SENSITIVITY TO DIMETHYLTUBOCURARINE AND TOXIFERINE WITH SPECIAL REFERENCE TO SERUM PROTEINS

J. STOVNER, L. THEODORSEN AND E. BJELKE

SUMMARY

In a consecutive series of 100 female patients undergoing abdominal surgery muscular relaxation was obtained in half with dimethyltubocurarine and in half with toxiferine. The required dose of these relaxants (mg/m² body surface) showed a lower individual variation than the requirements of any other non-depolarizing relaxants investigated under similar conditions. Neostigmine 0.5 mg reversed the block by dimethyltubocurarine better than the block by toxiferine. The requirement of dimethyltubocurarine showed no detectable correlation with any serum protein fraction. The requirement of toxiferine displayed a negative correlation with serum albumin (r = −0.46) and only weak positive correlation with the globulins. From the present and previous studies it is concluded that charge-dissipating ethyl and allyl quaternization leads to positive correlation with albumin. Methylquaternized compounds, on the other hand, do not show this effect and may even display a negative albumin correlation as seen with toxiferine. Free phenolic hydroxyl groups induce positive correlations with the globulins while free alcoholic hydroxyl groups do not.

It has been shown that sensitivity to alcuronium and gallamine is related to serum albumin levels and that sensitivity to tubocurarine is related to the level of gamma globulin, while pancuronium shows no relation at all to the serum protein pattern (Stovner, Theodorsen and Bjelke, 1971a, b). It has been suggested that the charge-dissipating ethyl and allyl quaternization present in gallamine and alcuronium respectively is the factor responsible for the positive albumin correlation. The absence of such albumin association for tubocurarine and pancuronium is assumed to depend on their methyl quaternization. The positive correlation between tubocurarine and gamma globulin was assumed to depend on the free phenolic hydroxyl groups in the former.

To test this hypothesis it was decided to study two other relaxant drugs, dimethyltubocurarine and toxiferine. In the first compound the free phenolic hydroxyl groups have been replaced by methylation and in the second, methyl quaternization has replaced the allyl quaternization of alcuronium. The requirements of these relaxants, correlated with the serum proteins, were therefore of considerable interest.

The present paper reports the correlation between the requirements of dimethyltubocurarine (Metubine; Lilly) and toxiferine (Toxiferine, Ro 4–2906; Roche) during surgery and the levels of the various serum protein fractions. At the same time some general properties of the two relaxants have been studied, such as relative potencies, individual variations in dosage and reversibility by neostigmine.

METHODS

Patients.

A consecutive series of 100 female patients with ovarian or uterine cancer scheduled for lower abdominal surgery were studied. No other selection of patients was made, all being included irrespective of age and weight. In the first 50 patients muscular relaxation was obtained with dimethyltubocurarine, and in the next 50 with toxiferine. Anaesthetic induction and technique were the same in both groups.

Anaesthetic technique and requirements of relaxants.

Premedication consisted of morphine 10 mg and hyoscine 0.6 mg given i.m. 1 hour before induction. After induction of sleep with diazepam 20–30 mg i.v., the relaxant was injected. The initial dose of dimethyltubocurarine was 10–12 mg and of toxiferine 2–2.5 mg. When respiration diminished, artificial
ventilation by bag and mask with 100 per cent oxygen was performed for 2 minutes before tracheal intubation. Anaesthesia was maintained with 25–50 mg doses of pethidine i.v. every 30-60 min. Controlled ventilation with a non-rebreathing technique employing a minute volume of 8–10 l./min of gas mixture was used throughout the operation. The degree of neuromuscular block was assessed using a manually triggered peripheral nerve stimulator (R. C. Wakeling and Co.) with needle electrodes applied to the ulnar nerve at the elbow. At 15-min intervals a train of four single stimuli of 0.3 msec duration and supramaximal voltage was delivered at a frequency of 2 Hz (i.e. 0.5 sec between each stimulus). The resulting twitch responses were recorded with a tensile compressive transducer (Ether UFI ± 32 ounces) assembled in the form of a hand grip (Ali, 1970) and connected to an Esterline Angus Recorder (Series S 601 S Labgraph). When the twitch responses indicated recovery of muscle tone during surgery, incremental doses of either dimethyltubocurarine 2 mg or toxiferine 0.5 mg were given. The requirements of relaxants during the first 90 min of the operation were calculated in mg/m² body surface. The body surface was read from the Du Bois nomogram for given height and weight (Du Bois and Du Bois, 1916).

