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ORIGINAL ARTICLE

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Tubular proteinuria in pre-term and full-term infants

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Abstract Predictors of tubular proteinuria (alpha 1-M/crea ratio >10 mg/mmol) were sought in 100 infants of 24–32 weeks' (group 1) and 69 of 34–42 weeks' gestation (group 2). Random spot urine samples were obtained in the former group at the ages of 0–3 days, at 1–2 weeks and thereafter at 2-week intervals until the disappearance of tubular proteinuria, and in the latter one sample at a mean (SD) of 3.0 days' (1.3) age. In group 1, gestational age correlated negatively with the first urinary alpha 1-M/crea ratio. The highest urinary alpha 1-M/crea ratios [median (range) 39.1 mg/mmol (9.5–268.9)] occurred at a median (range) of 5 days' (1–42) age. Low gestational age and the need for inotropes predicted tubular proteinuria early after birth, whereas low gestation and long duration of ventilator treatment predicted the highest alpha 1-M/crea ratios. Prolonged vancomycin treatment and low gestational age were associated with delayed normalization of tubular proteinuria. In group 2 no significant risk factors for tubular proteinuria were found. The urinary alpha 1-M/crea ratio seems to be a sensitive indicator of renal tubular function in neonates, with low gestational age, the need for inotropes and prolonged assisted ventilation being predictors of increased tubular proteinuria. Long vancomycin courses should be avoided in pre-term infants in view of the prolonged adverse renal effects.

Keywords Nephrotoxic drugs · Alpha-1-microglobulin · Antenatal · Postnatal · Non-steroidal anti-inflammatory drugs

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Introduction

In the newborn a number of factors can influence renal development and function after birth. Especially gestational age and postnatal age seem to play a major role in renal functional maturation [1, 2]. Also, antenatal or postnatal exposure to non-steroidal anti-inflammatory drugs (NSAIDs) [3, 4], birth asphyxia [5], mechanical ventilation and respiratory distress [6, 7], hypotension, septicemia or postnatal exposure to nephrotoxic drugs [8, 9] may have adverse effects on kidney function.

Renal glomerular function as measured by the glomerular filtration rate (GFR) appears to increase in both pre-term and full-term infants after birth [10, 11]. Among pre-term infants, the increase between 28–35-weeks' gestation may reflect functional changes in existing nephrons and the appearance of new nephrons, whereas during the last 5 weeks of gestation, the increase in GFR may reflect the increase in kidney size [10]. After birth the renal and systemic circulation adapt to extrauterine life, and GFR increases in both pre-term and term infants [8, 11, 12]. Likewise tubular function improves after birth in both groups [13].

Urinary alpha-1-microglobulin (alpha 1-M) is a suitable marker for proximal tubular function because of its relatively high concentration in the urine and its stability

Table 1 Clinical characteristics of patients

Variable	Group 1 (n=100)	Group 2 (n=69)
Birth weight (g)	1,398 (450)	3,517 (564)
Range	520–2,550	1,810–4,820
Gestational age (weeks)	29.5 (2.3)	39.3 (1.6)
Range	24–32	34–42
Number of infants of gestational ages <28 weeks	21	
Male/female ratio	63/37	41/28
Apgar score <7 at 5 min of age	10	2
SGA	6	2
Need for assisted ventilation	39	0
Range (days)	0–62	
Need for surfactant therapy	35	0
Bronchopulmonary dysplasia		
At 28 days of age	21	0
At the age of 36 gestational weeks	7	0
Maternal infection	34	1

Values are expressed as occurrences, mean (SD) or range values

in acid urine as well as in serum levels [14]. Its sensitivity is high, reflecting dysfunction of the proximal tubulus long before elevation of other markers [15]. For these reasons urinary alpha 1-M has been used as an indicator of renal tubular impairment and dysfunction caused by nephrotoxic drugs and other agents [16, 17].

The aim of the study was to determine the effects of nephrotoxic drugs for tubular proteinuria and to establish other potential risk factors for tubular dysfunction in premature and full-term infants.

Subjects and methods

Subjects

The study population comprised 100 pre-term neonates (group 1) and 69 near-term and full-term infants (group 2) born in Tampere University Hospital. Neonates with major malformations were excluded from the study. More detailed data on the infants studied are presented in Table 1. The ethical committee of Tampere University Hospital approved the study protocol, and informed consent was obtained from the parents.

