Renal Effects of Theophylline and Caffeine in Newborn Rabbits¹

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ABSTRACT. Renal hemodynamics and functions were assessed in four groups of anesthetized newborn rabbits receiving a single intravenous dose of methylxanthines, *i.e.*: aminophylline: 3 mg/kg (A1) or 6 mg/kg (A2); sodium benzoate caffeine: 5 mg/kg (C1) or 10 mg/kg (C2). Each animal acted as its own control. The mean PAH extraction ratio was not modified by the methylxanthines. Renal blood flow and glomerular filtration rate were determined by clearances of paraaminohippuric acid and inulin, respectively. No changes in renal hemodynamics or renal functions were observed in group C1. In group C2, renal blood flow and filtration fraction did not vary significantly but renal vascular resistance showed a delayed increase. Systemic infusion of the two aminophylline regimens induced a delayed increase in renal vascular resistance with a concomitant fall in renal blood flow and an increase of filtration fraction in group A2. Glomerular filtration rate was either reduced (3 mg/kg aminophylline) or increased (6 mg/kg aminophylline and 10 mg/kg caffeine). Moreover, diuresis increased and tubular water reabsorption declined in groups A1, A2, and C2. High dose caffeine enhanced sodium fractional excretion. The acute renal effects of methylxanthines appeared dose- and time-related in immature animals and caffeine proved safer than aminophylline at doses used in human neonates. (*Pediatr Res* 21: 615-618, 1987)

Abbreviations

V, urine flow rate
GFR, glomerular filtration rate
MBP, mean blood pressure
RBF, renal blood flow
RVR, renal vascular resistance
FF, filtration fraction
FENa, sodium fractional excretion
PAH, para-aminohippuric acid
Hct, hematocrit
E PAH, renal PAH extraction ratio
U/P inulin, urine to plasma inulin ratio
MX, methylxanthine
PG, prostaglandin

mature infants (1-3). Thus a precise knowledge of their respective adverse renal effects can be helpful for the therapeutic choice. In adult and experimental animals, methylxanthines act as diuretic and natriuretic agents (4), but conflicting results have been obtained in several studies assessing the renal effects of theophylline in the preterm infant (5). Moreover the renal effects of caffeine have not been extensively investigated in the neonatal period although some data suggest the absence of gross diuresis or electrolyte abnormalities (1, 6). Therefore we evaluated the acute renal effects of a single dose of theophylline ethylenediamine (aminophylline, 81% theophylline) or sodium benzoate caffeine in New Zealand White newborn rabbits whose renal maturation shows close similarities with that of premature infants (7). The methylxanthine doses were selected in the range of the usual therapeutic doses used in human neonates (1).

MATERIALS AND METHODS

Studies were performed in 59 newborn New Zealand rabbits aged 5 to 10 days. Animals were born by spontaneous vaginal delivery and afterward housed with the maternal rabbit and breast-fed. Newborn rabbits were initially anesthetized with sodium pentobarbital, 25 mg/kg by intraperitoneal route. Small doses of Na pentobarbital were subsequently administered as necessary. A tracheal cannulation allowed mechanical ventilation with a mixture of air and oxygen (Rodent ventilator, model 683, Harvard, Millis, MA). A stretched PE 10 polyethylene tubing was inserted into the right femoral artery for arterial blood sampling and monitoring of systemic blood pressure.

A second catheter was similarly placed into the right femoral vein for solute infusion and drug administration. Surgical procedures and vascular cannulations were performed under stereoscopic magnifying glass (Zeiss, Oberkochen, Germany).

The bladder was catheterized for urine collection in preweighed microtest tubes. During the surgical procedure and subsequent experimental periods the body temperature of the newborn rabbits was kept at 38-38.5°C using an infrared lamp and a warming operating table.

Throughout the experiment heart rate (Sanborn 780-3 video-scope, Hewlett Packard, 78332, Palo Alto, CA), blood pressure (Grass Polygraph, model 7B, Quincy, MA), and esophageal temperature (Digital thermometer, Poliak and Gramiger, EPFL, Lausanne, Switzerland) were continuously recorded. After completion of the surgical procedure priming doses of inulin (100 mg/kg) and PAH (1.25 mg/kg) were administered and a sustained infusion was given to maintain constant plasma inulin and PAH concentrations. The infusion rate was 1 ml/100 g/h using a constant infusion pump (Perfusor EDL 2, Braun, Melsungen, Germany). The infusate contained per liter: 150 mmol sodium, 5 mmol potassium, 105 mmol chloride, 50 mmol bicarbonate, 50 g mannitol, 3 g inulin, and 150 mg PAH. About 1 h was spent for animal preparation and 90 min for subsequent equilibration. Previously we demonstrated that blood pressure, heart rate, arterial pH, PO₂, PCO₂, and renal functions remain stable for up to 3 h in this animal preparation (7, 8).