In the 10 first patients from each group with signs of residual neuromuscular relaxation at the end of the operation, the effect of 0.5 mg neostigmine was studied by recording the responses to the four stimuli trains every 15 sec for 4 min after the injection. Figure 1 shows the recording of a train before and 1 min after injection of neostigmine 0.5 mg in a dimethyltubocurarine patient and a toxiferine patient.

**Blood protein estimations.**

Venous blood (5–10 ml) was drawn from each patient before induction of anaesthesia and allowed to clot. Total serum protein was determined by the biuret technique (Weichselbaum, 1946). The different serum protein fractions were determined by cellulose acetate electrophoresis (Beckman Microzone Electrophoresis System Model R–100).

**Data analysis and presentation.**

The comparability of the two groups of 50 patients can be assessed from table 1. The means and standard deviations for selected variables such as age, body surface and total protein, as well as the various serum protein fractions, were closely similar in the two groups. The intercorrelations of the various serum protein fractions were not significant.

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**TABLE I. Selected characteristics of the series of 100 female patients by type of relaxant.**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Dimethyltubocurarine</th>
<th>Toxiferine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Age (years) Mean</td>
<td>54.3</td>
<td>53.4</td>
</tr>
<tr>
<td>Age (years) SD</td>
<td>13.8</td>
<td>14.1</td>
</tr>
<tr>
<td>Body surface (m²)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body surface Mean</td>
<td>1.67</td>
<td>1.70</td>
</tr>
<tr>
<td>Body surface SD</td>
<td>0.16</td>
<td>0.18</td>
</tr>
<tr>
<td>Total protein (g/100 ml) Mean</td>
<td>6.8</td>
<td>6.7</td>
</tr>
<tr>
<td>Total protein (g/100 ml) SD</td>
<td>0.6</td>
<td>0.5</td>
</tr>
<tr>
<td>Albumin (g/100 ml) Mean</td>
<td>3.2</td>
<td>3.3</td>
</tr>
<tr>
<td>Albumin (g/100 ml) SD</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Total globulin (g/100 ml) Mean</td>
<td>3.5</td>
<td>3.5</td>
</tr>
<tr>
<td>Total globulin (g/100 ml) SD</td>
<td>0.5</td>
<td>0.4</td>
</tr>
<tr>
<td>Alpha 1 globulin (g/100 ml) Mean</td>
<td>0.31</td>
<td>0.33</td>
</tr>
<tr>
<td>Alpha 1 globulin (g/100 ml) SD</td>
<td>0.07</td>
<td>0.07</td>
</tr>
<tr>
<td>Alpha 2 globulin (g/100 ml) Mean</td>
<td>0.83</td>
<td>0.83</td>
</tr>
<tr>
<td>Alpha 2 globulin (g/100 ml) SD</td>
<td>0.15</td>
<td>0.15</td>
</tr>
<tr>
<td>Beta globulin (g/100 ml) Mean</td>
<td>0.99</td>
<td>0.98</td>
</tr>
<tr>
<td>Beta globulin (g/100 ml) SD</td>
<td>0.18</td>
<td>0.14</td>
</tr>
<tr>
<td>Gamma globulin (g/100 ml) Mean</td>
<td>1.41</td>
<td>1.36</td>
</tr>
<tr>
<td>Gamma globulin (g/100 ml) SD</td>
<td>0.28</td>
<td>0.22</td>
</tr>
<tr>
<td>Relaxant dose* (mg/m²) Mean</td>
<td>9.17</td>
<td>1.62</td>
</tr>
<tr>
<td>Relaxant dose* (mg/m²) SD</td>
<td>0.86</td>
<td>0.15</td>
</tr>
</tbody>
</table>

* The doses represent mg/m² body surface required for 90 minutes relaxation.
protein fractions, not given here, showed a similar pattern in the two groups of patients. The mean values and the standard deviations of the doses of relaxants required by the patients in each group are also given in table I. The bivariate correlations between the dose of relaxants and the level of the various serum protein fractions are given in table II. Product-moment correlation coefficients were used as measures of the strength of a linear association between the two variables.

RESULTS AND DISCUSSION

General properties of the relaxants.

