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PLACENTAL TRANSMISSION OF ATROPINE AT FULL-TERM PREGNANCY

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SUMMARY

Measurements of placental transmission of atropine were performed during Caesarean section. Twenty-five patients received ^{3}H-atropine 0.5 $\mu g \cdot kg^{-1}$ i.v. 1–30 min before delivery. Maternal venous blood was sampled before the induction of anaesthesia and at the moment of delivery, together with umbilical arterial and venous blood. Total hydrogen-3 activity was determined by liquid scintillation counting. The stability of ^{3}H-atropine was confirmed by paper chromatography. The concentrations in the umbilical vein 1 and 5 min after injection were respectively 12% and 93% of the corresponding maternal value. Those in the umbilical artery were approximately 50% of those in the umbilical vein during the same period.

Atropine has been used as a premedicant in obstetric anaesthesia, as a test of foeto–placental insufficiency and in the diagnosis of foetal asphyxia (Soiva and Salmi, 1959; Järvinen and Hirvonen, 1964; John, 1965; Schifferli and Caldeyro-Barcia, 1973; Brunel and Vinkler, 1975). However, there is a lack of quantitative information about the placental transfer of atropine at the end of pregnancy. It is known only that in the first half of gestation, foetal plasma concentrations of ^{3}H-atropine 20 min after an i.v. injection to pregnant women were only one-half those in maternal plasma (Kivalo and Saarikoski, 1970). Atropine, administered to the mother, influences also the function of the foetal autonomic nervous system which plays an important role in the adaptation of the newborn after the delivery. We have studied the rate of placental transfer of atropine in full-term parturient women, and have evaluated the effects of this drug on the neonate.

PATIENTS AND METHODS

Twenty-five patients with uncomplicated pregnancies underwent Caesarean section on account of foeto–pelvic disproportion. Each patient gave informed consent to the study. The data pertinent to the study are presented in table I.

The patients received atropine 0.01 mg . kg^{-1} i.m. 30 min before operation. They were placed on the operating table, which was tilted 15–20 degrees to the left, and 100% oxygen was administered for 3–4 min. A sleep-dose of thiopentone was followed by suxamethonium 75 mg. After tracheal intubation, the lungs were ventilated with a 50% mixture of nitrous oxide in oxygen until delivery of the infant.

^{3}H-atropine 0.5 $\mu g \cdot kg^{-1}$ or 0.7 $\mu Ci \cdot kg^{-1}$ (Radiochemical Centre, Amersham; specific activity 306 $mCi \cdot mmol^{-1}$) was administered i.v. at 1, 3, 5, 10 or 30 min before clamping the umbilical cord at delivery. The maximum permissible dose of hydrogen-3 (International Commission on Radiological Protection) is 1000 μCi; only 5% of this dose was used in the present study. The surgeon was informed of the injection of atropine so that the timing of events was exact. The induction–delivery interval ranged from 3.4 to 5.1 min, and the injections for the 10 and 30 min periods were given before commencing anaesthesia. After clamping the umbilical cord, fentanyl, or pethidine, and myoneural blocking drugs were administered and anaesthesia was maintained with a mixture of nitrous oxide in oxygen.

Blood was sampled from the antecubital vein of the mother before anaesthesia and at the time of delivery of the infant, simultaneous with the sampling of umbilical vein and artery blood. The samples were centrifuged and plasma aliquots of 0.5 ml were dried at 4 °C. The total activity was determined by liquid scintillation counting after proper combustion by an oxidation method. The recovery was $99.0 \pm 2.4\%$ (mean $\pm$ SD) (Saarikoski, 1974).

To confirm the stability of ^{3}H-atropine, plasma proteins were precipitated with 0.4-normal perchloric acid. After neutralization, paper chromatography was performed using Whatman No. 1 paper, and butanol–formic acid–water 100 : 20 : 50 as a solvent. The R_f value of atropine was 0.65.

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Plasma concentrations of hydrogen-3 were compared using a test of paired differences (Richterich, 1968).

RESULTS

Most infants received Apgar scores of 8 or better. Only four in the 1–10 min group had Apgar scores 2–6 at 1 min and 8–10 5 min after the delivery.

The maternal plasma hydrogen-3 concentration at 1 min amounted to 2.27 nCi . ml^{-1} and decreased in the following 2 min to 0.84 nCi . ml^{-1} (table II). During the remainder of the observation time the hydrogen-3 concentrations were about 1/4 of the first maternal plasma measurements.

