Residual curarization in the neonate after Caesarean section

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The transplacental transfer and the neonatal effects of atracurium 0.3 mg · kg^{-1} (ED_{95}) were compared with those of d-tubocurarine at the usual clinical dose of 0.3 mg · kg^{-1} (ED_{90}) in 46 patients undergoing elective Caesarean section. The atracurium group (25 patients) was similar to the d-tubocurarine group (21 patients) as far as age, parity and time intervals between precurarization, induction, skin incision, muscle relaxant administration, hysterotomy and birth. The transplacental transfer of atracurium was lower than that of d-tubocurarine, with a feto-maternal ratio of 9 ± 3% for atracurium and 12 ± 5% for d-tubocurarine ($P < 0.05$). The transplacental transfer of laudanosine was low at 14 ± 5%, with blood levels of 0.101 ± 0.032 μM · L^{-1} in the umbilical vein. Newborns in the two groups were comparable in terms of Apgar scores at one, five and ten minutes, as well as for NACS scores (neurological and adaptive capacity scoring test) at two and 24 hours after birth. However, at 15 min after birth, only 55% of newborns in whom the mothers received atracurium had a normal NACS score (≥ 35/40) compared with 83% of newborns in whom the mothers received d-tubocurarine ($P < 0.05$). Further analysis of the five variables related to active muscle tone revealed that the modal score for active extension of the neck of newborns from the atracurium group was lower than for newborns from the d-tubocurarine group ($P < 0.01$). This was compatible with the effect of residual curarization among newborns in whom the mothers received atracurium. However, this effect was transient since there was no difference found between the two groups at two and 24 hr after birth. Furthermore, no newborn had clinical signs of respiratory distress. In conclusion, atracurium given at a dose of 0.3 mg · kg^{-1} for Caesarean section may lead to partial residual curarization of neonates 15 min after birth.

Le passage transplacentaire et les effets sur le nouveau-né de l'atracurium à 0,3 mg · kg^{-1} (ED_{95}) ont été comparés à ceux de la d-tubocurarine à dose clinique habituelle de 0,3 mg · kg^{-1} (ED_{90}) chez 46 patientes devant subir une césarienne élective. Le groupe atracurium (25 patientes) était semblable à celui de la d-tubocurarine (21 patientes) concernant l'âge, la parité et les intervalles entre la précurarisation, l'induction, l'incision cutanée, l'administration du myorésolutif, l'hystérotomie et la naissance. Le passage transplacentaire de l'atracurium était légèrement inférieur à celui de la d-tubocurarine, avec un rapport foeto-maternel de 9 ± 3% pour l'atracurium et de 12 ± 5% pour la d-tubocurarine ($P < 0,05$). Le passage transplacentaire de la laudanosine était faible avec un rapport de 14 ± 5% et des niveaux sériques de 0,101 ± 0,032 μM · L^{-1} dans la veine ombilicale. Les nouveau-nés des deux groupes étaient comparables pour l'Apgar à une, cinq et dix minutes ainsi que pour le NACS ("neurological and adaptive capacity scoring test") à deux heures et 24 heures de vie. Cependant, à 15 min de vie, seulement 55% des nouveau-nés dont les mères avaient reçu de l'atracurium avaient un pointage normal pour le NACS (≥ 35/40) par rapport à 83% des nouveau-nés dont les mères avaient reçu de la d-tubocurarine ($P < 0,05$). Une analyse plus détaillée des cinq variables évaluant le tonus musculaire actif a démontré que la valeur modale pour l'extension active du cou était moins élevée chez les nouveau-nés du groupe atracurium que chez ceux du groupe d-tubocurarine ($P < 0,01$). Ceci est compatible avec une curarisation résiduelle chez les nouveau-nés dont les mères ont reçu de l'atracurium. Cependant, cet effet était transitoire puisqu'il n'y avait plus aucune différence entre les deux groupes à deux et 24 heures de vie. De plus, aucun nouveau-né n'a eu de signes cliniques de détresse respiratoire. Nous concluons que l'atracurium administrée à une dose de 0,3 mg · kg^{-1} lors d'une césarienne peut causer une curarisation résiduelle partielle chez le nouveau-né à 15 minutes de vie.