A methylated derivative of tubocurarine was described by King as early as 1935, but it was not until 1950 that Collier reported on its action in animals and Wilson, Gordon and Raffan used it clinically. Despite a number of advantages, the drug has never gained wide popularity, possibly because the complexity of the molecules makes it difficult to produce batches of identical activity (Mogey and Trevan, 1950). All the drug used in the present study was from the same batch.

King isolated the first toxiferines in 1949 and Paton and Perry described their pharmacology in 1951. The structural formula, however, was not known until 1958 as a result of the work of Bernauer and his group, and the synthesis followed in 1959 by Berlage and associates. The pharmacology of the purified alkaloid was described by Waser and Harbeck (1959) and it was tried clinically in Europe by Frey and Seeger (1961) and in the United States by Foldes, Wolfson and Sokoll (1961). Although producing excellent relaxation, it has never become popular, possibly because the long duration of action makes it less suitable for operations of short and medium duration.

The potency of dimethyltubocurarine in relation to tubocurarine can be found by comparing the doses of the two drugs under similar conditions. It may be seen from table I that dimethyltubocurarine 9.17 mg was needed per m² during 90 min, while tubocurarine 18.3 mg was needed under similar conditions (Stovner, Theodorsen and Bjelke, 1971a). This makes dimethyltubocurarine twice as potent as tubocurarine, a finding which is in good agreement with that of Wilson, Gordon and Raffan (1950). It is interesting that methyl substitution in tubocurarine has resulted in a compound with higher blocking activity, while in the case of toxiferine Waser (1962) showed that the compound with two free hydroxyl groups had the highest action. Obviously the phenolic hydroxyl groups in tubocurarine play a different role from the alcoholic hydroxyl group in toxiferine.

The potency of toxiferine in relation to tubocurarine can be found in the same way by comparing the requirements of the two relaxants under similar conditions. From table I it is seen that the mean dose of toxiferine in mg/m² body surface during 90 min was 1.62 while that of tubocurarine in a comparable series was 18.3 (Stovner, Theodorsen and Bjelke, 1971a). This suggests a potency of toxiferine eleven times that of tubocurarine. By comparing single doses of the two relaxants needed for tracheal intubation Foldes, Wolfson and Sokoll (1961) found toxiferine about six times as potent as tubocurarine, but they observed at the same time that the effect of toxiferine lasted at least twice as long as tubocurarine. During our 90 min of abdominal relaxation incremental doses of tubocurarine had to be given two to three times, while an extra dose of toxiferine was rarely given more than once during this period. The high potency of toxiferine noted in our study compared with the findings of Foldes, Wolfson and Sokoll (1961) is therefore due to the longer action of toxiferine and the fact that we have studied doses needed for 90 min relaxation. Toxiferine is exceptional in its high potency and also in its uniformity of action in several other species and thus differs from all other relaxants among which there is a bewildering species variation as regards sensitivity. When they discovered the high potency of toxiferine in 1951 Paton and Perry wrote: "Given such a compound, stories frequent in the more adventurous traveller's tales of inexorable death after the merest scratch by a poisoned arrow take on some semblance of credibility".

Individual variation in requirements.

The standard deviation expressed as a percentage of the mean for dimethyltubocurarine is 9.4%, and for toxiferine 9.0%. These are the lowest coefficients of variation found for any of the non-depolarizing relaxants tested under similar conditions (Stovner, Theodorsen and Bjelke, 1971a). A coefficient of variation for dimethyltubocurarine considerably lower than for both tubocurarine and decamethonium was found by Unna and associates (1950). Toxiferine is unique among relaxants in displaying the most uniform inter-species sensitivity (Paton and Perry, 1951). It is therefore not surprising that it also displays a very uniform individual sensitivity in humans.
However, we cannot deny the possibility that the long duration of action of a single dose of toxiferine makes it more difficult to detect individual variation in sensitivity to the drug even during 90-min periods of relaxation.

Reversibility by neostigmine.

It was noticed during the study that with dimethyltubocurarine smaller doses of neostigmine were needed for reversal than was the case with other non-depolarizing relaxants studied under similar conditions. Using the method of Ali, Utting and Gray (1970), we recorded the responses to a train of four single stimuli with half-second intervals and 15-sec train intervals. The effect of 0.5 mg neostigmine on partly relaxed patients could with this method be expressed as a percentage. In 10 patients relaxed with dimethyltubocurarine 0.5 mg neostigmine caused a mean increase in the ratio $C_4/C_1$ of 65% where $C_1$ and $C_4$ are the responses to the first and fourth stimuli in the train. In 10 patients relaxed with toxiferine 0.5 mg neostigmine caused a mean increase in the same fraction of only 35%. Typical recordings are shown in figure 1. Collier (1950) demonstrated an extreme difference among various animal species in the degree to which neostigmine reversed dimethyltubocurarine. The present results show that in man this reversal occurs readily and more completely than with toxiferine.

