Brit. J. Anaesth. (1971), 43, 473

QUANTITATIVE ASSESSMENT OF RESIDUAL ANTIDEPOLARIZING BLOCK (PART I)

BY

HASSAN H. ALI, J. E. UTTING AND T. CECIL GRAY

SUMMARY

A method is presented for the assessment of residual curarization after the use of antidepolarizing muscle relaxants which does not involve the necessity for establishing control observations. The ulnar nerve at the elbow was stimulated with a train of four pulses repeated intermittently. The muscle response to this train of four stimuli was recorded and analyzed using three ratios of twitch height (or electromyographic responses). Ratio (a) was taken as the height of the first response of the train to the height of the control response (i.e. the response before muscle relaxant was given), ratio (b) as the height of the second response to the height of the first response, and ratio (c) as the height of the fourth response to the height of the first response. There was a highly significant positive linear association between ratio (a), which involves the use of a control response, and the other two ratios, (b) and (c), which do not involve a control response.

It is well known that the degree of neuromuscular block produced by antidepolarizing muscle relaxants is dependent on the frequency of stimulation employed (Chou, 1947; Preston and Van Maanan, 1953; Wislicki, 1958). In conditions of partial neuromuscular blockade produced by tubocurarine it has been found that if a steady state of twitch height is obtained using one frequency of stimulation the twitch height declines when the frequency is increased, a new lower steady state of twitch height usually being attained after five stimuli at the faster rate. Thus when a change to the faster rate is made there is a progressive decline in twitch height for the first four or five responses and then the twitch height either flattens out or slightly increases. This phenomenon has been shown to occur with frequencies of stimulation of from 0.1 Hz to 10 Hz (Rosenblueth and Morrison, 1937; Maaske, Boyd and Brosnan, 1938; Blackman, 1963). Grob, Johns and Harvey (1956) further showed that the progressive depression of successive evoked potentials associated with partial neuromuscular blockade produced by tubocurarine could be reversed by the action of neostigmine. It should be noted that the progressive decline in the evoked action potentials found in these circumstances runs pari passu with the exponential decline in the endplate potentials shown to occur with repetitive nerve stimulation (Brooks and Thies, 1962; Elmqvist and Quastel, 1956).

This decline in twitch heights in response to repetitive nerve stimulation was put to practical use by Roberts and Wilson (1968) who used a train of four nerve stimuli at a frequency of 4 Hz, in patients with myasthenia gravis, to assess the progress of the disease and the effect of treatment.

In a previous study (Ali, Utting and Gray, 1970) the twitch response to various frequencies of nerve stimulation was investigated in an attempt to produce a method of assessing the degree of recovery from antidepolarizing neuromuscular block in patients and volunteers. A pattern of nerve stimulation was eventually selected which consisted of a group of four stimuli, the group being repeated at intervals. The heights of the four twitch responses to this train of stimuli were studied in an attempt to give an objective method of assessing degree of neuromuscular blockade. In some cases the electromyographic response to the stimuli was studied.

METHODS

The investigation was performed on 21 patients from whom informed consent was obtained in

HASSAN H. ALI, M.D.; J. E. UTTING, M.A., M.B., F.F.A.R.C.S.; T. CECIL GRAY, M.D., F.R.C.S., F.F.A.R.C.S.; Department of Anaesthesia, University of Liverpool.

every case; of these 10 were males and 11 females and their ages ranged from 21 to 68 years. All were undergoing lower abdominal or limb surgery and none of them had any neuromuscular disease.

No premedication was used. Anaesthesia was induced with thiopentone 250–300 mg and maintained with nitrous oxide and oxygen, but while the electrodes were being positioned and control response obtained it was sometimes necessary to add halothane (0.5 per cent) to the inspired mixture to avoid movement. The ulnar nerve was stimulated at the elbow using 25-gauge needle electrodes. Square wave stimuli of duration 0.3 msec and frequency of 0.3 Hz were delivered from a Grass stimulator (S8) by way of a Grass stimulus isolation unit (SIU478). The voltage of the stimulus was adjusted to be 10–20 per cent above that required to give a supramaximal twitch response. Following the establishment of control twitch height, trains of four stimuli of frequency 2 Hz were applied in this way, the trains being repeated at a frequency of 0.1 Hz. Where electromyography was used the frequency of the four stimuli was adjusted, for technical reasons, to 2.4 Hz.