The xanthine derivatives theophylline and caffeine are widely used and equally effective to control idiopathic apnea in pre-

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The experimental protocol successively included a 1-h control period (I), the intravenous methylxanthine administration and two 1-h study periods (II and III). Blood samples (0.4 ml) were withdrawn at the midpoint of each urine collection period. Blood gas analysis, hematocrit and protein concentration measurements were conducted immediately. The red blood cells were reconstituted in human albumin and immediately returned to the animal. Plasma and urine samples were kept at 4° C for subsequent analysis.

A single dose of aminophylline or caffeine diluted in a 100 μ l saline vehicle was slowly (5 min) infused at the end of period I. Aminophylline (Euphyllin R, BYK Gulden, Konstanz, Germany; 1 mg of aminophylline ethylenediamine contains 0.81 mg of theophylline) was administered as follows: 3 mg/kg (group A1; $n = 8$) and 6 mg/kg (group A2; $n = 9$). Caffeine prepared with sodium benzoate was administered as follows: 5 mg/kg (group C1; $n = 8$) and 10 mg/kg (group C2; $n = 10$).

Additional experiments were carried out to assess the renal PAH extraction ratio in 15 untreated newborn rabbits, five aminophylline (6 mg/kg) and four caffeine (10 mg/kg) treated rabbits (1 h after methylxanthines administration). Following a small laparotomy a fine needle was inserted into the left renal vein and venous blood was slowly extracted (approximately 0.04 ml/min) by a constant extraction pump (Perfusor EDL 2, Braun, Melsungen, Germany). At the end of the experiments the rabbits were killed with a lethal dose of pentobarbital.

The standard clearances (C) of inulin and PAH were calculated from the formula:

$$C \text{ (ml/min)} = U \times V/P$$

where U = urine concentration, P = plasma concentration, V = urine flow rate in ml per min per kg. GFR, RBF, RVR, FF, and FENa were calculated from the following equations:

$$\begin{aligned} \text{GFR (ml/kg/min)} &= C \text{ inulin} \\ \text{RBF (ml/kg/min)} &= C \text{ PAH}/[E \text{ PAH} \times (1 - \text{Hct})] \\ \text{RVR (mm Hg/ml/kg/min)} &= \text{blood pressure}/\text{RBF} \\ \text{FF (\%)} &= (C \text{ inulin}/C \text{ PAH}) \times E \text{ PAH} \times 100 \\ \text{FENa} &= (C \text{ Na}/C \text{ inulin}) \times 100. \end{aligned}$$

Analytical methods. The urine volume was calculated from the change in weight of preweighed tubes without correction for specific gravity (Analytical balance, Mettler, Greifensee, Zurich, Switzerland). Arterial blood for pH, PCO₂, PO₂, and hematocrit determinations was collected anaerobically in heparinized capillary tubes. Blood gas determinations were performed using a pH/blood gas analyzer (Gas analyzer 168, Corning, Halsted, Essex, England). The automatic anthrone (9) and the Bratton and Marshall (10) methods were used for the determination of inulin and PAH concentrations, respectively (Autoanalyzer II, Technicon Instrument Corporation, Tarrytown, NY). Sodium concentrations were determined by flame photometry (Flame-photometer 543, Instrument Laboratory, Lexington, MA). Plasma protein concentration was estimated from the plasma index of refraction, using a temperature compensated refractometer (AOTS meter, American Optical, Buffalo, NY). Statistical analysis (11) was performed by a one-way analysis of variance for age, weight, and E PAH comparisons. Time/treatment effect was tested using the two-way analysis of variance for repeated measures. When a significant ($p < 0.05$) effect was found, differences within each pair of means was tested by the Student's method using the residual variance given by the analysis. All computations were done using the Triomphe software which has been developed at the Department of Medical Information in Dijon Hospital, Dijon, Cedex, France. All values are expressed as means $\pm$ SEM.

