i.m. in the older children approximately one hour prior to induction of anesthesia. Following preoxygenation, anesthesia was induced with thiopentone i.v. or 66 percent nitrous oxide and halothane in oxygen via a face-mask. After the stabilization of cardiovascular indices and respiration, a neuromuscular blocking agent was injected. Tracheal intubation was attempted when respiratory efforts diminished. Intubating conditions were graded as excellent, satisfactory, fair and not possible according to the criteria proposed by Lund and Stovner[8]. Anesthesia was maintained with 66 percent nitrous oxide in oxygen and halothane in an inspiratory concentration not exceeding one percent. The time interval to the onset of apnea, duration of the apnea and the time interval to spontaneous recovery of respiration were noted. Surgical relaxation was assessed according to respiratory movements, resistance felt to the rebreathing bag and elasticity of the lungs. Duration of satisfactory relaxation and the neuromuscular transmission at the point when relaxation became inadequate were also recorded.

Neuromuscular transmission was monitored by a portable nerve stimulator. The ulnar nerve was stimulated at the elbow by surface electrodes using four square-wave supramaximal stimuli at a rate of 2 Hz (train of four, T4). The number of twitch responses was counted and presence or absence of visible fade to T4 stimuli was noted to evaluate the neuromuscular transmission[9,10]. T4 stimuli were applied to record the speed (the time from the end of injection of relaxant to the maximum effect), the depth (maximal depression in response to T4 stimuli) and the duration of effect (the time of the first sign of recovery and to complete recovery in cases where neuromuscular transmission recovered spontaneously). The absence of visible fade was taken as being equivalent to a train-of-four ratio of 75 percent or more, therefore, indicating an adequate neuromuscular transmission[11]. At the end of surgery the anesthesia was discontinued and the children having signs of muscle paralysis in response to T4 stimuli were given neostigmine 0.06 mg/kg and atropine 0.02 mg/kg to reverse the residual relaxant effect.

Each subject served as his own control. Data is given as the mean ± SEM and the significance of the difference between groups was tested by the Student's *t* test; $p<0.05$ was considered significant.

Results

Effect on Neuromuscular Transmission

Speed of onset of effect taken as the time from the end of injection of the relaxant to maximum depression in muscle response to T4 stimuli was significantly faster with Vm than Fm and Pm (Table II).

Depth of effect. There was complete blockade in neuromuscular transmission with no response to T4 stimuli in 19, 18 and 19 patients in Vm, Fm and Pm groups, respectively. In the remaining patients transmission continued to a variable degree showing one, two, three, and four responses with marked fade to T4 stimuli. The percentage of cases with no response to T4 stimuli was similar in all groups (Table II).

Duration of effect was taken as the time of the first sign of recovery and to spontaneous recovery of neuromuscular transmission. The mean time to the first sign of recovery was the shortest in the Vm group, the difference from the Fm and Pm groups being highly significant (Table III). In cases where transmission recovered spontaneously the mean times to complete recovery of blockade were

TABLE II: Speed and Depth (as evaluated by the number of responses to T4 at the time of maximum depression) of Effect

Relaxant	Vecuronium	Fazadinium	Pancuronium
Time to maximum effect (min)	3.6 ± 0.2*	6.1 ± 0.4**	6.9 ± 0.4
Number of twitch responses to T4			
No response	19 pts (63%)***	18 pts (60%)	19 pts (63%)
One response	7 pts	5 pts	7 pts
Two responses	–	3 pts	4 pts
Three responses	1 pts	–	–
Four responses	3 pts	4 pts	–

* High significant difference between Vm and others ($p<0.001$)
** Significantly shorter than Pm ($p<0.01$).
*** Percentage of cases showing complete blockade.

40.9 ± 1.9, 72.0 ± 6.6 and 75.0 ± 8.0 min in Vm, Fm and Pm groups, respectively. A limited number of cases who showed spontaneous recovery of transmission at the end of surgery in the Fm and Pm groups precludes any statistical comparison (Table III).