Mechanical muscle response was monitored in 10 patients. An Ether force displacement transducer (UFI) assembled in the form of a hand grip was used (Ali, 1970), and the responses recorded on a Devices single channel recorder (R2). Electromyographical responses were studied in 11 patients: evoked compound action potential was monitored from the belly of the first dorsal interosseous muscle of the hand using surface electrodes. The output was amplified and displayed on a Medelec Ms 5 electromyograph, the display being photographed using a polaroid camera.

After control values had been obtained an antidepolarizing muscle relaxant was administered; tubocurarine was given to 13 patients (average total dose 0.66 mg/kg); pancuronium to 4 patients (dose 0.1 mg/kg) and alcuronium to 4 patients (average total dose 0.28 mg/kg). Controlled ventilation was established, endotracheal intubation performed and anaesthesia continued with nitrous oxide and oxygen without any volatile adjuvant or analgesic drug. At the end of the operation, 37–178 min after the relaxant had been given, atropine 1.2 mg and neostigmine 5 mg was administered. Monitoring of the twitch response was continued for a variable period (from 5 to 30 min) after the action of the muscle relaxant had been reversed, the time available for further monitoring depending on circumstances in the recovery room.

The height of the control twitch responses was measured and subsequently the first, second and fourth responses of the train of four after the relaxant had been given were measured. From these data three ratios were calculated; this is illustrated diagrammatically in figure 1.

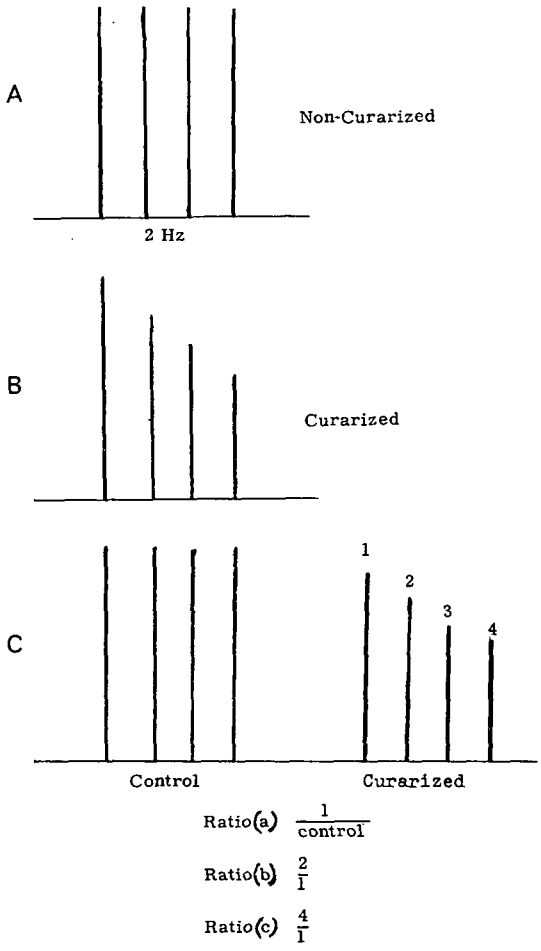

FIG. 1

Diagrammatic illustration of the evoked muscle twitch response to a train of four stimuli at 2 Hz in a non-curarized subject (A).

In (B), the effect of a small dose of tubocurarine on twitch response to the same train of four stimuli.

(C) shows how the three ratios (a), (b) and (c) were calculated.

Ratio (a) is the height of the first response to the height of the control response (expressed as a percentage).

Ratio (b) is the height of the second response to the height of the first (expressed as a percentage).

Ratio (c) is the height of the fourth response to the height of the first (expressed as a percentage).

RESULTS

The muscle responses to the train of four stimuli before relaxant was administered (control responses) were all equal in amplitude. After the muscle relaxant had been given the magnitude of the responses diminished and there was the characteristic "fade" in the trains of four: sometimes, however, there was hardly any muscle response to stimuli. There was a gradual and progressive increase in amplitude of the four responses after neostigmine had been given: the first response started to increase in amplitude followed by the second then the third and finally the fourth.

The three ratios (a), (b) and (c) were calculated from observations for every 5 minutes after reversal. A scattergram of ratio (b) against ratio (a) in 92 observations is shown in figure 2. Statistical analysis of the regression revealed a highly significant ($P<0.001$) positive linear association between ratio (b) and ratio (a) despite the random choice of patients and the various antidepolarizing relaxants given ($r=+0.86$; $t=15.74$). Similarly ratio (c) was plotted against ratio (a) and a scattergram obtained (fig. 3). Regression analysis again revealed a highly significant ($P<0.001$) positive linear association between the two ratios in the same group of 92 observations ($r=+0.84$; $t=14.67$).

