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Renal Functional Impairment in Preterm Neonates Related to Intrauterine Indomethacin Exposure

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ABSTRACT. Renal function was measured during the first 4 postnatal days in 9 preterm neonates (gestational age 26.2 to 31 wk) exposed to indomethacin during the last 2 days of pregnancy (group I). The data were compared to those obtained from nine control neonates (gestational age 28 to 34.5 wk) (group II). Five of the nine neonates in group I were markedly edematous at birth, none of group II were edematous. Urine production in group I was low (32.2 ± 16.8 ml/kg·day on day 1 increasing to 68.6 ± 21.4 ml/kg·day on day 4) and differed significantly from group II [75.2 ± 26.8 ml/kg·day on day 1 increasing to 84.8 ± 20.9 ml/kg·day on day 4 ($p < 0.001$)]. Fluid intake was adapted to urine production when necessary.

A continuous inulin infusion was started directly after admission and continued for 5 days. Renal function was evaluated for 3 consecutive days after at least 48 h of inulin infusion. The values of the inulin clearance, serum creatinine, urine osmolarity, osmolar clearance, and free water clearance were stable in both groups during the study period. Inulin clearance was lower in group I than in group II ($p < 0.001$), whereas serum creatinine was higher in group I than in group II ($p < 0.0001$). Urine osmolarity was higher in group I ($p < 0.01$), whereas osmolar clearance and free water clearance were lower in group I ($p < 0.02$, respectively, $p < 0.01$). There was no difference in fractional sodium excretion between the groups. In conclusion, indomethacin treatment given as a short course to pregnant women, leads to a significant functional impairment of the kidneys in their offspring immediately after exposure. This necessitates adaptation of fluid intake. (*Pediatr Res* 24: 644–648, 1988)

Abbreviations

BW, body weight
C_{H2O}, free water clearance
C_{in}, inulin clearance
C_{osmol}, osmolar clearance
FENa, fractional sodium excretion
GFR, glomerular filtration rate
i, inulin concentration in infusion
ID, indomethacin
p, plasma inulin concentration
PDA, patent ductus arteriosus
R, infusion rate
S_{creat}, serum creatinine
U_{osmol}, urine osmolality
PAP, para amino phenazone

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ID has been used as an inhibitor of preterm labor in the pregnant woman since 1974 (1). Recent papers report that short courses of this drug administered before 35 wk of gestation are safe and free of side effects (2). However, side effects have previously been reported. In the animal model intrauterine closure of the ductus arteriosus has been described (3, 4), as well as a decrease in cerebral blood flow (5) and an arrest in fetal nefrogenesis (6). In contrast to the described intrauterine closure of the ductus arteriosus in the animal model there are various reports of persistent fetal circulation in the human neonate (7–9). Cardiac insufficiency (10) and irreversible renal insufficiency (11–13) are also reported. Recently we described an infant who remained totally anuric after birth, after his mother has been treated with ID for 6 wk (14). Furthermore, it has been reported that treatment of preterm neonates with ID for medical closure of the patent ductus arteriosus results in a temporary decrease in renal function (15–18). These observations prompted us to evaluate the renal function in preterm neonates, exposed to ID during the last days of intrauterine life.

PATIENTS AND METHODS

Patients. Renal function studies were performed on 20 preterm neonates born after intrauterine exposure to ID. Eleven infants were excluded because of one or more of the following criteria: the temporary discontinuation of the inulin infusion due to technical difficulties which lead to unstable inulin concentrations; the use of aminoglycosides and severe perinatal asphyxia as possible causes of impairment of renal function. Nine patients remained for further analysis of renal function. Gestational age varied from 26.2 to 31 wk (mean 28.1 wk) and birth weight from 1000 to 1640 g (mean 1290 g) (group I).

The patients were compared with nine neonates (group II), whose mothers did not receive ID during pregnancy. Gestational age in this group varied from 28 to 34.5 wk (mean 31.1 wk) and birth weight from 920 to 2055 g (mean 1503 g). These patients were selected from a group of 22 preterm neonates who were originally entered into the study, using the same criteria as in group I. Blood pressure was monitored in all infants using an indwelling catheter in the radial or tibial artery or by means of an electronic blood pressure monitor (Dinamap, Kriticon). Blood pressure was within the normal limits for age in all children (19).

