A Randomized, Double-Blind, Placebo-Controlled Trial of the Effects of Prophylactic Theophylline on Renal Function in Term Neonates With Perinatal Asphyxia

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ABSTRACT. *Background.* The kidney is the most damaged organ in asphyxiated full-term infants. Experiments in rabbits and rats have shown that renal adenosine acts as a vasoconstrictive metabolite in the kidney after hypoxemia and/or ischemia, contributing to the fall in glomerular filtration rate (GFR) and filtration fraction. Vasoconstriction produced by adenosine can be inhibited by the nonspecific adenosine receptor antagonist, theophylline. Gouyon and Guignard performed studies in newborn and adult rabbits subjected to normocapnic hypoxemia. Their results clearly showed that the hypoxemia-induced drop in GFR could be avoided by the administration of low doses of theophylline.

Objective. This study was designed to determine whether theophylline could prevent and/or ameliorate renal dysfunction in term neonates with perinatal asphyxia.

Setting. Buenos Aires, Argentina.

Study Design. We randomized 51 severe asphyxiated term infants to receive intravenously a single dose of either theophylline (8 mg/kg; study group: $n = 24$) or placebo (control group: $n = 27$) during the first 60 minutes of life. The 24-hour fluid intake and the urine volumes formed were recorded during the first 5 days of life. Daily volume balances (water output/input ratio and weights) were determined. Severe renal dysfunction was defined as serum creatinine elevated above 1.50 mg/dL, for at least 2 consecutive days after a fluid challenge, or rising levels of serum creatinine (.3 mg/dL/day). The GFR was estimated during the second to third days of life by endogenous creatinine clearance (mL/minute/1.73 m2) and using Schwartz's formula: GFR (mL/minute/1.73 m2) = .45 × length (cm)/plasma creatinine (mg/100 mL) during the first 5 days of life. Tubular performance was assessed as the concentration of β2-microglobulin (β2M) determined by enzyme immunoassay, on the first voided urine 12 hours after theophylline administration. The statistical analysis for the evaluation of the differences between the groups was performed with Student's *t* and χ^2 tests as appropriate.

Results. During the first day of life, the 24-hour fluid balance was significantly more positive in the infants receiving placebo compared with the infants receiving theophyline. Over the next few days, the change in fluid balance favored the theophyline group. Significantly higher mean plasma values were recorded in the placebo group from the second to the fifth days of life. Severe renal dysfunction was present in 4 of 24 (17%) infants of the theophylline group and in 15 of 27 (55%) infants of the control group (relative risk: .30; 95% confidence interval: .12–.78). Mean endogenous creatinine clearance of the theophylline group was significantly increased compared with the creatinine clearance in infants receiving placebo (21.84 ± 7.96 vs 6.42 ± 4.16). The GFR (estimated by Schwartz's formula) was markedly decreased in the placebo group. Urinary β2M concentrations were significantly reduced in the theophylline group (5.01 ± 2.3 mg/L vs 11.5 ± 7.1 mg/L). Moreover, 9 (33%) patients of the theophylline group versus 20 (63%) infants of the control group had urinary β2M above the normal limit (<.018).

There was no difference in the severity of the asphyxia between infants belonging to the theophylline and control groups in regards of Portman's score. Except for renal involvement, a similar frequency of multiorganic dysfunction, including neurologic impairment, was observed in both groups.

The theophylline group achieved an average serum level of 12.7 μg/mL (range: 7.5–18.9 μg/mL) at 36 to 48 hours of live versus traces (an average serum level of .87 μg/mg) in the placebo group.

Conclusions. Our data suggest that prophylactic theophylline, given early after birth, has beneficial effects on reducing the renal dysfunction in asphyxiated full-term infants. A single dose of 8 mg/kg of theophylline within the first postnatal hour in term neonates with severe perinatal asphyxia results in a significant decrease in serum creatine and urinary β2M, together with a significant increase in the creatine clearance. The potential clinical relevance of the data would be the avoidance of the contributory role of hypoxemia in the development of acute renal failure. Additional studies will be necessary before the use of theophylline in asphyxiated newborns can be considered for clinical practice. *Pediatrics* 2000;105(4). URL: http://www.pediatrics.org/cgi/content/full/105/4/e45; *perinatal asphyxia, theophylline, renal function.*

