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## **The Influence of Carbon Dioxide on the Neuromuscular Blocking Properties of Tubocurarine Chloride and Diallyl-nor-Toxiferine Dichloride (Alloferin Roche) in Man**

### **A Comparative Study**

A. J. COLEMAN, S. H. RIPLEY, C. M. SLIOM, and S. L. KNOWLES

The influence of carbon dioxide on the neuromuscular blocking effect of tubocurarine chloride has been well demonstrated in man and animals (BARAKA 1964 [1]; BUSH and BARAKA 1964 [2]; GAMSTORP and VINNARS 1961 [3]; PAYNE 1958 [11]). Indeed it has been suggested that the syndrome of neostigmine resistant curarisation (HUNTER 1956 [5]) may be produced by the enhancement of the action of tubocurarine in the acidaemic subject (BUSH and BARAKA 1964 [2]; BARAKA, GRAY and THOMAS: personal communication).

Similarly, the activity of other muscle relaxants may be affected by changes in acid-base variants; e.g. gallamine, suxamethonium, decamethonium and dimethyltubocurarine (KATZ et al. 1963 [7]; PAYNE 1958 [10], 1958 [11]).

The purpose of this study is to attempt to describe the neuromuscular effects of diallyl-nor-toxiferine on the myoneural junction at different levels of arterial carbon dioxide tension and hydrogen ion concentration and to compare these with the effects of tubocurarine given under comparable conditions.

### *Material and methods*

The series comprises 30 patients who were investigated during elective major abdominal surgery. The patients were assigned to two groups of 15 in a random fashion.

In group 1, patients were maintained as nearly as possible in a steady state of respiratory alkalaemia for the duration of the experiment. In group 2, a condition of mild respiratory acidaemia was aimed at. 10 of the patients in each group were given diallyl-nor-toxiferine 0.32 mg/kg of body weight to produce muscle relaxation. The remaining 5 subjects in each group were given tubocurarine 0.72 mg/kg of body weight. After a short control period these doses of muscle relaxants were given and were not reinforced by further doses.

Neuromuscular blockade was assessed continuously by recording the mechanogram produced in response to supramaximal stimulation of the ulnar nerve at the elbow by

means of a needle electrode. The electrical stimulus was a train of square waves of 0.3 msec duration with a repetition frequency of 30/sec. This stimulus was applied to the nerve for 0.3 sec at 30 sec intervals. With 30 sec intervals between trains of stimuli no fatigue could be demonstrated, whereas with 10 sec intervals some subjects showed progressive fatigue. The resultant contraction of the ring finger flexors (twitch response) was measured isometrically with a force-displacement transducer attached to the ring finger; the other fingers and the thumb were held firmly on a metal yoke which also served as the indifferent electrode. The amplitude of contraction was recorded on a direct writing oscillograph. The quantitative significance of a similar method of assessing neuromuscular blockade has been discussed elsewhere (BARAKA 1964 [1]).

The anaesthetic technique was as follows. All patients were premedicated with pethidine 75–100 mg and atropine 0.6 mg, given intramuscularly 1 hour prior to surgery. Anaesthesia was induced with a sleep dose of 2.5% sodium thiopentone and maintained with nitrous oxide and oxygen delivered through a non-rebreathing circuit to a face mask. Ventilation was assisted manually at this stage in the patients in group 1 to increase their minute volumes to approximately twice their calculated resting minute volumes. Carbon dioxide was added to the inspired gases of patients in group 2. During this time, neuromuscular activity was recorded in the manner described above. After recording the constant height control twitch for ca. 10 min, a sample of arterial blood was withdrawn. The dose of relaxant was then given into the tubing of a rapidly running intravenous infusion. Following paralysis, the patient's trachea was intubated and ventilation was maintained with a mechanical ventilator adjusted to deliver a minute volume of between 15 and 20 l/min through a non-rebreathing circuit. Carbon dioxide was continuously added to the fresh gas supply of the patients in group 2 at a rate sufficient to produce the desired degree of respiratory acidaemia.

