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Effects of theophylline on renal insufficiency in neonates with respiratory distress syndrome

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Abstract We report here 6 cases of critically ill newborn infants with both RDS and acute renal insufficiency, unresponsive to conventional treatment (furosemide, dopamine). Theophylline, an adenosine antagonist, has been shown to prevent hypoxemia-induced renal insufficiency in rabbits and our patients thus received compassionately a low-dose of theophylline ($1\ mg \cdot kg^{-1}$ IV). Urinary water excretion and creatinine clearances increased significantly in 5 out of 6 neonates, thus suggesting a beneficial role of theophylline in neonatal prerenal failure.

Key words Renal insufficiency · Prerenal failure · Vasomotor nephropathy · Hypoxemia · Theophylline · Newborn infant

Introduction

Prerenal failure is frequently encountered in neonates with respiratory distress syndrome (RDS) [1]. This clinical condition is characterized by renal hypoperfusion and decreased glomerular filtration rate along with a decline in urinary water and sodium excretion. Neonatal vasomotor nephropathy has been ascribed to the occurrence of hypoxemia, acidosis, hypovolemia, systemic hypotension or to the concomitant use of vasoactive drugs such as tolazoline or indomethacin [2].

The conventional treatment of prerenal failure presently includes correction of acidosis, hypoxemia, hypovolemia, systemic hypotension, and the administration of furosemide and/or low-dose dopamine ($2-4\ \mu g \cdot kg^{-1} \cdot min^{-1}$) [3]. However, conventional treatment may fail, thus leading to the need of extrarenal epuration by techniques (peritoneal dialysis, hemofiltration and hemodiafiltration) which all carry a substantial risk [4].

Low-dose theophylline ($0.5-1\ mg \cdot kg^{-1}$), an adenosine antagonist, has been shown to prevent hypoxemia-induced renal insufficiency in both adult and newborn rabbits [5]. Higher theophylline doses have been safely administered to neonates for treatment of idiopathic apnea. Zakkaudin et al. [6] found that theophylline ($5\ mg \cdot kg^{-1}$) induced an increase in glomerular filtration rate in a group of otherwise healthy preterm infants treated for apnea of prematurity. Therefore, we compassionately administered low-dose theophylline ($1\ mg \cdot kg^{-1}$) to 6 critically ill newborn infants presenting both RDS and acute renal insufficiency which was unresponsive to conventional treatment, in order to avoid extracorporeal epuration.

Methods

All neonates who received theophylline for renal insufficiency in the NICU of Dijon (France) from 1988 to 1992 were included in this report. Urinary collections (12 h) were obtained before and after theophylline administration. Urine was collected by attaching a U-bag to the perineum. Suprapubic compression was performed at the end of each collection to ensure that the bladder was empty. Blood samplings were performed at the midpoint of each period as part of the routine management of the patients. The short-term effects of theophylline on urine flow rate, water output/input ratio and

creatinine clearance were assessed by comparing the 12 h-periods preceding and following theophylline administration. Water and sodium intakes remained unmodified during the two periods. Plasma and urinary creatinine concentrations were measured by the Jaffe method (Astra, Beckman).

Case Reports

Case 1

This male premature infant was born by vaginal delivery at 28 weeks gestational age (GA), with a 1200 g birth weight. Apgar score was 5 and 9 at 1 and 5 min, respectively. The patient developed a severe RDS and required mechanical ventilation. On day 3, systemic hypotension was associated with mixed acidosis and oliguria. The infant was administered human albumin ($0.5\,g \cdot kg^{-1} \times 2$), dopamine ($2.5\,\mu g \cdot kg^{-1} \cdot min^{-1}$), dobutamine (7.5 to $10\,\mu g \cdot kg^{-1} \cdot min^{-1}$), sodium bicarbonate ($2\,mmol \cdot kg^{-1} \times 2$) and furosemide ($1\,mg \cdot kg^{-1} \times 2$). The intakes of fluids and sodium were respectively $110\,ml \cdot kg^{-1} \cdot d^{-1}$ and $2.2\,mmol \cdot kg^{-1} \cdot d^{-1}$. In spite of blood pressure normalization, urine flow rate remained low (Table 1) with a water output/input (O/I) ratio of 0.24 and fractional excretion of sodium (FENa) of 3.2%. Renal echography showed cortical hyperechogenicity with a decreased cortico-medullary differentiation.