Fetal and neonatal asphyxia are the primary causes of transient renal impairment or acute renal failure (ARF) in neonates.[1,2] Circulatory adaptive responses to perinatal asphyxia may lead to renal injury as a consequence of decreased perfusion of the kidney.[3,4] Recently, Gunn et al[5] reported that

all the infants with hypoxic-ischemic encephalopathy included in their study developed signs of ARF. A persistent tubular dysfunction at 1 year old has been described in infants with a neonatal history of renal failure associated with asphyxia.[6]

The study of the protection of renal adverse effects of hypoxemic and/or ischemic impairments has been the focus of numerous investigations. Experimental data obtained from animal models suggest that various pharmacological agents, such as methylxanthines,[7] calcium entry blockers,[8] and atrial natriuretic peptide,[9] are effective in the prevention of renal impairment associated with hypoxemia.

Experiments in rabbits[10] and rats[11] have shown that renal adenosine acts as a vasoconstrictive metabolite in the kidney after hypoxemia and/or ischemia, contributing to the fall in glomerular filtration rate (GFR) and filtration fraction (FF).[12] Vasoconstriction produced by adenosine can be inhibited by the nonspecific adenosine receptor antagonist, theophylline.[13]

Gouyon and Guignard[7] performed studies in newborn and adult rabbits subjected to normocapnic hypoxemia. Their results clearly showed that the hypoxemia-induced drop in GFR could be avoided by the administration of low doses of theophylline. To determine whether theophylline could prevent and/or ameliorate the renal dysfunction in term infants with severe asphyxia, we designed a randomized, multicenter, double-blind, placebo-controlled trial.

METHODS

Infants eligible for study admission were of term or postterm gestation and had severe birth asphyxia manifested by: 1) history of fetal distress (late decelerations, decreased heart rate variability, or bradicardia (<100 beats/minute with or without meconium stained amniotic fluid); 2) 5-minute Apgar score of 6 or lower; 3) base deficit equal to or greater than 15 mEq/L in cord blood or admission arterial blood sample; and 4) requirement of immediate neonatal ventilation with mask or traqueal tube for >2 minutes after delivery.

Exclusion criteria applied on infants were: 1) any condition that was abnormal or unrelated to asphyxia; 2) small for gestational age; 3) congenital abnormalities of kidneys and/or urinary tract; 4) cardiovascular pathology not related to prenatal asphyxia; 5) prenatal or neonatal exposure to medications that might have modified renal hemodynamics and renal function; 6) polycythemia; 7) clinical evidence of potential antenatal injury, ie, microcephaly, multiple pregnancy, hypothyroidism, or chromosomal disorders; and 8) pharmacological depression.[14]

The study population included infants born at 3 hospitals of Buenos Aires, Argentina (Hospital Italiano, Sanatorio Güemes, and Clínica Maternal Lomas).

Infants were managed according to an identical special protocol approved by the local ethics committees of each hospital.

After parental consent was obtained, infants were randomized by sequential computer-generated numbers to receive intravenously a single dose of either theophylline (8 mg/kg; 1.6 mL/kg) or an equal volume of placebo (5% dextrose in water). The loading infusion was administrated as soon as possible after admission to the neonatal intensive care unit over a 5-minute period within the first hour after birth. Investigators and caregivers were blinded to the assignment of the patient. Preparation of both treatment and placebo drugs were provided by Phoenix Pharmaceutical (Buenos Aires, Argentina) in vials with the same external appearance and placed in consecutive numbered sealed opaque envelops based on a randomized table with predetermined group allocation.

The theophylline dose selected for this trial was based on studies by Kelly and Shannon[15] that used a 7.5-mg/kg dose in

term newborns with apnea without finding adverse side effects, except for vomiting in 2 patients.

The Score of Portman et al[16] was used to determine the severity of the asphyxia and to assess whether patients belonging to both groups had potentially the same multiorganic risk predictability. The score (range: 0–9) was based on fetal heart rate, 5-minute Apgar score, and base deficit in the first hour of life. According to Portman et al,[16] the score for severe asphyxia was defined as >6 and for moderate asphyxia as <5.

The indication for treatment of hypotension was a systemic mean arterial blood pressure <45 mm Hg.[17]

Infants initially received an intravenous infusion of D10W at a rate of 60 mL/kg/day. Fluid and electrolyte intake was subsequently adjusted as indicated by the clinical status of each patient. After a poor response of a reduced urine output with a fluid challenge, a 2-mg/kg dose of furosemide was given. Fluid restriction was instituted in the infants with oliguric renal failure.