Key words

ANAESTHESIA: obstetrical;
MEASUREMENT TECHNIQUES: Apgar, NACS score;
NEUROMUSCULAR RELAXANTS: atracurium, d-tubocurarine.

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This study was conducted at Ste-Justine Hospital, 3175 Côte Ste-Catherine, Montreal, Que, H3T-1C5 and supported in part by a grant from Burroughs Wellcome.

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Accepted for publication 7th March, 1991.

The ideal muscle relaxant for use during Caesarean section ought to have the following characteristics: rapid onset, short duration of action, minimal passage across the placental barrier and rapid elimination by the new-

born. The physicochemical properties of atracurium give it the characteristics which approach that of the ideal muscle relaxant. It is a quaternary ammonium ion of high molecular weight with a low liposolubility and has a protein binding of 50%.[1] Thus its passage across the placental barrier should be limited. In addition, its redistribution and rapid metabolism ($t_{\frac{1}{2}}\alpha$ = 1.5 min, $t_{\frac{1}{2}}\beta$ = 15.7 min in adults and $t_{\frac{1}{2}}\alpha$ = 3.8 min, $t_{\frac{1}{2}}\beta$ = 20 min in infants) ought to permit rapid elimination from the circulation.[2]

Flynn *et al.* have evaluated the use of atracurium administered at 0.3 $mg \cdot kg^{-1}$ during Caesarean section.[3] They concluded that atracurium produced adequate relaxation of short duration and that its transplacental transfer was weak with a feto-maternal ratio of 12%. They reported also that the newborns showed no signs of distress since they had Apgar scores within the normal limits. However, they did not compare atracurium with a traditional muscle relaxant and the newborn evaluation was not completed by more sophisticated tests to permit an assessment of neurobehavioural well-being. This study aimed to measure the transfer across the placenta of atracurium given at 0.3 $mg \cdot kg^{-1}$ (ED_{95}) and its metabolite laudanosine, to evaluate its effect on the newborn and to compare it with d-tubocurarine administered at a commonly used clinical dose of 0.3 $mg \cdot kg^{-1}$ (ED_{90}).[11]

Methods

The protocol was accepted by the hospital medical ethics committee and informed consent was obtained from the patients. In a randomized double-blind study, 46 patients were studied at term who had been admitted for elective Caesarean section. These patients were all in good health (ASA physical status I and II), had no known fetal distress, did not suffer from diseases which could have interfered with the effects of muscle relaxants and did not take medications other than vitamins and iron supplements. They received no premedication other than sodium citrate 0.3 M.

The patients were divided at random into two groups and received either d-tubocurarine 0.3 $mg \cdot kg^{-1}$ (prepregnancy weight) or atracurium 0.3 $mg \cdot kg^{-1}$. The anaesthetic technique was similar in the two groups. The patients were placed in left pelvic tilt and received a bolus of 500 ml Ringer's lactate before induction of anaesthesia. All patients were monitored with a cardioscope, non-invasive blood pressure monitor (Dinamap®), pulse oximeter and nerve stimulator at the cubital nerve. After preoxygenation, a precurarization dose was given with either 0.05 $mg \cdot kg^{-1}$ of d-tubocurarine or 0.05 $mg \cdot kg^{-1}$ of atracurium. A rapid sequence induction was performed with thiopentone 4 $mg \cdot kg^{-1}$ and succinylcholine 1.5 $mg \cdot kg^{-1}$. Atracurium or d-tubocurarine 0.3 $mg \cdot kg^{-1}$ was administered as soon as the patient was intubated. Anaesthesia was maintained with nitrous oxide 50% and halothane 0.5% in oxygen until clamping of the umbilical cord and with fentanyl and nitrous oxide 66% thereafter. At the end of the surgery, the neuromuscular block was reversed with neostigmine 2.5 mg and atropine 1.2 mg, and reversal was confirmed with a tetanus stimulation of 100 Hz for five seconds.

