PLACENTAL TRANSFER OF $^{14}$C-DIMETHYLTUBOCURARINE DURING CAESAREAN SECTION

I. KIVALO AND S. SAARIKOSKI

SUMMARY

Placental transfer of $^{14}$C-dimethyltubocurarine ($^{14}$C-dmtc) was studied during Caesarean section. Liquid scintillation counting was used for determination of $^{14}$C activity from the maternal and foetal blood samples. Paper chromatography was used to confirm the stability of $^{14}$C-dmtc. In all cases $^{14}$C-dmtc was able to cross the placenta. Detectable amounts of $^{14}$C-dmtc were found in umbilical blood 2 min after injection into the mother. Six and 10 min after injection, the $^{14}$C concentration in the umbilical blood was 12% of the corresponding maternal value.

In an earlier study of placental transmission and foetal uptake of $^{14}$C-dimethyltubocurarine ($^{14}$C-dmtc) during the first trimester of pregnancy, it was found that $^{14}$C foetal plasma concentration was approximately one-tenth of the maternal value 20 min after the injection of the substance to the mother (Kivalo and Saarikoski, 1972). The result was in agreement with the findings of Elert and Cohen (1962), who reported that the concentration of tubocurarine in the cord plasma taken at Caesarean section was 5-10% of the maternal value 6-10 min after injecting into the mother.

Because infants are delivered within 10 min of the induction of anaesthesia in many cases, (Kivalo, Timonen and Castren, 1971; Mattila, Pystynen and Makkonen, 1972) and tubocurarine is one of the drugs commonly employed as a neuromuscular blocking agent in obstetric anaesthesia, it is important to know the concentrations of tubocurarine during the period before delivery, to determine the optimum time for removal of the infant.

PATIENTS AND METHODS

Eighteen parturient women with foeto-pelvic disproportion underwent Caesarean section, all having normal pregnancies without signs of foetal distress.

Premedication was atropine 0.01 mg/kg i.m. 30 min before induction of anaesthesia. The patients were placed in the left lateral position on the operating table. After a period of pre-oxygenation, a sleep-dose of thiopentone was administered, followed by suxamethonium 75 mg to facilitate endotracheal intubation. The patients were ventilated with a 1 : 1 mixture of nitrous oxide–oxygen. $^{14}$C-dmtc 0.5 μCi, corresponding to 0.005 mg of the drug per kg body weight (tubocurarine di(methyl-$^{14}$C)ether iodide; the Radiochemical Centre, Amersham; specific activity 89.3 mCi/mmol), was injected at 2, 4, 6 or 10 min before clamping of the umbilical cord at delivery. The maximum dose of $^{14}$C confirmed by the International Commission on Radiological Protection is 300-400 μCi, of which only one-tenth was used in the present study. The injection of $^{14}$C-dmtc was administered in co-operation with the obstetrician so that the timing was exactly as planned. In the 6- and 10-min groups the drug was administered before, and in the other two groups after the induction of anaesthesia. After the delivery, tubocurarine and pethidine or fentanyl were injected and anaesthesia was maintained with a mixture of 66% nitrous oxide in oxygen.

Maternal blood was taken from the antecubital vein before the induction of anaesthesia and at the moment of delivery, simultaneous with the umbilical blood samples. Proteins were precipitated with 0.4 N perchloric acid and ethanol. After neutralization, aliquots were taken for the determination of total $^{14}$C activity.

To verify the integrity of $^{14}$C-dmtc, paper chromatography was performed with Whatman 3MM paper using butanol–ethanol–water 3 : 1 : 1 as solvent. The $R_F$ value of dmtc recorded with this method was 0.46 (fig. 1).

In comparing the maternal and corresponding foetal values, a test of paired differences was used (Richterich, 1968).

