A STUDY OF THE NEUROMUSCULAR BLOCKING PROPERTIES AND CARDIOVASCULAR EFFECTS OF VECURONIUM

BY

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THIS DISSERTATION IS SUBMITTED IN PART FULFILMENT FOR THE REQUIREMENTS OF THE DEGREE OF MASTER OF MEDICINE IN ANAESTHESIA OF THE UNIVERSITY OF NAIROBI,1991.

DECLARATION.

This dissertation is my original work and has not to my knowledge been submitted for a degree in any other University.

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This dissertation has been submitted for examination with my approval as University supervisor.

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A C K N O W L E D G E M E N T S

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LIST OF FIGURES.

CONTENTS

S U M M A R Y.

Vecuronium bromide in a standard dose of 0.1mg per kilogram body weight was used on one hundred patients of the American Society of Anaesthesiologists status I and II undergoing abdominal or limb surgery. The time of onset of action with each intravenous dose of vecuronium and its duration of action time were measured. The pulse rate and blood pressure were monitored before and after administration of vecuronium.

Informed verbal consent was obtained from each patient. The premedication, induction, maintenance and reversal drugs were standardized. A nerve stimulator on the ulnar nerve was used to obtain onset of maximal block and time of at least 75% recovery from the block. An automatic electronic blood pressure machine model DS.91 was used to monitor the pulse rate and blood pressure at the necessary intervals.

It was found that the average onset time of action of vecuronium 0.1mg/kg was 194 seconds (3 minutes 14 seconds). The average duration of action time was 29.55 minutes. A decline in pulse rate and mean arterial pressure was noted after the induction of anaesthesia. This was not found to be clinically significant. Intraoperatively, from time of injection of vecuronium to twenty minutes later, there was minimal change in pulse rate and mean arterial pressure.

INTRODUCTION.

The introduction of the use of drugs which block the neuromuscular junction of skeletal muscles to reduce muscle tone was one of the major milestones of anaesthesia. In clinical use the drugs are reckoned to be remarkably safe provided that the users understand their actions and how these can be changed by disease and by other drugs. But a survey of deaths attributable to anaesthesia identified respiratory inadequacy following myoneural blockade as an important factor of anaesthetic mortality (1).

Curare was the first muscle relaxant to be used in 1942 in clinical practice. Curare's use was associated with many drawbacks which led to the search for other neuromuscular blocking agents. None of those newer neuromuscular blocking agents has proved to be ideal and the search for better drugs in clinical practice is still on (2).

The requirements of the ideal relaxant, it is generally acknowledged,are [3,6].

1) The neuromuscular blocking drug should be competitive and non-depolarizing.

2) The cessation of neuromuscular blockade should not depend on renal or hepatic function.

3) Chemical decomposition of the drug in the body would be acceptable provided the breakdown products do not posses any neuromuscular blocking powers or produce other unwanted effects.

4) The drug should have a relatively short duration of action time. When a longer duration is desired repeated or continous administration can be used. With such usage lack of cumulative effects would be desired.

5) It should be highly specific so that no harmful effects on other systems occur.

6) The neuromuscular blockade should be antagonized easily by acetylcholinesterase inhibitors.

With the above requirements in mind a lot of new drugs have been developed tested and introduced into clinical practice None has proved to be the ideal muscle relaxant. Thus as new neuromuscular blocking agents appear on the market their use must be carefully introduced into our practice if some advantage is foreseen over those already in use.

More recent advance research on Pancuronium has led to the development of Vecuronium.[4,5]

Vecuronium is said to have the advantages associated with pancuronium but unlike pancuronium has minimal side effects on the cardiovascular system.

AIMS AND OBJECTIVES OF THE STUDY.

The main aims and objectives of the study were:-

(1) To observe the neuromuscular blocking effects of vecuronium when used in clinical practice.

(2) To evaluate the average onset time of action and duration of action time of vecuronium.

(3) To evaluate the side effects of vecuronium on the cardiovascular system.

(4) To make appropriate recommendations about the use of vecuronium (if any) in contemporary clinical practice.

METHODS AND MATERIALS.

1. PATIENT SELECTION.

The study was carried out on a hundred adults patients. The patients were above eighteen years old and belonged to the American Society of Anaesthesiologists status I and II.

The American Society of Anaesthesiologist classification of patients accoridng to their general condition is as follows:-

ASA 1 - A normal healthy patients.

II - A patient with mild systemic disease.

III - A patient with severe systemic disease that limits activity but is not incapacitating.

V - A patient with an incapacitating systemic disease that is a constant threat to life.

V - A moribund patient who is not expected to survive 24 hours

with or without an operation.

The patients were undergoing limb or abdominal surgery. They all had haemoglobin levels above 10 gm % and no electrolyte inbalance. Informed verbal consent was obtained from each patient. The patients were starved overnight.

PROCEDURE.