The mean hydrogen-3 concentration in the umbilical vein at 1 min after the injection of atropine was 12% of the maternal value, and at 5 min was 93%. It remained at 71% for the next 25 min. During the period from 1 to 5 min after the administration of the drug, the concentration in the umbilical artery was almost half of that of the umbilical vein, reaching equilibrium at 30 min.

The remainder of the foetal plasma hydrogen-3 concentrations were found to be significantly less than the maternal values, except the umbilical vein concentration at 5 min ($P < 0.05$ and $P < 0.001$).

Paper chromatography showed that, in the 1–5 min group, 72.5 ± 2.2% (mean ± SD) of the hydrogen-3 activity in the maternal plasma, 73.4 ± 3.2% in the umbilical vein and 57.9 ± 6.6% in the umbilical artery, moved to the same point as the carrier atropine (fig. 1). The corresponding percentages for the 10–30 min group (fig. 2) were 52.7 ± 4.6% of the activity in the maternal plasma, 60.1 ± 5.0% in the umbilical vein and 60.4 ± 6.4% in the umbilical artery.

DISCUSSION

This study showed that there may be rapid placental transmission of atropine. One minute after the administration of the drug the concentrations of hydrogen-3 in the umbilical vein and artery amounted to 12 and 4%, respectively, of the maternal value. In two patients the time from the injection to sampling was only 30 s and no detectable transfer of ^{3}H-atropine occurred. The concentration of hydrogen-3 in the umbilical artery remained stable in the period 3–10 min, being 0.25 nCi . ml^{-1} or about half of the maternal plasma concentration. Toward the

TABLE I. *Injection of atropine–delivery interval, maternal age, maternal and newborn weights (mean ± SEM)*

Group	No. of patients	^{3}H-atropine–delivery interval (min)	Age (yr)	Weight	
				Maternal (kg)	Newborn (g)
A	5	1	28 ± 2.9	66.3 ± 2.3	3694 ± 106
B	4	3	26 ± 1.7	66.7 ± 3.2	3435 ± 162
C	6	5	27 ± 3.0	66.3 ± 4.2	3432 ± 92
D	4	10	33 ± 3.3	77.3 ± 10	3490 ± 211
E	4	30	32 ± 3.9	74.1 ± 4.2	3500 ± 279

TABLE II. *Hydrogen-3 concentrations in maternal and foetal plasma (nCi . ml^{-1}; mean ± SEM). P relates to the comparison with the corresponding maternal value*

Group	Maternal vein	Umbilical vein	Umb. vein / Mat. vein	Umbilical artery	Umb. art. / Mat. vein	Umb. art. / Umb. vein
A	2.27 ± 0.36	0.27 ± 0.64 $P < 0.005$	0.12 ± 0.29	0.11 ± 0.04 $P < 0.005$	0.04 ± 0.01	0.41 ± 0.16
B	0.84 ± 0.10	0.56 ± 0.50 $P < 0.05$	0.67 ± 0.10	0.24 ± 0.07 $P < 0.01$	0.29 ± 0.07	0.43 ± 0.19
C	0.57 ± 0.04	0.53 ± 0.04 $P > 0.05$	0.93 ± 0.11	0.25 ± 0.03 $P < 0.001$	0.44 ± 0.06	0.47 ± 0.06
D	0.45 ± 0.03	0.32 ± 0.03 $P < 0.01$	0.71 ± 0.04	0.25 ± 0.04 $P < 0.001$	0.56 ± 0.06	0.78 ± 0.11
E	0.52 ± 0.04	0.37 ± 0.03 $P < 0.01$	0.71 ± 0.04	0.35 ± 0.04 $P < 0.05$	0.67 ± 0.09	0.95 ± 0.08

