PLACENTAL TRANSFER OF ORG NC45 IN WOMEN UNDERGOING CAESAREAN SECTION

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SUMMARY

Org NC 45 60–80 \( \mu g \) kg\(^{-1} \) was administered to 20 pregnant women undergoing general anaesthesia for Caesarean section. Org NC 45 plasma concentrations were measured fluorimetrically in samples of maternal, venous and arterial cord blood obtained at delivery. The venous cord to maternal concentration ratio averaged 11% and was not influenced by the interval between induction and delivery. The venous cord plasma concentration averaged 40 ng ml\(^{-1} \). The arterial cord concentration was less than the venous cord concentration in every instance and was undetectable in four patients. It is concluded that Org NC 45 crosses the human placental barrier to a very limited extent and that its use during anaesthesia for Caesarean section is safe for the newborn.

Neuromuscular blocking agents do not cross the placenta readily because they are relatively insoluble in lipids and are highly ionized in plasma. Savage, Sleigh and Carlyle (1980) predicted that, on account of its chemical structure, Org NC 45 might be more lipophilic than either pancuronium or tubocurarine. However, this hypothetical lipid solubility is low compared with the high water solubility of the drug. In addition, like most quaternary ammonium compounds, Org NC 45 is insoluble in diethyl ether (Savage, Sleigh and Carlyle, 1980). However, since the placental transfer of Org NC 45 may be greater than that of other neuromuscular blocking drugs, the present study was undertaken in women undergoing Caesarean section.

PATIENTS AND METHODS

Twenty pregnant women undergoing elective Caesarean section were included in the study. Consent for the administration of Org NC 45 and the sampling of maternal venous and umbilical cord blood was obtained from each patient after the risks of the investigation had been explained. Anaesthesia was induced with thiopentone 5 mg kg\(^{-1} \) i.v. and the trachea intubated following the administration of suxamethonium 1 mg kg\(^{-1} \). Org NC 45 4–6 mg, was injected to maintain neuromuscular blockade and anaesthesia was maintained with 60% nitrous oxide in oxygen delivered by intermittent positive pressure ventilation (minute ventilation 100 ml kg\(^{-1} \)). In eight patients 0.5% halothane was administered intermittently. The management of the newborn included assessment and recording of the Apgar scores at 1 and 5 min and preparation for ventilation. Maternal and cord blood samples were obtained simultaneously at delivery. A 10–20 cm section of the cord was secured between two clamps and venous and arterial blood samples withdrawn. Blood was collected in heparinized tubes and was centrifuged within 5 min of its collection. One millilitre of plasma was mixed in a tube containing 150 \( \mu l \) litre\(^{-1} \) of sodium dihydrogen phosphate (\( \text{Na}_2\text{HPO}_4 \)) 1 mol litre\(^{-1} \) to prevent the hydrolysis of Org NC 45 (Paanakker and Van de Laar, 1980). The tubes were kept at \(-20^\circ \text{C} \) until analysis. Org NC 45 was assayed according to a modification of the Rose Bengal fluorimetric method used for the determination of pancuronium (Kersten, Meijer and Agoston, 1973). The lowest concentration that could be reliably determined was 25 ng ml\(^{-1} \).

RESULTS

Org NC 45 was found in detectable amounts in all venous cord blood samples. The venous cord concentration averaged 40 ng ml\(^{-1} \) and was much lower than the maternal concentration (390 ng ml\(^{-1} \)). Individual values are detailed in table I. The venous to maternal concentration ratio was 11% and was not influenced by the interval between injection of Org.
NC 45 and delivery. The concentration of Org NC 45 in the cord artery was always lower than in the cord vein: in four samples out of the 14 examined, Org NC 45 was not detectable. Apgar scores at 1 and 5 min averaged 9.1 and 9.9.