The body weight of the patient was taken in kilograms. A standardized premedication of 0.6 mg of atropine and 50mg Pethidine intramuscularly was given half an hour before the patient presented in theatre. Induction of anaesthesia was done using a sleep dose of thiopentone, that which abolished the eyelash reflex. Tracheal intubation was done after 100 mg of suxamethonium for muscle relaxation had been given and the lungs inflated with 100% Oxygen. When signs of the wearing off of suxamethonium were evident, and a good response of the thumb to stimulation

of the ulnar nerve established, an intravenous dose of vecuronium of 0.1mg/kg was administered The ulnar nerve was stimulated at the wrist with surface electrodes. The subsequent movement of the thumb then used to assess neuromuscular function. The pattern of stimulation used was the train of four. This consisted of the application of a short train of supramaximal stimuli at a low frequency of 2 Hertz for 2 seconds (four stimuli in 2 seconds), hence the term train of four. The response obtained before the administration of vecuronium was four equal twitches,this was taken as 0% block. The intravenous dose of vecuronium was administered and stimulation continued at thirty seconds intervals until no response was observed. This was taken as the onset time of an intense block on the neuromuscular junction. The stimulation was then done at five minutes intervals. A record was kept when at least three responses in the count

of four occured. This was taken to be the end of the neuromuscular block.

The pulse rate and blood pressure were recorded before the induction of anaesthesia two minutes after the injection of vecuronium and at two minutes intervals thereafter for ten minutes. More readings were taken after fifteen and twenty minutes.

Intermittent positive pressure ventilation was provided by a manley ventilator (Medishield Model MPT). The neuromuscular block was reversed with neostigmine 2.5 mg and atropine 1.2 mg. The patients were extubated ater spontaneous respiration was adequate and oro-pharyngeal suction had been carried out.

MATERIALS

1) Automatic blood pressure machine Model DS-91. It utilized the Riva Rocci Korotkow method and has a K sound detector. The accuracy of the machine is given as Pressure +/-3 mmHg Pulse rate +/-5% of reading.

The same machine was used on all patients.

2) Weighing Scale - A mechanical scale was used the weight was taken after the machine was set to read zero.

3) Nerve stimulator and surface electrodes. The Microstim supramaximal nerve stimulator with ordinary pre-jelled E.C.G. electrodes was used.

R E S U L T S.

ONSET OF ACTION.

This was taken to be from time of injection of vecuronium to time of complete depression of the evoked twitch reponse. The average onset time of action of vecuronium at a dose of 0.1 mg/kg was found to be 194 seconds $\pm$ 48 seconds. (1 standard deviation) (Figure 1).

DURATION OF ACTION.

The duration of action time was taken as from time of injection (time 0) to time when the train of four had recovered from complete depression to show a count of at least three in the train of four. This was taken to be at least 75% recovery. The average duration of action time was found to be 29.55 minutes $\pm$ 4.7 minutes (1 standard deviation) (Figure 11).

HAEMODYNAMIC DATA.

1. PULSE RATE.

The mean pulse rate preoperatively was 101 beats per minute. This rate was taken after atropine premedication.

The mean rate after the injection of vecuronium was as follows at 2,4,6,8,10,15 and 20 minutes:- 102,96,92,91,89,90 and 90 beats per minute respectively (Figure III).

The line graph shows a steady decline in the pulse rate from 2 minutes onwards. The decline was highest at 10minutes whereby a mean difference of 13 beats per minute was observed. The change was not found to be statistically or clinically significant.

2. MEAN ARTERIAL BLOOD PRESSURE.

The mean arterial blood pressure was calculated from the systolic and diastolic pressure viz:-

⅓ pulse pressure + diastolic pressure.

The mean arterial blood pressure before induction of anaesthesia was 96 mmHg. The mean pressures after injection of vecuronium at 2,4,6,8,10,15 and 20 minutes were 88.3, 87.5 87.3, 86.1, 87.7, 89.2 and 90 mmHg respectively (Figure IV). The changes were not found to be of any significance.

DISCUSSION.

Vecuronium bromide was developed from a continuation of the search which originally resulted in the invention of pancuronium bromide in 1964. The steroid nucleus is the rigid framework molecule for supporting the quaternary ammonium compounds in the design of non-depolarizing neuromuscular blocking agents. Vecuronium differs from pancuronium only in the nature of its 2 B nitrogen atom which is tertiary as distinct from quaternary (Figure V). This single apparently minor molecular modification gives a drug molecule which has proved to be significantly different in physical and chemical properties from pancuronium.

Animal studies showed Org NC 45 later renamed vecuronium to posses high neuromuscular blocking potency but very low potency in blocking the cardiac muscarinic receptors.[5] The same study

estimated the relative neuromuscular and vagal blocking potencies and showed it to have upto 63 times the power to block the neuromuscular junction compared with its ability to block the vagus.