TABLE III: Mean Duration (min) of Effect of Vm, Fm and Pm

Relaxant	Time to first sign of recovery	Time to spontaneous recovery
Vecuronium	13.0 ± 0.9* (n: 30)	40.9 ± 1.9 (n: 27)
Fazadinium	26.7 ± 1.2 (n: 30)	72.0 ± 6.6 (n: 5)
Pancuronium	27.0 ± 1.0 (n: 30)	75.0 ± 8.0 (n: 5)

* Highly significant difference from others ($p < 0.001$).

Intubating times and conditions. The mean intubating time was shortest in the Vm group, the difference from the Pm group being significant (Fig. 1). Intubation was possible in all patients with varying conditions. The percentage of patients that could be intubated with satisfactory or excellent conditions were 70, 70 and 57 percent in the Vm, Fm and Pm groups, respectively. Although Vm provided the best conditions, the difference between the groups was not statistically significant (Fig. 1).

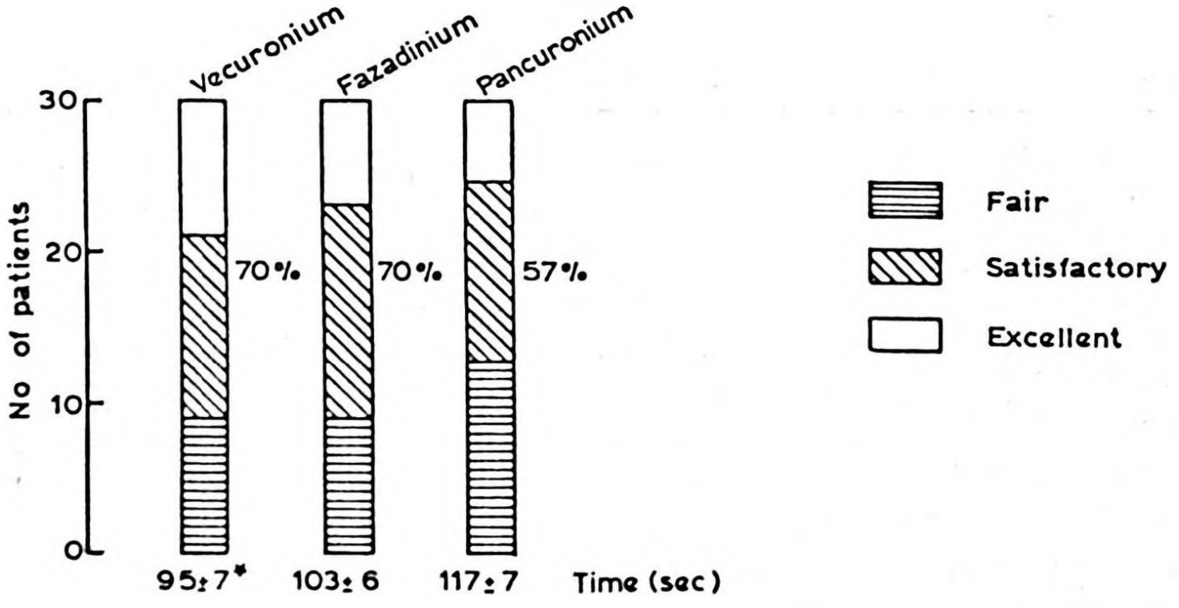

Fig. 1 : Mean intubating times and conditions following Vm, Fm and Pm injection.
* Significantly shorter than Pm group.

Surgical relaxation. In three cases (one in each group) abdominal relaxation was not satisfactory from the beginning. The mean durations of satisfactory relaxation provided by Vm, Fm and Pm were 19.2 ± 1.2, 30.6 ± 1.4 and 34.6 ± 1.3 min, respectively. A highly significant difference was found between Vm and the others in this respect. When relaxation was considered inadequate, transmission varied from one to four responses with a marked fade to T4 stimuli (Table IV).