Interactions with serum proteins.

The structural formulae for dimethyltubocurarine and alcuronium (diallyl-nor-toxiferine) as well as their mother compounds, tubocurarine and toxiferine, are given in figure 2.

![Structural formulae for tubocurarine, dimethyltubocurarine, alcuronium and toxiferine.](Fig. 2)

From table II it can be seen that the requirements of dimethyltubocurarine showed no notable correlation with any of the serum protein fractions. This indicates that the association between tubocurarine and the globulins previously shown by Stout (1963), Baraka and Gabali (1968) and Stovner, Theodorsen, and Bjelke (1971a) is due to the free phenolic hydroxyl groups of that compound.

It came as a surprise to us that toxiferine requirements showed a negative correlation to serum albumin ($r = -0.46$) as seen in the scatter diagram in figure 3. The working hypothesis was, as mentioned in the introduction, that methyl-quatnization in toxiferine would lead to a disappearance of the positive albumin correlation found in the allyl-quatnized alcuronium. A negative correlation was not expected, and would appear to indicate that high serum albumin values would enhance the blocking action of toxiferine. That human serum or some of its components actually can enhance the blocking action of certain relaxants was shown by Payne and Webb (1962).

Toxiferine has a longer duration of action than alcuronium. This agrees well with the findings in the
barbiturate series where allyl substitution confers greater affinity for albumin than the corresponding saturated agents (Goldstein, 1949) and albumin binding and shortness of action were found to go hand in hand (Goldbaum and Smith, 1954). Gallamine showed a positive correlation to albumin (Stovner, Theodorsen and Bjelke, 1971b) and is one of the shortest acting non-depolarizing relaxants in clinical use. Allyl substitution on the tertiary N-methyl group in morphine yields the antagonistic compound nalorphine, which has both a shorter duration of action and a weaker analgesic action than the mother compound. Drug-serum correlation might be analogous to drug-receptor binding, and it would be interesting to study the affinities of the two relaxants toxiferine and alcuronium to serum albumin in vitro.

Only weak positive correlations were found between the requirements of toxiferine and the globulins. Thus the primary alcoholic hydroxyl groups in toxiferine are different from the ionizable phenolic hydroxyl groups in tubocurarine in this respect as well. The primary hydroxyl groups are also present in alcuronium, but here they are masked by hydrogen bonding (Buckett and Frisk-Holmberg, 1970). Our results are in agreement with the findings in other series of compounds. In his study of sulphonated azo dyes, Klotz (1946) concluded that polar substituents such as hydroxyl groups diminish the affinity for albumin unless their position permits masking by hydrogen bonding. According to Albert (1968) the aromatic acids, sulphonamides and barbiturates, lose their affinities for serum albumin when they carry hydrophilic substituents like alcoholic hydroxyl groups.

**Chemical structure and serum protein correlations.**

The muscle relaxants were the first substances used to obtain information about drug receptors on the cell surface. Considerable information about endplate receptors has been obtained by testing series of compounds (Boehm, 1920; Bovet, 1951; Cavallito, 1962). We must, however, consider both specific and non-specific receptors for muscle relaxants, as pointed out by Chagas (1962). Non-specific receptors are found on the mast cells and certain relaxants fill the requirements of these receptors and cause histamine liberation (Buckett and Frisk-Holmberg, 1970). Drug-serum protein interactions are in many ways a model system for drug receptor interactions (Goldstein, 1949). From the present and previous studies we are able to draw some conclusions about the molecular features of the relaxant drugs governing the interactions with the serum proteins. These features are listed in Table III where variation in albumin or total globulin accounted for 12% or more of the variation between individuals in drug requirements. This has been indicated in table III