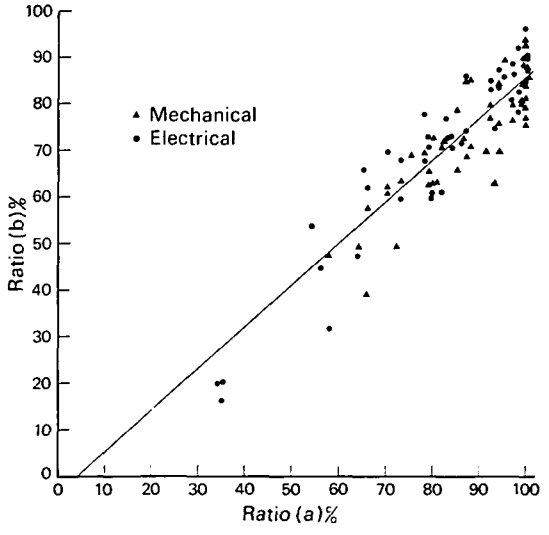

FIG. 2

Scattergram and calculated regression line of ratio (b) in per cent against ratio (a) in per cent. Data obtained from 21 patients given different antidepolarizing muscle relaxants. As ratio (a) increases, ratio (b) also increases.

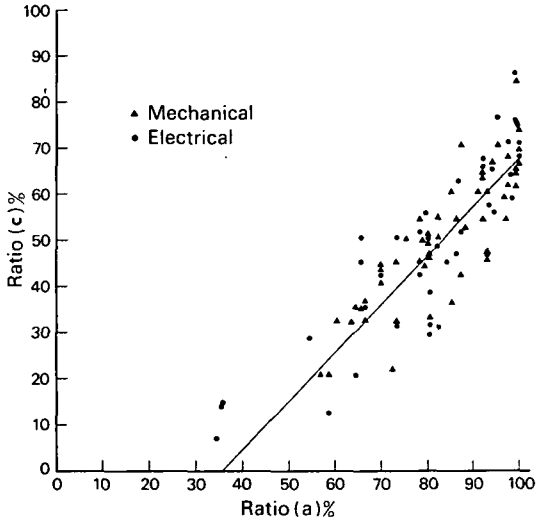

FIG. 3

Scattergram and calculated regression line of ratio (c) in per cent against ratio (a) in per cent. Data obtained from the same group of observations as in fig. 2. Note that this regression line is nearly parallel but lower than the line of ratio (b) against ratio (a).

DISCUSSION

The results show that there is a strong correlation between a ratio which involves the control response (ratio (a)) and two ratios (b) and (c) which do not involve the previous establishment of a control twitch response. The two regression lines were nearly parallel but the second line (ratio (c) against ratio (a)) was lower than the first (ratio (b) against ratio (a)); ratio (c), therefore, is a more sensitive index of the degree of curarization than either (a) or (b).

Thus a method is presented for assessment of residual curarization which does not require a control twitch height. This would seem to afford a method of estimating the degree of residual

curarization after an antidepolarizing relaxant has been given, and can be applied to situations before and after attempted reversal of the block with neostigmine. It appears to obviate the necessity of obtaining a control twitch height before an antidepolarizing muscle relaxant has been administered. This is of some practical importance since it is unusual to have a control twitch height available for comparison in situations in which residual curarization is suspected. Moreover, even when a control twitch height is available, complete stability of recording over hours cannot be guaranteed. Nor does the pattern of stimulation suggested cause the degree of discomfort to the conscious patient which is associated with the use of tetanic rates of stimulation at 50–200 Hz as suggested by Gissen and Katz (1969).

The neurophysiological basis of the train of four stimuli at 2 Hz is discussed elsewhere (Ali, Utting and Gray, 1970). The limitation of the stimuli to four at 2 Hz is to ensure maximum depletion of acetylcholine release from the immediately available store at the motor nerve ending, without the complicating factors on the muscle response attributed to the effect of tetanic stimulation at high rates of stimulation.

REFERENCES

Ali, H. H. (1970). A new device for monitoring force of thumb adduction. *Brit. J. Anaesth.*, **42**, 83.

—— Utting, J. E., and Gray, C. (1970). Stimulus frequency in the detection of neuromuscular block in humans. *Brit. J. Anaesth.*, **42**, 967.

Blackman, F. R. (1963). Stimulus frequency and neuromuscular block. *Brit. J. Pharmacol.*, **20**, 5.