**DISCUSSION**

This study demonstrates that Org NC 45 crosses the human placental barrier to a very limited extent. In comparison with pancuronium, which possesses approximately the same potency as Org NC 45 (Agoston et al., 1980), the placental transfer of Org NC 45 is at least half. The fetal concentration of pancuronium averaged 70 ng ml⁻¹ after the administration of equipotent doses of pancuronium to women undergoing Caesarean section (Booth, Watson and McLeod, 1977; Duvaldestin et al., 1978). Several factors may influence the placental transfer of foreign compounds: molecular weight, lipid solubility, the concentration gradient across the placental membrane and the duration of feto-placental exchange. Org NC 45 is believed to be more lipophilic than pancuronium, the latter being also more lipophilic than tubocurarine (Savage, Sleigh and Carlyle, 1980). However, this lipophilic property is weak compared with the hydrophilic property of all neuromuscular blocking drugs. This may partly explain why Org NC 45 does not cross the placenta more rapidly than pancuronium. Another factor influencing the placental transfer is the rate at which the drug disappears from the maternal plasma. Org NC 45 is eliminated rapidly from the plasma (Van der Veen and Bencini, 1980), a property which tends to decrease the concentration gradient across the placent membrane. A feto-maternal concentration ratio of 11% was observed for Org NC 45 whereas this ratio was of 22% for pancuronium (Booth, Watson and McLeod, 1977; Duvaldestin et al., 1978). The feto-maternal ratio did not correlate with the interval between injection of Org NC 45 and delivery as has been shown for dimethyl tubocurarine (Kivalo and Saarikoski, 1976) and pancuronium (Duvaldestin et al., 1978). Deacetylation of Org NC 45 by placental enzymes remains a possible explanation for its low concentration in the newborn. The arteriovenous concentration difference in the cord vessels suggests an extensive uptake of Org NC 45 by the fetus. The hepatic uptake of Org NC 45 contributes normally to its rapid elimination from the plasma and may be more important in the fetal liver which receives 50% of the umbilical blood flow. Therefore, fetal hepatic uptake will decrease the effects of any placental transfer since the arterial cord blood concentration reflects more accurately the concentration delivered to the muscle end-plates. The highest arterial cord concentration of Org NC 45 was 50 ng ml⁻¹ and is much smaller than the concentration of 140 ng ml⁻¹ which corresponds to a 50% neuromuscular block in adults (Van der Veen and Bencini, 1980).

We can conclude from this study that the fetus receives an insignificant proportion of any clinical dose of Org NC 45 received by the mother and that its use during obstetric anaesthesia is safe for the newborn.

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TRANSFERT PLACENTAIRE DE L’ORG NC45 CHEZ
DES FEMMES SUBISSANT UNE CESARiENNE

RESUME
De l’Org NC 45 a la dose de 60–80 µg kg⁻¹ a été administre a 20
femmes enceintes recevant une anesthesie generale pour
Cesarienne Les concentrations plasmatiques de l’Org NC 45 ont
été mesurées par fluorimétrie dans des échantillons de sang
maternel et de sang artériel et veineux du cordon lors de l’extraction.
Le rapport entre les concentrations maternel et veineuse
dans le cordon, avoisinaient 11% et n’étaient pas influencées par
le déléai entre l’induction et l’extraction. La concentration plas-
matique du sang veineux dans le cordon avoisinait 40 ng ml⁻¹. La
concentration dans le sang artériel du cordon était plus basse que
dans le sang veineux dans chaque cas et était non-dosable chez
quatre patientes. Nous en concluons que l’Org NC 45 traverse la
barrière placentaire chez l’homme de façon très limitée et que son
utilisation au cours de l’anesthésie pour Césarienne est sans
danger pour le nouveau-né.

PASO DE LA BARRERA DE LA PLACENTA POR
PARTE DEL ORG NC 45 EN MUJERES SOMETIDAS A
OPERACION DE CESAREA

SUMARIO
Se administró de 60 a 80 µg kg⁻¹ de Org NC 45 a 20 mujeres
preñadas sometidas a anestesia general para fines de operación de
cesárea. Las concentraciones de Org NC 45 en el plasma se
midieron fluorimétricamente en muestras de sangre del cordón
arterial y venoso de la madre, que se obtuvieron en el parto. La
razón entre la concentración del cordón venoso y la concentración
materna fue del 11% y no vino influenciada por el lapsus entre
la inducción y el parto. El promedio de la concentración del plasma
del cordón venoso fue de 40 ng ml⁻¹. La concentración del cordón
arterial fue inferior a la del cordón venoso en todo momento y no
pudo detectarse en cuatro de las pacientes. La conclusión es que el
Org NC 45 cruza la barrera de la placenta humana, en cantidades
muy limitadas y que su uso durante la anestesia tendente a la
operación de cesárea es seguro para el recién nacido.