TABLE IV: Duration of Satisfactory Relaxation and Neuromuscular Transmission at the Time of Inadequate Relaxation

Relaxant	Vecuronium	Fazadinium	Pancuronium
Duration of relaxation (min)	19.2 ± 1.2* (n: 29)	30.6 ± 1.7 (n: 29)	34.6 ± 1.3 (n: 29)
Number of twitch responses to T4			
One response	2 patients	6 patients	9 patients
Two responses	6 patients	8 patients	5 patients
Three responses	8 patients	6 patients	3 patients
Four responses	13 patients	9 patients	12 patients

* High significant difference between Vm and the others ($p<0.001$).

Respiration. Apnea did not occur in a total of six patients (one in the Vm, four in the Fm and one in the Pm group). The time interval to apnea was significantly shorter with Vm in comparison to the others. In addition, the intervals to spontaneous recovery of respiration evaluated clinically were significantly shorter in the Vm group (Table V). In the remaining patients, respiration was found to be adequate within a few minutes after reversal.

TABLE V: Effect on Respiration

Relaxant	Interval to apnea (sec)	Duration of apnea (min)	Interval to recovery of respiration (min)
Vecuronium	95.7 ± 10.2* (n: 29)	17.1 ± 1.3** (n: 29)	37.3 ± 1.7*** (n: 28)
Fazadinium	142.5 ± 10.3 (n: 26)	21.4 ± 1.8 (n: 26)	58.2 ± 3.8 (n: 17)
Pancuronium	165.7 ± 11.7 (n: 29)	22.5 ± 1.1 (n: 29)	60.6 ± 3.7 (n: 14)

* ** *** Significantly less than others ($p<0.05$, 0.001 and 0.01 respectively).

Duration and mode of recovery of neuromuscular transmission. In cases with complete neuromuscular blockade i.e., with no response to T4 stimuli, intervals to complete abolition of responses and to the re-appearance of each response to T4 stimuli were calculated and are shown in Fig. 2. All these values were found to be significantly less ($p<0.001$) in the Vm group than the others, showing a faster recovery in transmission following Vm injection.