In group 1, intravenous antibiotic treatment with ampicillin (50 mg/kg every 12 h) and netilmicin (3.0 mg/kg every 12 or 18 h, according to the length of gestation of the patient) was initiated in 74 infants immediately after birth. Twenty of these primarily treated cases, as also six other infants, received subsequent antibiotic treatment (netilmicin, vancomycin, ceftazidime or meropenem), and seven received fluconazole during the study period. Twenty infants received no antibiotic or antifungal treatment; 12 infants received netilmicin treatment concomitantly with vancomycin. Infusion of inotropes (dopamine and/or dobutamine) for hypotension was needed in 40 cases. Eight infants received dexamethasone for weaning from the ventilator. Single doses of furosemide were administered to 38, mainly with packed red cell infusions (Table 2). No long-term diuretic therapy was used. Postnatal indomethacin treatment for patent ductus arteriosus was administered to two infants, one of these receiving two courses: the first at 0.2 mg/kg to 0.1 mg/kg to 0.1 mg/kg at 12-h intervals and the second at a first dose of 0.1 mg/kg and the remaining two at 0.2 mg/kg at 12-h intervals. The other infant received three doses of indomethacin at 0.2 mg/kg at 12-h intervals. Only one infant had an anuric period of about 24 h resulting from hemodynamic instability. Septicemia confirmed by positive blood culture, an increased proportion of immature neutrophils and elevated C reactive protein [18] were diagnosed in eight cases.

In group 2, one infant received antibiotic therapy 1 day before sampling (ampicillin 50 mg/kg every 8 h and netilmicin 3 mg/kg every 8 h) for a suspected infection directly after birth. Otherwise, no medication was needed.

Methods

Data on the mothers' medications during pregnancy were collected from the case records and in full-term cases also obtained from the mothers by structured questionnaire. Altogether 25 infants in group 1, with gestational ages of a mean (SD) 29.7 weeks (2.1), and 9 infants in group 2 had been exposed antenatally to NSAIDs (indomethacin, ibuprofen, ketoprofen or metamizole-pitophenone, or Litalgin). The time between the last dose of medication and delivery was a median (range) of 2 days (0–26) and in five cases in group 1 less than 48 h. Group 2 infants had been exposed to these drugs between a gestational age of 30 and delivery. More detailed data on antenatal medication are summarized in Table 3.

In group 1, the first random spot urine sample for analysis of alpha 1-M and creatinine content was obtained by collecting the urine into plastic bags attached to the skin surrounding the external genitalia during the first 3 days after birth. In 14 cases the first sample was missed because of technical problems. The next sample was taken at the age of 1 to 2 weeks. Sampling was continued at 2-week intervals, if the infants' condition was stable, as long as the previous alpha 1-M/crea value exceeded 10 mg/mmol, or until discharge from the hospital. In group 2, one random spot urine sample was taken at a mean (SD) of 3.0 days (1.3) of age. In group 1, plasma creatinine content was measured in altogether ten infants, in nine cases because of increased proteinuria or delayed normalization of urinary alpha 1-M/crea ratio and in one case because of antenatally diagnosed hydronephrosis. Serum cystatine C was determined in six infants on account of increased proteinuria or delayed normalization of urinary alpha 1-M/crea ratio. Renal ultrasonographic examination was performed in nine infants at a median (range) of 43 days (2–98) of age. In group 2, plasma creatinine was determined in one infant because of asphyxia.

Urinary alpha 1-M was measured nephelometrically (Behring BN II nephelometer, Dade Behring, Marburg, Germany) with a

Table 2 Postnatal drug therapy in group 1 during the whole study time

	Number of infants treated	Cumulative dosage of the drug (mg/kg)	Duration of therapy (days)
Netilmicin	79	17 (5–128)	4 (1–23)
Vancomycin	16	304 (117–730)	10 (4–36)
Ceftazidime	14	457 (49–924)	6 (1–14)
Meropenem	5	244 (124–407)	6 (3–12)
Fluconazole	7	84 (58–147)	14 (8–30)
Inotropes	40		1.5 (0.2–19)
Dexamethasone	8		11 (4–22)
Furosemide	38		1.5 (1–8)