Once the animal studies showed this exceptionally wide margin between the actions of vecuronium further investigations and screening tests were done and then clinical trials of vecuronium in humans were started.

This study has compared and contrasted the findings on our population to those found with use of vecuronium in other centres around the world.

The onset time of vecuronium has been reported to be dose dependant. In one study a dose of 0.05 mg/kg had an onset time of 4.5 minutes ± 0.6 minutes, a dose of 0.1 mg/kg also had on onset of 4 minutes.[7,8]

In a study when vecuronium and pancuronium were compared at equipotent doses the onset of action of vecuronium

appeared to be slightly faster but the difference was not statistically significant.[9,10] In our study the onset time was 3 minutes 14 seconds which also disqualifies the use of vecuronium from rapid sequence intubation. Comparison of suxamethonium and vecuronium for intubation of the trachea clearly shows suxamethonium to be a more superior agent in a class of its own.[14] Certain studies have shown that the time of onset, the amount of block and the duration of action of vecuronium are dose dependant and that the use of nitrous oxide and halothane would necessitate the use of a smaller dose of vecuronium. Studies have shown that the ED 90/95 (that dose which produces 90-95% depression of the evoked twitch reponse of the adductor pollicies) can be seen to range from 36 to 56 ug/kg with nitrous oxide and opoids.

The duration of action is not only influenced by the dose but also by the other anaesthetic drugs used. In one study when an intubating dose of vecuronium of 0.1mg/kg was succeded by a maintenance anaesthetic technique of nitrous oxide and narcotic supplementation, the duration of action time was shown to be 44.1 ± 3.9 minutes.[7]

The potentiation of vecuronium by volatile agents has been shown to be much shorter than that seen with either pancuronium or d-tubocurarine.[10]

A difference in the manner by which volatile anaesthetics enhance the neuromuscular block produced by vecuronium has been found, in that the peak effect of vecuronium is less dependant on the concentration of the volatile anaesthetics.[12]

The dose-response relationships and the neuromuscular blocking effects of vecuronium and pancuronium during Ketamine anaesthesia have also been studied.[15] An increase in duration of

action . following successive doses of vecuronium was seen. In another study when an intubating dose of vecuronium of 0.1mg/kg was used with narcotic supplementation the first thumb twitch was detectable at approximately 25 minutes, it was further shown that following single injection, multiple injection or long lasting intravenous infusion the recovery times are remarkably short and relatively constant.[13]

The type of monitoring of neuromuscular blockade used in this study cannot be used to give quantitative conclusion about the action of relaxants at the receptor. Studies have been done to demonstrate that response to stimulation of a nerve is not reduced unless more than 70 percent of the receptors are occupied by a non-depolarizing relaxant.[21] Twitch is completely eliminated when 90

percent of the receptors are occupied. Studies have shown that for clinical purposes merely counting the number of twitches in the Train of four response can quantify the extent of block and dose of Tubocurare and probably other non-depolarizing muscle relaxants required to achieve certain degrees of relaxation[22,23]

Vecuronium has consistently been shown to be associated with cardiovascular stability although a small clinically insignificant decrease in heart rate has been reported by some authors.[24,25] Thirty five patients of ASA I without any cardiovascular disease were studied to better confirm the cardiovascular effects of vecuronium.[16] The heart rate and arterial blood pressure were monitored after an intubating dose of vecuronium and pancuronium in patients anaesthetized with either halothane or enflurane in whom surgical stimulation was not present. Pancuronium was seen to regularly produce tachycardia whereas vecuronium produced minimal changes in cardiovascular signs. A similar study comparing vecuronium and pancuronium showed a decrease of heart rate in majority of patients following vecuronium and an increase following Pancuronium[17] the conclusion reached was that vecuronium was devoid of vagal blocking action.The

use of vecuronium could be safer when an increase in heart rate is contraindicated or when a liability to dysrrhythmias is considered. On the other hand drug or reflex induced bradycardia during surgery may appear more easily.

Adverse anaesthetic reactions when vecuronium is used with commonly used anaesthetic drugs has been reported. Vecuronium was reported to occasionally give reaction when used with thiopentone methohexitone and etomidate (18). No such reaction was observed in this study.

Any residual vecuronium blockade was readily antagonized by anticholinesterase agents. This was found to be necessary before adequate spontaneous respiration was established.

Animal experiments indicate that vecuronium is not dependant on the kidney as its principle route of elimination. When the liver was

excluded from the circulation in anaesthetized cats prolongation of the vecuronium induced neuromuscular blockade was seen (19). There is evidence that in man vecuronium is rapidly cleared from the plasma by the liver. It would seem likely that rapid plasma clearance resulting from hepatic uptake is a major contributory factor to the short duration of vecuronium blockade (20). Thus impaired renal function dose not contraindicate the use of vecuronium.