The 24-hour fluid intake and the urine volumes formed were recorded during the first 5 days of life. Hourly urinary output was carefully collected by attaching a urine bag to the perineum or was measured via a urine catheter. The spilled urine was measured by weighing the diapers. All fluid volume infusions, transfusions, and medications administered were recorded. Daily volume balances (water output/input ratio and weights) were determined.

Body weight was measured on admission to the unit and then every 24 hours for the first week of life.

To assess renal function, we determined daily serum creatinine levels (Yaffe method, Astra, Beckman) and electrolytes in the first week of life; 12-hour urine collections were obtained between the second and third days of life to evaluate urine creatinine levels and electrolytes.

The GFR was estimated during the second to third days of life by endogenous creatinine clearance (mL/minute/1.73 m2) and also using Schwartz's formula[18]: GFR (mL/minute/1.73 m2) = .45 × length (cm)/plasma creatinine (mg/100 mL) during the first 5 days of life.

Criteria for post asphyxia severe renal dysfunction were: a serum creatinine elevated above 1.50 mg/dL, for at least 2 consecutive days after a fluid challenge consisting of a total of 20 mL/kg of normal saline, or rising levels of serum creatinine (.3 mg/dL/day). These values are according to literature data[1,17] and also correspond to +2 standard deviation over mean normal standard value that we obtained from 55 healthy neonates born at a gestational age of >37 weeks (unpublished data). Oliguria was defined as a urine output of <1 mL/kg per hour for at least 24 hours, based on our experience and literature data.[19]

Hematuria was assessed using standard dipstick reagent strips (Multistix, Bayer Diagnostics, Buenos Aires, Argentina).

Tubular performance was assessed as the concentration of β2-microglobulin (β2M) determined by enzyme immunoassay (Enzygnost (R) − β2M), on the first voided urine 12 hours after theophylline administration. All urine samples were collected before the administration of the first dose of aminoglycoside antibiotics. Suprapubic compression was performed at the beginning of each urine collection to ensure that the urine preserved in the bladder had not been formed before the inutero asphyxia event. Urine samples were frozen promptly and stored at −20°C until determinations were performed. Our data from healthy infants showed that the 95% confidence limit (mean + 2 standard deviation) for urinary β2M concentration was 3.8 mg/L.[20] We used this value as the upper limit of normal. Our data were consistent with those reported by Tack et al[21] who found that the 95% confidence limit for β2M concentrations in healthy infants was 4.00 mg/L on the first voided specimens.

Serum theophylline levels were determined at 36 to 48 hours of life.

Continuous variables with normal distribution were analyzed by Student's t test. The χ^2 test was used for analysis of discrete data. Differences were considered significant at $P < .05$. The results are reported as mean ± standard deviation.

RESULTS

General Features

During a 74-month study, 60 consecutive patients met the entry criteria of severe birth asphyxia. Nine of these infants were excluded: 4 because of congen-

TABLE 1. Clinical Characteristics on the First Day of Life in the Two Groups of Asphyxiated Neonates*

	Theophylline Group $n = 24$	Placebo Group $n = 27$	P Value
Birth weight (g)	3.256 ± 309	3.387 ± 376	.99†
Gestation age (wk)	39.3 ± 1.6	39.4 ± 1.4	.81†
Cesarean section (%)	14 (58)	13 (48)	.46‡
Meconium staining of amniotic fluid (%)	17 (70)	18 (67)	.98‡
Initial arterial blood gases values			
pH	7.04 ± .13	7.02 ± .17	.64†
Base excess (mEq/L)	−18.32 ± 2.45	−19.15 ± 4.07	.38†
Asphyxia score >6 (%)	18 (75)	21 (77)	.92‡
Age of starting loading infusion of theophylline or placebo (m)	45 ± 7	38 ± 5.0	.24†
Inotropic agents infused (%)	14 (58)	17 (63)	.96‡
Mean blood pressure (mm Hg; 12 h of life)	51 ± 8	49 ± 6	.31†

* Values are expressed as mean ± standard deviation.
† Student's t test.
‡ Values calculated from χ^2 analysis (Yate's correction).

ital malformations, 2 because of pharmacological depression, 1 because of maternal heroin addiction, 1 because the mother died just after delivery, and 1 because the mother had renal failure with a serum creatinine value of 2.1 mg/dL. Fifty-one asphyxiated term infants were enrolled in the study. Twenty-four infants randomized were assigned to the theophylline group, and 27 to the placebo group.