On day 4, a single dose of theophylline ($1\,mg \cdot kg^{-1}$) was infused intravenously, 24 h after the onset of oliguria. This infusion was followed by a dramatic increase in urine flow rate (multiplied by 15), O/I ratio (multiplied by 15.4) and creatinine clearance (multiplied by 1.75) (Table 1). The infant died 5 days later from irreversible respiratory acidosis. The histological findings (autopsy) showed normal kidneys.

Case 2

This male premature infant was delivered at 36 weeks GA by emergency caesarean section, because of maternal pre-eclampsia and fetal distress. Birth weight was 2700 g. Apgar score was 2, 4 and 2 at 1, 5 and 10 min, respectively. The baby had multiple (pulmonary, cerebral, renal and mesenteric) organ failure due to severe peri natal asphyxia and required mechanical ventilation. On day 2, glomerular filtration rate was low ($6.73\,ml \cdot min^{-1} \cdot 1.73\,m^{-2}$) for conceptional age [7]. FENa was 1.8%. Renal echography was normal. Fluids and sodium intakes were respectively $80\,ml \cdot kg^{-1} \cdot d^{-1}$ and $1.5\,mmol \cdot kg^{-1} \cdot d^{-1}$. Blood pressure was in the normal range for age. Treatment with human albumin ($0.5\,g \cdot kg^{-1}$), dopamine ($5\,\mu g \cdot kg^{-1} \cdot min^{-1}$) and furosemide ($1\,mg \cdot kg^{-1} \times 3$) did not improve creatinine clearance but slightly enhanced diuresis to subnormal values ($2.08\,ml \cdot kg^{-1} \cdot h^{-1}$). This acute renal insufficiency was associated with gross edema and hemodilution. Thus, theophylline was administered in order to increase urinary water excretion.

On day 3, urine flow rate, O/I ratio and creatinine clearance increased after the infusion of $1\,mg \cdot kg^{-1}$ theophylline (multiplied by 3.1, 2.8 and 2.6, respectively) (Table 1). This infant developed severe multifocal leukoencephalopathy and died one month later.

Case 3

This female premature infant was born at 33 weeks GA by caesarean section, because of uterine apoplexy. Birth weight was 2250 g. Apgar score was 3, 5 and 5 at 1, 5 and 10 min, respectively. The infant developed severe RDS associated with persistent pulmonary arterial hypertension and decreased systemic blood pressure. On day 2, tolazoline ($0.3\,mg \cdot kg^{-1} \cdot h^{-1}$), dopamine ($15\,\mu g \cdot kg^{-1} \cdot min^{-1}$), dobutamine ($7.5\,\mu g \cdot kg^{-1} \cdot min^{-1}$) and epinephrine ($0.1\,\mu g \cdot kg^{-1} \cdot min^{-1}$) were administred. Blood pressure was normalized and subsequently ramained stable. Renal insufficiency was disclosed on day 3 by a plasma creatinine increase (108 to 153 $\mu mol \cdot l^{-1}$). Renal echography performed before theophylline administration demonstrated cortical hyperechogenicity. During the 12 h period preceding theophylline administration, the mean urinary water excretion was $1.96\,ml \cdot kg^{-1} \cdot h^{-1}$ (Table 1) but complete anuria was observed in the last 6 h of this period. Administration of a single dose of intravenous theophylline ($1\,mg \cdot kg^{-1}$) on day 4, was followed by a dramatic increase in diuresis and an improvement in creatinine clearance (multiplied by 1.94 and 6.40, respectively). The baby was weaned from the ventilator after 4 days and made an uneventful recovery.

