THE USE OF TACRINE AND SUXAMETHONIUM IN ANAESTHESIA FOR CAESAREAN SECTION

BY

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SUMMARY
Suxamethonium was combined with tacrine to obtain muscle relaxation in anaesthesia for Caesarean section in fifty patients. The mean total dose of suxamethonium used was 60 mg as against 400 mg in thirty patients not given tacrine. The mean duration of muscle paralysis following suxamethonium 25 mg with tacrine 20 mg was 14 minutes compared with 5.5 minutes after suxamethonium 50 mg alone. Postoperative respiratory insufficiency of a mild degree occurred in one patient. Tacrine was found in specimens of urine from each of six neonates. Serious side effects in mother or child were not observed and this combination of drugs was thought worthy of further study for Caesarean section.

Pharmacology of Tacrine
Tacrine is reported to be a potent respiratory stimulant, especially effective against morphine and barbiturate induced depression in animals and man (Shaw, 1960). It is also an anticholinesterase agent and is said to be almost as potent as neostigmine, thus antagonizing the action of tubocurarine at the neuro-muscular junction in animals and prolonging the action of suxamethonium (Gershon and Shaw, 1958). Hunter (1965), however, found that it proved relatively unsatisfactory as an antidote to curarization in man. While it has little effect on the cardiovascular system, it may cause slight bradycardia and is said to prevent ventricular fibrillation due to digitalis or electric shock and to "prevent the cardiac effects caused by volatile anaesthetic agents" (Stone, Moon and Shaw, 1961).

PRESENT STUDY
The present study is presented in two parts. In the first part the clinical use of tacrine in fifty patients undergoing Caesarean section is described, while in the second part evidence is presented to show that the drug crosses the placental barrier.

Clinical use of Tacrine during Caesarean Section.

The patients.
Fifty patients were included in this series, of whom 21 were in labour and 29 not in labour. The mean age was 28.6 years (range 18-42). In
view of the fact that tacrine may cause bradycardia, even momentarily, the pulse rate was closely followed in 16 patients. Electrocardiographic control was used in 4 patients, and the pulse counted by palpation in 12 patients. The pulse readings were taken for 2 minutes continuously following the initial injection of suxamethonium and tacrine and then for 2 minutes following each subsequent injection of suxamethonium. The pulse rate changes in a series of 16 other patients anaesthetized with thiopentone, suxamethonium, nitrous oxide and oxygen, without tacrine were studied as controls.

**Anaesthetic technique.**

Premedication in all cases was atropine 0.6 mg. In 47 patients it was given intramuscularly about 40 minutes pre-operatively, and in 3 patients intravenously just prior to induction. Atropine 0.6 mg intramuscularly 40 minutes pre-operatively was also the premedication in each patient in the two series in which the pulse rate was closely followed.

Each patient was pre-oxygenated for 3 minutes using a facepiece with an oxygen flow rate of 5 l./min from a Boyle Mark II circuit with carbon dioxide absorption. During this time the sphygmomanometer cuff was placed on an arm, and a Mitchell needle inserted into a vein on the dorsum of one hand. Thiopentone (2.5 per cent) up to a maximum dose of 250 mg was injected through the Mitchell needle, and was followed by a mixture of tacrine 20 mg and suxamethonium 25 mg. When muscle paralysis had occurred a cuffed endotracheal tube was inserted and anaesthesia maintained with nitrous oxide and oxygen (70:30 per cent). Ventilation of the lungs was carried out using the Cyclator ventilator with a Beaver valve, maintaining a minute volume of 8-10 l./min. In a few patients ventilation was maintained by hand, using nitrous oxide 3.5 l./min and oxygen 1.5 l./min in the Boyle Mark II circuit with carbon dioxide absorption.

When muscle tone returned, as indicated by triggering of the ventilator or by swallowing movements, paralysis was again obtained by intravenous injection of suxamethonium 10 mg (1 ml of 1 per cent solution), this dose being repeated as necessary until the operation was completed.

Twenty-five patients received pethidine 25–50 mg intravenously during the operation, but after delivery of the baby. Pethidine was given if the level of anaesthesia seemed too light, e.g. if sweating or opening of the eyes occurred.

**RESULTS**

**Dose.**

The most obvious result was the reduction in the total amount of suxamethonium used, the mean dose being 60 mg (SD 20.3; range 35–115 mg), the higher doses being used in those operations of longer duration. The mean duration of anaesthesia was 42 minutes (SD 11.4; range 26–68 min). In a series of 30 patients undergoing Caesarean section with suxamethonium but without tacrine the corresponding mean dose was 400 mg (SD 98; range 250–650 mg). The mean duration of anaesthesia in this series was 43 minutes (range 29–59 min).