Intubation was performed in 41 patients; biochemical resuscitation in 28.

There were no significant differences in birth weight, gestational age, sex, cesarean rate, presence of meconium-stained amniotic fluid, individual components of the asphyxia morbidity score (fetal heart rate, 5-minute Apgar score, and base excess), arterial blood pH, and blood pressure. No infants were breech or small for gestational age (<10th percentile). Each group received either theophylline or an equal volume of placebo at similar chronological ages (45 ± 7 vs 38 ± 5.0 minutes; Table 1).

Four of these critically ill infants died. One patient belonging to the theophylline group died from persistent pulmonary hypertension. There were 3 neonatal deaths in the placebo group: 2 of them attributable to multisystemic organ failure, and 1 caused by overwhelming sepsis.

All asphyxiated infants required respiratory support; none hyperventilated. Involvement of 1 or more organs occurred in 75% of the infants. Central nervous system (CNS) involvement (seizures, transient cerebral irritability, and feeding problems) occurred in 38 (74%) of the infants. Clinical seizures required treatment with anticonvulsants in 13 control infants and 9 infants receiving theophylline. Pulmonary involvement (meconium aspiration, persistent pulmonary hypertension, and mild respiratory distress syndrome) was evidenced in 18 (35%) infants. Seven infants had abnormal echocardiographic findings (tricuspid or mitral regurgitation and/or myocardial dyskinesia not affecting ventricular output). Gastrointestinal involvement (bloody stools, necrotizing enterocolitis, and bilious residuals) occurred in 11 (21%) infants. We found no significant differences in frequency and severity of CNS, pulmonary, heart, and gastrointestinal involvement between the 2 groups. However, severe renal dysfunction was present in 4 (17%) infants of the theophylline group and in 15 (55%) of the control group (relative risk: .30; 95% confidence interval: .12-.78; $P < .001$; Fig 1).

Renal Evaluation

Table 2 summarizes the balances during the first 5 days of life in the 2 groups of asphyxiated neonates. During the first day of life, the 24-hour fluid balance was significantly more positive in the infants receiving placebo compared with the infants receiving theophylline. Over the next days, the change in fluid
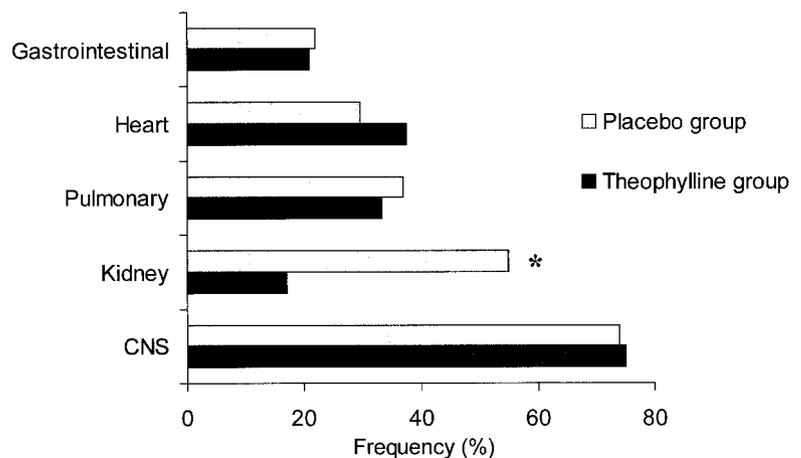

Fig 1. The frequency of organ involvement for the 2 groups of asphyxiated neonates.