TABLE I Comparison of time intervals during Caesarean section

	d-Tubocurarine	*Atracurium*
Precurarization – induction (min)	3.8 ± 1.8	3.6 ± 1.4
Induction – delivery (min)	9.1 ± 2.5	9.5 ± 2.9
Skin incision – delivery (min)	7.5 ± 2.7	7.8 ±3.0
Muscle relaxant – delivery (min)	6.0 ± 2.5	6.7 ± 3.2
Hysterotomy – delivery (sec)	121 ± 66	98 ± 39

Mean ± SD.

The times of precurarization, induction of anaesthesia, administration of the muscle relaxant, uterine incision and delivery (clamping of the umbilical cord) were noted. All newborns were examined by the same paediatrician who was unaware of the type of muscle relaxant used. They were evaluated by Apgar scores at one, five and ten minutes and by NACS scores (neurologic and adaptive capacity scoring) at 15 minutes, two hours and 24 hours after birth.[5] After clamping of the umbilical cord, two blood samples of 10 ml each were withdrawn simultaneously: one from either the dorsum of the hand or antecubital fossa of the mother and the other from the umbilical vein of the placenta. The blood samples containing d-tubocurarine were placed in preservative-free tubes, whereas those of atracurium were placed in tubes containing an acidic medium. The samples were transported in ice, centrifuged and the resulting serum kept at −20° C.

Plasma concentrations of atracurium and laudanosine were measured using a specific HPLC assay.[6] In brief, plasma samples (250 µl) containing 250 ng of verapamil (internal standard) were reacidified with 10 µl of 0.5 M sulfuric acid, and plasma proteins precipitated using 0.6 ml of acetonitrile. After centrifugation, an aliquot of 50 µl of the supernatant was injected for analysis. The chromatographic separations were carried out on a Hichrom Spherisorb C8 column (100 × 4.6 mm ID, 5 µm particle size; Reading, UK) with a linear gradient mobile phase (pH 5) at a flow rate of 1.7 $ml \cdot min^{-1}$. The mobile phase varied from 100% of 0.03 M phosphate buffer-methanol-acetonitrile (47.5:15:37.5) to 100% of 0.1 M phosphate buffer-methanol-acetonitrile (47.5:15:37.5) in a period of eight minutes. The excitation and emission monochromators of the Shimadzu fluorescence detector (Kyoto, Japan)

TABLE II Serum concentrations of d-tubocurarine, atracurium and laudanosine at delivery

	Maternal vein $\mu M \cdot L^{-1}$ ($\mu g \cdot ml^{-1}$)	*Umbilical vein* $\mu M \cdot L^{-1}$ ($\mu M \cdot ml^{-1}$)	*UV/MV*
D-tubocurarine			
mean	2.348 (1.432)	0.272 (0.166)	0.12*
± SD	0.657 (0.401)	0.118 (0.072)	0.05
range	1.131–3.803 (0.63–2.32)	0–0.492 (0–0.3)	
Atracurium			
mean	0.540 (0.502)	0.044 (0.041)	0.09*
± SD	0.155 (0.144)	0.010 (0.089)	0.03
range	0.307–0.779 (0.285–0.724)	0.024–0.061 (0.022–0.057)	
Laudanosine			
mean	0.802 (0.286)	0.101 (0.036)	0.14
± SD	0.323 (0.115)	0.032 (0.011)	0.05
range	0.375–1.441 (0.134–0.514)	0.035–0.155 (0.012–0.055)	

*$P < 0.01$ between d-tubocurarine and atracurium.

were set at 240 and 320 nm, respectively. The method is sensitive (limit of detection of 20 $ng \cdot ml^{-1}$), reproducible (mean coefficient of variation under 5%) and linear for plasma concentrations ranging from 30 to 8000 $ng \cdot ml^{-1}$ for atracurium and laudanosine. Plasma concentrations of d-tubocurarine were determined by HPLC using a slight modification of the assay described by Meulemans *et al.*[7]

Statistical analysis was done using the Mann-Whitney U test and the Kruskal Wallis ANOVA for non-parametric values. A one-way analysis of variance and the F test were used for parametric values.

Results

Of the 46 patients studied, 21 received d-tubocurarine and 25 received atracurium. Eight patients were removed from the study because of incomplete data: three patients were in the d-tubocurarine groups and five in the atracurium group. All the patients were haemodynamically stable, and there were no episodes of maternal hypoxia.