RESULTS

The induction–delivery times, the Apgar scores and the times of $^{14}$C-dmtc injection before delivery are
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Fig. 1. Chromatography of dmtc in the organic phase of butanol–ethanol–water, 3:1:1, showing the location of reference material (hatched area) as it appears after fluorescein staining in ultraviolet light. For the counting of radioactivity, the paper was sectioned as indicated by marks on the margin.

TABLE I. Means ± SEM of the induction–delivery times, the Apgar scores and the time from the injection of 14C-dimethyl-tubocurarine (14C-dmtc) to delivery

<table>
<thead>
<tr>
<th>Time from 14C-dmtc to delivery (min)</th>
<th>Induction–delivery time (min)</th>
<th>Apgar scores</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>1-min</td>
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<tr>
<td>2</td>
<td>3.8 ± 0.6</td>
<td>8.8 ± 0.6</td>
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<tr>
<td>4</td>
<td>4.4 ± 0.3</td>
<td>8.8 ± 0.4</td>
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<tr>
<td>6</td>
<td>5.1 ± 0.1</td>
<td>9.0 ± 0.6</td>
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<tr>
<td>10</td>
<td>6.0 ± 0.6</td>
<td>8.5 ± 0.7</td>
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</table>

Fig. 2. Chromatography of 14C-dmtc performed on aliquots of the maternal and foetal plasma.

TABLE II. 14C concentrations in maternal and foetal plasma (nCi/ml; mean ± SEM)

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>Time (min)</th>
<th>Maternal vein</th>
<th>Umbilical vein</th>
<th>Ratio Umb. vein / Mat. vein</th>
<th>Ratio Umbil. artery</th>
<th>Ratio Umb. art. / Umb. vein</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>2</td>
<td>4.42 ± 0.33</td>
<td>0.16 ± 0.02</td>
<td>0.04 ± 0.01</td>
<td>0.05 ± 0.01</td>
<td>0.01 ± 0.0</td>
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<tr>
<td>6</td>
<td>4</td>
<td>2.09 ± 0.58</td>
<td>0.14 ± 0.05</td>
<td>0.07 ± 0.01</td>
<td>0.07 ± 0.03</td>
<td>0.03 ± 0.01</td>
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<td></td>
<td>6</td>
<td>1.92 ± 0.34</td>
<td>0.24 ± 0.02</td>
<td>0.12 ± 0.03</td>
<td>0.11 ± 0.01</td>
<td>0.06 ± 0.01</td>
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<td></td>
<td>10</td>
<td>1.74 ± 0.18</td>
<td>0.21 ± 0.02</td>
<td>0.12 ± 0.01</td>
<td>0.13 ± 0.01</td>
<td>0.07 ± 0.0</td>
</tr>
</tbody>
</table>

P relates to the comparison with the corresponding maternal value.

given in table I. All the infants were born within 7 min (range 2.3–7.2 min) and were in good condition (Apgar scores 7–10).

Plasma concentrations. Table II shows the maternal and foetal plasma concentrations of 14C-dmtc, with the respective ratios at various times after the injection of the drug. The highest maternal plasma concentration of 14C, 4.42 nCi/ml at 2 min, diminished during the next 2 min by 50%, being 1.74 nCi at 10 min. The 14C concentration in the umbilical vein
within 2 min of administration of $^{14}$C-dmtc was only 0.16 nCi/ml, or 4% of the maternal value, and at 6 min the content had increased to 0.24 nCi/ml, 12% of the maternal $^{14}$C concentration, the ratio being the same at 10 min. The $^{14}$C activity in the umbilical artery did not reach that in the umbilical vein during the first 10 min, but during the period from 2 to 10 min it increased from 30 to 60%. The foetal plasma values were always significantly less than the maternal values during the observation time ($P<0.02$ and $P<0.005$).

Paper chromatography. Figure 2 shows that $85.9 \pm 1.5\%$ (mean $\pm$ SEM) of the $^{14}$C activity in the maternal plasma, $77.2 \pm 2.6\%$ in the umbilical vein and $67.3 \pm 2.9\%$ in the umbilical artery behaved as unlabelled dimethyltubocurarine in chromatography.