**Table III. Relaxant structure and serum protein dependence.**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Charge on N+</th>
<th>Hydroxyl groups</th>
<th>Correlation with*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tubocurarine†</td>
<td>Concentrated by methyl groups</td>
<td>Free phenolic groups</td>
<td>Total globulins positive</td>
</tr>
<tr>
<td>Dimethyl-tubocurarine</td>
<td>Concentrated by methyl groups</td>
<td>Masked by methylation</td>
<td>—</td>
</tr>
<tr>
<td>Gallamine‡</td>
<td>Dissipated by ethyl groups</td>
<td>None</td>
<td>Albumin positive</td>
</tr>
<tr>
<td>Pancuronium‡</td>
<td>Concentrated by methyl groups</td>
<td>None</td>
<td>—</td>
</tr>
<tr>
<td>Toxiferine</td>
<td>Concentrated by methyl groups</td>
<td>Free primary</td>
<td>Albumin negative</td>
</tr>
<tr>
<td>Alcuronium† (diallyl-nortoxiferine)</td>
<td>Dissipated by allyl groups</td>
<td>Masked by H+ bonding</td>
<td>Albumin positive</td>
</tr>
</tbody>
</table>

* Only correlations with albumin and total globulin stronger than r = ±0.34 have been included. On this basis the serum proteins account for 12% or more of the variation in drug doses.

† Stovner, Theodorsen and Bjelke, 1971a.
‡ Stovner, Theodorsen and Bjelke, 1971b.

as either a positive or negative correlation. It is seen that charge-dissipating ethyl and allyl quaternization such as in gallamine and alcuronium produces a positive correlation with albumin. Charge concentrating methyl quaternization, on the other hand, does not have this effect and may even cause negative correlation. Free phenolic hydroxyl groups lead to a positive correlation with the globulins, while free primary hydroxyl groups lack this ability and may contribute to a negative albumin correlation.

**Acknowledgement**

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**References**

BERLAGE, F., BERNAUER, K., VON PHILPSBORN, W., SCHMID, H., AND KARRER, P. (1959). Notiz zur synthese des C-
Calebassen-alkaloides C-Dihydropotoxiferine und C-Toxi-
ferine I des Alkaloids Conchocurarine—1 aus Strychnos
Springer.
chemical constitution and curare-like activity. Ann. N.Y.
Acad. Sci., 54, 407.
of neuro-muscular blocking agents to investigate receptor
structure requirements for histamine release. Brit. J.
Pharmacol., 14, 165 p.
Cavallito, C. J. (1962). Structure-action relations throwing
light on the receptor, in Curare and Curare-like Agents
(ed. A. V. S. de Reuck). Ciba Foundation Study Group
No. 12.
CHAGAS, C. (1962). The fate of curare during curarization;
in Curare and Curare-like Agents (ed. A. V. S. de Reuck).
Ciba Foundation Study Group No. 12.
COLLIER, H. O. J. (1950). Pharmacology of D-O.O-Di-
methyltubocurarine iodide in relation to its clinical use.
Brit. med. J., 1, 1293.
DU BOIS, D., AND DU BOIS, E. F. (1916). A formula to
estimate the approximate surface if height and weight
use of toxiferine for the production of surgical relaxa-
tion. Anesthesiology, 22, 93.
experience with toxiferine (alkaloid of calabash curare).
GOLDBAUM, L. R., AND SMITH, P. K. (1954). The interac-
tion of barbiturates with serum albumin and its possible
relation to their disposition and pharmacological actions.
J. Pharmacol. exp. Ther., 111, 197.
GOLDSTEIN, A. (1949). The interactions of drugs and plasma
chem. Soc., 1381.
KLOZ, I. M. (1946). Spectrophotometric investigations of
the interactions of proteins with organic ions. J. Amer.
chem. Soc., 68, 2299.
Paton, W. D. M., AND PERRY, L. M. (1951). The pharma-
from jaundiced patients on the action of relaxants. Brit.
J. Anaesth., 34, 863.
WASER, P. G. (1962). Discussions in Curare and Curare-
like Agents (ed. A. V. S. de Reuck), p. 52. Ciba Founda-
tion Study Group No 12.
HARBECK, P. (1959). Erste klinische Anwendung der
Calabassenalkaloide Toxiferine I und Curarine I. Der
Anaesthesist, 8, 193.
WEICHSELBAUM, T. E. (1946). An accurate and rapid method
for the determination of protein in small amounts of
Sec. 40.
Dimethyl ether of d-tubocurarine iodine as a curarizing
agent in anaesthesia for thoracic surgery. Brit. med. J.,
1, 1296.