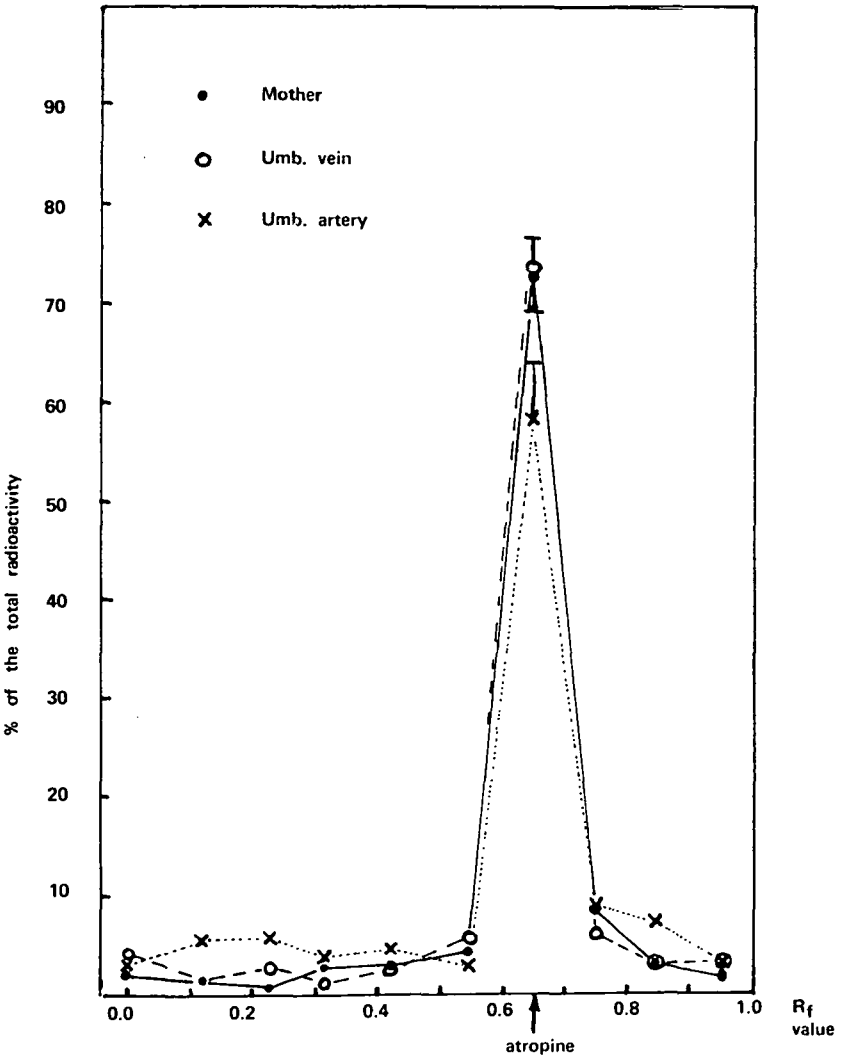

FIG. 1. Chromatography of ^{3}H-atropine performed on aliquots of the maternal and foetal plasma for time intervals of 1–5 min.

end of the time of observation, there was a slight increase to 0.35 nCi . ml^{-1}, which was 67% of the corresponding maternal value. Although the transfer of atropine across the placenta was rapid, equilibrium between the umbilical vein and artery was slower, being established only 30 min after the administration of atropine.

In an earlier study of placental transfer of ^{3}H-atropine in the first half of pregnancy, the radioactivity in the foetal plasma amounted to half of the hydrogen-3 content of the maternal plasma in 20 min (Kivalo and Saarikoski, 1970). This agrees with the present findings and indicates that there is little change with development in the ability of the placenta to transfer atropine.

Our paper chromatography studies strengthen the view that atropine found in the neonate was largely intact atropine. According to a human study with radioactive atropine, 85–88% of radioactivity was excreted in urine within the first 24 h (Gosselin, Gabourel and Wills, 1960), which indicates that the radiation dose in the present study was small and did not endanger mother or foetus.

Evidence of autonomic activity in the human foetus and newborn is derived from studies of the heart rate during labour and delivery: the transient bradycardia