Values are expressed as occurrences or median (range) values

Table 3 Antenatal exposure to drugs

	Indomethacin	Ibuprofen	Ketoprofen	Metamizole-pitophenone
Group 1				
Number of infants exposed	11 (11)	5 (5)	3 (3)	8 (8)
Cumulative dosage (mg)	150 (50–200)	400 (400–600)	100 (100–200)	500 (500–5,000)
Group 2				
Number of infants exposed	5 (7)	4 (6)	2 (3)	2 (3)
Cumulative dosage (mg)	250 (50–525)	1,400 (400–3,600)	2,525 (50–5,000)	750 (500–1,000)

Values are expressed as occurrences with percentages or median (range) values

sensitivity of about 5 mg/l. Urinary creatinine was measured enzymatically using a Cobas Integra 700 Analyzer (F. Hoffmann-La Roche Ltd., Diagnostic Division, Basel, Switzerland). Urinary alpha 1-M was expressed as a ratio to millimoles of creatinine in urine samples. Serum cystatine C concentrations were measured as previously described [19].

Statistical analysis

The statistical analyses were performed using SPSS for Windows version 10.1 and 12.0.1. Continuous data were analyzed using Spearman rank correlation, the Mann-Whitney U-test or Kruskal Wallis Test, and discrete data were analyzed using the Pearson chi-squared test or Fisher's exact test. To identify potential risk factors for high first and high maximum urine alpha 1-M/crea ratios (upper quartile of the first and upper quartile of the maximum urine alpha 1-M/crea ratios during hospitalization), including antenatal exposure to NSAIDs, gestational age, birth weight, gender, Apgar <7, postnatal age, being small for gestational age (SGA), septicemia, the duration of postnatal exposure to inotropes, furosemide, dexamethasone, netilmicin, vancomycin, ceftazidime, meropenem or fluconazole and the need for mechanical ventilation, logistic regression analysis by a backward stepwise method was used. Cox regression analysis was used to evaluate the significance of the same potential predictors for normalization of urine alpha 1-M/crea ratio and Kaplan-Meier survival analysis for Fig. 1.

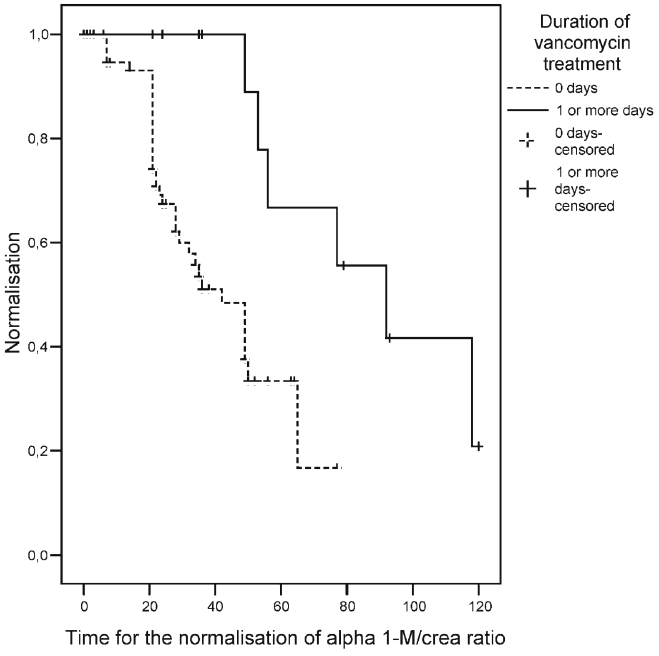

Fig. 1 The effect of vancomycin treatment on normalization of urine alpha 1-M/crea ratio

Results

For group 1, the first urinary alpha 1-M/crea values from samples obtained at a mean (SD) 1.7 days (0.8) of age were a median (range) 33.8 mg/mmol (3.1–255). In five cases (5.8%) the value was already primarily normal (<10 mg/mmol). A significant negative correlation (r =–0.0647,P <0.001) was observed between gestational age and this first urinary alpha 1-M/crea ratio (Fig. 2).