Experiments were continued until a predetermined degree of recovery of twitch response had occurred, namely 50–60% of the amplitude of that of the control level. Neostigmine, preceded by 1.2 mg of atropine, was then given to ensure complete reversal of neuromuscular block.

Arterial blood was sampled at intervals during the experiments and analysed immediately for  $p\text{CO}_2$ , pH and  $p\text{O}_2$  in a Beckman modular electrode assembly maintained at  $37^\circ\text{C}$  ( $\pm 0.1^\circ\text{C}$ ). The output of the three electrodes was read directly on a Beckman multi-channel amplifier (Model 160).

Mid-oesophageal temperatures were monitored by means of a thermistor thermometer.

Pulse rates and sphygmomanometrically determined blood pressure were recorded at least every 10 min during the experiments.

### *Results*

Records of the twitch response were analysed in the following two ways. The time from disappearance of twitch following administration of the paralyzing agent to the reappearance of the smallest recordable twitch was measured and is presented graphically in relation to arterial  $p\text{CO}_2$  and pH (Fig. 1 a and b). The period from the first recordable muscle twitch to the point where the twitch had attained a height of 50–60% of the pre-paralysis control level was measured. This is also presented graphically in relation to arterial  $p\text{CO}_2$  and pH (Fig. 2 a and b). In 4 of the diallyl-nor-toxiferine subjects in group 1 and 1 in group 2, the twitch response had reappeared as shown in Fig. 1 but for clinical reasons it was not possible to follow the recovery of twitch to 50–60% of the control level. Consequently, the results from these cases do not appear in Fig. 2.

Following tubocurarine administration, there appeared to be a well-defined difference (in all but one case), not only in the duration of complete flexor paralysis but also in the rate of recovery of muscular tension according to whether there was a respiratory acidaemia or alkalaemia. Compared with an alkalaemia, in most cases an acidaemia prolonged the rate of recovery from curarization.

4 of the 5 patients in the acidaemic group who had received tubocurarine showed the first signs of recovery in 80–120 min (Fig. 1 a and b). After a further 140 min none of these 4 had attained a muscular tension of 50% of the control level. For clinical reasons the experiments were terminated at this time.

In those patients who had received diallyl-nor-toxiferine, differences in arterial pH and  $p\text{CO}_2$  did not appear to be associated with any systematic variation in the duration of complete myoneural blockade nor with the rate of recovery of muscular tension. This contrasts sharply with the consistent effects of acidaemia or alkalaemia on tubocurarized subjects.

It is of interest to note the considerable degree of individual variation in response observed in patients given diallyl-nor-toxiferine on a body weight basis.

Although our patients were not followed through to complete recovery of muscular tension it is evident that even though *complete* paralysis may persist for as short a time as 10 min it takes at least 45 min from the time of administration of the relaxant for them to regain 50% of the muscular control tension. The average 50% recovery time for 21 cases is 1 h and 27 min. At the dose levels used in the study (normal recommended clinical dose levels) one must therefore reckon the period required for 100% muscular recovery in terms of hours, not minutes.

One interesting observation was that the 10 patients in group 2 who received neostigmine to reverse the residual neuromuscular blockade produced by diallyl-nor-toxiferine, recovered rapidly and completely despite the fact that a respiratory acidaemia was still present. This is in contrast to the findings of BARAKA, GRAY and THOMAS that neostigmine did not completely reverse the block produced by tubocurarine in respiratory acidaemia. It was also found that 5 mg of neostigmine was frequently necessary to produce complete recovery from diallyl-nor-toxiferine regardless of the level of arterial  $p\text{CO}_2$ .