ETUDE DE LA SENSIBILITE A LA DIMETHYLTUBOCURARINE ET A LA TOXIFERINE EN SE
REFERANT TOUT PARTICULIEREMENT AUX PROTEINES SERIQUES

SOMMAIRE

Dans le cadre d’une série de 100 malades du sexe féminin
ayant subi des interventions de chirurgie abdominale, la
myorelaxation a été obtenue dans la moitié des cas par
la dimethyltubocurarine et dans l’autre moitié, par la
toxiferine. La dose requise de ces agents myorelaxants
(mg/surface corporelle en m²) a présenté une variation
individuelle inférieure aux doses requises, dans des con-
ditions similaires, par toute autre substance myorelaxante
non dépolarisante. A la dose de 0,5 mg, la néostigmine a
permis de neutraliser plus efficacement le blocage provoqué
par la dimethyl-tubocurarine que celui engendré par la
toxiferine. Les doses requises en dimethyltubocurarine
n’ont pas présenté de relation décelable avec aucune frac-
tion protéique sérique. La dose requise en toxiferine a
présenté une corrélation négative avec l’albumine sérique
(r=0,46) et seulement une faible corrélation positive avec
les globulines. A partir des études présentes et antérieures,
it est possible de conclure qu’une transformation quater-
naire des dérivés de type éthyle et alyle qui abouti à une
dispersion des charges, conduit à une corrélation positive
avec l’albumine. D’autre part, les composés de type
méthyle quaternaires ne sont pas dosés d’un tel effet et
peuvent même présenter une corrélation négative avec
l’albumine. Ainsi qu’on le sait, a pu le constater avec la toxiferine.
Les radicaux hydroxyles phénoliques induisent des cor-
relations positives avec les globulines, tandis que les radicaux hydroxydes alcooliques libres en sont incapables.

DIMETHYLTUBOCURARINE- UND TOXIFERINEMPFINDLICHKEIT UNTER
BESONDERER BERÜCKSICHTIGUNG DER SERUMPROTEINE

ZUSAMMENFASSUNG

Bei einer Serie von einhundert weiblichen Patientinnen, die
sich einer abdominalen Operation unterzogen, wurden die
Muskelkraft in einer Hälfte mit Dimethyltubocurarine und
in der anderen Hälfte mit Toxiferin relaxiert. Die erforderliche
Dosis dieser Relaxantien (mg/m² Körperoberfläche) zeigte
eine geringere individuelle Variationsbreite als die aller
anderen nicht-depolarisierenden Relaxantien, die unter
ähnlichen Bedingungen untersucht wurden. 0,5 g Neo-
stigmin hoben den Block durch Dimethyltubocurarine
erhöht, den Block durch Toxiferin dagegen. Die erforderliche Menge
Dimethyltubocurarine zeigte keine erkennbare Korrelation
mit irgendwelcher Serumproteinkonzentration. Bei Toxiferin zeigte
sich eine negative Korrelation zur Serumalbumin (r= 
-0,46) und nur eine schwache positive Korrelation zu den

SENSIBILIDAD PARA LA DIMETILTUBOCURARINA Y TOXIFERINA CON MENCION ESPECIAL DE LAS PROTEINAS SERICAS

RESUMEN
En una serie consecutiva de cien pacientes sometidas a cirugía abdominal se obtuvo relajación muscular en una mitad con dimetiltubocurarina y en la otra mitad con toxiferina. La dosis requerida de estos relajantes (mg/m² de superficie corporal) mostró una variación individual más baja que los requisitos de cualquier otro de los agentes no despolarizantes investigados bajo condiciones semejantes. 0,5 mg de neostigmina invirtieron el bloqueo por dimetiltubocurarina mejor que el bloqueo por toxiferina. Los requisitos de dimetiltubocurarina no mostraron ninguna correlación detectable con alguna fracción proteínica del suero. Los requisitos de toxiferina mostraron una correlación negativa con la albúmina sérica ($r=0,46$) y solamente una débil correlación positiva con las globulinas. Se deduce de los presentes estudios y otros previos que la cuaternización de etil y alil que disipan cargas conduce a una correlación positiva con la albumina. Los compuestos con metil cuaternizado, por otra parte, no desarrollan este efecto e incluso pueden mostrar una correlación negativa de albúmina como se observa con la toxiferina. Los grupos hidroxílicos fenólicos libres inducen correlaciones positivas con las globulinas, en tanto que los grupos hidroxílicos alcohólicos no lo hacen.