During the median (range) 28-day (1–120) follow-up, the urinary alpha 1-M/crea ratio remained normal in one case, in 42 cases the value first increased and then decreased, and in 47 it progressively decreased compared to the initial level. In 10 cases only one sample was collected. The urinary alpha 1-M/crea ratio was highest at a median (range) 5-day (1–42) age, having a median (range) of 39.1 mg/mmol (9.5–268.9). In 42 infants follow-up was discontinued because of normalization of the urine alpha 1-M/crea ratio and due to hospital discharge in 54 cases. Four infants died before the normalization of the value.

Tubular proteinuria seemed not to be increased with increasing cumulative drug dosage among the cases with antenatal NSAID exposures. Twelve infants had been exposed concomitantly to netilmicin and vancomycin, and the urinary alpha 1-M/crea ratio was elevated in six of these cases.

According to logistic regression analysis, low gestational age (OR 0.263; 95% CI 0.125, 0.551) and the need for inotropes (OR 4.341; 95% CI 1.235, 15.253) remained the risk factors associated with an elevated first alpha 1-M/crea ratio. Low gestational age at the time of sampling (OR 0.614; 95% CI 0.471, 0.799) and a long duration of ventilator treatment (OR 1.650; 95% CI 1.211, 2.247) entailed a risk of reaching the highest quartile maximum alpha 1-M/crea ratio. In Cox regression analysis, low gestational age (OR 0.66; 95% CI 0.474, 0.929) and a long duration of vancomycin medication (OR 1.579; 95% CI 1.068, 2.336) (Fig. 1) were associated with delayed normalization of the alpha 1-M/crea ratio.

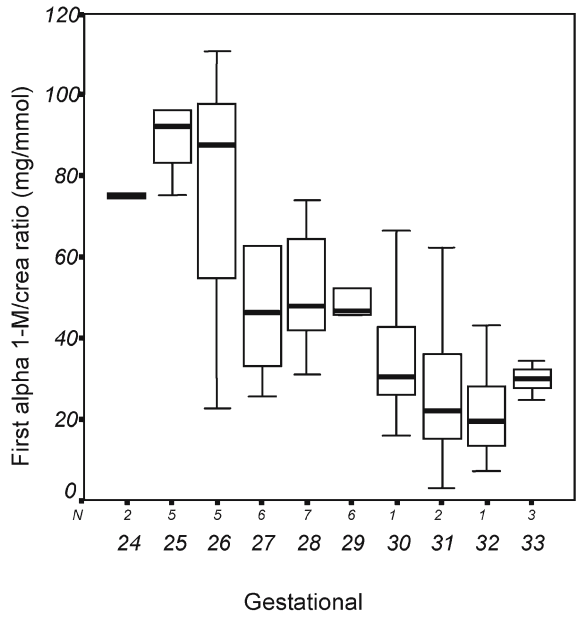

Fig. 2 The relationship between first urine alpha 1-M/crea and gestational age ratio at the time of sampling. *Black lines* denote medians, *boxes* inter-quartile ranges and *line bars* ranges. Six observations lay outside the ranges (not shown)

In group 2, the median (range) urinary alpha 1-M/crea ratio in the sample obtained at a mean (SD) age of 3.0 days (1.3) was 8.4 mg/mmol (1.6–33.1). In altogether 41 (59%) infants, four of them with antenatal NSAID exposure and 37 without exposure had urinary alpha 1-M/crea ratios below the threshold level (P =0.469). The median (range) urinary alpha 1-M/crea ratios were 11.2 mg/mmol (4.9–33.1) in the exposed infants and 7.9 mg/mmol (1.6–23.4) in the non-exposed infants (P =0.084). Even in the infant with the highest cumulative antenatal ketoprofen exposure of 5,000 mg, urinary alpha 1-M/crea was only slightly elevated (12.6 mg/mmol). In the infant who received postnatal netilmicin treatment, the urine alpha 1-M/crea ratio was 15.6 mg/mmol. In these near-term and full-term infants, no relationship between gestational age and urinary alpha 1-M/crea ratio was seen, and no significant risk factors for tubular proteinuria were detected in logistic regression analysis.

Plasma creatinine content, measured at a median (range) age of 36 days (1–120), was 33.5 μmol/l (10–83) in group 1. Serum cystatine C values at 61 days' (23–120) age were a median 1.59 mg/l (range: 1.15–1.92). Renal sonography findings were normal in eight infants. One infant, born at 25 gestational weeks, had mild renal nephrocalcinosis examined at 68 days of age. In group 2, the plasma creatinine value in the asphyxiated infant was 69 μmol/l examined at 1 day age.