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Fig. 1 a and b. The relations between arterial  $p\text{CO}_2$  and pH on the duration of complete paralysis of the ring finger flexors. ● = paralysis induced by tubocurarine; ○ = paralysis induced by diallyl-nor-toxiferine. Vertical bars indicate the variation of arterial  $p\text{CO}_2$  and pH during the experiment. Only single arterial  $p\text{CO}_2$  and pH determinations were made in those records which have no terminal vertical bar. The duration of paralysis was taken as the time between disappearance and reappearance of the ring finger twitch.

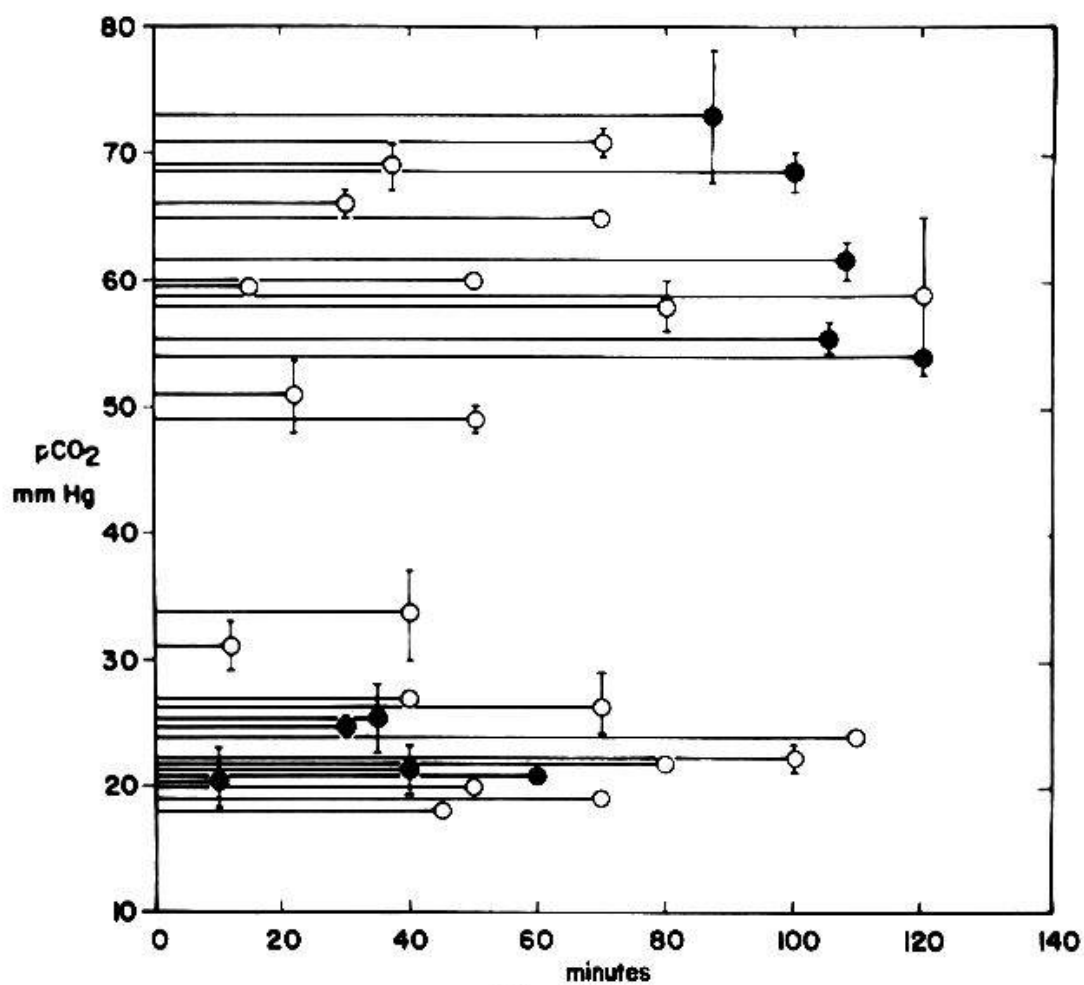


Fig. 1a

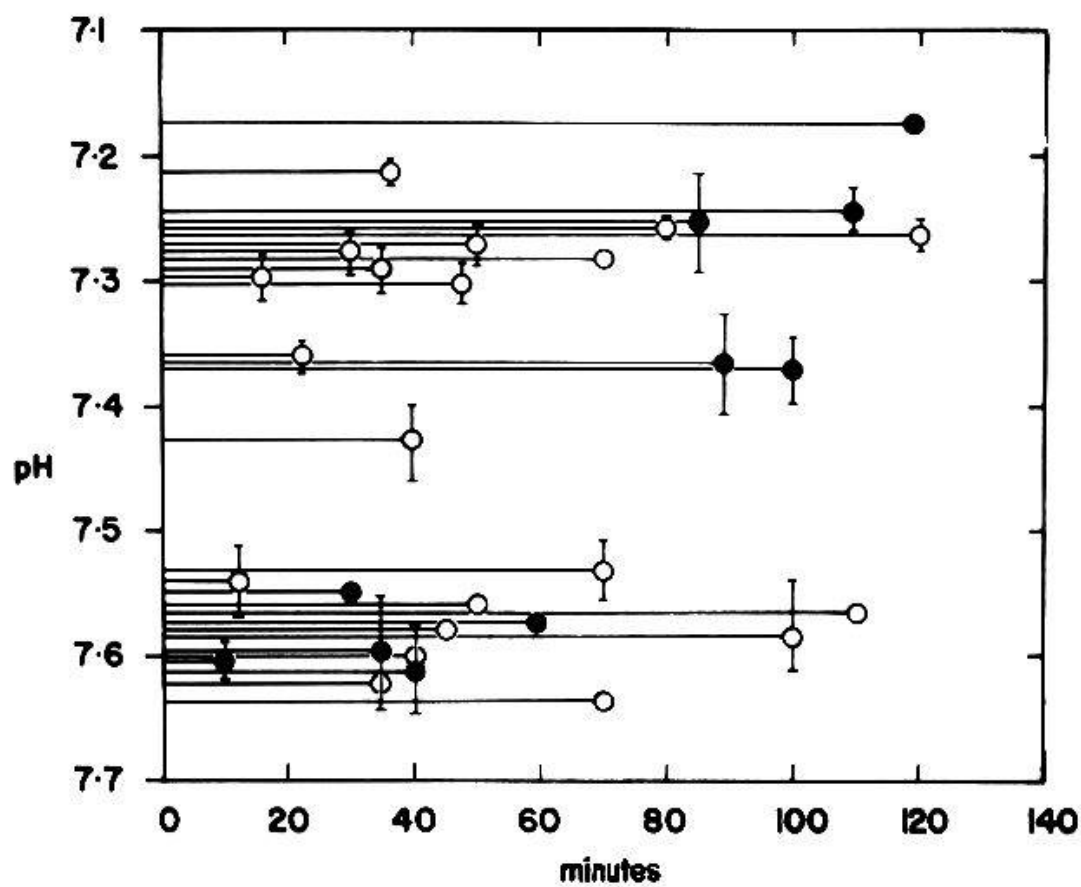