Brooks, V. B., and Thies, R. D. (1962). Reduction of quantum content during neuromuscular transmission. *J. Physiol. (Lond.)*, **162**, 298.

Chou, T. C. (1947). A method of estimating curare-like activity on the isolated phrenic nerve diaphragm preparation of the rat. *Brit. J. Pharmacol.*, **2**, 1.

Elmqvist, D., and Quastel, D. M. J. (1965). A quantitative study of endplate potentials in isolated human muscles. *J. Physiol. (Lond.)*, **178**, 505.

Gisssen, A. J., and Katz, R. L. (1969). Twitch, tetanus and post-tetanic potentiation as indices of nerve-muscle block in man. *Anesthesiology*, **30**, 481.

Grob, D., Johns, R. J., and Harvey, A. M. (1956). Studies in neuromuscular function. V: Effects of anticholinesterase compounds, d-tubocurarine and decamethonium in normal subjects. *Bull. Johns Hopk. Hosp.*, **99**, 195.

Maaske, C. A., Boyd, T. E., and Brosnan, J. J. (1938). Inhibition and impulse summation at the mammalian neuromuscular junction. *J. Neurophysiol.*, **1**, 332.

Preston, J. B., and Van Maanan, E. F. (1953). Effects of frequency of stimulation on the paralysing dose of neuromuscular blocking agents. *J. Pharmacol. exp. Ther.*, **107**, 165.

Roberts, D. V., and Wilson, A. (1968), in *Myasthenia Gravis* (ed Greene, R.), p. 14. London: Heinemann.

Rosenblueth, A., and Morrison, R. S. (1937). Curarization, fatigue and Wedensky inhibition. *Amer. J. Physiol.*, **119**, 236.

Wislicki, L. (1958). Effects of rate of stimulation and of fatigue on the response of neuromuscular blocking agents. *Brit. J. Pharmacol.*, **13**, 138.

EVALUATION QUANTITATIVE D'UN BLOCAGE RESIDUEL ANTIDEPOLARISANT (PREMIERE PARTIE)

SOMMAIRE

Il est fait état d'une méthode destinée à évaluer la curarisation résiduelle consécutive à l'emploi d'agents myorelaxants non dépolarisants et ne comportant pas la nécessité de recourir à des observations témoins. Le nerf cubital a fait l'objet, au niveau du coude, d'une stimulation par un train de quatre impulsions répété par intermittence. La réponse musculaire à ce train de quatre stimuli a été enregistrée et analysée en se servant de trois rapports d'intensité des secousses musculaires (ou réponses électromyographiques). Le rapport (a) a été choisi comme traduisant l'intensité de la première réponse du train par rapport à celle de la réponse témoin (c'est-à-dire la réponse enregistrée avant que l'agent myorelaxant ne soit adminstré); le rapport (b) comme traduisant l'intensité de la seconde réponse par rapport à celle de la première et la rapport (c) comme traduisant l'intensité de la quatrième réponse par rapport à celle de la première. On a noté l'existence d'une corrélation linéaire positive hautement significative entre le rapport (a) qui implique le recours à une réponse témoin et les deux autres rapports (b) et (c) qui n'impliquent pas l'utilisation de cette réponse témoin.

QUANTITATIVE MESSUNG DES RESTLICHEN ANTIDEPOLARISIERUNGS-BLOCKS (TEIL I)

ZUSAMMENFASSUNG

Es wird eine Methode dargestellt, wie man bei Patienten, denen man nicht-depolarisierende Muskelrelaxantien verabreichte, und die nicht mehr beobachtet werden müssen, die noch vorhandene Curarisation messen kann. Dabei wurde der Nervus Ulnaris am Ellenbogen wiederholt mit vier Stromstößen stimuliert. Die Muskelreaktonen auf diese Stromstöße wurden aufgezeichnet und analysiert, indem man drei Relationen zwischen der Höhe der Muskelzuckungen (oder den elektromyographischen Reaktionen) herstellte. Die Relation (a) wurde aus der Höhe der ersten Zuckung zur Höhe der Kontrollreaktion (d.h. die Reaktion vor Verabreichung des Relaxans) gebildet; die Relation (b) bezog sich auf die Höhe der zweiten Reaktion zur Höhe der ersten Reaktion, und die Relation (c) auf die Höhe der Vierten Reaktion zur Höhe der ersten Reaktion. Es bestand eine hoch signifikante, positiv lineare Korrelation zwischen der Relation (a), welche die Kontrollreaktion umfaßt und den anderen Reaktionen (b) und (c), die den Wert der Kontrollreaktion nicht enthalten.