No differences were found between the two groups with respect to age, parity, precurarisation-delivery, induction-delivery, skin incision-delivery, muscle relaxant-delivery and hysterotomy-delivery intervals (Table I).

The serum concentrations of d-tubocurarine, atracurium and laudanosine in the mother and fetus as well as feto-maternal blood ratios are given in Table II. Atracurium blood levels were 0.540 ± 0.155 $\mu M \cdot L^{-1}$ for the mothers and 0.044 ± 0.010 $\mu M \cdot L^{-1}$ for the fetuses. d-Tubocurarine blood levels were 2.348 ± 0.657 $\mu M \cdot L^{-1}$ for the mothers and 0.272 ± 0.118 $\mu M \cdot L^{-1}$ for the fetuses. The transplacental transfer of d-tubocurarine was slightly higher than that for atracurium with a feto-maternal ratio of 9 ± 3% for atracurium and 12 ± 5% for d-tubocurarine ($P < 0.05$). Laudanosine blood levels were 0.802 ± 0.323 $\mu M \cdot L^{-1}$ for the mothers and 0.101 ± 0.032 $\mu M \cdot L^{-1}$ for the fetuses, for a feto-maternal ratio of 14 ± 5%.

TABLE III Comparison of newborns

	d-Tubocurarine	*Atracurium*
Birth weight (g)	3227 ± 387	3214 ± 461
Apgar scores ≥ 8*		
at 1 min	15 (83)	18 (90)
at 5 min	18 (100)	20 (100)
at 10 min	18 (100)	20 (100)
NACS ≥ 35*		
at 15 min	15 (83)	11 (55)†
at 2 hr	16 (89)	18 (90)
At 24 hr	17 (94)	20 (100)

Mean ± SD.
*Number of patients (%).
†$P < 0.05$.

The two groups were comparable for both weight and Apgar scores at one, five and ten minutes (Table III). All the newborns had Apgar >8 at five and ten minutes and all had sustained respiration before 90 seconds. Analysis of the neurobehavioural test (NACS) of the two groups revealed similar scores at two and 24 hours. However, at 15 minutes after birth, the number of patients with a normal score (>35/40) was lower in the atracurium group (55%) than in the d-tubocurarine group (83%) (Table III).

More detailed analysis of the five components of the

TABLE IV Neonatal scores on NACS items 15 min after birth

	d-Tubocurarine	*Atracurium*
Adaptive capacity	9 (7–10)	7 (6–10)
Passive tone	8 (7–8)	8 (6–8)
Active tone	9 (7–10)	7 (6–9)*
Primary reflexes	6 (5–6)	6 (3–6)
General assessment	6 (6)	6 (5–6)
Total score	36 (30–39)	34,35 (32–39)

Mode (range)
*$P = 0.0238$.

TABLE V Neonatal scores on NACS items evaluating active tone 15 min after birth

	d-Tubocurarine	*Atracurium*
Active contraction of neck flexors	2 (1–2)	1,2 (1–2)*
Active contraction of neck extensors	2 (1–2)	1 (1–2)†
Palmar grasp	2 (1–2)	2 (1–2)
Response to traction	1 (1–2)	1 (0–2)
Supporting reaction	2 (1–2)	2 (1–2)

Mode (range)
*$P = 0.07$.
†$P = 0.0099$.

NACS test (adaptive capacity, passive tone, active tone, primary reflexes and general assessment) revealed a difference in the "active tone" component ($P < 0.05$) (Table IV). Further analysis of the five variables related to active muscle tone revealed that the modal scores for active contractions of the flexor and extensor muscles of the neck was lower for the atracurium group than for the d-tubocurarine group, i.e., 1,2 versus 2 with respect to flexion and 1 vs 2 with respect to extension, although only the difference for the extensor muscles reached statistical significance (Table V). No newborn in either group had clinical evidence of respiratory distress.