Discussion

We here sought the incidence of and risk factors for tubular proteinuria by measuring sequentially urinary alpha 1-M levels after birth during hospitalization in premature infants and the corresponding levels in single spot urine samples in full-term infants. We related alpha 1-M to creatinine in order to reduce the influence of individual urinary excretion variation in the infants. Despite the simple and noninvasive sampling, we failed to secure some samples because of technical problems, which circumstance may have created bias and made data analysis less confirming. The small number of previous studies on the excretion of urinary alpha 1-M, and the fact that in very low birth weight and gestational age categories it is not possible to find healthy controls, caused problems to assess the importance of results. Very immature infants have high morbidity and an increased need of different combinations of pharmacologic treatment. Therefore, the effects on tubular function of immaturity per se cannot be distinguished from the effects of diseases or their treatment, and only indirect conclusions can be made. However, the population studied was fairly large, being a representative group of infants of different gestational ages. Also, the follow-up time was long and the observation of risk factors comprehensive compared with previous studies [17]. Urinary alpha 1-M determination is only one means to assess tubular function and treatment effects on the kidney. Measuring other indicators, including N-acetyl-β-D-glucosaminidase (NAG), beta-2 -microglobulin, P-glycoprotein, creatinine clearance and cystatine C levels, and following up the infants after discharge from the hospital in cases with persisting abnormal alpha 1-M/crea ratios, would have given a more complete picture of the renal function of our cases.

In premature infants we found an inverse correlation between the first urinary alpha 1-M values and gestational age. Also, an increased risk of high maximum tubular proteinuria and slower normalization of alpha 1-M level was seen in the most premature infants. Renal function appears to be decreased, especially at less than 34 weeks' gestation [20]. Renal functional maturation as measured by glomerular indicators, including serum creatinine levels, urinary microalbumin, immunoglobulin G and GFR, or tubular indicators, including fractional excretion of sodium or urinary alpha 1-M, has previously been seen to be closely associated with gestational age [2, 13, 21]. Postnatal maturation of renal glomerular and tubular function has a direct correlation with postnatal age, but it is possible that in most premature infants born at <31 weeks gestational age, postnatal maturation of renal function is delayed, reaching normal status only during early childhood [2, 22, 23, 24]. In preterm infants, maturation of renal function can also be delayed as a result of sickness of the infants [13].

Renal function, especially in preterm infants, is vulnerable to extrinsic effects [8, 25]. Acute renal failure is usually caused by prerenal causes including hypotension [26]. Hypotension itself can stimulate vasoconstrictive mediators such as angiotensin II, cause renal vasoconstriction and hypoperfusion and further reduce already low GFR in the newborn [8, 20, 23]. In addition, dopamine, usually the first inotrope used for the treatment of

hypotension, has a direct effect on renal function via renal dopaminergic receptors located in the renal arteries, glomerules and proximal and distal tubules [27]. At low doses (0.5–2 μg/kg/min) dopamine causes renal vasodilatation and increases GFR and electrolyte excretion [28]. In neonatal care higher doses of dopamine (6–10 μg/kg/min) are needed to achieve systemic cardiovascular effects. Such doses have an opposite effect on renal function, causing renal vasoconstriction and reduction in sodium and water excretion [28]. In contrast, dobutamine seems to have very little impact on renal function [29]. In this study, a long duration of inotrope infusion emerged as a risk factor for tubular proteinuria. As a first-choice inotrope, the duration of dopamine use was in most cases significantly longer than the use of dobutamine. The correlation of inotrope use with tubular proteinuria cannot, however, be distinguished from the effects of hypotension per se.

Mechanical ventilation is associated with decreased creatinine clearance and increased urinary beta-2-microglobulin and fractional sodium excretions in premature infants, although adverse effects on GFR have not been shown [6, 21, 30]. Mechanical ventilation can reduce venous return and cardiac output and can thus cause renal hypoperfusion and impair renal function [8]. Supporting this concept, a long duration of mechanical ventilation was associated with an increased risk of excessive tubular proteinuria as measured by the urinary alpha 1-M/crea ratio in our study. It is also possible that the infants with a prolonged need for ventilatory support have also suffered from prolonged hypoxia, this exerting an adverse effect on the proximal tubule [5, 8].