Fig. 1b

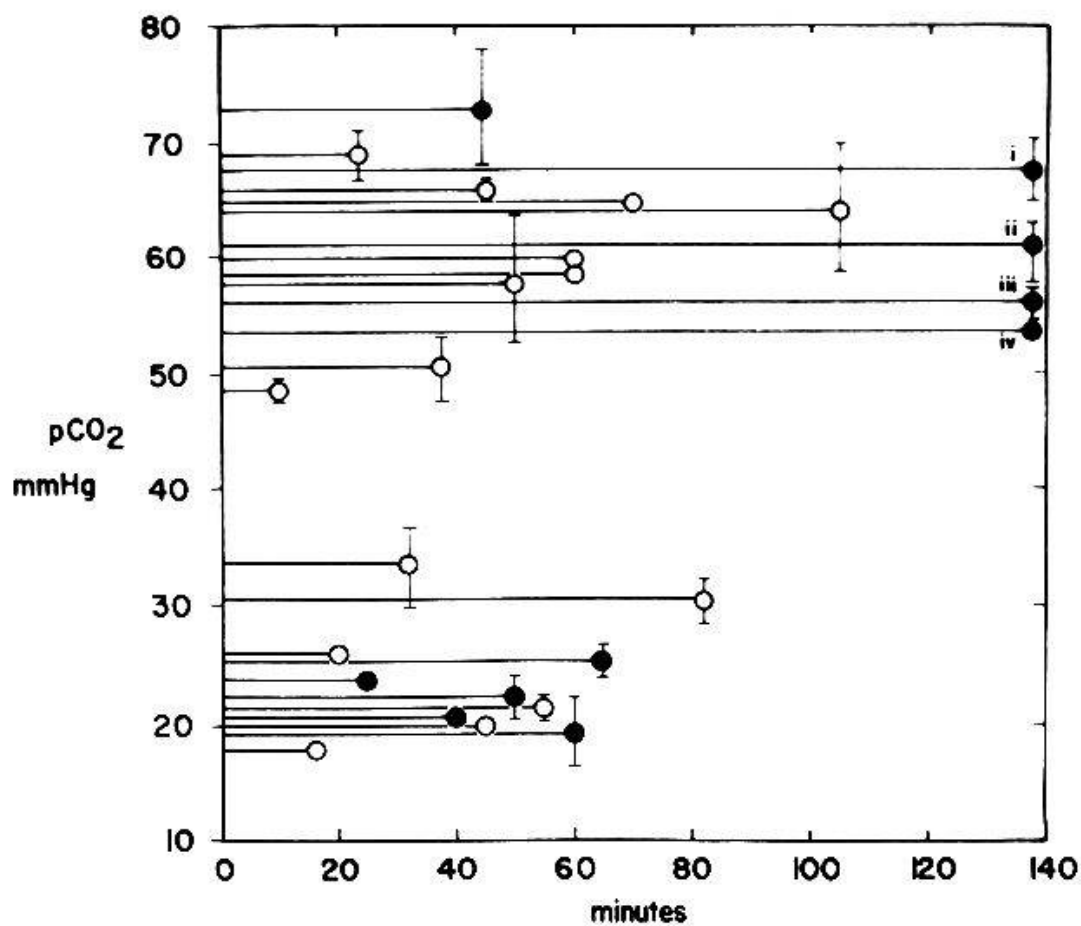


Fig. 2a

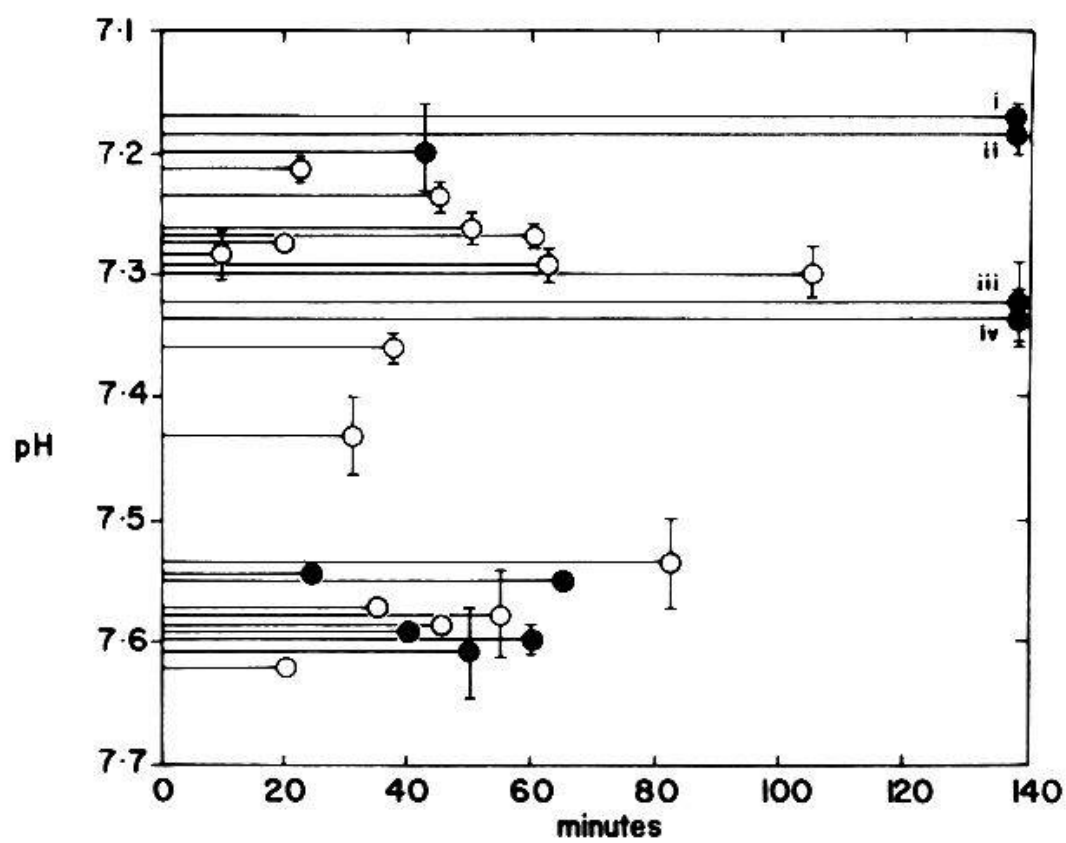


Fig. 2b



In this experimental series the relaxant was given some 15–20 min after induction of anaesthesia. During this period, systolic blood pressure was monitored every few minutes before and after administration of the relaxant. Surgery did not commence for 10–15 min after the relaxant was given and in no case did the blood pressure prior to the start of surgery fluctuate by more than 10% of the control level.

The oesophageal temperature remained within one degree centigrade of the preoperative level.