**DISCUSSION**

During the first months of pregnancy, the foetal plasma concentration of $^{14}$C-dmtc was approximately one-tenth of the maternal value 20 min after injection (Kivalo and Saarikoski, 1972). The integrity of the drug was confirmed by chromatography. According to the present study, the same ratio was reached in 6 min and there were no changes during the next 4 min. Elert and Cohen (1962) were unable to detect any significant amounts of tubocurarine in the foetal plasma before 5–6 min, while the foetal concentration of the drug was 5–10% of the maternal concentration after 9 min.

In a recent study by Bloggs and colleagues (1975), using a labelled version of a new non-depolarizing neuromuscular blocking agent, $3^H$-AH 8165, in patients undergoing termination hysterectomy at 10 and 16 weeks of gestation a ratio of approximately 10:1 maternal: foetal whole blood was observed, which is in accordance with the findings of our previous and present studies. These results strengthen further the assumption that the human placental barrier is not absolute for the passage of the non-depolarizing neuromuscular blocking agents (Elert and Cohen, 1962; Moya and Smith, 1965; Older and Harris, 1968).

At Caesarean section for a poor-risk foetus all depressive factors have to be kept to a minimum. The length of the induction–delivery time has been found to influence the condition of the foetus (Lumley, Walker and Marum, 1970; Timonen, Castren and Kivalo, 1970). In the present study all the infants were delivered within 7 min. There was no need to give additional doses of thiopentone, nor was the administration of tubocurarine necessary to facilitate the removal of the foetus.

Since curare is able to cross the placenta in small, but detectable amounts it might be advantageous to the well-being of the foetus to exclude the drug before the delivery especially when foetal compromise is suspected.

**ACKNOWLEDGEMENT**

Orion-yyhtymä Oy, Helsinki, gave financial aid in providing $^{14}$C-dimethyltubocurarine.

**REFERENCES**


**TRANSFERT PLACENTAIRE DE TUBOCURARINE-DIMÉTHYL $^{14}$C PENDANT LES OPERATIONS CESARIENNES**

**RESUME**

On a étudié le transfert placentaire de tubocurarine-diméthyl $^{14}$C ($^{14}$C-dmtc) pendant les opérations césariennes. On s'est servi du comptage par scintillation liquide pour déterminer l'activité de $^{14}$C à partir d'échantillons du sang maternel et du sang du foetus. On a utilisé la chromatographie sur papier pour confirmer la stabilité du $^{14}$C-dmtc. Dans tous les cas le $^{14}$C-dmtc a pu traverser le placenta. On a trouvé des quantités décelables de $^{14}$C-dmtc dans le sang
ombilical 2 min après l'injection dans la mère. Entre 6 et 10 min après l'injection, la concentration de $^{14}$C dans le sang ombilical a été de 12% de la valeur correspondante de la mère.

**ZUSAMMENFASSUNG**

Es wurde die plazentare Überleitung von $^{14}$C-Dimetnyltubokurarin verfolgt. Bei Durchleuchtungsbeobachtungen wurde die $^{14}$C-Dimetnyltubokurarzinwirkung in mütterlichen, sowie in foetalen Blutproben ermessene. Papierchromatographische Untersuchungen wurden durchgeführt, um die Stabilität von $^{14}$C-Dimetnyltubokurarin zu bestätigen. Bei sämtlichen Patientinnen erfolgte der Übergang von $^{14}$C-Dimetnyltubokurarin durch das Plazenta. Erweisbare Mengen von $^{14}$C-Dimetnyltubokurarin wurden im Nabelschnurblut 2 Min nachdem es der Mutter mittels Spritze verabreicht worden war festgestellt. Sechs und 10 Min nach der Injektion zeigte sich das $^{14}$C-Dimetnyltubokurarin-Konzentrat im Nabelschnurblut als 12% des betreffenden Wertes im Blut der Mutter.