Discussion

This study showed that use of d-tubocurarine and atracurium at a dose of 0.3 $mg \cdot kg^{-1}$ during Caesarean section produced low maternal blood concentrations of both muscle relaxants at the time of delivery. In addition, the transplacental transfer of the two muscle relaxants was weak and slightly lower for atracurium which had a feto-maternal ratio of 9 ± 3% versus 12 ± 5% for d-tubocurarine ($P < 0.01$). These results are similar to those reported in the literature (7% for atracurium and 12% d-tubocurarine).[3,8] Transplacental transfer of laudanosine was low, 14 ± 5%, with blood concentrations in the newborn of 0.101 ± 0.032 $\mu M \cdot L^{-1}$ (0.036 ± 0.011 $\mu g \cdot ml^{-1}$). This level is less than the levels which produce cardiovascular depression (16.8 $\mu M \cdot L^{-1}$ (6 $\mu g \cdot ml^{-1}$)) and neurotoxicity (47.6 $\mu M \cdot L^{-1}$ (17 $\mu g \cdot ml^{-1}$))[9] in animals. Studies in humans have shown that blood concentrations between 5.3 and 14 $\mu M \cdot L^{-1}$ (1.9 and 5 $\mu g \cdot ml^{-1}$) do not produce signs of toxicity.[10]

The Apgar scores did not reveal any fetal distress since all the newborns of the two groups had Apgar scores greater than eight at both five and ten minutes. This is comparable to Flynn's study which showed that of 53 patients studied, only two newborns had Apgar scores less than seven and those newborns had evidence of intrauterine fetal distress.[3]

Our study was more sensitive. We assessed the well-being of the newborn with the use of the NACS test, developed by Amiel-Tison *et al.* in 1982.[5] It evaluates 20 criteria grouped under five headings (Table IV). Unlike other neurobehavioural tests, it puts more emphasis on neonatal tone and the evaluation of different muscle groups which is, we think, well suited for the detection of a residual neuromuscular block. Furthermore, the NACS test is highly reproducible as shown by an interobserver reliability of 92.8%.[5] Newborns of mothers receiving atracurium at a dose of 0.3 $mg \cdot kg^{-1}$ had lower NACS scores than the newborns of mothers receiving d-tubocurarine at a dose of 0.3 $mg \cdot kg^{-1}$. This difference is transient, occurring only at 15 minutes and was limited to active muscle tone, more precisely to the active contraction of the extensor muscles of the neck. In adults, the inability to sustain a headlift in the supine position for five seconds is considered to be a clinical test of residual curarization. The modal score for contraction of the extensor group of muscles of the neck was 1 for the atracurium group compared with 2 for the d-tubocurarine group (Table V).

Although the blood levels of atracurium measured in the newborns (mean 0.044 ± 0.010 $\mu M \cdot L^{-1}$ (0.041 ± 0.089 $\mu g \cdot ml^{-1}$)) were less than the EC_{50} (the blood level known to cause curarization among 50% of subjects) in this age group (0.391 $\mu M \cdot L^{-1}$ (0.363 $\mu g \cdot ml^{-1}$)), the evaluation of the active contraction of the neck muscles seemed to indicate that the newborns in the atracurium group had detectable residual curarization at 15 minutes of life.[2]

In this study, no newborns had clinical respiratory distress. However, atracurium was used in patients who were at term and who had no known pathology or fetal distress. Newborns and especially premature newborns are more susceptible to respiratory muscle fatigue because of a reduction of type I muscle fibres of the diaphragm.[11] In the case where respiratory work is increased, e.g., transient tachypnoea of the newborn, hyaline membrane disease or diaphragmatic hernia, it is possible that residual

curarization could dangerously aggravate the respiratory distress already present. The doses of muscle relaxant used in our study were not pharmacologically equipotent, i.e., ED_{90} for atracurium and ED_{95} for d-tubocurarine, but reproduced the recommendation of Flynn *et al.* for atracurium and what was used in clinical practice for d-tubocurarine.[4] Since the blood concentrations of atracurium measured in the newborns were low and clearly less than that known to cause curarization in this age group, one cannot be sure that a lower dose of atracurium would eliminate the risk of a residual curarization in the newborn.[2]

In conclusion, this study shows that although transplacental transfer is weak, the use of atracurium at a dose of 0.3 $mg \cdot kg^{-1}$ for Caesarean section induces clinical signs of residual curarization at 15 minutes after birth.

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