Fluid intake consisted of a glucose-NaCl solution, providing 10 g glucose/100 ml and 3–5 Meq Na^+/kg body weight·day. Aminoacids and a triglyceride emulsion were added on the 2nd day of life. The amount of proteins and fat was increased during the 1st wk of life from 1 g up to 2 1/2 g/kg body weight/day. When possible, feeding was started through a nasogastric tube. Informed parental consent was obtained for the studies. Clinical data of both groups are summarized in Table 1.

Methods. The experimental protocol is outlined in Figure 1. Immediately after birth or after admission to the neonatal intensive care unit, *i.e.* in the first 6 h of extrauterine life, a blood sample was taken to measure the ID level. ID levels were measured by means of high-pressure liquid chromatography (20).

An inulin glucose infusion with an inulin concentration of 25 g/liter and an infusion rate of 0.6 ml/kg·h was started after admission, together with the other intravenous solutes. This was continued for a period of 5 days. Total urine production, calculated from changes in diaper weight (21) and 6-h collection periods, and fluid intake were evaluated after 1, 2, 3, and 4 days of infusion; renal function after 2, 3, and 4 days of infusion. A blood sample was taken daily to measure plasma levels of inulin, creatinine, sodium, and osmolality. Urine was collected during 6-h periods using urine collection bags. Urinary volume as well as osmolality and sodium concentrations were determined. The S_{creat} levels in group 1 were repeated 2 wk later.

Inulin concentrations in serum were determined using the following method. Serum was deproteinized with an equal volume of 0.6 N $HC1O_4$ and the inulin concentration was calculated in the supernatant as the difference in glucose + fructose content before and after hydrolysis during 15 min at 70° C. The amount of glucose + fructose was measured with an enzymatic test (Boehringer-Mannheim 716260; Boehringer-Mannheim Biochemicals, Indianapolis, IN) adapted to a Cobas Bio Analyser (Hoffman-La Roche, Basel, Switzerland). The blank values were determined directly after deproteinization to avoid (slow) hydrolysis at room temperature. These values varied between 1.6 and 48.4 mg/liter "inulin" ($n = 73$).

S_{creat} was determined on a Cobas Mira (Hoffman-La Roche) by an enzymatic method (creatinine-PAP, Boehringer-Mannheim 856885). By adding $K_3Fe(CN)_6$ and h-albumen to the reagent to achieve a final concentration of 0.57 mmol/liter and 5.7 g/liter, respectively. The negative influence of bilirubin up to 400 μmol/liter was suppressed. Coefficients of variation were 5.1% (83 μmol/liter, n = 573) and 3.4% (233 μmol/liter, n = 562).

C_{in} was used as a marker for GFR and calculated from the i, the R, and the p ($C_{in} = i \cdot R/p$) and expressed in ml/kg·min. FENa, C_{osmol}, and C_{H2O} were calculated from serum values and the values in the collected urine. Inulin was used as reference to calculate FENa.

Statistics. The two-sample *t* test was used to compare the mean values of gestational age and body weight in the two groups. Multiple linear regression analyses with stepwise selection of the independent variables were performed to assess the best predictors of the variables used to quantitate glomerular and tubular function.

The following independent variables were included: the treatment groups, gestational age, postnatal day, and fluid intake. If a variable failed to meet entry requirement (probability of F to enter >0.05), the procedure was terminated. Procedures were carried out with commercially available soft-ware (SPSS/PC, SPSS Inc. Chicago, IL) on a personal computer.