### *Discussion*

The ability of carbon dioxide to depress the twitch response is well documented (GAMSTORP and VINNARS 1961 [4]; LEHMAN 1937 [8]; LORENTE DE NÓ 1946 [9]). The fact that a consistent prolongation of myoneural blockade during respiratory acidaemia was observed only in those patients who had received tubocurarine would seem to indicate that diallyl-nor-toxiferine is not grossly affected by changes in blood pH or  $p\text{CO}_2$  although the wide individual variation in response to diallyl-nor-toxiferine may be masking a subtle effect.

The effect of variations in carbon dioxide tension on the neuromuscular blocking action of different drugs is not easy to explain. In the case of tubocurarine it has been suggested that the myoneural blocking activity may vary with the changes in the degree of ionization of its two phenolic hydroxyl groups (KALOW 1954 [6]). Diallyl-nor-toxiferine has no such groups and at the time of writing the authors can find no reference to the  $pK_a$  of the two substituted quaternary ammonium groups. The marked difference in the activity of the two relaxants observed in this study suggests that diallyl-nor-toxiferine remains fully ionized within the range of pH used in the experiments.

The failure to demonstrate prolonged activity of diallyl-nor-toxiferine compared with tubocurarine in the acidaemic patients suggests it to be the non-depolarizing relaxant of choice in those patients known to be, or likely to become, acidaemic.