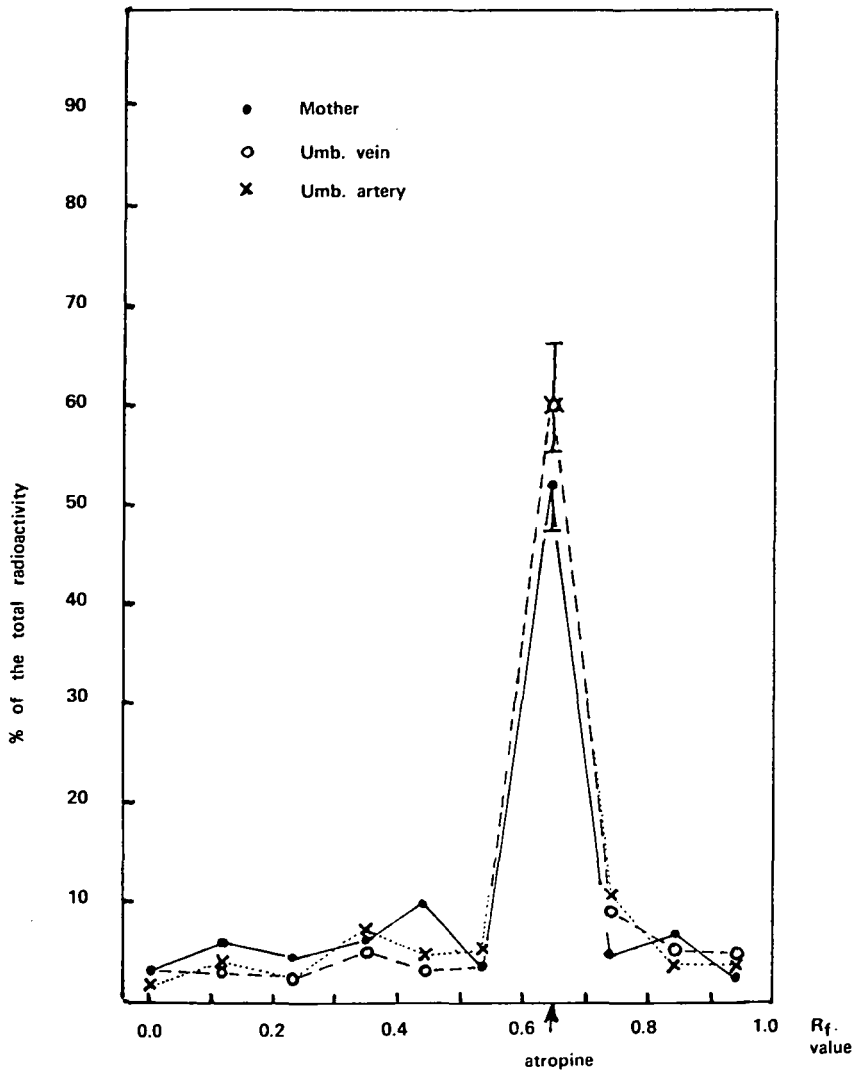

FIG. 2. Chromatography of ^{3}H-atropine performed on aliquots of the maternal and foetal plasma for time intervals of 10–30 min

associated with uterine contraction or early deceleration differentiated on the basis of the time interval from the peak concentration to the lowest heart rate. Atropine inhibits the early deceleration of foetal heart rate (Type 1 "dips"), which indicates increased vagal activity. This has been used as an index of the health of the foetus (Schifferli and Caldeyro-Barcia, 1973).

In foetal lambs it was found that, although atropine inhibited foetal bradycardia, there was a marked decrease in the cardiac output and a diminution in the umbilical blood flow (Cohn, Piasecki and Jackson, 1976). This suggests that atropine should not be used as a treatment of foetal asphyxia.

In patients undergoing Caesarean section, atropine is often administered about half an hour before induction of anaesthesia. This results in a transfer of atropine to the foetus before delivery and may protect the foetus and the newborn from vagal reflexes which can occur during birth and resuscitation (Gregory, 1975).

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REFERENCES

Brunel, G., and Vinkler, J. L. (1975). The value of atropine test in therapeutic orientation during feto–placental insufficiency; in *Therapy of Feto–Placental Insufficiency* (ed. B. Salvadori), p. 21. Berlin, Heidelberg, New York: Springer Verlag.

Cohn, H. E., Piasecki, G. J., and Jackson, B. T. (1976). Effect of atropine blockade on the fetal cardiovascular response to hypoxemia. *Gynecol. Invest.*, **7**, 57.

Gosselin, R. E., Gabourel, J. D., and Wills, J. H. (1960). The fate of atropine in man. *Clin. Pharmacol. Ther.*, **1**, 597.

Gregory, G. A. (1975). Resuscitation of the newborn. *Anesthesiology*, **43**, 225.