RESULTS

Clinical data of the patients in group I were comparable to those in group II. Only gestational age differed significantly

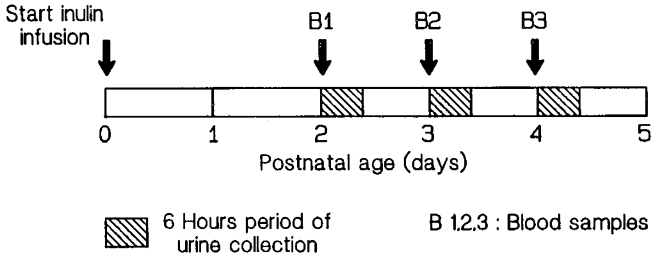

Fig. 1. Experimental protocol.

Table 1. *Clinical data of study groups**

	Gestational age	Birth wt	Diagnosis†	Ventilation	ID dosage‡ (mg)	ID levels (μg/ml)
Group I						
1	27.5	1060	RDS, PROM	SV	400	0.3
2	28	1400	PROM	SV	300	1.9
3	27.4	1100	RDS	AV	200	0.3
4	29	1260	PDA	AV	200	0.5
5	28.8	1405	RDS	SV	200	0.6
6	28.4	1500	RDS	AV	800	0.3
7	28	1250	PROM	SV	100	0.2
8	30	1640	RDS	SV	400	0.1
9	26.2	1100	RDS	AV	550	0.2
Group II						
1	34.5	2275	RDS	SV		
2	30	920		SV		
3	30.4	1230	RDS	AV		
4	28	1055	RDS	SV		
5	31.7	1745	RDS, PROM	AV		
6	32.7	2055	RDS	SV		
7	32.7	1745	RDS	SV		
8	30	1060	RDS	AV		
9	30	1450	RDS	AV		

* RDS, respiratory distress syndrome; PROM, prolonged rupture of membranes; SV, spontaneous ventilation; AV, artificial ventilation.

† The diagnoses small for gestational age and prematurity are not mentioned.

‡ Doses of ID administered during the last 48 hours of pregnancy.

between the groups (28.1 ± 1.0 *versus* 31.1 ± 2.0 wk, $p < 0.01$). No differences were present in P_{aco2}, oxygen saturation or P_{ao2} between the groups (data not presented). In both groups, four of nine neonates needed artificial ventilation during the study period. No significant differences in body weight were present (1290 ± 214 *versus* 1503 ± 478 g). In group I ID levels varied from 0.1 to 1.9 μg/ml (Table 1).

Five of the nine infants in group I were edematous at birth and remained so during the study period. Ultimately two patients died, one in group I of sepsis related to meconium peritonitis (patient 6) and one in group II of bilateral pneumothorax (patient 8). The data on fluid balance in both groups are summarized in Table 2. Fluid intake in group II was increased because of adequate urine production, in contrast to group I.

Intrauterine exposure to ID was found to be the best predictor for a low urine output among the variables included in the study (multiple $r = 0.41$). Postnatal age was the next best predictor. By adding postnatal age to the regression equation multiple r rose to 0.50, indicating that urine output increased with postnatal age. Other variables failed to meet entry requirements. Inulin levels in group I and II did not change during the study period. However, inulin levels in group I were significantly higher compared to group II (444 ± 37 SEM *versus* 291 mg/liter ± 16 SEM) resulting in a low C_{in} in group I compared to group II ($p < 0.002$, $r = 0.77$). S_{creat} levels were higher in group I compared to group II ($p < 0.0001$, $r = 0.70$). No correlation was found between the measured values and gestational age (Table 3). S_{creat} in group I was 55 μmol/liter ± 16 at 2 wk of age. Renal tubular functional parameters are summarised in Table 4. None of the parameters changed during the study in the two groups. Multiple regression analysis demonstrated that the exposure to ID was the only predictor for a high U_{osmol} ($p < 0.01$, $r = 0.38$). C_{osmol} was less in group I compared with that in group II ($p < 0.02$, $r = 0.38$) as was C_{H2O} ($p < 0.01$, $r = 0.39$). Neither fluid intake nor postnatal age were significant predictors of the observed changes. FENa did not differ between the groups.

DISCUSSION

Our data indicate that intrauterine exposure to ID results in a marked suppression of renal function during the first 5 days of postnatal life. Both GFR and urine production are suppressed. The decreased urine production in group I prevented us from increasing fluid intake on day 3 and 4 (Table 2) in contrast to group II.