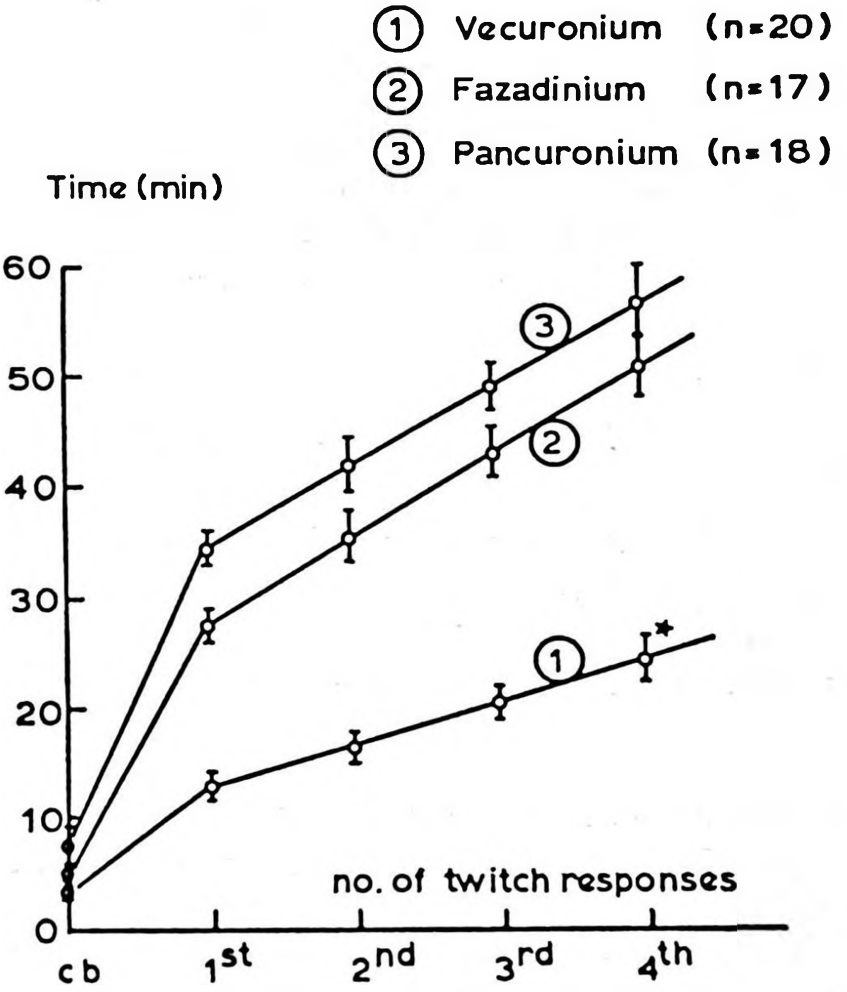

Fig. 2 : Mean times form the Injection of relaxant to complete abolition and re-appearance of consecutive train of four responses. O: end of injection of relaxant, CB: complete blockade in transmission with no response to T4 stimuli.

* Significant difference from others at all points ($p < 0.001$).

At the end of surgery, transmission was found adequate with no fade in response to T4 stimuli in twenty-seven, five and five patients in the Vm, Fm and Pm groups, respectively (Table III). In the remaining patients transmission was reversed with atropine and neostigmine. At the time of reversal all the patients had a muscle response of two or more twitches to T4 stimuli. Reversal was easy and complete within 7.9 ± 4.0 and 8.4 ± 3.9 min in the Fm and Pm groups, respectively. In the

Vm group only three patients having four responses with marked fade at the end of surgery required reversal.

There were two cases in each Vm and Fm group and one in the Pm group with skin eruptions on the face, neck and upper chest area, disappearing within five minutes without treatment. But none of these children developed hypotension or severe tachycardia. No localized reactions at the site of i.v. injection were observed.

Discussion

It has been suggested that Vm is an advancement in this field in respect to being a potent, fast-acting, non-polarizing muscle relaxant[1]. The data obtained from the present study demonstrates that Vm has a significantly faster onset and shorter duration of action than both Fm and Pm in children. The results obtained with Vm and Pm are in agreement with those reported by pharmacokinetic and dynamic[3,4], experimental[1,2] and clinical studies carried out both on adults[12-14] and children[6,15]. To our knowledge a study comparing Vm with Fm which is a fast acting, non-depolarizing relaxant[16,17], has not been reported.

Vm was found to be fastest in action when compared to Fm and Pm. The mean time to maximum effect recorded as 3.6 min with Vm, was twice as long with Pm while Fm was intermediate in this respect. Using similar dosages of Vm the mean time to maximum effect has been reported to be 3.9 min[14], 4 min[18] and 2.4 min[5] in adults and approximately 2 min in a study carried out on children by Ferres et al[6]. The duration of action of Vm was also shorter than both Fm and Pm. The mean time to the first sign of recovery of transmission was 13.0 min with Vm, whereas it was 26.7 and 27.0 min with Fm and Pm, respectively. Another aspect of Vm was that in the majority of patients transmission recovered spontaneously within a mean time of 40.9 min (n: 27). This may be an advantage in cases undergoing shorter operations requiring intubation and/or muscle relaxation and where the use of either neostigmine or a depolarizing relaxant is not desired. Duration of action taken as the time between the end of injection and the recovery of the twitch height to 90 percent of control was found to be 44.1 min by Agoston et al[5]. Since no visible fade in response to T4 stimuli can be taken as 75 percent or better twitch height[11], our results with 40.9 min are in agreement with the above-mentioned study. Gramstaad et al[13] have also reported the duration of action of Pm to be twice as long as that of Vm.