CONCLUSION AND RECOMMENDATION.

The study has shown that vecuronium is a potent non-depolarizing neuromuscular agent with a shorter duration of action than those currently available in our practice. The use of vecuronium would be recommended in surgical procedures of short or intermediate duration.

Vecuronium is safer than pancuronium in patients with poor cardiovascular reserve where an increase in heart rate is contraindicated. On the other hand when vecuronium is used drug or reflex induced bradycardia during anaesthesia and surgery may appear more easily. In our practice where the equipment for continous monitoring of cardiac activity is not always available the vagolytic and sympathomimetic properties of pancuronium could be to some advantage. Thus the use of vecuronium when available should be reserved for deserving cases clinically indicated.

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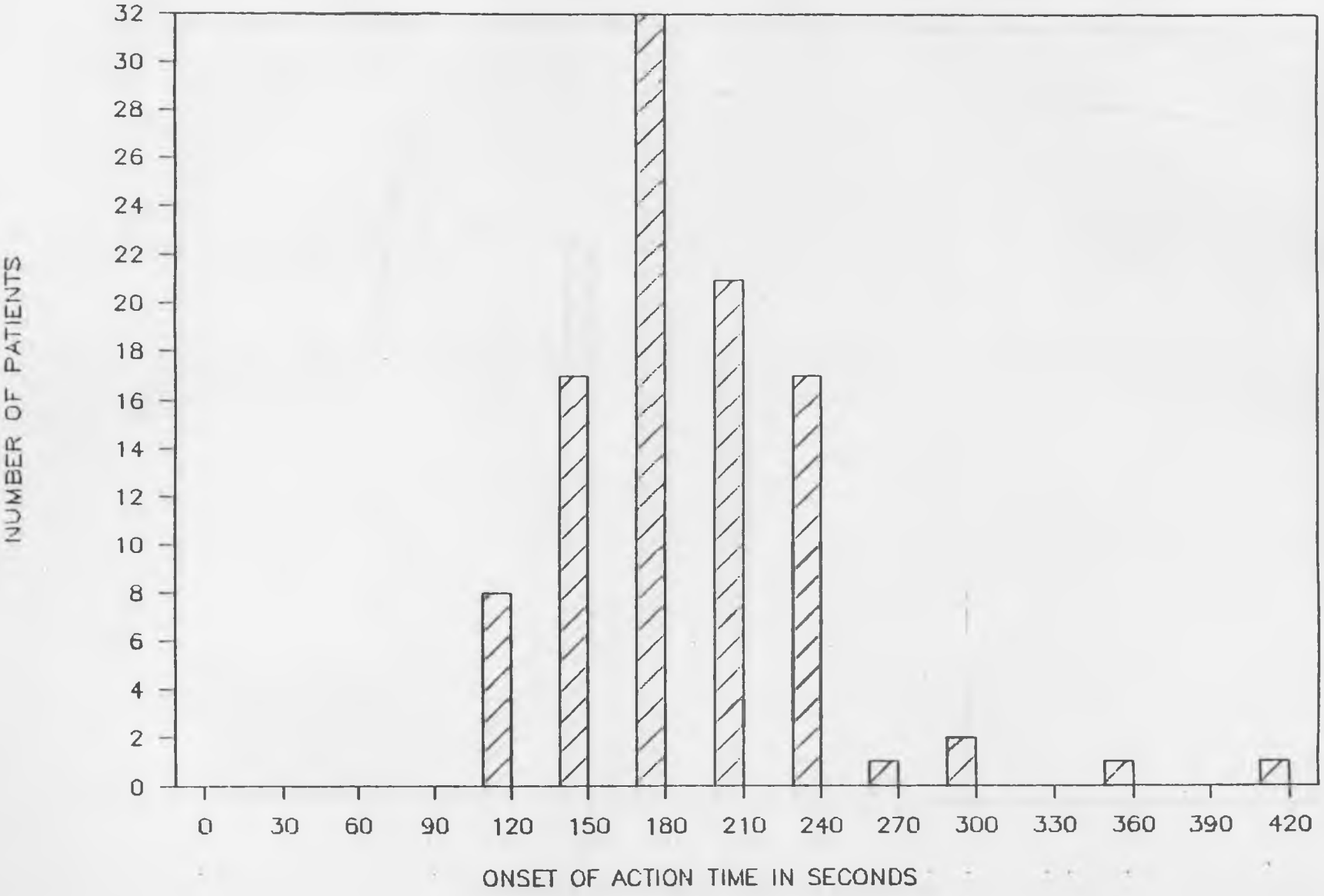
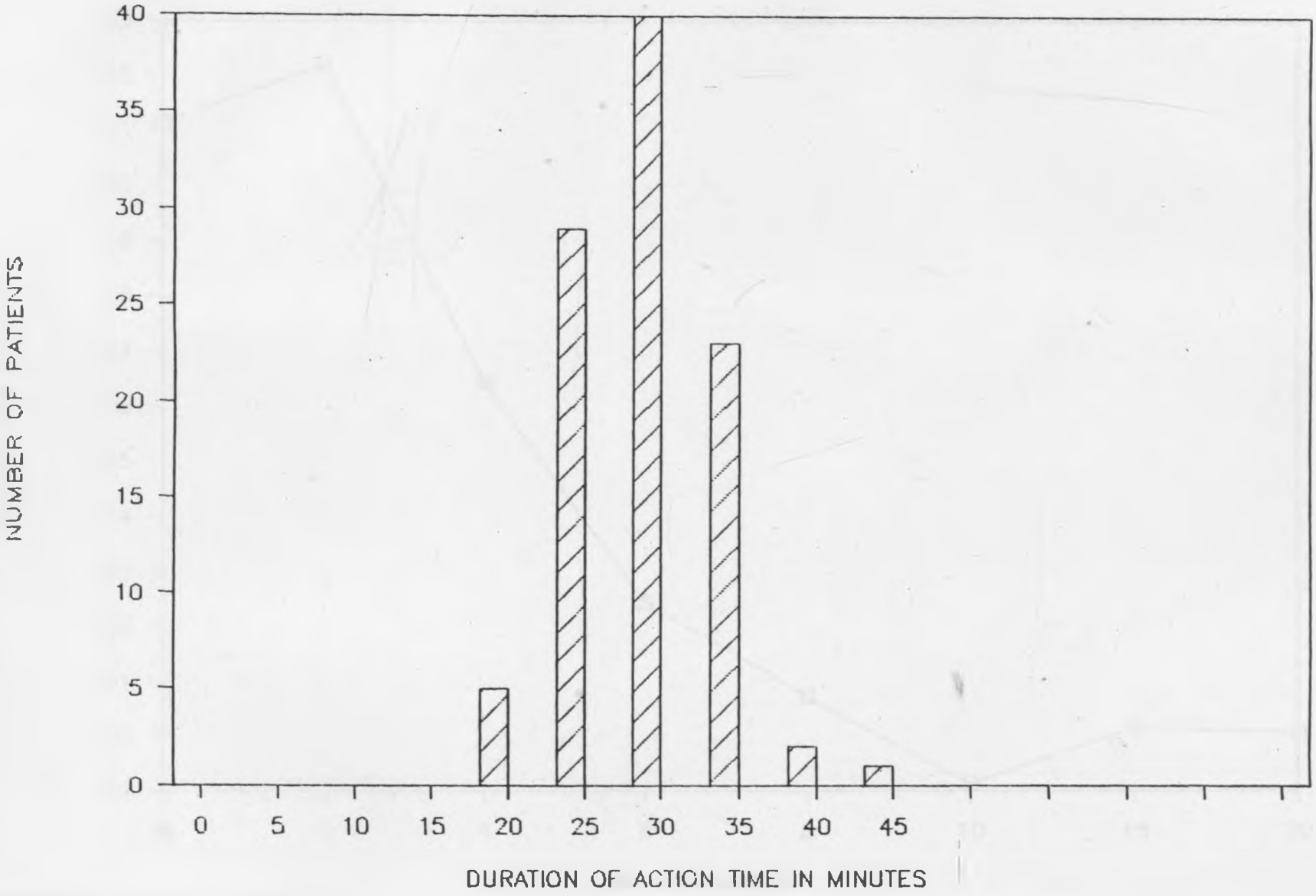
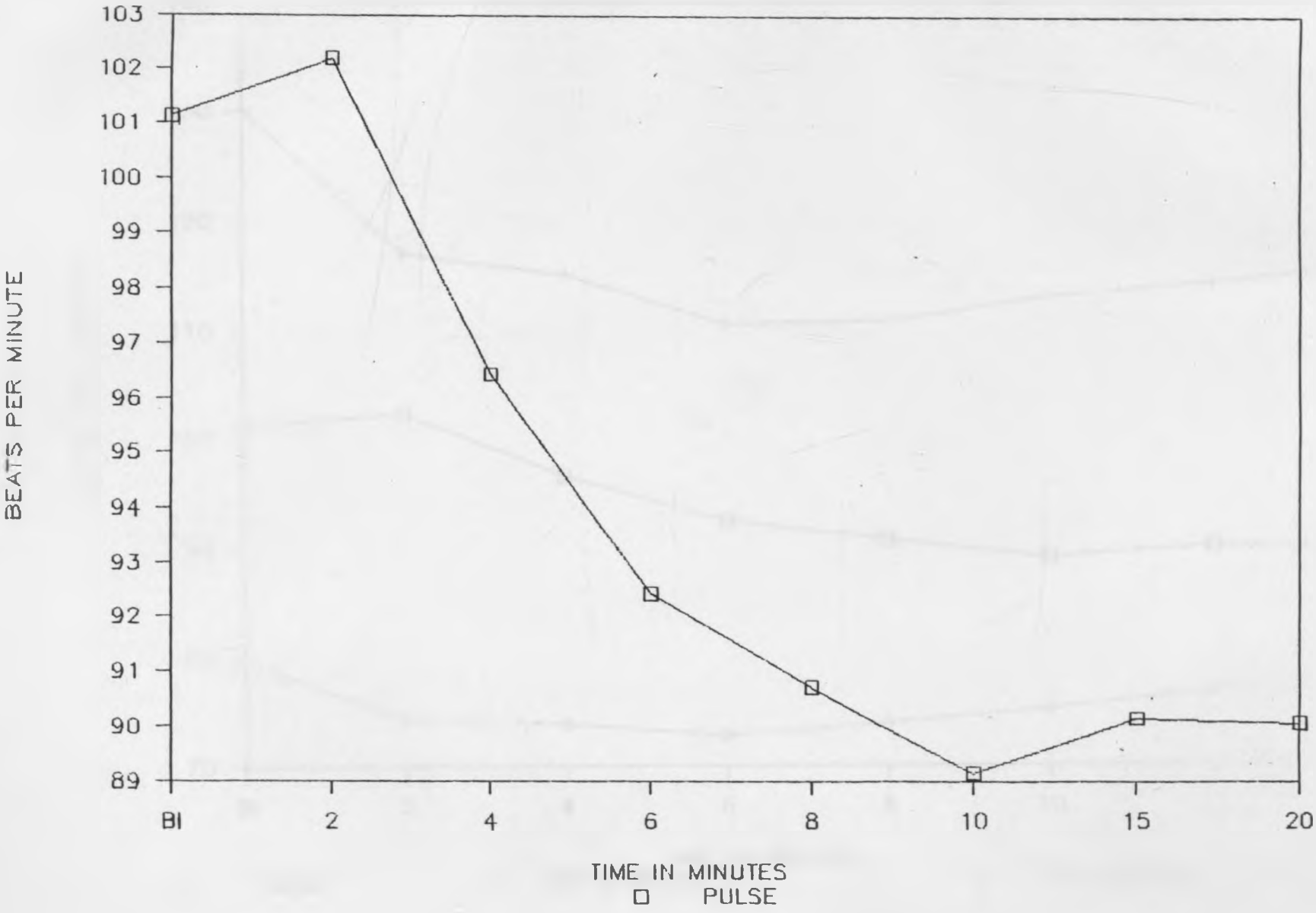
ONSET HISTOGRAM