Animal and human studies show that ID slowly passes through the placental barrier (22, 23). In neonates ID levels at birth were equal to the maternal levels 5 h after administration of ID (23). This suggests that the fetus is exposed to relatively high levels, when the mother receives ID several times daily during a prolonged period. The half-life of ID in preterm infants is longer than in adults. In adults the half-life is 2.6–11.2 h (24), in preterm infants reports of half life vary from 11–20 h (25) up to 63 ± 38 h (26).

If the half-life of up to 63 h (26) is considered, the effects of ID given prenatally can presumably last for almost 1 wk postnatally. The levels of ID in our present study varied from 0.1 to 1.9 μg/ml. This is in the same range as that found when using ID for medical closure of the PDA (27, 28).

We used the continuous inulin infusion technique to measure GFR, because creatinine clearances during the first days of extrauterine life are not reliable (29). A disadvantage of the C_{in}, measured with a continuous inulin infusion, is that the GFR can only be calculated after a prolonged period of inulin infusion because of the known long equilibration time in the preterm infant (30). A small, but significant, difference in gestational age between the study groups is present. This is due to the fact that preterm labor in the referring hospital is nowadays generally treated with ID. Therefore few preterm babies are born in this hospital without ID exposure. The C_{in} was expressed in ml/min·kg in order to minimize the effects of differences existing between the two groups. The difference in gestational age between both groups probably does not influence the results of the present study. In another study of 33 neonates in whom C_{in} was measured on day 3, 4, or 5, no correlation of the GFR/kg BW was observed with gestational age in neonates between 27 and 34.5 wk (31). The data of Coulthard (32) concerning neonates of a comparable gestational age, support these results. In our study groups no correlation existed between the measured values and gestational age. We failed to demonstrate a positive correlation between GFR and postnatal age in both groups, in contrast to results in the literature (31, 33). This is probably related to the relative short observation period in this study. The increments in GFR reported in other studies were observed over periods of more than 1 wk. S_{creat} was stable in both groups during the observation period but significantly higher in group I. Therefore S_{creat} declined normally in group II during the first 48 h. In group I the usual decrease did not take place. We assume that GFR increased to normal values after the observation period, because normal S_{creat} values were found in all infants after the age of 2 wk (34). C_{in} was not repeated at that time because of ethical and practical reasons. Intravenous infusion was not longer necessary in a number of patients and some were referred to another hospital. No longlasting effects on GFR were observed, judging from the

Table 3. *Glomerular function parameters in neonates exposed to indomethacin (group I) and controls (group II)**

		Days of extrauterine life		
	Group	2	3	4
Inulin clearance ml/min·kg	I	0.65 ± 0.15	0.63 ± 0.13	0.51 ± 0.13
	II	0.85 ± 0.15	0.89 ± 0.17	0.91 ± 0.12
Screatinine (μmol/liter)	I	103.9 ± 24.6	100.0 ± 22.8	103.7 ± 36.7
	II	56.2 ± 10.7	50.6 ± 12.6	50.7 ± 17.1

* Multiple regression analysis revealed that inulin clearance correlates negatively with the exposure to ID ($p < 0.001$, $r = 0.77$). Serum creatinine values were higher in the ID-treated infants.

Table 2. *Fluid balance during study period in neonates exposed to Indomethacin (group I) and controls (group II)**

		Days of extrauterine life			
	Group	1	2	3	4
Fluid intake ml/kg·day	I	95.9 ± 28.6	91.2 ± 18.9	96.3 ± 38.6	103.8 ± 29.7
	II	88.6 ± 17.5	104.5 ± 16.0	20.8 ± 27.8	132.2 ± 28.0
Urine production ml/kg·day	I	32.2 ± 16.8	65.1 ± 29.5	62.3 ± 23.0	68.6 ± 21.4
	II	75.2 ± 26.8	78.2 ± 20.9	77.7 ± 26.9	84.8 ± 20.9

* Multiple regression analysis revealed that the use of ID is the best predictor of a low urine volume ($p < 0.001$, $r = 0.41$) followed by postnatal age ($p < 0.001$, multiple $r = 0.50$).