In this study, depth of effect of relaxants used was determined by the number of twitches and the presence of fade to T4 stimuli. Lee[9] found that elimination of the fourth, third and second twitches in the train correlated with 75, 80 and 90 percent block of the first response in the train, respectively. When all twitches in the train

were absent 100 percent or complete blockade was present. Thus for clinical purposes, merely counting the twitches in the T4 response quantifies the extent of blockade. Although a dose of 0.1 mg/kg Vm is reported to provide complete blockade in adults[5,14,18-20], in the present study none of the relaxants tested provided complete blockade in all patients. Fisher and Miller[21] have also reported that larger dosages of Vm were required in pediatric patients to achieve the same degree of blockade. If complete blockade is to be obtained, dosages of the three relaxants should be increased. Although Crul and Booij[22], Agoston et al[5] and Viby-Mogensen et al[23] have reported Vm to be slightly more potent than pancuronium, in our study the number of cases with complete blockade were similar in all groups, indicating that these dosages were approximately equipotent.

Vm provided slightly better conditions for intubation in a shorter time than both Fm and Pm. Intubation was possible in all cases before the maximum effect was reached. Although Bencini and Newton[24] have reported that Vm in a dose of 0.1 mg/kg provided good intubating conditions about 3.5 min after injection and at least 30 sec after the establishment of complete blockade, findings in other studies both in adults[5,18] and children[6] show that Vm in a similar dosage provides satisfactory conditions for intubation, around 90 sec; these are in agreement with our results. In our opinion there is no need to delay intubation to obtain better conditions, until maximum effect of relaxant is established.

Satisfactory abdominal relaxation provided by Vm lasted for a mean time of 19.2 min, considerably shorter than both Fm and Pm. This may be an advantage in cases with short duration which require muscle relaxation. When relaxation was found to be inadequate, neuromuscular transmission varied from one to four responses to T4 stimuli. Miller[25] points out that in an adequately anesthetized patient in which two of the T4 responses are eliminated, muscle relaxation for abdominal surgery is adequate. This difference may be due to the different levels of anesthesia.

The effect of Vm on respiration also differed significantly from Fm and Pm in respect to speed and duration. Apnea produced by Vm occurred at a mean time of 95,7 sec and lasted 17.1 min, both figures being significantly less than Fm and Pm. Also in the majority of cases respiration recovered spontaneously within a mean time of 37.3 min, again being significantly faster than the others.

In children receiving Fm and Pm, the relaxant effect was reversed and antagonism was easy and prompt since transmission had recovered, showing two or more responses to T4 stimuli before reversal was attempted. Contrary to this, in the majority of the cases (n: 27) receiving Vm, transmission recovered spontaneously with no visible fade to T4 stimuli not requiring antagonism. This finding also noted by Kerr and Baird[26], provided transmission is monitored, may indicate an advantage especially in cases where the use of neostigmine is undesirable.

In the Vm series no evidence of bronchospasm was noted but two children manifested typical histamine flush following i.v. injection. Marshall et al[2] have reported that both in experimental animals and human volunteers, Vm produced less evidence of histamine release than Pm and tubocurarine.

In conclusion, Vm was found to be more rapid in onset and shorter in duration of action than both Fm and Pm in children and may offer advantages over the currently available neuromuscular blocking drugs in surgical interventions of short or intermediate duration providing good intubating conditions and satisfactory abdominal relaxation. The doses used in this study were found to be approximately equipotent.

Summary

Ninety children in groups of 30, whose ages ranged between six months to twelve years were given vecuronium, fazadinium and pancuronium as a single i.v. bolus of 0.1, 1.0 and 0.1 mg/kg, respectively. Their effects on neuromuscular transmission and respiration, intubating times and conditions with abdominal relaxation they provided are evaluated. Mean times to onset and duration of effect, mean durations of apnea and relaxation were all significantly shorter with Vm than either with Fm or Pm. Transmission recovered spontaneously in the majority of patients in the Vm group within a mean time of 40.9 min. Dosages used were found to be approximately equipotent. Intubation could be carried out in a shorter time with slightly better conditions with Vm. Vm may be advantageous in children undergoing surgical intervention with short or intermediary duration and where the use of either a depolarizing relaxant or an anticholinesterase is not desirable.

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