SERUM CHOLINESTERASE: EFFECT ON THE ACTION OF SUXAMETHONIUM FOLLOWING ADMINISTRATION TO A PATIENT WITH CHOLINESTERASE DEFICIENCY

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SUMMARY
Purified serum cholinesterase 90 mg was administered to a patient with cholinesterase deficiency. The effect on the action of suxamethonium was studied. The half-life (44.7 h), time constant (64.5 h), rate constant (0.0155 h⁻¹) and distribution volume (2740 ml) of the cholinesterase activity were determined.

The clinical use of the short-acting depolarizing relaxant suxamethonium (SuM) is occasionally associated with prolonged apnoea and muscular weakness. The commonest cause is a low activity of cholinesterase (ChE) in the plasma as a result of either a genetic abnormality or disease. A patient with ChE deficiency was given purified serum cholinesterase. The resulting effect on the action of SuM and the pharmacokinetic behaviour of the enzyme are discussed.

CASE REPORT
A 65-year-old man, weighing 62.5 kg, underwent elective vascular surgery to remove an occlusion of the left femoral artery. The history revealed that this was the patient's first anaesthetic and operation and that he was receiving digoxin and Prostagutt,* a phytotherapeutic urological preparation. There was no other known physical or biochemical abnormality, in particular there was no hepatic or neuromuscular disease.

Anaesthesia
Premedication consisted of atropine 0.5 mg, fentanyl 0.05 mg and droperidol 2.5 mg i.m. about 30 min before the operation. Anaesthesia was induced with methohexitone 80 mg i.v. and maintained with fentanyl 0.15 mg and droperidol 2.5 mg, and a 4-litre/min total flow of about 70% nitrous oxide and 0.8% enfluran in oxygen. Controlled ventilation was performed throughout the procedure at a respiratory rate of 12 b.p.m. and a minute volume of 90 ml/kg body weight (b.w.) (Ocbo and Terry, 1969). An electrolyte solution containing 5% fructose (Sterofundin-HL5) and a gelatine solution (neoplasmagel) was infused at a rate of up to 8–10 ml/kg b.w. h⁻¹; no blood was transfused during or after surgery. \(P_{aCO_2}\) was not measured during anaesthesia.

Neuromuscular blockade and ChE activity
After pre-oxygenation, the trachea was intubated following the i.v. injection of suxamethonium 40 mg. Since no return of spontaneous breathing nor other signs of muscular activity occurred after 30 min, a neuromuscular disorder was suspected. Venous blood was sampled to measure plasma ChE activity (Merckotest No. 3337) (Schuh, 1975). Monitoring of neuromuscular transmission by means of ulnar nerve stimulation and myomechanography of the hand muscles (Schuh, 1974) was performed. Shortly after a stable contraction amplitude had been accomplished (about 45 min after the induction of anaesthesia) a test-dose of SuM 10 mg was injected i.v. resulting in an augmented and prolonged neuromuscular blockade (fig. 1A). In the meantime plasma ChE activity had been determined to be 2.2 u/ml (normal: 5.5 ± 1.25 u/ml, mean ± SD; at 25 °C, pH 7.7, with butyrylthiocholine as substrate).

Subsequently, 90 mg of a commercially available lyophilized human serum cholinesterase preparation (Serum-Cholinesterase, Behringwerke AG, Marburg/Lahn) was administered i.v. Five minutes later a second test-dose of SuM 10 mg was given i.v., resulting in a normal response to the muscle relaxant (fig. 1B); the esterase activity in the patient's blood was now 5.9 u/ml. The haematocrit, haemoglobin concentration and ChE activity were measured frequently during surgery and in the period after operation (table I). The patient was discharged well on the 10th day after surgery.


*Prostagutt is a preparation containing a multiplicity of plant extracts.
FIG. 1. Intraoperative myomechanogram of the hand muscles showing the effect of suxamethonium 10 mg (SuM; 0.16 mg/kg) in a patient with cholinesterase (ChE) deficiency before (A) and 5 min after (B) the administration of serum cholinesterase 90 mg. Muscular contractile force is expressed in terms of pressure (mm Hg) exerted by the contracting hand muscles stimulated indirectly (0.2 Hz, 0.3 ms, 120 V).