DURATION HISTOGRAM



PULSE LINE GRAPH



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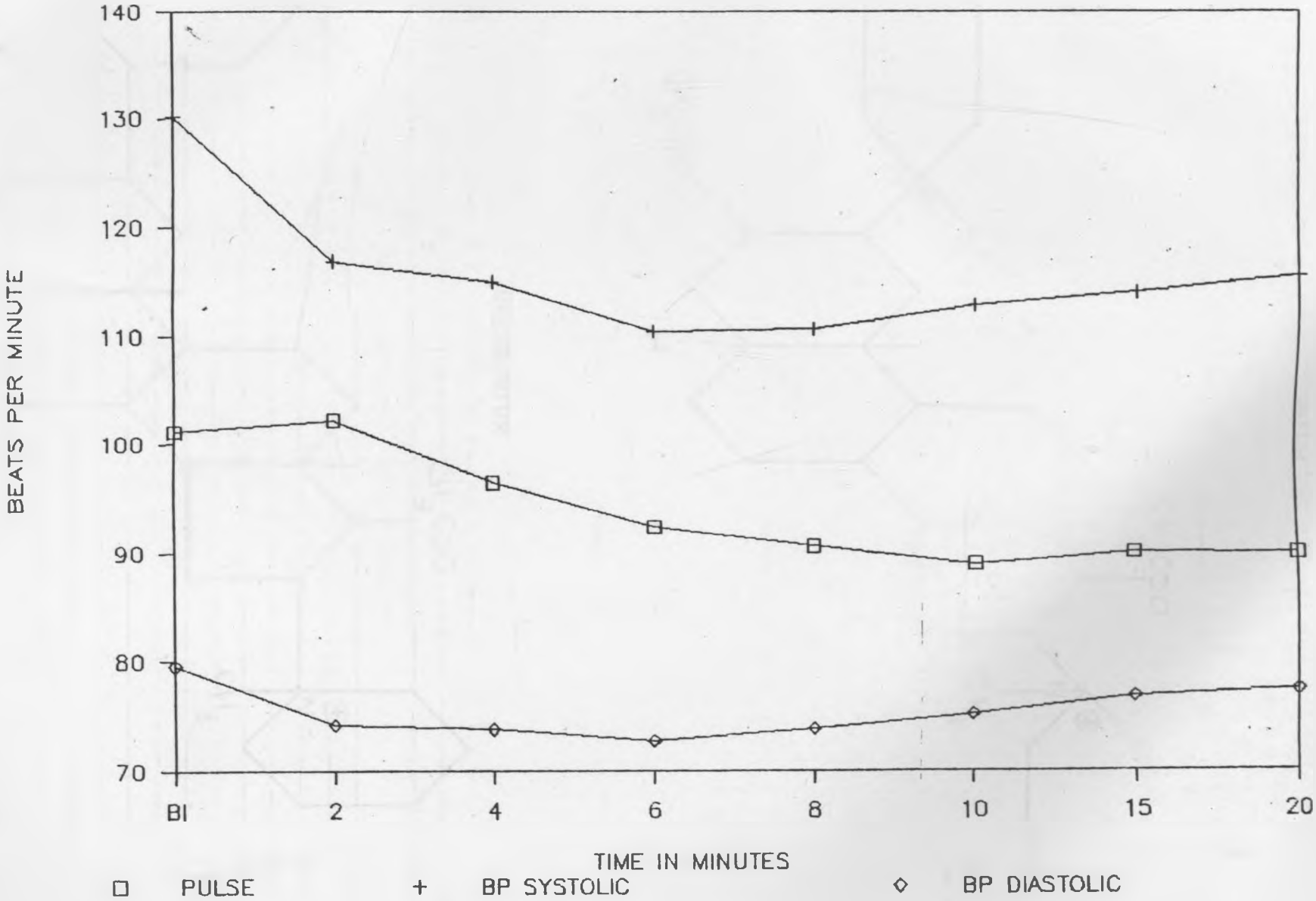
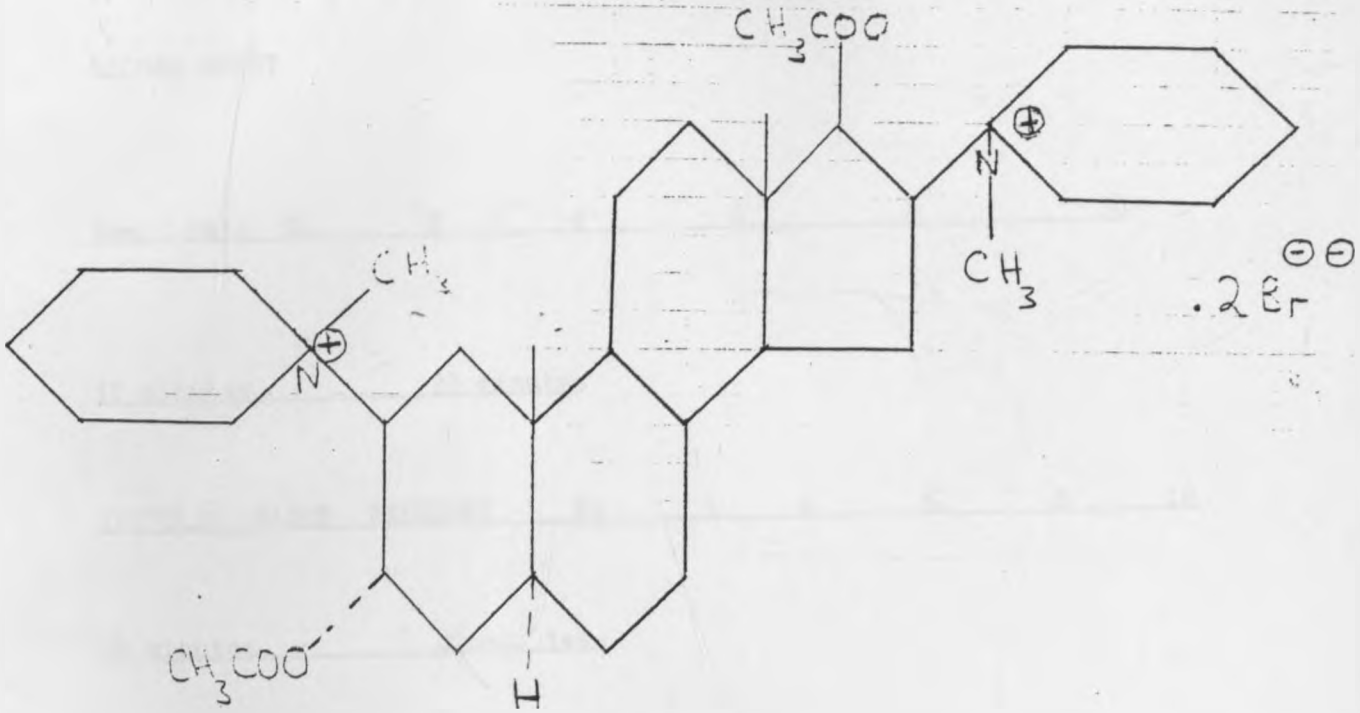