**Duration of paralysis.**

Suxamethonium was given in doses of 50 mg and the mean duration of muscle paralysis following 50 mg suxamethonium was 5.5 minutes (SD 1; range 3–8 min). The mean duration of muscle paralysis following suxamethonium 25 mg given with tacrine 20 mg was 14 minutes (SD 3.4; range 8–24 min). The duration of muscle paralysis after each succeeding injection of 10 mg suxamethonium is shown in the following example; it becomes progressively less, but is comparable to the effect of single injections of 50 mg suxamethonium.

Para 4 + 0, aged 26 years, underwent Caesarean section, muscle paralysis being obtained at first with suxamethonium 25 mg and tacrine 20 mg followed by suxamethonium 10 mg as required.

<table>
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<tr>
<th>Suxamethonium (mg)</th>
<th>Duration of paralysis (min)</th>
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<tr>
<td>25 (with 20 mg tacrine)</td>
<td>11</td>
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<td>10</td>
<td>7</td>
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<td>10</td>
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<td>10</td>
<td>6</td>
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<td><strong>Totals 75</strong></td>
<td><strong>41</strong></td>
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Respiration recommenced as the last skin stitch was inserted. When the wound dressing was completed, respiration was adequate as judged by an expired tidal
volume of approximately 400 ml, measured by a Wright Respirometer placed on the distal end of the endotracheal catheter mount. Consciousness was regained at the same time.

The rapid return of consciousness was a feature in these patients, all of them responding to questions before leaving the operating theatre.

**Pulse changes.**

The mean pre-operative pulse rate was 99 beats/min (range 80–120). The mean fall in the pulse rate from the pre-operative level was 10 beats/min (SD 11.3, range 2–20 beats/min) in 12 patients. In the remaining 4 patients, one showed no change, while 3 showed increases of 6, 10 and 10 beats/min respectively from the pre-operative values. The mean fall for the 16 patients was 6 beats/min (SD 10.09, range +18 to −20).

In the control series, 10 patients were elective and 6 emergency cases. The mean pre-operative pulse rate was 100 beats/min (range 66–136). In this series the mean fall in pulse rate was 25 beats/min (SD 10.7, range 6–52), all patients showing some fall in the pulse rate.

In all cases the change in pulse rate was calculated by measuring the difference from the pre-operative value to the lowest recorded at any time during the anaesthetic. This gives a measure of the safety of the technique.

**Muscle fasciculations.**

These were less marked than when suxamethonium alone was given, and muscle tone returned gradually, the first sign being triggering of the ventilator or a swallowing movement.

**Postoperative effects.**

*Postoperative respiratory insufficiency.* Only one case of postoperative respiratory insufficiency occurred in this series.

Mrs. G., aged 41 years, para 4 + 0, underwent elective Caesarean section because of previous Caesarean section. Her general health was good. She received tacrine 20 mg and a total dose of suxamethonium 45 mg. Anaesthesia lasted for 40 minutes and was quite uneventful. The patient started to breathe at the end of the operation and as she reacted to the presence of the endotracheal tube it was removed. Within a few minutes she complained that she could not breathe and the tidal volume was only 150 ml; 15 minutes later she stated that she could now breathe easily and the tidal volume was then 450 ml. She was able to cough when asked to do so, and her subsequent postoperative course was uneventful.

**Muscle pains.** Only 3 patients (6 per cent) complained spontaneously of generalized muscle aching and stiffness, lasting up to 24 hours. Seven other patients (14 per cent) admitted to some muscle aching only on direct questioning but considered it to be due to an awkward posture. The aching was mostly confined to the neck and shoulders and did not last more than 24 hours in any patient.

**Postoperative ventilation** was measured by a Wright Respirometer in 10 patients prior to extubation. The respirometer was placed on the distal end of the endotracheal catheter mount. The expired tidal volume varied from 250 to 600 ml and the minute volume from 8.7 to 16 l./min. The exact figures were difficult to estimate since the patients were waking and reacting to the presence of the endotracheal tube, breath holding and coughing being frequently seen. These figures indicate that postoperative ventilation was adequate and clinically all the other patients, except the case quoted above, did not appear to have any respiratory depression.

**Return of consciousness** occurred very rapidly in all 50 patients upon withdrawal of anaesthetic agents, and they were able to respond to simple commands. The administration of pethidine during anaesthesia did not seem to make recovery less rapid, possibly due to the stimulant action of tacrine.