VALORACION CUANTITATIVA DEL BLOQUEO ANTIDESPOLARIZANTE RESIDUAL (PARTE I)

RESUMEN

Se presenta un método para la valoración de la curarización residuel después del uso de relajantes musculares no depolarizantes que no requiere establecer observaciones de control. El nervio cubital en el codo fue estimulado con un tren de cuatro pulsos repetidos intermitentemente. La respuesta muscular a este tren de cuatro estímulos fue registrada y analizada utilizando las tres proporciones de altura de la sacudida (o respuestas electromiográficas). La proporción (a) fue tomada como la altura de la primera respuesta del tren y la altura de la respuesta de control (es decir, la respuesta antes de administrar el relajante muscular); la proporción (b), como la altura de la segunda respuesta y la altura de la primera respuesta, y la proporción (c), como la altura de la cuarta respuesta y la altura de la primera respuesta. Hubo una asociación lineal positiva muy significativa entre la proporción (a), que requiere el uso de una respuesta de control, y las otras dos proporciones, (b) y (c), que no requieren el uso de una respuesta de control.

BOOK REVIEWS

A Method of Study (*Clinical Anaesthesia* 1/1969). By Joseph Artusio jr., M.D. Published by Blackwell Scientific Publications, Oxford, 1970. Pp. ix+275. Price £3.

This number in the "Clinical Anaesthesia" series is intended to give the examination candidate or the clinical anaesthetist a plan of study lasting about a year, which will take him through the whole field of anaesthesia at a fairly high scientific and clinical standard. The book is divided into forty-nine "study plans" each one of which is supposed to contain a week's work (five days) of a few hours a day. Each study plan starts with a few paragraphs as an introductory homily, and this is followed by an outline for study divided into five periods, and a list of books for suggested reading. At the end of each study plan is a series of questions mostly of the D.A. type. Teachers and postgraduates will find perusal of this volume rewarding for it gives an insight into the educational needs in anaesthesia of another country, and a guide to individuals on how to meet them. The book also provides a very useful literature list under each topic heading.

W. W. Mushin

Principles of Measurement for Anaesthetists. By M. K. Sykes and M. D. Vickers. Published by Blackwell Scientific Publications, Oxford and Edinburgh. Pp. 309; illustrated; indexed. Price £3.75.

This text has been designed for the student preparing for the Primary FFARCS examination and is the first book of its type to be prepared exclusively by clinical anaesthetists. Paradoxically it may prove to be one of the best, if only because the writers have a helpful degree of insight into the reader's difficulties.

The preface assumes of the reader "nothing beyond first M.B. physics and 'O' level mathematics". This is a little depressing since many students find that they have forgotten much of both. However, a predominantly helpful and original opening section on general principles of measurement seems to fulfil the authors' promise to avoid jargon. I would specially recommend the chapters on recording systems and on spectrophotometry. A chapter on isotopes is informative but brief and I would have wished to see more on the subject of protection and hazards.

Part 2 deals with specific measurements. It accounts for well over half of the book and is the section which perhaps is most worthwhile. Pressure and flow measurements are discussed clearly and relevantly. Volume measurement comes as a miscellany of spirometry, blood electrolyte composition, blood volume and blood loss estimations. This is an original arrangement but turns out well in the end. Gas and blood-gas analysis are given an emphasis which, although perhaps departing from a mere description of basic principles, will be of undoubted value beyond the needs of the examinee. It is a small point, but the paragraphs on gas chromatography would have been improved by a diagram. This section also deals with thermometry and the measurement of biological potentials. I was glad to find a readable description of a clinical nerve stimulator.

While reading through a chapter in the first section entitled "Electricity and Electronics" I felt myself out of sympathy with the authors in their chosen scope for the book. I believe that a similar criticism can be extended to nearly all of the third section which deals with the analysis of numerical data. Even the authors feel uncertain about the relevance of this section for they begin with a note of explanation. However, they are soon in full flight and the reader is spared very little. My surprise is not at the balance in presentation, although one wonders about Yates correction and the Wilcoxon ranking test, but the fact that the authors feel the need to include the subject of statistical analysis at all. I can think of at least one book on this subject which sells, page for page, at a tenth of the price of this one. I have emphasized these shortcomings not because the authors have failed in their purpose but because they have come very close to the ideal formula for communicating the essentials of clinical measurement.

The coming of the second edition is foretold on page 288. Immodest though they seem, I am sure the authors are right!

Alastair A. Spence