Järvinen, P. A., and Hirvonen, E. (1964). Value of the intravenous atropine test as a criterion of placental function. *J. Obstet. Gynaecol. Br. Commonw.*, **71**, 740.

John, A. H. (1965). Placental transfer of atropine and the effect of foetal heart rate. *Br. J. Anaesth.*, **37**, 57.

Kivalo, I., and Saarikoski, S. (1970). Quantitative measurements of placental transfer and distribution of radioactive atropine in fetus. *Ann. Chir. Gynaecol. Fenn.*, **59**, 80.

Richterich, R. (1968). *Klinische Chemie, Theorie und Praxis*, 2nd edn, p. 17. Basel: Karger.

Saarikoski, S. (1974). Fate of noradrenaline in the human foeto–placental unit. Thesis. *Acta Physiol. Scand.* (Suppl.), **421**, 29.

Schifferli, P., and Caldeyro-Barcia, R. (1973). Effects of atropine and beta-adrenergic drugs on the heart rate of the human fetus; in *Fetal Pharmacology* (ed. L. Boréus), p. 259. New York: Raven Press.

Soiva, K., and Salmi, A. (1959). Phonocardiographic studies of the foetal heart rate. *Ann. Chir. Gynaecol. Fenn.*, **48**, 287.

TRANSMISSION DE L'ATROPINE AU PLACENTA EN FIN DE GROSSESSE

RESUME

Au cours d'une opération Césarienne, on a mesuré la quantité d'atropine transmise au placenta. Vingt-cinq femmes enceintes ont reçu 0,5 μg/kg de ^{3}H-atropine entre 1 min et 30 min avant l'accouchement. Il a été prélevé sur les mères des échantillons de sang veineux avant l'induction de l'anesthésie et au moment de l'accouchement, ainsi que des échantillons de sang ombilical veineux et artériel. On a déterminé l'activité totale de l'hydrogène-3 grâce à un comptage par scintillation liquide. La stabilité de la ^{3}H-atropine a été confirmée par la chromatographie sur papier. Les concentrations dans la veine ombilicale ont été, à 1 et à 5 min après l'injection, respectivement de 12 et de 93% des valeurs correspondantes chez les mères. Les concentrations dans l'artère ombilicale ont été de 50% environ de celles se trouvant dans la veine ombilicale pendant la même période.

PLAZENTARE ATROPIN-BEFÖRDERUNG BEI VOLLZEITIGER SCHWANGERSCHAFT

ZUSAMMENFASSUNG

Messungen der plazentaren Atropin-Beförderung wurden während eines Kaiserschnitts durchgeführt. Fünfundzwanzig Patientinnen erhielten intravenös 0,5 $\mu g.kg^{-1}$ von ^{3}H-Atropin, und zwar 1–30 Minuten vor der Geburt. Der Mutter wurde vor der Narkose und bei der Geburt eine venöse Blutprobe entnommen, zusammen mit einer umbilikalen arteriellen und venösen Blutprobe. Die totale ^{3}H-Aktivität wurde mittels Flüssigkeitsfunkenzählung ermittelt. Die Stabilität von ^{3}H-Atropin wurde durch Papier-Chromatographie ermittelt. Die Konzentrationen in der Nabelschnurvene betrugen nach 1 min nach der Injektion 12%, 5 min nach der Injektion 93% des entsprechenden Wertes bei der Mutter. Die Konzentrationen in der Nabelschnurarterie betrugen etwa 50% von denen in der Nabelschnurvene während des gleichen Zeitraums.

TRANSMISION PLACENTAL DE ATROPINA A PRENEZ COMPLETA

SUMARIO

Se realizaron mediciones de transmisión placental de atropina durante operaciones cesáreas. Veinticinco pacientes recibieron atropina ^{3}H, 0,5 μg/kg i.v., 1–30 min antes del parto. Se analizó la sangre venosa materna antes de la inducción de anestesia y en el momento del parto, junto con sangre venosa la arterial umbilical. La actividad total de hidrógeno-3 se determinó mediante la medición de centelleamiento líquido. La estabilidad de atropina-^{3}H se confirmó mediante cromatografía de papel. Las concentraciones en la vena umbilical a 1 y 5 min después de la inyección fueron 12 y 93%, respectivamente, del correspondiente valor maternal. Aquellos en la arteria umbilical resultaron ser un 50% de aquellos en la vena umbilical durante el mismo período.