* p = .001

Days of Life	Water Output/Input Ratio		P Value	Weight		P Value*
	Theophylline Group	Placebo Group		Theophylline Group	Placebo Group	
1	.23 ± .18	.71 ± .3	<.001	3.190 ± 301	3.481 ± 383	.004
2	1.45 ± .11	.36 ± .8	<.001	3.126 ± 293	3.421 ± 368	.003
3	1.6 ± .55	.92 ± .6	<.001	3.050 ± 289	3.319 ± 364	.005
4	1.38 ± .6	1.7 ± .54	.05	2935 ± 106	3097 ± 389	.047
5	NE	NE		3019 ± 284	3107 ± 401	.375

NE indicates not evaluated in all the patients.
* Student's *t* test.

balance favored the theophylline group. The diuretic response was significantly greater in the theophylline group (Fig 2). On the first day of life, plasma creatinine values were similar in the 2 groups, but significantly higher mean plasma creatinine values were recorded in the placebo group from the second to the fifth days of life (Table 3). During the second to the third days of life, mean endogenous creatinine clearance (mL/minute/1.73 m2) of the theophylline group was significantly increased compared with the creatinine clearance in infants receiving placebo (21.84 ± 7.96 vs 8.42 ± 4.16; $P < .001$). The GFR (estimated by Schwartz's formula) were markedly decreased in the placebo group (Table 3). No difference was found in sodium excretion obtained from 12-hour urine collections between the second and third days of life in the theophylline group with respect to the control group (45 ± 55 mEq/L vs 57 ± 49 mEq/L; $P = .24$). Urinary $\beta2M$ concentrations were significantly reduced in the theophylline group (5.01 ± 2.3 mg/L vs 11.5 ± 7.1 mg/L; $P = .005$). Moreover, 9 (33%) patients of the theophylline group versus 20 (63%) infants of the control group had urinary $\beta2M$ above the normal limit ($P < .018$).

Dipstick testing for hematuria over the first 3 days of life demonstrated large blood on at least one occasion in 15 of 24 in the theophylline group and 19 of 27 in the control group ($P = .766$).

Serum Theophylline Levels

The theophylline group achieved an average serum level of 12.7 μg/mL (range: 7.5–18.9 μg/mL) at 36 to 48 hours of life versus traces (an average serum level of .87 μg/mg) in the placebo group.

DISCUSSION

Our findings indicate that treatment with a single dose of 8 mg/kg of theophylline within the first postnatal hour in term neonates with severe perinatal asphyxia results in a significant decrease in serum creatinine and urinary $\beta2M$, together with a significant increase in the creatinine clearance. In addition, the present study shows that using theophylline in neonatal asphyxia helps to reduce the severe renal dysfunction. All infants reported in this study were critically ill according to their immediate postpartum conditions and exhibited numerous signs of multisystemic dysfunction.

The kidney is the most damaged organ in asphyxiated full-term infants.[2,22] Acute hypoxemia is associated with an increase in renal vascular resistance and a decrease in GFR and FF.[23] During oxygen deficit, when adenosine triphosphate hydrolysis prevails over adenosine triphosphate synthesis, adenosine (a direct degradative product of 5'adenosine monophosphate) increases and activates its receptors resulting in an increment of the renal vascular resistance (preglomerular vasoconstriction and postglomerular vasodilatation) thus decreasing GFR and FF.[24]

Hemodynamic renal changes produced by adenosine were observed during ischemic or hypoxemic experimental studies.[25] Moreover, adenosine admin-
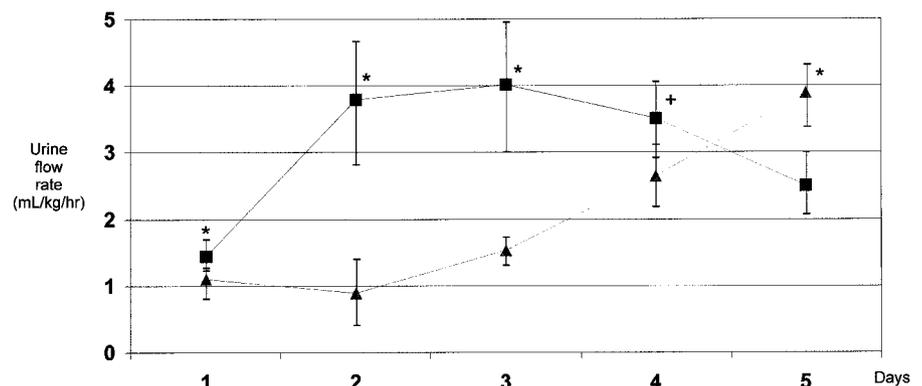

Fig 2. Diuretic expressed as rate of urine formation in mL/kg/hour (mean ± standard deviation). Theophyline group (filled boxes) and placebo group (filled triangles).