RESULTS

Mean ages and weights were similar in the four groups (A1: 7.8 ± 0.5 days; 127 ± 5 g, A2: 6.6 ± 0.5 days; 110 ± 5 g, C1: 6.7

± 0.6 days; 117 ± 7 g, C2: 6.4 ± 0.3 days; 108 ± 5 g). The mean PAH extraction ratio was similar in untreated ($55 \pm 4\%$), theophylline ($46 \pm 7\%$), and caffeine ($48 \pm 13\%$) treated rabbits. Thus RBF, RVR and FF were subsequently calculated assuming the same E PAH value (55%) for treated and untreated animals.

Arterial PO₂ was purposely maintained above 100 mm Hg in order to avoid any hypoxemia-induced change in renal hemodynamics (12). No physiological parameters varied significantly in groups A1 and A2 (Table 1). As a consequence of repeated blood sampling Hct decreased from period I to period II in group C2 and from period I to period III in groups C1 and C2 (Table 2). Mean blood pressure, PaCO₂, arterial pH, and protein levels remained stable throughout the experiments in the caffeine-treated animals.

The changes in absolute V, GFR, RBF, RVR, FF, FENa, and U/P inulin ratio values are given in Tables 3 and 4. The following significant percent changes are noteworthy. Group A1: a decrease in GFR ($-45 \pm 9\%$) and RBF ($-46 \pm 8\%$) associated with an increase in RVR ($+123 \pm 45\%$) in period III. Group A2: an increase in GFR ($+31 \pm 6\%$) in period II; a decrease in RBF ($-37 \pm 8\%$) and an increase in RVR ($+57 \pm 18\%$) in period III. Group C2: an increase in GFR ($+29 \pm 11\%$) in period II; an increase in RVR ($+36 \pm 15\%$) in period III.

DISCUSSION

Systemic administration of MX to newborn rabbits induced changes in GFR and renal hemodynamics in a manner related to the kind and dose of MX and to the time elapsed after MX administration. GFR and renal hemodynamics did not change in the low-dose caffeine group (5 mg/kg). An early increase of GFR was observed after high-dose aminophylline or caffeine and a delayed decrease after low-dose aminophylline. RVR remained unchanged in rabbits infused with 5 mg/kg caffeine but experienced a delayed increase with the higher caffeine regimen (10 mg/kg). No significant change in RBF or FF was observed at either dose of caffeine. The systemic infusion of 2.5 and 5 mg/kg theophylline (*i.e.* 3 and 6 mg/kg aminophylline) was associated with an increase in total RVR concomitant with a delayed but marked fall in RBF.

These renal hemodynamic changes after systemic administration of theophylline appear different from those observed after intrarenal infusion of theophylline, a condition inducing either a rise in GFR and RBF with an associated decline in RVR (13, 14) or no change in RBF, FF, or GFR, when low doses of theophylline were administered to mature animals (15, 16). The discrepancies between MX systemic and intrarenal administration could be related to differences in experimental conditions, namely, a) the duration of renal follow-up after theophylline administration, b) the specific characteristics of the renal response of the immature kidney to theophylline, and c) additive systemic extrarenal effects of the MX. The small but insignificant increase in blood pressure observed in groups A2 (6 mg/kg aminophylline) and C2 (10 mg/kg caffeine) suggests a possible inotropic cardiovascular effect mediated by an increase in sympathetic neuronal tone and/or in adrenomedullary catecholamine release (17–19).

In newborn rabbits administered theophylline in a slow 5-min injection, plasma theophylline concentrations decline by $24 \pm 4\%$ within 2 h (Gouyon J-B, Guignard J-P, unpublished data). Theophylline levels determined at the end of the experiments in groups A1 and A2 were 2.29 ± 0.04 μ g/ml ($n = 3$) and 4.74 ± 0.4 μ g/ml ($n = 5$), respectively. The renal hemodynamic effects of theophylline were observed at low doses and low plasma concentrations that cannot inhibit renal rabbit phosphodiesterase (20) but effectively antagonize renal adenosine receptors (21). Recent experimental data strongly suggest that renal adenosine could directly or indirectly induce a preglomerular vasoconstriction and an efferent arteriolar vasodilatation through stimulation of A1 and A2 adenosine receptors (16, 22–29). Thus, the significant increase in FF associated with 6 mg/kg aminophylline