### *Summary and conclusions*

In a series of patients anaesthetized for surgical procedures, the duration of neuromuscular blockade produced by diallyl-nor-toxiferine during in-

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Fig. 2 a and b. The relation between arterial  $p\text{CO}_2$  and pH and the rate of recovery of contraction of the ring finger flexors. ● = recovery from tubocurarine induced paralysis; ○ = recovery from diallyl-nor-toxiferine induced paralysis. Terminal vertical bars indicate the variation of arterial  $p\text{CO}_2$  and pH during the experiment. Only single  $p\text{CO}_2$  and pH determinations were made in those records which have no terminal vertical bar. Rate of recovery from paralysis is taken as the period from the first recordable twitch to the point at which the twitch had attained 50–60% of the preparalysis control height. – Individual records labelled i, ii, iii and iv did not attain 50% recovery before termination of the experiment (see text).

duced respiratory acidaemia and alkalaemia was studied by recording the isometric muscular contractions of the forearm flexors following repetitive electrical stimulation of the ulnar nerve at the elbow. These responses were compared with the effects of tubocurarine under similar circumstances. There appeared to be no relation between duration of paralysis with diallyl-nor-toxiferine and the  $p\text{CO}_2$  and pH of arterial blood, in contrast to the marked prolongation of block seen with tubocurarine during respiratory acidaemia.

The results are discussed and it is concluded that diallyl-nor-toxiferine may be the safer drug to use in patients who are acidaemic or likely to become so.

### *Zusammenfassung*

An einer Reihe von zur Vornahme von chirurgischen Eingriffen narkotisierten Patienten wurde die Dauer des durch Diallyl-nor-toxiferin und durch d-Tubocurarin bewirkten neuromuskulären Blocks bei provozierter respiratorischer Acidose und Alkaliämie vergleichend untersucht. Es erfolgte dies an Hand der Aufzeichnung der isometrischen Muskelkontraktionen der Vorderarmflexoren nach wiederholter elektrischer Reizung des Nervus ulnaris am Ellenbogen. Im Falle des Diallyl-nor-toxiferins schien kein Zusammenhang zwischen der Dauer der Lähmung und der  $\text{CO}_2$ -Spannung bzw. dem pH im arteriellen Blut zu bestehen, im Gegensatz zu der deutlichen Verlängerung des Blocks, wie sie mit d-Tubocurarin bei respiratorischer Acidose auftrat. Es wird aus diesen Befunden geschlossen, daß das Diallyl-nor-toxiferin für Patienten, die bereits acidotisch sind oder bei denen eine Acidose zu erwarten ist, das sicherere Präparat ist.

### *Résumé*

Dans une série de patients narcotisés pour des interventions chirurgicales, la durée du blocage neuromusculaire produit par la diallyl-nor-toxiférine et la d-tubocurarine, respectivement en état d'acidose et d'alkalinémie respiratoire provoquée a été comparée au moyen d'enregistrements des contractions musculaires isométriques des fléchisseurs antérieurs du bras après stimulation électrique répétée du nerf cubital au coude. Pour la diallyl-nor-toxiférine, une relation entre la durée du blocage, le  $p\text{CO}_2$  et le pH artériels ne semble pas exister, et ceci en contraste avec la prolongation marquée du blocage constatée avec la d-tubocurarine sous acidose respiratoire. En conclusion, la diallyl-nor-toxiférine apparaît être le musculo-relaxant le plus sûr pour des patients se trouvant déjà ou susceptibles d'être en acidose.

### *Riassunto*

In un gruppo di pazienti anestetizzati per interventi chirurgici, si è studiata, registrando le contrazioni muscolari isometriche dei flessori dell'avam-



braccio dopo stimolazione elettrica ripetitiva del nervo ulnare al gomito, la durata del blocco neuro-muscolare da diallil-nor-toxiferina, in condizioni di acidosi e di alcalemia respiratoria provocata. I risultati sono stati confrontati con quelli ottenuti usando d-tubocurarina nelle medesime condizioni sperimentali. Con diallil-nor-toxiferina non sembra esservi alcuna relazione tra la durata della paralisi, il  $p\text{CO}_2$  ed il pH arterioso, mentre con la d-tubocurarina durante l'acidemia respiratoria si riscontra un marcato prolungamento del blocco neuro-muscolare. In conclusione, la diallil-nor-toxiferina può essere considerata come il muscolorilassante più sicuro in pazienti che sono già o possono divenire acidemici.

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