**Awareness during operation.** No patient had awareness of the operation, although some stated on enquiry that they had had vivid dreams, some presumably pleasant, e.g. "I dreamt I was dancing in a night-club". Only one had an unpleasant dream—she dreamt she had died!

**Pulmonary complications.** Four patients (8 per cent) developed a cough with mucopurulent sputum, pyrexia and signs of acute bronchitis. These patients all had pre-existing respiratory complications; one had asthma, two had chronic bronchitis and one had a severe head cold at the time of her emergency Caesarean section. All responded quickly to antibiotic treatment and physiotherapy.


**Other findings.** Excessive salivation was not a feature during the operation, though most patients produced copious saliva on return of consciousness. Following aspiration of the pharynx and extubation excessive salivation ceased. No significant alteration in blood pressure occurred.

**Neonates.** There were no neonatal deaths in the series which could be attributed to the anaesthetic agents used.

**PLACENTAL TRANSMISSION OF TACRINE**

It was decided to try to find out if tacrine did, in fact, cross the placental barrier, since this could be an advantage if it was suspected that the foetus might be depressed by morphine or pethidine given to the mother prior to delivery.

**Method.** The first 24-hour specimen of urine was collected from each of 6 male children born by Caesarean section to mothers who had received tacrine. These samples of urine were examined by the method described by Kaul (1962). The method is based on the fact that tacrine in aqueous solution shows a characteristic absorption spectrum in the ultra-violet region with peaks at 323 and 335 m\(\mu\) (fig. 1). The procedure adopted was as follows. Concentrated ammonia solution and chloroform were added to the urine in a centrifuge tube, which was then shaken and centrifuged. The organic layer was then shaken with 0.5 N hydrochloric acid and centrifuged. The acid layer was then measured at 323 m\(\mu\) against 0.5 N hydrochloric acid saturated with chloroform.

The urine specimen from each of the 6 neonates was examined for the presence of tacrine by the above method and each sample showed that the drug was present (e.g. fig. 2).

**DISCUSSION**

The choice of a 20-mg dose of tacrine was made following a trial of various combinations of doses of tacrine and suxamethonium as being the most useful with regard to its length of time of action in relation to the duration of operation. In no case was it found necessary to give additional tacrine. The duration of action of suxamethonium can be prolonged by any anticholinesterase drug, but McCaul and Robinson (1962) regard tacrine as being the most potent in this respect. It is nearly as potent an anticholinesterase as neostigmine (Gordh and Wåhlin, 1961). These authors point out that tacrine is only slightly less potent than neostigmine in inhibiting plasma cholinesterase and acetylcholinesterase (A.Ch.E). As tacrine is an anticholinesterase it could be expected to cause bradycardia, especially in conjunction with a drug known to cause bradycardia such as suxamethonium.

In the two series of 16 patients each, whose pulse rates were closely followed, the fall in pulse rate was less with the combination of tacrine and suxamethonium (6 10.09), than with suxamethonium alone (25 10.7). The difference in the mean pulse rate fall is significant (\(P<0.05\)). It must be remembered that the first group of patients were given suxamethonium 10 mg while the second group of patients were given suxamethonium 50 mg as intermittent injections.

The reduction in total dosage of suxamethonium is of value since it minimizes the accumulation of succinyl monocholine and the risk of dual block which arises when large doses of suxamethonium are given. The use of tacrine provides an alternative to intermittent injections of suxamethonium since the number and frequency of injections are reduced.

When drugs are administered to obstetric patients for analgesia or anaesthesia the fact that they may cross the placenta and affect the foetus must be remembered. The mechanism of transfer of drugs across the placenta is not clear and a number of theories have been advanced to explain this (Moya and Thorndike, 1962). Simple diffusion from an area of high concentration to one of low concentration may account for the transfer of foreign substances such as drugs. Most drugs used in anaesthesia for obstetrics in normal clinical dosage cross the placenta with the notable exception of suxamethonium and tubocurarine. Moya and Kvisselgaard (1961) suggest that the concept of the lipoid barrier may apply to the permeability of the placenta to drugs. They suggest that drugs having high degrees of dissociation and low lipoid solubilities, e.g. suxamethonium, have difficulty in crossing the placenta. In clinically used doses (up to 100 mg) as a single injection it appears that suxamethonium does not affect the neonate, though it may be that if very large doses of this drug are given to the mother.
Fig. 1
Absorption spectrum of nicotine 0.01 mg/ml.