Table 1. *Physiological data before (period I) and after (periods II and III) acute administration of aminophylline 3 mg/kg (group A1) or 6 mg/kg (group A2) in neonatal rabbits*

Periods	Group A1 (n = 8)			Group A2 (n = 9)		
	I	II	III	I	II	III
PaO ₂ (mm Hg)	143 ± 23	172 ± 14	177 ± 21	169 ± 13	155 ± 15	164 ± 19
PaCO ₂ (mm Hg)	41.0 ± 3.3	40.1 ± 2.6	38.5 ± 2.3	37.6 ± 0.7	38.5 ± 1.3	36.3 ± 1.4
pH	7.46 ± 0.02	7.46 ± 0.01	7.47 ± 0.02	7.50 ± 0.01	7.48 ± 0.01	7.49 ± 0.01
Hct (%)	31.4 ± 1.3	29.4 ± 1.5	29.4 ± 0.8	30.6 ± 1.9	29.5 ± 2.0	29.9 ± 1.7
Protein level (g/liter)	35.3 ± 1.2	34.1 ± 1.4	33.9 ± 1.2	31.3 ± 1.7	31.6 ± 1.9	32.0 ± 1.9
MBP (mm Hg)	32.0 ± 1.5	31.9 ± 1.4	31.2 ± 2.3	32.3 ± 1.7	35.7 ± 1.8	36.2 ± 2.2

Table 2. *Physiological data before (period I) and after (periods II and III) acute administration of caffeine 5 mg/kg (group C1) or 10 mg/kg (group C2) in neonatal rabbits*

Periods	Group C1 (n = 8)			Group C2 (n = 10)		
	I	II	III	I	II	III
PaO ₂ (mm Hg)	102 ± 7	129 ± 8*	131 ± 11*	165 ± 18	170 ± 21	166 ± 14
PaCO ₂ (mm Hg)	40.2 ± 1.4	41.6 ± 1.8	41.8 ± 2.1	36.5 ± 2.4	41.2 ± 2.9	38.4 ± 2.6
pH	7.44 ± 0.01	7.43 ± 0.01	7.43 ± 0.01	7.48 ± 0.03	7.45 ± 0.03	7.46 ± 0.03
Hct (%)	32.3 ± 1.3	31.4 ± 1.4	30.8 ± 1.6*	30.7 ± 1.2	29 ± 1.3*	28 ± 1.6†
Protein level (g/liter)	37.8 ± 2.4	35.6 ± 1.5	34.4 ± 2.3	31.9 ± 2.0	30.3 ± 1.2	31.0 ± 1.9
MBP (mm Hg)	27.8 ± 1.8	28.0 ± 1.9	28.3 ± 2.0	28.4 ± 1.6	30.4 ± 1.6	29.6 ± 2.0

Significant variations when comparing values of periods II and III to period I: * $p < 0.025$; † $p < 0.01$.

Table 3. *Kidney function parameters before (period I) and after (periods II and III) acute administration of aminophylline 3 mg/kg (group A1) or 6 mg/kg (group A2) in neonatal rabbits*

Periods	Group A1 (n = 8)			Group A2 (n = 9)		
	I	II	III	I	II	III
V (ml/kg/min)	0.05 ± 0.003	0.06 ± 0.004*	0.04 ± 0.007	0.064 ± 0.003	0.107 ± 0.007†	0.084 ± 0.012
GFR (ml/kg/min)	1.6 ± 0.19	1.61 ± 0.23	0.87 ± 0.16†	1.84 ± 0.17	2.43 ± 0.26†	1.75 ± 0.26
RBF (ml/kg/min)	16.7 ± 1.3	16.6 ± 1.4	9.2 ± 1.8†	19.9 ± 2.4	19.8 ± 2.6	14.0 ± 2.6†
RVR (mm Hg/ml/kg/min)	2.0 ± 0.18	1.98 ± 0.13	4.24 ± 0.66†	1.82 ± 0.23	2.13 ± 0.45	4.04 ± 1.13*
FF (%)	14.4 ± 1.8	14.1 ± 2.0	14.1 ± 1.5	14.6 ± 1.4	19.2 ± 1.5†	20.6 ± 1.5†
FENa (%)	0.36 ± 0.11	0.69 ± 0.25	0.63 ± 0.26	0.75 ± 0.24	1.43 ± 0.28	1.55 ± 0.43
U/P inulin	31.6 ± 2.7	25.4 ± 3.3†	20.2 ± 2.0†	29.0 ± 2.1	22.5 ± 1.4†	20.8 ± 1.6†

Significant variations when comparing values of periods II and III to period I: * $p < 0.05$; † $p < 0.01$.