TABLE I. Cholinesterase activity, haemoglobin concentration, and haematocrit in a patient with cholinesterase deficiency following the injection of 90 mg of a purified serum cholinesterase preparation

<table>
<thead>
<tr>
<th>Time after injection</th>
<th>Cholinesterase activity (u/ml)</th>
<th>Haemoglobin (g/dl)</th>
<th>Haematocrit (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Before)</td>
<td>2.2</td>
<td>13.1</td>
<td>42.0</td>
</tr>
<tr>
<td>5 min</td>
<td>5.9</td>
<td>12.3</td>
<td>39.0</td>
</tr>
<tr>
<td>20 min</td>
<td>4.2</td>
<td>10.6</td>
<td>35.0</td>
</tr>
<tr>
<td>1 h</td>
<td>4.1</td>
<td>10.3</td>
<td>33.5</td>
</tr>
<tr>
<td>2 h</td>
<td>3.7</td>
<td>9.4</td>
<td>31.5</td>
</tr>
<tr>
<td>3.5 h</td>
<td>3.2</td>
<td>9.8</td>
<td>33.0</td>
</tr>
<tr>
<td>21.5 h</td>
<td>3.8</td>
<td>10.3</td>
<td>34.0</td>
</tr>
<tr>
<td>32.5 h</td>
<td>3.5</td>
<td>11.7</td>
<td>37.5</td>
</tr>
<tr>
<td>49.5 h</td>
<td>3.3</td>
<td>10.8</td>
<td>34.5</td>
</tr>
<tr>
<td>77.5 h</td>
<td>2.9</td>
<td>10.4</td>
<td>33.5</td>
</tr>
<tr>
<td>127.5 h</td>
<td>2.4</td>
<td>9.6</td>
<td>30.0</td>
</tr>
<tr>
<td>196.5 h</td>
<td>1.9</td>
<td>9.1</td>
<td>28.5</td>
</tr>
<tr>
<td>213.5 h</td>
<td>2.0</td>
<td>9.0</td>
<td>28.5</td>
</tr>
<tr>
<td>246.5 h</td>
<td>1.8</td>
<td>8.6</td>
<td>28.0</td>
</tr>
<tr>
<td>260.5 h</td>
<td>2.0</td>
<td>9.1</td>
<td>28.5</td>
</tr>
<tr>
<td>340.5 h</td>
<td>2.0</td>
<td>10.4</td>
<td>33.0</td>
</tr>
</tbody>
</table>

DISCUSSION

The neuromuscular blocking action of SuM is terminated normally within a few minutes by the hydrolytic activity of the plasma enzyme choline-esterase (ChE; acetylcholine acyl-hydrolase, E.C. 3.1.1.8.). A reduced activity of this esterase (molecular weight: 2–3 × 10⁶) will result in a delayed metabolic breakdown of SuM and a prolonged paralysing action. In our patient the plasma ChE activity (2.2 u/ml) was about 40% of normal. Unfortunately, it has not been determined whether this reduced activity was caused by a qualitative reduction in ChE (genetic variant) or by a quantitative reduction (disease). As a result of clinical observation, the prolonged SuM action was noticed early and was studied by myomechanography. According to our experience of monitoring and quantification of neuromuscular blockade, SuM 1.0 mg/kg given to a patient with normal ChE activity will cause approximately the same magnitude and duration of action as the test-dose of 10 mg (0.16 mg/kg b.w.) given to our patient, who thus appears to be six times more sensitive to SuM.

Recently a purified human serum cholinesterase preparation (Serum-Cholinesterase, Behringwerke AG, Marburg/Lahn) has become commercially available, which contains 45 mg/vial, corresponding to 500 ml of human serum. The i.v. injection of 45–135 mg has been recommended for enzyme substitution in patients with ChE deficiency (Happle, Scholler and Münsch, 1973; Scholler and Goedde, 1975), thus increasing the esterase activity in the patient's blood, enhancing the hydrolysis of SuM, and restoring spontaneous breathing. Indeed, 5 min after the injection of serum cholinesterase 90 mg, the plasma activity (5.9 u/ml) and the neuromuscular response to SuM 10 mg were found to be within the normal range. From these quantitative observations the application of purified serum cholinesterase can be expected to be an effective therapeutic measure in complications which result from ChE deficiency after operation.