* p < .001
+ p: .03

TABLE 3. Renal Evaluation: The GFR (Estimated by Schwartz's Formula) and Plasma Creatinine in the First Five Days of Life in the Two Groups of Asphyxiated Neonates*

Days of Life	Glomerular Filtration Rate		P Value	Plasma Creatinine (mg/dL)		P Value†
	Theophylline Group	Placebo Group		Theophylline Group	Placebo Group	
1	23.17 ± 10.3	22.07 ± 9	.68	1.0 ± .3	1.05 ± .4	.62
2	24.01 ± 8.6	14.9 ± 6.8	<.001	.97 ± .17	1.51 ± .41	<.001
3	25.94 ± 11.2	11.36 ± 5.1	<.001	1.02 ± .69	1.94 ± 1.1	<.001
4	27.29 ± 9.1	32.41 ± 7.4	<.03	.89 ± .7	1.59 ± .7	<.001
5	32.41 ± 7.4	18.0 ± 9.8	<.001	.71 ± .2	1.36 ± .9	<.001

* Values are expressed as mean ± standard deviation.
† Student's test.

istrated into the renal artery led to decreased GFR[26] in humans.

Adenosine receptor antagonists like theophylline can inhibit renal vasoconstriction in response to exogenous and endogenous adenosine and have been successfully used to improve renal function after experimental ARF induced by glycerol,[27] endotoxin,[28] and radiocontrast administration in several animal models.[29] It has been observed in rats that theophylline attenuates the extent of GFR reduction when it is administrated during maintenance phase of post-ischemic ARF.[30] Kemper[31] demonstrated in anesthetized rats that administration of theophylline (8mg/kg), before adenosine infusion, prevents a sharp fall in glomerular filtration in comparison to adenosine alone. Gouyon and Guignard[7] demonstrated in newborn and adult animals that the fall in glomerular filtration induced by hypoxemia can be prevented by theophylline in low doses. These authors used rabbits as a animal model that showed, in hypoxemia episodes, renal changes similar to those observed in human hypoxemic newborns. Used commonly for apnea of prematurity, theophylline has also been shown to prevent both the reduction of GFR after contrast media application in humans and the renal insufficiency induced by hypoxemia in newborns with respiratory distress syndrome.[32,33]

In our study, the incidence of glomerular dysfunction and proximal tubular damage, evidenced by elevated serum creatinine concentrations and high urinary levels of β2M, respectively, were considerably lower in the group receiving theophylline. The mechanism by which the administration of theophylline results in lower serum creatinine and better diuresis could be attributable, at least in part, to an increase in GFR explained by the adenosine blockade.[36] Moreover, daily fluid balance was significantly more negative in the theophylline group. The GFR was estimated by endogenous creatinine clearance and using Schwartz's formula. With both methods, we obtained significantly increased values in the theophylline group. Zacchello et al[35] concluded that Schwartz's formula provides an adequate estimation of neonatal creatinine clearance as a marker for GFR in neonatal asphyxia. Although the levels of urine sodium showed no difference between the 2 groups, these results need to be interpreted with caution because it is known that theophylline causes natriuresis.[34] Theophylline levels were within the therapeutic range in patients of the theophylline group and no side effects were observed.

In newborn asphyxiated piglets, a supply of 8 mg/kg of theophylline attenuates in a nonsignificant way the increase in brain circulation that normally takes place in hypoxia episode.[36] It has been reported that pretreatment of rats with aminophylline in experimental cerebral ischemia reduced the mortality rate from 56% to 10%.[37] Bona et al[38] showed that acute treatment with adenosine A1 antagonist before hypoxic-ischemic reduces brain damage in rat pups. Significant cerebroprotection was reported in newborn rats by potentiation of endogenous extracellular adenosine levels with either the adenosine deaminase inhibitor deoxycoformycin or the adenosine transport inhibitor propentofylline.[39] However, we found no significant differences in the incidence of CNS involvement and seizures between the 2 groups of asphyxiated neonates.

CONCLUSION

Our data suggest that prophylactic theophylline treatment, given early after birth, has beneficial effects reducing the renal involvement in asphyxiated full-term infants, with no significant changes in CNS involvement. The potential clinical relevance of these data would be the avoidance of the contributory role of hipoxemia in the development of ARF. Additional and larger studies will be necessary before the use of theophylline in asphyxiated newborns can be considered for clinical practice.

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