Wave Length

Optical Density

Fig. 2
Absorption spectrum of nicotine in neutral urine.

Wave Length

Optical Density
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then transfer across the placenta might take place. Any drug prolonging the action of suxamethonium could therefore be dangerous to the neonate under these circumstances, but since the dose of suxamethonium when combined with tacrine is so reduced no effect is likely to be seen in the neonate.

Morphine and pethidine are known to cross the placenta (Roberts et al., 1957) but the time of the peak effect on the foetus after administration to the mother is not known. It is generally held that delivery before 1 hour or after 6 hours following the giving of narcotic drugs to the mother does not appear to cause depression of the child. If delivery occurs during the 2nd to 6th hour after morphine or pethidine has been given to the mother, then it may be expected that the neonate will suffer from respiratory depression and that active resuscitation may be necessary.

So far as the neonate is concerned, it is essential that respiration is established as soon as possible after delivery so that expansion of the lungs and oxygenation of the blood can take place, thus enabling the neonate to continue its separate existence.

The use of anti-respiratory depressant drugs has become established over the past decade or so and can increase the safety of narcotic drugs but should not be used as an excuse for the liberal use of narcotics to women in labour. The fact that tacrine crosses the placenta as shown by its appearance in the urine of neonates can be of use in antagonizing the respiratory depressant effect of morphine and pethidine, although it was given to the mother for a different purpose, namely, to prolong the action of suxamethonium.

Caesarean section may be carried out when foetal distress is present as indicated by slowing of the foetal heart rate and the appearance of meconium and if due to obstetrical reasons such as inco-ordinate uterine action, then anti-respiratory depressant drugs such as tacrine or nalorphine would not be expected to have any effect even though narcotics had been given to the mother.

Case report.

A primigravida had been in labour for 30 hours and had not progressed during this time. A total dose of no less than 750 mg of pethidine had been given, the last dose of 150 mg having been given 4 hours before foetal distress appeared. After delivery by Caesarean section the baby gasped but respiration was not established for 8 minutes. Tacrine 20 mg had been given intravenously 20 minutes before delivery.

If Caesarean section was carried out when no foetal distress was present, but when large doses of narcotics had been given to the mother, then the anti-respiratory depressant effect of tacrine might be of most value, although not given primarily for this purpose.

Case report.

A primigravida was in labour for 24 hours but had not progressed. She had received morphine 15 mg and a total of 300 mg of pethidine during this time. No foetal distress was apparent as judged by a normal heart rate and the absence of meconium, but there was considerable maternal distress present. The child was delivered by Caesarean section and breathed and cried within 1 minute of delivery. Tacrine 20 mg was given intravenously 10 minutes before delivery.

It was not obvious in this series whether tacrine is of value in such cases (because of insufficient numbers), but it does seem worthy of further study from this aspect.

It is concluded that the use of tacrine in combination with suxamethonium offers advantages over the conventional thiopentone-suxamethonium-nitrous oxide-oxygen sequence as an anaesthetic technique for Caesarean section. In the series of cases reported here, no serious side effects on mother or child have been noted and a marked reduction in the total dosage of suxamethonium was made possible. Tacrine crosses the placental barrier, but far from being a disadvantage, this may be of value where large doses of narcotics have been given to the mother prior to delivery.

ACKNOWLEDGEMENTS

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REFERENCES


**L'EMPLOI DE LA TACRINE ET DU SUXAMETHONIUM DANS L'ANESTHESIE POUR CESARIEENNE**

**SOMMAIRE**

Le suxaméthonium a été associé à la tacrine pour obtenir le relâchement musculaire dans l'anesthésie pour une césarienne chez cinquante femmes. La dose totale moyenne du suxaméthonium utilisé a été de 60 mg contre 400 mg chez trente femmes auxquelles on n'a pas donné de tacrine. La durée moyenne de la paralysie musculaire après 25 mg de suxaméthonium et 20 mg de tacrine a été de 14 minutes par rapport à 5,5 minutes après 50 mg de suxaméthonium seul. Une insuffisance respiratoire légère s'est produite chez une malade après l'opération. La tacrine a été mise en évidence dans des échantillons d'urine de six nouveau-nés. On n'a pas observé de sérieux effets secondaires ni chez la mère ni chez l'enfant, et on pense que cette association médicamenteuse mérite d'être étudiée davantage pour les césariennes.

**DIE VERWENDUNG VON TACRINE UND SUXAMETHONIUM FUR DIE NARKOSE BEIM KAISERSCHNITT**

**ZUSAMMENFASSUNG**