The ChE activity was measured frequently during the postoperative course and control levels were determined after approximately 5–6 days (table I). For a pharmacokinetic analysis (Dost, 1968), the basic esterase activity, that is the level before the application of the serum cholinesterase preparation (ChE_pre), was subtracted from the actual activity after injection (ChE_post). A semi-logarithmic plot of the data thus obtained (ChE_post - ChE_pre = Y) versus time (t) disclosed a straight line (fig. 2) described by the following exponential equation:

\[ Y = 2.0063e^{-0.0155t} \] (1)

The half-life, \( t_\frac{1}{2} \) (time required for a decrease to one-half of the original value), or the time constant
SUXAMETHONIUM AND I.V. CHOLINESTERASE

The short half-life of the serum cholinesterase preparation (44.7 h) is surprising for three reasons:

1. Plasma ChE is known to be a very stable enzyme which does not show any significant spontaneous decrease in activity in bank blood and in blood protein solutions during 4 and more weeks of cold storage (Schuh, 1975).

2. The half-life of human plasma proteins in general is considerably greater and is in the range of 1–2 weeks (Dost, 1968).

3. When normal plasma was transfused into a "silent gene" patient, the injected ChE had a half-life of about 10 days (Jenkins, Balinsky and Patient, 1967); this corresponds to the spontaneous regeneration rate for plasma ChE after administration of the organophosphate DFP. An explanation for the short half-life observed in our patient could be the influence of organic solvents during the purification and lyophilization procedure (alcohol fractionation) reducing the biological stability of the enzyme protein and making it more susceptible to metabolic cleavage and inactivation in the recipient's blood. A rapid disappearance from blood was observed also by other authors who injected purified acetylcholinesterase or plasma ChE into laboratory animals for experimental purposes (Mendel and Hawkins, 1943; Beck, 1951; Karczmar, Koppanyi and Sheatz, 1951). In clinical practice, a reliable effect on the prolonged neuromuscular blockade after SuM (fast recovery of the postoperative apnoea and muscular weakness) can be expected only within a short period after administration, the exact time depending on the basic ChE activity before the injection of SuM and on the amount of serum cholinesterase administered.

ACKNOWLEDGEMENTS

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REFERENCES


CHOLINESTERASE DU SERUM: EFFET SUR L'ACTION DU SUXAMETHONIUM APRES ADMINISTRATION A UN MALADE SOUFFRANT D'UNE INSUFFISANCE DE CHOLINESTERASE

RESUME
De la cholinestérase de sérum purifiée (90 mg) a été administrée à un malade souffrant d'une insuffisance de cholinestérase. On a étudié son effet sur l'action du suxaméthonium et on a déterminé la demi-vie (44,7 h), la constante de temps (64,5 h), la constante du taux (0,0155 h⁻¹) et le volume de répartition (2740 ml) de l'activité de la cholinestérase.

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SERUM-CHOLINESTERASE: EFFEKT AUF DIE WIRKUNG VON SUXAMETHONIUM NACH GABE BEI EINEM PATIENTEN MIT CHOLINESTERASE-MANGEL

ZUSAMMENFASSUNG
Gereinigte Serum-Cholinesterase (90 mg) wurde einem Patienten mit Cholinesterase-Mangel injiziert. Der resultierende Effekt auf die Wirkung von Suxamethonium sowie die Halbwertszeit (44,7 h), Zeitkonstante (64,5 h), Geschwindigkeitskonstante (0,0155 h⁻¹) und das Verteilungsvolumen (2740 ml) der verabreichten Cholinesterase-Aktivität wurden ermittelt.

COLINESTERASA SERICA. EFECTO SOBRE LA ACCION DEL SUXAMETONIO TRAS LA ADMINISTRACION A UN PACIENTE CON INSUFICIENCIA COLINESTERASICA

SUMARIO
Colinesterasa sérica purificada 90 mg fue administrada a un paciente con insuficiencia colinesterásica. El efecto sobre la acción del suxametonio fue estudiado. La media vida (44,7 horas), constante de tiempo (64,5 horas), constante de índice (0,0155 horas⁻¹), y volumen de distribución (2740 ml) de la actividad de la colinesterasa fueron determinados.