Table 4. *Kidney function parameters before (period I) and after (periods II and III) acute administration of caffeine 5 mg/kg (group C1) or 10 mg/kg (group C2) in neonatal rabbits*

Periods	Group C1 (n = 8)			Group C2 (n = 10)		
	I	II	III	I	II	III
V (ml/kg/min)	0.065 ± 0.006	0.088 ± 0.016	0.085 ± 0.018	0.056 ± 0.005	0.097 ± 0.001*	0.096 ± 0.011*
GFR (ml/kg/min)	1.54 ± 0.26	2.16 ± 0.41	2.00 ± 0.45	1.49 ± 0.17	1.83 ± 0.19†	1.52 ± 0.19
RBF (ml/kg/min)	16.1 ± 2.9	17.8 ± 2.9	18.1 ± 3.4	16.4 ± 3.7	17.1 ± 3.3	12.5 ± 2.8
RVR (mm Hg/ml/kg/min)	2.11 ± 0.33	1.96 ± 0.35	2.04 ± 0.40	2.09 ± 0.34	1.97 ± 0.29	2.87 ± 0.56†
FF (%)	15.1 ± 1.2	17.7 ± 1.5	19.8 ± 2.2	13.5 ± 2.6	14.3 ± 1.7	16.9 ± 1.8
FENa (%)	0.86 ± 0.31	0.59 ± 0.17	0.57 ± 0.12	0.76 ± 0.14	1.23 ± 0.17†	1.39 ± 0.21†
U/P inulin	24.1 ± 3.6	24.5 ± 3.2	22.5 ± 3.3	27.1 ± 2.7	20.1 ± 1.3*	16.6 ± 0.9*

Significant variations when comparing values of periods II and III to period I: * $p < 0.01$; † $p < 0.025$.

administration in newborn rabbits could reflect changes in the ratio of arteriolar afferent to efferent tone rather than a decrease in the ultrafiltration coefficient K_f [adenosine, the target of theophylline, does not alter glomerular capillary hydraulic conductivity (30)] or changes in oncotic pressure in the glomerular capillaries (seric protein levels remained stable throughout the experiments). Noteworthy is the fact that the changes in FF were only significant in the rabbits receiving theophylline, a more potent adenosine antagonist than caffeine (31), and that theophylline induced FF changes in a dose-related manner.

Acute theophylline and caffeine administration increases diuresis and natriuresis in rats (32), dogs (13), man (4), and possibly

in human neonates (33). In newborn rabbits changes in diuresis were also present and can be related both to an increase in GFR and a decline in tubular water reabsorption, as suggested by the decrease in U/P inulin ratio. The natriuretic effect was only significant in animals administered 10 mg/kg caffeine.

As recently reported by Baer *et al.* (32) and Takeuchi *et al.* (34) theophylline causes simultaneous increases in urine flow rate and sodium and urinary PGE₂ excretion. However, enprofylline (3-propylxanthine), a xanthine derivative with low adenosine antagonistic properties, also increases urinary PGE₂ excretion (32) but does not elicit a natriuretic or a diuretic effect (32, 35). Thus the diuretic and natriuretic effects of theophylline

cannot be ascribed simply to an increase in renal PGs. Furthermore, Woodcock *et al.* (36, 37) recently described A₂ (RA) adenosine receptors in rats and human renal papillae, probably located in the collecting tubule. These authors hypothesized that stimulation of adenylate cyclase-coupled adenosine receptors in the renal papilla could produce an increase in hydraulic conductivity of the collecting tubule (36, 37) while inhibition of these receptors by theophylline and caffeine could reduce water tubule reabsorption at this tubular site.

The present data demonstrate that the renal effects of methylxanthines are dose- and time-related and suggest that acute low-dose caffeine (5 mg/kg) could prove safer than theophylline to control apnea, especially in very low birth weight infants who present with physiological low GFR and RBF (38) that can be further depressed by various perinatal stresses (39).

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