Case 4

This small for gestational age female infant was born at 32 weeks by caesarean section because of acute fetal distress. Birth weight

Table 1 Water output/input ratio (*O/I*), urine flow rate (*V*) and creatinine clearance (*Ccr*) in 5 patients with non anuric renal insufficiency responsive to theophylline infusion. Renal functions were assessed over the 12 h preceding and following theophylline infusion and were statistically compared using the Wilcoxon signed rank test. A 6th patient with acute renal failure did not respond to theophylline and is not included in the table

Patients	GA	Diagnosis	Before theophylline			After theophylline		
			O/I	V	Ccr	O/I	V	Ccr
1	28	RDS	0.24	0.93	3.20	3.70	14.00	5.60
2	36	MOF	0.60	2.08	6.73	1.70	6.53	17.62
3	33	RDS-PPHN	0.93	1.96	2.25	1.16	3.80	14.40
4	32	MOF	0.32	1.00	1.46	0.70	2.20	2.49
5	38	RDS	0.57	2.40	2.80	0.85	3.85	3.30
Mean			0.53	1.67	3.29	1.62*	6.08*	8.69*
±SE			±0.12	±0.30	±0.91	±0.55	±2.10	±3.08

* = $p < 0.05$ Significant difference when comparing renal values obtained after theophylline infusion with basal values of the same variables

GA Gestational age (weeks); *O/I* water output/input ratio; *V* urine flow rate ($ml \cdot kg^{-1} \cdot h^{-1}$); *Ccr* creatinine clearance ($ml \cdot min^{-1} \cdot 1.73\,m^{-2}$); *RDS* respiratory distress syndrome; *NBI* neonatal bacterial infection; *MOF* multiple organ failure; *PPHN* persistent pulmonary hypertension of the newborn

was 920 g. The Apgar score was 1 at 1 min and the infant required immediate tracheal intubation. This patient had multiple organ failure (RDS, acute oliguric renal failure and systemic hypotension). Renal echography showed cortical hyperechogenicity. Treatment included mechanical ventilation, dopamine ($5\ \mu g \cdot kg^{-1} \cdot min^{-1}$) and epinephrine ($0.2\ \mu g \cdot kg^{-1} \cdot min^{-1}$) administration. On day 4, creatinine clearance was low for conceptional age (Table 1) [7]. FENa was 1.9%. At that time, hemodilution required a decrease in water and sodium intakes to $75\ ml \cdot kg^{-1} \cdot d^{-1}$ and $2.3\ mEq \cdot kg^{-1} \cdot d^{-1}$, respectively. Intermittent intravenous furosemide ($1\ mg \cdot kg^{-1} \times 4$) administration and subsequent continuous furosemide infusion ($4\ mg \cdot kg^{-1} \cdot d^{-1}$) failed to improve oliguria (Table 1).

On day 5, an intravenous $1\ mg \cdot kg^{-1}$ theophylline dose was followed by an increase in diuresis ($\times 2.20$) and creatinine clearance ($\times 1.71$). On day 6, the infant died from massive intraventricular haemorrhage.

Case 5

This 3600 g birth weight male infant was born at 38 weeks GA. Apgar score was 2 and 7 at 1 and 5 min, respectively. The patient developed severe RDS complicated by bilateral pneumothoraces and persistent pulmonary hypertension. The occurrence of refractory hypoxemia led to extracorporal membrane oxygenation on day 4. On day 9, this infant presented oliguric acute renal failure ($1.04\ ml \cdot kg^{-1} \cdot h^{-1}$) associated with renal cortical hyperechogenicity. Diuresis attained $2.40\ ml \cdot kg^{-1} \cdot h^{-1}$ by infusing $10\ mg \cdot kg^{-1} \cdot d^{-1}$ of furosemide but creatinine clearance remained very low for conceptional age (Table 1) [7]. Diuresis was not sufficient to avoid edema, rapid weight gain (+18% from day 9 to day 10) and hemodilution.