Table 4. *Tubular function parameters in neonates exposed to indomethacin (group I) and controls (group II)**

	Group	Days of extrauterine life		
		2	3	4
U_{osmol} (mosmol/kg H_2O)	I	295.1 ± 100.4	307.5 ± 116.6	316.0 ± 117.7
	II	220.0 ± 104.2	220.6 ± 77.4	238.0 ± 100.3
C_{osmol} (ml/min·kg)	I	0.022 ± 0.010	0.037 ± 0.019	0.032 ± 0.017
	II	0.041 ± 0.018	0.040 ± 0.009	0.049 ± 0.016
C_{H2O} (ml/min·kg)	I	0.007 ± 0.010	−0.004 ± 0.015	0.004 ± 0.013
	II	0.015 ± 0.026	0.020 ± 0.016	0.017 ± 0.032
FENa (%)	I	4.0 ± 1.9	4.0 ± 2.6	3.2 ± 1.8
	II	4.8 ± 1.8	2.5 ± 1.6	2.8 ± 1.3

* Multiple regression analysis revealed that the use of ID in group I was the only predictor of a high urine osmolarity ($p < 0.01$, $r = 0.38$) C_{osmol}

serum creatinine values in the other 11 newborns exposed to ID but excluded from the statistical analysis.

Renal water excretion was decreased in neonates exposed to ID, compared with controls as judged from the lower urine output and lower C_{H2O}. The observed effects on renal water handling are in accordance with those observed during medical treatment for a patent ductus arteriosus, and can be attributed to either the low GFR or the improvement of concentrating capacity. In our study no changes in FENa were demonstrated. Although the effect on renal function in group I was temporary, we consider the use of this drug to be controversial.

It is known from animal studies that differentiation processes in the maturing fetus are accompanied by major changes in prostaglandin activity (35). We consider the data of Novy (6) on intrauterine development of monkeys exposed to ID, demonstrating an arrest in nephrogenesis related to the use of ID, alarming. Total kidney volume in these monkey fetuses was reduced about 38% compared with nonexposed fetuses.

Itskowitz *et al.* (11) reported three women in whom pregnancy ended with an oligohydramnios and perinatal death after exposure to ID for 4–6 days. Cantor *et al.* (12) reported transient anuria of a neonate after 9 wk of ID treatment for Still's disease of the mother. Veersema *et al.* (13) described a so-called renal nonfunctioning syndrome in a newborn related to 8 wk ID treatment of the pregnant mother. We described a newborn with the same symptoms (14) and we recently observed another infant who remained totally anuric after 9 wk intrauterine exposure to ID.

It is known that ID impairs GFR in adults as well as in preterm newborns. In adults this phenomenon occurs especially in situations where high levels of angiotensin II are present (36). In human preterm neonates an impairment of GFR has been observed during treatment of the PDA (15–18). The underlying mechanism of the effect of ID on GFR is probably the same in neonates exposed after birth and in the newborns exposed during pregnancy as in adults. Levels of angiotensin II are high in newborns and decline after birth (37). Inhibition of prostaglandin synthesis blocks the antagonizing effect of prostaglandins on angiotensin II-induced vasoconstriction. Many animal experiments provide evidence for this mechanism (38, 39). There is evidence from animal studies that renal vascular resistance is high and cortical perfusion low in neonatal life compared to later (40–42). The inhibition of prostaglandin synthesis may further increase renal vascular resistance, resulting in an impaired renal blood flow and a concomitantly reduced GFR. When ID is used for longer periods during pregnancy severe renal insufficiency can develop; sometimes irreversible functional damage occurs (11–14).

In conclusion, a significant decrease in GFR combined with a low urine output is present in neonates born after intrauterine exposure to ID. This has major implications for the fluid management of the newborns concerned and the administration of drugs such as digoxin or nephrotoxic drugs. Although the alterations in renal function may be transient, we consider prolonged ID treatment during pregnancy to be an important risk factor for the developing fetus.

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