The nephrotoxicity of vancomycin depends on a transport process from the blood to the renal tubular cell across the basolateral membrane, and presumably at least in part a tubular resorption process is also involved in it [9]. Risk factors reported for vancomycin nephrotoxicity are pre-dose levels of vancomycin >10 mg/l and concomitant treatment with aminoglycosides [9, 31]. In premature infants, especially in those of <29 weeks gestation, vancomycin clearance is initially reduced even if the pharmacokinetic disposition varies, even at the same gestational age [32]. The adverse influence of vancomycin on the normalization of proximal tubular function in preterm infants has not hitherto been described. Here we did not monitor through or peak concentrations of the drug, and our sampling was not scheduled with antibiotic treatment. Our results nonetheless suggest that long courses of vancomycin should be avoided to prevent prolonged tubulotoxicity in preterm infants.

In the present study, netilmicin did not seem to have a statistically significant effect on the normalization of tubular proteinuria. Although tubulotoxicity is a well-known side effect of aminoglycosides, their injurious effects depend on the degree of kidney maturity and the type of aminoglycoside administered [25]. It has indeed been suggested that aminoglycosides might be less nephrotoxic in newborn infants than in adults [9]. In our hospital we use netilmicin, which has been suggested to have low tubulotoxicity even in preterm neonates [25, 33]. The injurious effects of the drugs are reversible, but it might take 20–60 days before biochemical parameters return to normal limits [9]. It would thus seem unlikely that the timing of sampling can have influenced the tubular proteinuria detected in our study.

According to previous work, tubular and glomerular renal function in full-term infants is more mature than in pre-term infants, but also in full-term infants maturation continues after birth [11, 13, 16]. In the healthy term infant, urinary alpha 1-M/crea ratios are higher during the 1st days of life, decreasing during the 1st weeks of life to normal values during the 1st months [16]. Healthy term infants have also been shown to be more tolerant of nephrotoxic drugs than pre-term infants [25], but in critically ill term infants, urinary alpha 1-M excretion is high, the recovery of proximal tubular function occurring rapidly if the infants' conditions return to stable [16]. In this study the full-term infants were stable and in most of them the urinary alpha 1-M/crea ratios were normal, supporting previous reports. Also in the infant with postnatal exposure to netilmicin, the urinary alpha 1-M/crea ratio was only slightly above normal.

Indomethacin use as a tocolytic agent even at cumulative dosages of 150 mg has been proved to have severe adverse effects on the infant if delivery occurs pre-term and within 24–48 h of the last dosage. However, no long-term renal adverse effects have been seen in prematurely born children examined at 2–4 years of age [34, 35]. Although the median time between the last dosage of NSAIDs and delivery was here about 2 days, our results did not indicate any detectable adverse effects of antenatal exposure of NSAIDs either as the development of oliguric symptoms or in the occurrence of tubular proteinuria in pre-term or near- and full-term newborns. Only one pre-term patient had an oliguric episode of about 24 h, without exposure to NSAIDs. The cumulative dosages used in most of our cases were also mostly low, ranging between one to ten times a single dose of each drug. The number of cases receiving each single drug in our study was rather low, but maternal use of low dosages of NSAIDs after 30 weeks of pregnancy would seem to be fairly safe in terms of proximal tubular function of the near-term and full-term neonate.

In conclusion, the urinary alpha 1-M/crea ratio would appear to be a sensitive indicator in the evaluation of adverse effects of treatments on renal tubular function during neonatal intensive care. In pre-term infants low gestational age and the need for inotropes emerged as risk factors for increased tubular proteinuria early after birth, whereas low gestational age and long duration of ventilator treatment were the predictors of the highest urinary alpha 1-M/crea ratios. Long courses of vancomycin seem to have prolonged adverse renal effects in pre-term infants, the risk increasing with decreasing gestational age. Among near- and full-term infants, tubular function is apparently quite mature, and no risk factors for tubular proteinuria were found. The mothers' intake of indomethacin, ibuprofen, ketoprofen or metamizole-pitofe-

none at low cumulative dosages after 30 weeks pregnancy and within 4 weeks before delivery seems not to have any detectable effect on the proximal tubular function of their near-term and full-term infants.

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