On day 10, a single theophylline dose of $1\ mg \cdot kg^{-1}$ was followed by an increase in urine flow rate and creatinine clearance ($\times 1.60$ and $\times 1.18$) (Table 1). The infant died on day 30 from massive pulmonary embolism.

Case 6

This male premature infant was born at 29 weeks GA with a 1100 g birth weight. Apgar score was 9, 10 and 10 at 1, 5 and 10 min, respectively. The patient had severe RDS, neonatal *E. coli* infection, systemic hypotension and anuria. Renal echography showed cortical hyperechogenicity. Conventional treatment of systemic hypotension and anuria included the administration of albumin ($0.5\ g \cdot kg^{-1} \times 2$), dopamine ($2.5\ \mu g \cdot kg^{-1} \cdot min^{-1}$), dobutamine ($7.5\ \mu g \cdot kg^{-1} \cdot min^{-1}$) and furosemide ($3 \times 1 mg \cdot kg^{-1}$). Fluid and sodium intakes were respectively $110\ ml \cdot kg^{-1} \cdot d^{-1}$ and $3\ mmol \cdot kg^{-1} \cdot d^{-1}$. While blood pressure normalized, anuria persisted. On day 3, theophylline infusion ($1\ mg \cdot kg^{-1}$ i.v.) also failed to restore diuresis. On day 4, the baby died from refractory hypoxemia and respiratory acidosis.

Discussion

All infants reported in this study were critically ill and each presented with one or several etiological factors of prerenal failure (birth asphyxia, systemic hypotension or tolazoline administration). Basal creatinine clearance were low for conceptional age (Table 1) [7] reflecting a low glomerular filtration rate as described by Guignard et al. in severe RDS [1]. Renal echography performed before theophylline infusion excluded obstructive nephropathy and showed cortical hyperechogenicity in 5 out of 6 newborn infants. This pattern has been associated with changes in renal perfusion [8]. Because renal insufficiency was unresponsive to conventional treatment, a single low dose of theophylline ($1\ mg \cdot kg^{-1}$) was compassionately administered in order to avoid extrarenal epuration. This was followed by a significant increase in urine flow rate and O/I ratio (Table 1) in 5 out of 6 patients. No side effect was observed. The improvement in diuresis could be due at least, in part, to an increase in glomerular filtration rate as suggested by the increase in creatinine clearances. It is noteworthy that complete anuria was only observed in patient no. 6 and was irresponsive to theophylline. This therapeutic failure could be due to parenchymal renal insufficiency.

Experimental studies strongly suggest that intrarenal adenosine plays a key role in the hemodynamic renal changes observed during an ischemic or hypoxemic stress [5, 9]. Adenosine enhances angiotensin II-induced preglomerular vasoconstriction, while dilating postglomerular vessels thus decreasing glomerular filtration rate and filtration fraction [10]. We have recently shown that low-dose intravenous theophylline ($0.5-1\ mg \cdot kg^{-1}$), allowing micromolar serum concentrations to antagonize adenosine receptors, avoids hypoxemia-induced vasomotor nephropathy in both adult and newborn rabbits.

These overall data suggest that endogenous renal adenosine participates in renal insufficiency observed in RDS. These preliminary results await prospective studies in order to assess the beneficial effects of low-dose theophylline in infants suffering prerenal insufficiency.

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ANNOUNCEMENTS

1995

16th International Symposium on Current Problems in Emergency and Intensive Care Medicine 1995

28 June–1 July, Münster, Germany
Information: Prof. Dr. P. Lawin, FCCM, Klinik und Poliklinik für Anaesthesiologie und Operative Intensivmedizin, Westfälische Wilhelms-Universität, Albert-Schweitzer-Strasse 33, D-48149 Münster, Germany
Tel.: +49-251-837252/53
Fax: +49-251-88704

3rd International Congress of the Society of Organ Sharing

17–19 July, Paris, France
Information: Secretariat Office, France-Transplant, Hôpital St. Louis, 1 Avenue Claude Vellefaux, F-75475 Paris Cedex 10, France
Fax: +33-1-4206-9490

24th Central European Anaesthesia Congress

4–8 September, Vienna, Austria
Information: Udo M. Illievich, MD, Secretary, P.O. Box 52, A-1097 Vienna, Austria
Fax: +43-1-406-4811

Mechanical Circulatory Support '95 – 5th International Symposium

7–9 September, Bad Oyenhausen, Germany
Information: Ms. Susanne Traut, Herzzentrum NRW, Klinik für Thorax- und Kardiovaskularchirurgie, Georgstrasse 11, D-32545 Bad Oeynhausen, Germany
Tel.: +49-5731-971333

7th European Congress on Pediatric, Surgical and Neonatal Intensive Care

25–29 September, Cambridge, UK
Information: ESPIC/IBC Technical Services Ltd., Gilmoore House, 57–61 Mortimer Street, London W1N 8JX, UK
Tel.: +44-171-637-4383
Fax: +44-171-631-3214

8th European Congress on Intensive Care Medicine

18–22 October, Athens, Greece
Information: Prof. Ch. Roussos (Organizing Committee President), Evangelismos Hospital, Critical Care Department, 45–47 Ipsilandou St., GR-10676 Athens, Greece
Tel.: +301-360-9511-15 or 360-9552
Fax: +301-360-7962

International Symposium: 66 Years of Surfactant Research

5–10 November. The scientific sessions will be held at the universities of Vienna and Budapest with poster sessions on board ship. Accommodation will be on board ship from Passau (Germany) along the river Danube via Vienna (Austria) to Budapest (Hungary).
Information: Prof. Dr. B. Lachmann, Department of Anaesthesiology, Erasmus University Rotterdam, P.O. Box 1738, NL-3000 DR Rotterdam, The Netherlands
Phone: +31-10-4087-312
Fax: +31-10-4367-870

International Symposium on Ventilation of the Lung – Anaesthesia and Intensive Care

17–18 November, Antalya, Turkey
Information: K. Akpir, MD, Chair of Anaesthesiology and Reanimation, Istanbul University, Medical Faculty at Capa Istanbul, Turkey
Tel.: +90-212-631-8767
Fax: +90-212-533-2083
or J.-P. Jantzen, MD, Chair of Anaesthesiology and Intensive Care, Academic Teaching Hospital Hannover Nordstadt, Haltenhoffstrasse 41, D-30167 Hannover, Germany
Tel.: +49-511-970-1572
Fax: +49-511-970-1012

1996

2nd World Congress on Pediatric Intensive Care 1996

23–26 June, Rotterdam, The Netherlands
Information: Holland Organizing Centre, Parkstraat 29, NL-2514 JD The Hague, The Netherlands
Tel.: +31-703657850
Fax: +31-703614846

Emergency Management and Critical Care of Stroke

5–7 September, Heidelberg, Germany
This conference is sponsored by the Research Group of Neurological Intensive Care of the World Federation of Neurology (WFN).
Information: Werner Hacke, MD, Professor and Chairman, Department of Neurology, Im Neuenheimer Feld 400, D-69120 Heidelberg, Germany
Tel.: +49-6221-568211
Fax: +49-6221-565348

9th European Congress on Intensive Care Medicine

23–27 September, Glasgow, UK
Information: Secretariat: Castle House Conferences, 28–30 Church Road, Turnbridge Wells, Kent TN1 1JP, UK
Tel.: +44-1892-539606
Fax: +44-1892-517005