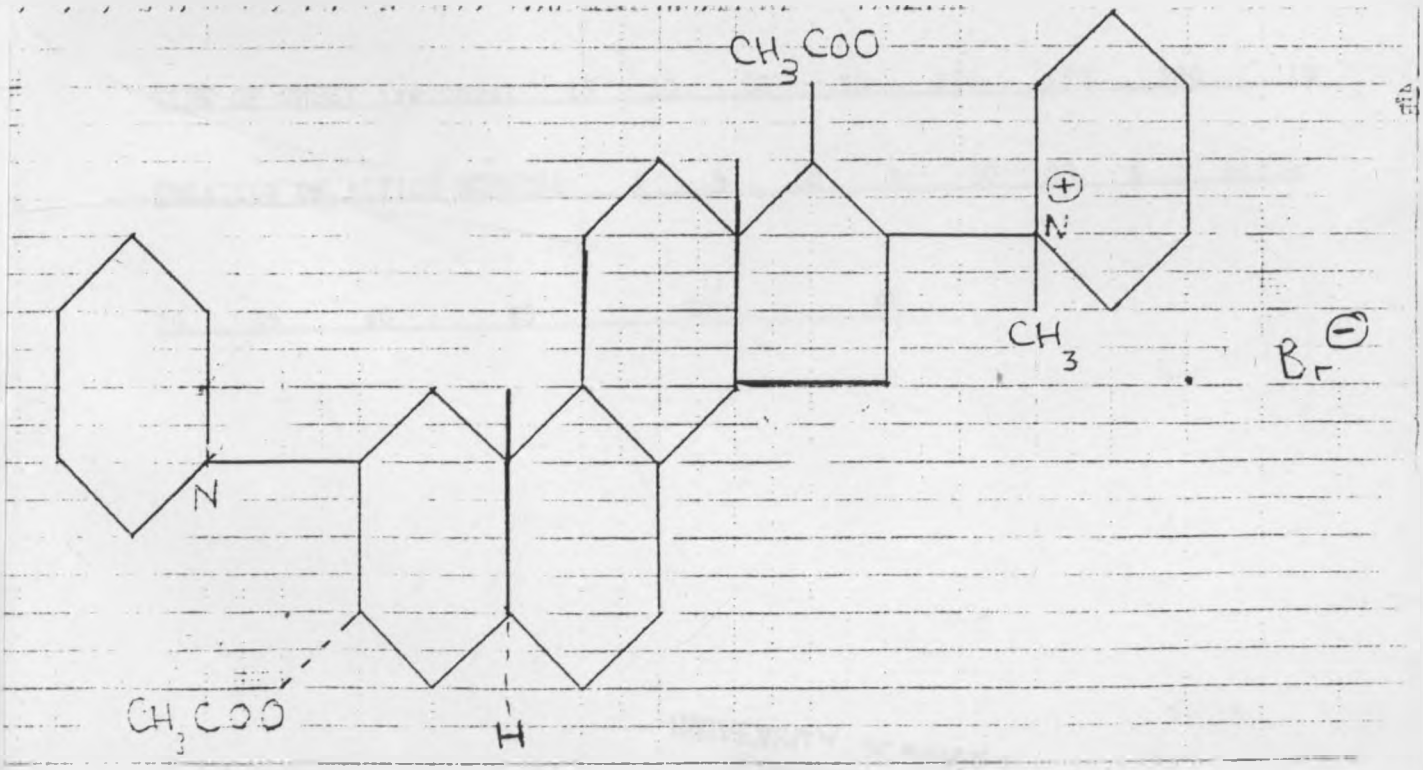
CHEMICAL STRUCTURE OF PANCURONIUM BROMIDE AND VECURONIUM BROMIDE

FIGURE V

PANCURONIUM



VECURONIUM



RECORD SHEET

Heart Rate B1 2 4 6 8 10

15 minutes 20 minutes

SYSTOLIC BLOOD PRESSURE B1 2 4 6 8 10

15 minutes 20 minutes

DIASTOLIC BLOOD PRESSURE B1 2 4 6 8 10

15 minutes 20 minutes

TIME OF ONSET (seconds) 15 30 60 90 120 150 180 210

DURATION OF ACTION MINUTES: 1 5 10 15 20 25 % block

30 35 40 45 50 55

RECORD SHEET

NO: AGE: SEX:

NAME:

IP. NO: DIAGNOSIS:

WEIGHT: ASA GROUP:

OPERATION SURGEON:

DOSE VECURONUIM:

ONSET OF ACTION TIME:

DURATION OF ACTION TIME:

CUMULATION

EFFECT ON HEART RATE:

EFFECT ON BLOOD PRESSURE:

AVERAGE DURATION OF OPERATION:

REVERSAL

OTHER COMMENTS: