A COMPARISON OF THE EFFECTS OF SUXAMETHONIUM AND TUBOCURARINE IN PATIENTS IN LONDON AND NEW YORK

BY

R. L. KATZ, J. NORMAN, R. F. SEED AND L. CONRAD

SUMMARY

The effects of suxamethonium and tubocurarine were studied in London and New York patients anaesthetized with thiopentone, nitrous oxide and halothane. The actions of the muscle relaxants were assessed by measurement of the twitch response of the adductor pollicis muscle to supramaximal stimulation of the ulnar nerve. The duration of action of suxamethonium (1 mg/kg) was less in London patients than in a comparable group of New York patients. With tubocurarine (0.1 mg/kg) the magnitude and duration of action was less in London than in New York patients. In a group of American patients at a United States Air Force (USAF) hospital the magnitude and duration of action of tubocurarine (0.1 mg/kg) was similar to that seen in New York patients. It was also observed that the response to tubocurarine (0.1 mg/kg) was affected by the prior administration of suxamethonium (1 mg/kg). Both the magnitude and duration of action of tubocurarine were greater in patients who had previously received suxamethonium than in those who had not.

During the course of a sabbatical year one of us (R.L.K.) was surprised to observe clinically that doses of tubocurarine (0.5–1.0 mg/kg) which in New York would regularly abolish the twitch response to stimulation of the ulnar nerve did not do so in London. Further, in a study of pancuronium (Norman, Katz and Seed, in preparation) when the responses to suxamethonium and tubocurarine were measured for comparison it seemed that the responses to both these agents were less in patients in London than in New York. The present study was undertaken to explore the differences. A preliminary report of the results has been given (Katz, Norman and Seed, 1969).

METHODS

Patients were studied during anaesthesia and surgery. Most patients were premedicated with either atropine (0.6 mg) or hyoscine (0.4 mg), pethidine (50–100 mg) or papaveretum (10–20 mg), and on occasion droperidol (5–10 mg). Anaesthesia was induced with thiopentone (200–500 mg) and maintained with nitrous oxide and halothane (0.75–1.5 per cent).

Neuromuscular transmission was studied in a manner previously described (Katz, 1965). Briefly the ulnar nerve was stimulated with pulses of supramaximal intensity generated by either a Block-Aid monitor or a Tektronix pulse generator at a rate of 1 pulse every 3 or 4 seconds via steel needles placed subcutaneously over the ulnar nerve at the elbow. The resultant adduction of the thumb was measured using either a force-displacement transducer (Grass model FT-03) attached to a Devices recorder or a portable mechanical transducer writing on a moving-paper recorder. The effects of suxamethonium and tubocurarine were recorded continuously. The duration of action of each drug was measured from the first twitch to show a decrease in height after administration of the drug, to recovery to either 10 or 90 per cent of the initial control height. The magnitude of the block produced was calculated as the maximum depression in the force of adduction expressed as a percentage of the initial twitch tension.

The effects of suxamethonium chloride (dose 1 mg/kg) were determined in fourteen patients...
at Hammersmith Hospital and the results were compared with those of ten patients previously studied at the Columbia-Presbyterian Medical Centre (Katz and Ryan, 1969). The suxamethonium used in the London patients was a 5 per cent solution (Scoline; Allen & Hanbury) whilst the New York patients received a 2 per cent solution (Anectine; Burroughs Wellcome). In three patients in London both solutions were used.

The effects of 0.1 mg/kg of tubocurarine were determined initially in eleven patients at Hammersmith Hospital and the results were compared with those in fifteen patients previously studied at Columbia-Presbyterian (Katz and Gissen, 1967). In London tubocurarine was used as a 1 per cent solution (Duncan, Flockhart & Evans) whilst the New York patients received a 0.3 per cent solution (Burroughs Wellcome). Twelve additional patients in Hammersmith Hospital received tubocurarine; a 0.3 per cent solution in seven and a 1 per cent solution in five. Similar results were seen with the 0.3 and 1 per cent solutions. The effects of 0.1 mg/kg of a 1 per cent solution of tubocurarine were studied in eleven patients at a United States Air Force hospital in London.

RESULTS

Suxamethonium.

The response to suxamethonium (1 mg/kg intravenously) in a London patient is shown in figure 1. It differs from that seen in the New York patients (Katz and Ryan, 1969) in that the speed of onset is faster and the duration of block is shorter. Table I compares the recovery to 10 and 90 per cent of the control level in the patients under comparable conditions in New York and London. The differences between the two groups are statistically significant for both the 10 per cent (P<0.005) and the 90 per cent recovery (P<0.001). Since there were differences in the brands and concentrations of suxamethonium used there was a possibility that the differences were due to these factors. However, three patients received both the 2 and the 5 per cent solutions. Figure 2 shows the response to successive injections in one patient and shows the similarity of

<table>
<thead>
<tr>
<th>Recovery time (min)</th>
<th>London</th>
<th>New York</th>
<th>Significance*</th>
</tr>
</thead>
<tbody>
<tr>
<td>10%</td>
<td>6.3±2.15</td>
<td>10.2±3.2</td>
<td>P&lt;0.005</td>
</tr>
<tr>
<td>(n=14)</td>
<td></td>
<td>(n=10)</td>
<td></td>
</tr>
<tr>
<td>90%</td>
<td>9.1±2.9</td>
<td>14.6±3.6</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>(n=13)</td>
<td></td>
<td>(n=10)</td>
<td></td>
</tr>
</tbody>
</table>

Values are mean, ±1 SD (No. of observations).

* Significance is the significance of the difference between the mean values assessed using Student's t test.

FIG. 1

Effect of suxamethonium on twitch response to ulnar nerve stimulation. Suxamethonium injected at ↑. The bar shows 1 minute duration.

FIG. 2

Response to injections of suxamethonium (1 mg/kg) in 5 and 2 per cent solutions. Each trace shows time marker (min), twitch record, and signal marker. The upper and lower traces are continuous. Upper panel, suxamethonium (5 per cent) injected at break in signal marker. Lower panel suxamethonium (2 per cent) injected at marker.
response to each solution. The other two patients also had a similar response to each solution. Thus the differences in brand and concentration do not account for the differences in response between London and New York patients. But although the differences are statistically significant we feel they are of minimal clinical importance.

**Tubocurarine.**

The responses to the intravenous injection of 0.1 mg/kg of tubocurarine were determined initially in eleven patients in London. A marked variation in response was seen (figs. 3, 4) similar to that previously reported (Katz, 1967). Although, in general, the duration of block was longer in patients with a greater magnitude of block, individual exceptions were seen. For example, the duration of block (to 90 per cent recovery) in the patient in figure 4 was 15 minutes. In another patient with a similar magnitude of block the duration (to 90 per cent recovery) was 33 minutes. Thus, in any one patient, a prediction of duration of block from the magnitude could be wrong.

The magnitude and duration of block produced by tubocurarine in the London patients were less than that seen in a similar group of patients in New York (table II). Both these differences were statistically significant (P<0.001). In contrast with the differences seen with suxamethonium we felt that these differences with tubocurarine were of practical importance and the problem was explored further.

The New York-London differences in response raised many questions. Were the differences due to chance (despite the statistical significance of the difference), to heredity, to environment, to the use of different brands and concentrations of the drug, to unrecognized changes in the experimental technique, or to the fact that the responses in London were being compared with those seen in New York some years earlier? We have attempted to answer some of these questions by studying additional patients in London and by studying American citizens operated on at a United States Air Force (USAF) hospital in London.

**Table II**

<table>
<thead>
<tr>
<th></th>
<th>London Mean</th>
<th>New York Mean</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>% block</td>
<td>43.2 ± 21.1</td>
<td>75.0 ± 14.1</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>90% recovery</td>
<td>14.6 ± 8.8</td>
<td>31.2 ± 12.4</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>time (min)</td>
<td>(n=9)</td>
<td>(n=11)</td>
<td></td>
</tr>
</tbody>
</table>

Values are mean, ±1 SD (No. of observations).

**Fig. 3**

Effect of tubocurarine on twitch response. Tubocurarine (0.1 mg/kg) injected at †. The bar shows 1 minute duration. No suxamethonium had been administered previously.

**Fig. 4**

Effect of tubocurarine on twitch response. Tubocurarine (0.1 mg/kg) injected at †. The bar shows 1 minute. This record was obtained from the patient whose response to suxamethonium is shown in figure 1.
Responses in USAF patients in London.

These patients had lived in London and its environs for periods of between 13 and 36 months. There was a variation in the extent of their integration with the local non-American community. Some bought food in the Commissary (obtained from the United States), some shopped mainly in the local markets, and others used both sources of supply. The group was consistent only in that they all breathed the English air!

The magnitude and duration of action of 0.1 mg/kg of tubocurarine in these eleven patients was greater than that observed in the London patients (table III). Figure 5 shows the results in one USAF patient in whom recovery to 90 per cent of the original twitch height took 64 minutes. A statistical comparison of the results in the USAF patients shows that when compared with the English patients (table III) the intensity and duration of the block just fail to achieve statistical significance (0.1>P>0.05 in each case). A larger series may well show a significant difference. The tubocurarine used in these

<table>
<thead>
<tr>
<th>TABLE III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response to tubocurarine (0.1 mg/kg).</td>
</tr>
<tr>
<td>% block</td>
</tr>
<tr>
<td>62.4 ± 26.7</td>
</tr>
<tr>
<td>(n=11)</td>
</tr>
<tr>
<td>90% recovery</td>
</tr>
<tr>
<td>time (min)</td>
</tr>
<tr>
<td>Values are mean, ±1 SD (No. of observations).</td>
</tr>
</tbody>
</table>

patients was that usually employed in London—namely a 1 per cent solution. The magnitude and duration of action of 0.1 mg/kg of tubocurarine in the USAF and previously studied New York patients was similar (tables II and III). These results suggest that different brands and concentrations of the drug, changes in experimental technique or differences in the year of study are not important factors in explaining the Anglo-American difference. In addition, it should be clear from figure 5 and tables II and III why American anaesthesiologists use doses of tubocurarine which appear homeopathic to English anaesthetists.

Differences in experimental design.

Whilst we were studying the USAF patients and additional London patients we reviewed the experimental circumstances for possible clues to explain the Anglo-American difference. The patients in both London and New York were patients of the Urology and Plastic Surgery Departments. The USAF patients were undergoing general or gynaecological surgery. The age, sex and weight distributions were similar. Pre-medication, induction and maintenance of anaesthesia were similar and all patients inhaled nitrous oxide-oxygen and halothane for 20 minutes before receiving tubocurarine. One factor which did change in each series was that some patients received suxamethonium (usual dose 1 mg/kg) before tubocurarine in order to permit endotracheal intubation, whilst others did not. In each

FIG. 5

Effect of tubocurarine on twitch response in a USAF patient who had previously received suxamethonium. Tubocurarine (0.1 mg/kg) injected at \( \uparrow \). The bar shows 1 minute. The upper and lower panels are continuous. Towards the end of the upper panel a 3-seconds tetanic stimulation was given and post-tetanic facilitation is seen.
A COMPARISON OF SUXAMETHONIUM AND TUBOCURARINE

TABLE IV

Effect of prior administration of suxamethonium (1 mg/kg) on the response to tubocurarine (0.1 mg/kg).

<table>
<thead>
<tr>
<th></th>
<th>No suxa-</th>
<th>Suxa-</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>methonium</td>
<td>methonium</td>
<td></td>
</tr>
<tr>
<td><strong>London</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% block</td>
<td>20.3 ± 22.1</td>
<td>65.4 ± 26</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>(n=12)</td>
<td>(n=11)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>90% recovery</td>
<td>7.5 ± 8.7</td>
<td>27.1 ± 10.1</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>time (min)</td>
<td>(n=11)</td>
<td>(n=8)</td>
<td></td>
</tr>
<tr>
<td><strong>USAF</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% block</td>
<td>43.0 ± 20</td>
<td>85.0 ± 8.4</td>
<td>P &lt; 0.005</td>
</tr>
<tr>
<td>(n=6)</td>
<td>(n=5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>90% recovery</td>
<td>17.5 ± 10.7</td>
<td>37.0 ± 15.0</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td>time (min)</td>
<td>(n=6)</td>
<td>(n=5)</td>
<td></td>
</tr>
</tbody>
</table>

Values are mean, ± 1 SD.

of the three groups (New York, London and the USAF) approximately half the patients received suxamethonium. In each case tubocurarine was not given until the twitch height had returned to the control level. Examination of the results in the first eleven patients studied in London suggested that the magnitude and duration of the action of tubocurarine was less in patients who did not receive suxamethonium (figs. 3, 4). However, to attain statistical significance, more patients had to be studied. The results of twenty-three patients in London are shown in table IV. Both the magnitude and duration of action are significantly greater (P < 0.001 in both cases) when suxamethonium had been given previously. The same is true for the USAF patients (table IV). It can be seen from table IV, for the groups given suxamethonium and those not, that the magnitude and duration of action of tubocurarine was less in the patients studied in London than in the USAF patients.

DISCUSSION

This study was stimulated by the surprising observation that the effects of suxamethonium and tubocurarine in London were different from those observed in New York by one of us (R.L.K.). But the results found in London were not considered unusual by one of us normally working there (J.N.). Since a marked variation in the responses to relaxants has previously been reported (Katz, 1967; Katz and Ryan, 1969) our first thoughts were that the differences were due to chance and would disappear as the experimental series grew. When additional patients were studied and significant statistical differences were found we wondered if the technique used in New York was different from that in London. But this was ruled out at the USAF hospital where the equipment and techniques used were the same as those employed in London and the results were similar to those found in New York. In addition, studies carried out since the return of R.L.K. to New York suggest that neither time nor technical differences are a factor.

Perhaps we should not have been surprised by the differing results found in London and New York. A company which sells both relaxants in both countries prepares the agents in differing concentrations for each country—in response to the demand. Further, it is known that clinical practice with tubocurarine differs in England and the United States. Visitors from one country to the other often wonder why larger doses of tubocurarine are used in England. A suggestion of this Anglo-American difference may also be found in the literature. The effect of tubocurarine in normocapnic patients, observed by Walts, Lebowitz and Dillon (1967) working in California, is similar to that seen in New York and USAF patients. The mean magnitudes of block produced by 0.1 mg/kg of tubocurarine were 73 per cent (California), 75 per cent (New York) and 62 per cent (USAF) and the times for recovery to 90 per cent of the initial height were 29, 31 and 26.6 minutes respectively. The experimental designs were similar although neither the Californian nor the New York studies were subdivided according to whether or not suxamethonium was used for intubation. A study in England by Bridenbaugh and Churchill-Davidson (1968) shows that tubocurarine appears to have a smaller effect than that seen in American patients by Walts, Lebowitz and Dillon (1967) and the present authors. But this experimental design was somewhat different and firm conclusions cannot be drawn from the retrospective analysis.

The USAF patients were studied not only to check our experimental technique but also to see if any environmental factor might modify the responses. The similarities of the responses in these patients to those seen in New York may mean that the environmental factors are not important or that 1–3 years does not provide sufficient exposure to produce a change. We hope
to study patients who have lived in England for a longer period of time and also to study patients born in England and now living in the United States. So far we have been unable to find any information about the relative amounts of cholinesterase inhibitor organophosphorus compounds used in agriculture in the two countries. Clearly we have raised more questions than we have answered.

An important finding of this study is that suxamethonium can modify the action of tubocurarine administered later, even if the twitch response is allowed to return to control prior to the injection of tubocurarine. It is, of course, known that recovery of twitch height to the normal level does not necessarily signify complete recovery from the action of the drug (Katz, Wolf and Papper, 1963; Katz, 1965; Paton and Waud, 1967). What is surprising is that suxamethonium increases the action of tubocurarine, since the classical view is that depolarizing and non-depolarizing agents antagonize each other. The mechanism by which suxamethonium increases the action of tubocurarine is not known, nor is the duration of this effect known. It has been suggested that with the first dose of suxamethonium some motor endplates are in a desensitized state (Katz, Wolf and Papper, 1963; Churchill-Davidson and Katz, 1966). It is possible that in these endplates tubocurarine has a greater action than normal. But this is difficult to reconcile with the observation that the response to a second dose of suxamethonium can be the same as the first (see fig. 2). It may be that the qualitative and quantitative presynaptic, postsynaptic and muscle spindle effects of suxamethonium and tubocurarine differ, leading to a composite effect on the twitch response which would be difficult to interpret.

One further question which must be answered is the role of halothane in influencing the results reported here. It is known that halothane affects neuromuscular transmission (Gissen, Karis and Nastuk, 1966) and increases the action of tubocurarine in American and English patients (Katz and Gissen, 1967; Baraka, 1968). Whether halothane increases the effect of tubocurarine to the same degree in both countries is not known. Studies are in progress in London and New York to compare the effects of tubocurarine in the absence of halothane and to determine the effects of suxamethonium on the action of tubocurarine in the absence of halothane.

Finally it appears that there is a rational explanation for the larger doses of tubocurarine used in the University of Liverpool compared with those in Columbia-Presbyterian Medical Centre. This is due in part to a difference in the response of patients to relaxants and in part to differences in clinical practice, particularly the use of suxamethonium and halothane. When suxamethonium is used for intubation tubocurarine will have a greater effect. Furthermore, inhalation of halothane will decrease the amount of tubocurarine required since halothane increases the action of tubocurarine and also produces muscle relaxation by its effect on the central nervous system (Katz and Gissen, 1967; Katz and Katz, 1968). Thus a British patient who has not received suxamethonium or halothane will require larger doses of tubocurarine than an American patient who has received suxamethonium and halothane.

REFERENCES


A COMPARISON OF SUXAMETHONIUM AND TUBOCURARINE


UNE COMPARAISON DES EFFETS DE SUXAMETHONIUM ET TUBOCURARINE CHEZ DES PATIENTS A LONDRES ET A NEW YORK

SOMMAIRE
Les effets de suxamethonium et tubocurarine ont été étudiés à Londres et à New York chez des patients anesthésiés au moyen de thiopentone, protoxyde d'azote et halothane. L'action des relachants musculaires a été évaluée en mesurant la réaction de contraction du muscle adducteur du pouce après stimulation supramaximale du nerf ulnaire. La durée d'action du suxamethonium (1 mg/kg) était moins longue à Londres que chez un groupe comparable de patients newyorkais. L'intensité et la durée d'action étaient moins grandes à Londres qu'à New York avec tubocurarine (0.1 mg/kg). L'intensité d'effet et la durée d'action de tubocurarine (0.1 mg/kg) chez un groupe de patients dans un hôpital de la Force Aérienne des États Unis (USAF) étaient similaires à celles observées chez les patients à New York. On a également remarqué que la réaction à la tubocurarine (0.1 mg/kg) était influencée par l'administration préalable de suxamethonium (1 mg/kg). Aussi bien l'intensité que la durée d'action de tubocurarine étaient plus grandes chez les patients qui avaient préalablement reçu du suxamethonium, que chez ceux qui n'en avaient pas reçu.

EIN VERGLEICH DER EFFEKTE VON SUXAMETHONIUM UND TUBOKURARIN BEI PATIENTEN IN LONDON UND NEW YORK

ZUSAMMENFASSUNG
Die Effekte von Suxamethonium und Tubokurarin wurden an jeweils einem mit Thiopenton, Lachgas und Halothan narkotisierten Patientenkollektiv in London und New York untersucht. Die Wirkung der Muskelrelaxantien wurde durch Messung der durch eine supramaximale Stimulation des N. ulnaris ausgelösten Zuckungsreaktion des M. adductor pollicis festgestellt. Die Wirkungsdauer von Suxamethonium (1 mg/kg) war bei den Patienten in London kürzer als bei einer vergleichbaren Patientengruppe in New York. Die Wirkungsstärke und -dauer von Tubokurarin (0,1 mg/kg) war bei dem Patientenkollektiv in London geringer als bei den New Yorker Patienten. Bei einer amerikanischen Patientengruppe in einem US Air Force Hospital waren Stärke und Dauer der Tubokurarinwirkung (0,1 mg/kg) denen der New Yorker Patienten ähnlich. Ebenfalls beobachtet wurde, daß die Reaktion auf Tubokurarin (0,1 mg/kg) durch die vorherige Applikation von Suxamethonium (1 mg/kg) beeinflußt werden konnte. Sowohl Stärke als auch Dauer der Tubokurarinwirkung waren bei den bereits vorher mit Suxamethonium behandelten Patienten größer als bei den Patienten, die kein Suxamethonium erhalten hatten.

THE SEVENTH CONGRESS OF THE EUROPEAN DIALYSIS AND TRANSPLANT ASSOCIATION

will be held in Barcelona, Spain, on June 25, 26 and 27, 1970.

The Congress will also include a Scientific and Commercial Exhibition.

Information can be obtained from the Secretary of the Congress:
INSTITUTO POLICLINICO, PLATON 21, BARCELONA, SPAIN.