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Antenatal aminophylline and steroid exposure: Effects on glomerular filtration rate and renal sodium excretion in preterm newborns

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1 Introduction

Aminophylline and steroids are frequently administered to mothers with threatened premature birth to stimulate surfactant synthesis and to reduce the incidence and severity of hyaline membrane disease [6, 11, 14].

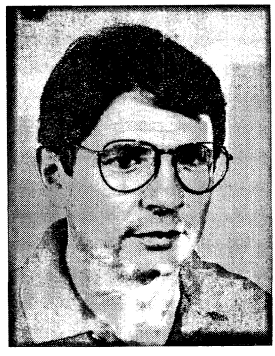
Aminophylline, has an effective tocolytic effect on the hypercontractile uterus and improves utero-placental flow, given continuously in the last trimester or during premature delivery to stimulate fetal pulmonary maturity when maternal diseases do not allow the use of steroids [7, 11].

Prenatal steroids have been shown to induce the precocious maturation of the renal tubule with respect to that of the glomerulus, by activation of tubular Na^+-K^+ ATPase of the premature infant [2, 3, 13, 17, 19].

Theophylline, among the various methylated xanthine derivatives, has the strongest diuretic action in both the adult and in pediatric populations, reducing the reabsorption of sodium and water at the tubular level, probably by inhibiting the degradation of cyclic AMP [5]. There have been no studies thus far on the possible fetal renal effects of prenatal treatment with theophylline [9, 12].

Since in our institution some high-risk pregnancies are treated during the last trimester until parturition with aminophylline with or without steroids, we thus had the opportunity to investigate, in an uninterventional way, their renal glomerular and tubular effects in premature newborns at birth.

Curriculum vitae



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2 Patients and methods

With informed parental consent, we prospectively studied three groups of twelve preterm neonates (gestational age of ≤ 35 weeks) whose mothers were treated, during pregnancy, with aminophylline, associated or not with steroids. A fourth group of twelve newborns of similar gestational age, whose mothers had none of the above medications, were followed as controls. The newborns of the four groups are comparable by clinical and anthropometric characteristics (table I). Excluded from our study were neonates of birth weight < 1250 gr, with associated major malformations, those who died in the perinatal period, and those with incomplete hematochemical data.

Student's t-test

Table I. Characteristics of aminophylline (A), steroid (S), steroid and aminophilline (A + S) treated and control (C) infants. Birth statistics, condition in the newborn period. Differences between groups calculated by Student's t-test or x^2 as appropriate. RDS = respiratory distress syndrome.

	C	A	S	A + S	Difference
Number in group	12	12	12	12	NS
C Section	9	12	11	11	NS
Birth weight (g)	1651 ± 476	1919 ± 293	1378 ± 406	1838 ± 266	NS
Gest. age (wk)	32 ± 2	33 ± 2	32 ± 1.5	32 ± 1.5	NS
Apgar S. ≤ 5 at 5′	2	4	3	3	NS
RDS	5	3	5	5	NS
Intake ml/kg/h	3.29 ± 1.5	3.19 ± 1.5	3.02 ± 2.1	3.11 ± 1.6	NS
Diuresis ml/kg/h	3.7 ± 1.5	2.38 ± 0.8	2.78 ± 1.2	2.91 ± 1.3	NS

After admission, they were entered in a protocol to examine renal function during the first 24 hours, a period of time in which usually newborn infants do not receive electrolytes, diuretics, indomethacin, vasoactive drugs, or blood transfusions. During the observation period the attending physician prescribed parenteral fluids (dextrose 10% in water, 3–4 ml/kg/h) according to the standard needs of each patient. Intake and output were measured and recorded commencing with admission. Volume output other than blood and urine was negligible.

Treatment with steroids followed LIGGINS classic protocol with administration of dexamethasone during the last two days of pregnancy [14]. Aminophylline treatment was undertaken as tocolytic therapy in the last three months of pregnancy until delivery, or in premature labour to induce surfactant synthesis in mothers for whom steroids were contraindicated, for at least three days before parturition, as previously described [11]. Aminophylline seems to induce fetal pulmonary maturity earlier in gestation, but some newborns were later treated with steroids as well.

Urine collection for evaluation of diuresis was done sterily in the first 24 hours of life, following TARLOW's method [20]. When urine sample was about half done, femoral vein samples were taken for hematochemical parameters, performed with a SMAC autoanalyzer (TECHNICON; Tarrytown, USA). Urinary osmolality was determined by freezing point lowering.

For each newborn we evaluated: serum and urine sodium (mEq/l) and creatinine, and osmolality of both urine and plasma, the latter according to:

$$\text{POsm (mOSm/kg)} = 2\,Na^+ + \frac{\text{serum urea (mg/dl)}}{2.8} + \frac{\text{blood sugar (mg/dl)}}{18}$$

From these data we also determined the osmolar ratio, creatinine clearance, osmolar clearance, free-water clearance, and the fractional excretion of sodium, using the following formulas:

$$\text{Osmolar ratio: } \frac{\text{U Osm}}{\text{P Osm}}$$

$$\text{Creatinine clearance (Ccr ml/min): } \frac{(\text{Ucr}) \times (\text{V})}{\text{Pcr}}$$

Osmolar clearance (COsm ml/min):

$$\frac{(\text{UOsm}) \times (\text{V})}{\text{POs}}$$

Free-water clearance (CH_2O ml/min): V-COsm

Fractional sodium excretion:

$$\frac{(U_{Na^+}) \times (\text{Pcr})}{(\text{Ucr}) \times (P_{Na^+})} \times 100$$

In the above formulas V stands for 24 hour urine output milliliters per minute, POsm is plasma osmolality (mOsm/KgH_2O).

For evaluation simplicity osmolar clearance and free-water were expressed per deciliter creatinine clearance.

Evaluation of the comparison of treated and control babies was done either by analyses of variance or by chi-square.

3 Results

The results of this study on the renal effects of antenatal steroids (S), aminophylline (A), aminophylline and steroids (A + S) and in the controls (C) are shown in table II.

We found no significant differences for plasma and urine creatinine or creatinine clearance in the groups considered.

Among the neonates, comparable for weight, gestational age and clinical characteristics, the S group presents the more evident differences:

1. urine osmolality (S vs A + S $p < 0.005$; S vs C $p < 0.005$; S vs A $p < 0.005$) and urine/plasma osmolality ratio (S vs C $p < 0.005$; S vs A $p < 0.05$; S vs A + S $p < 0.005$) significantly higher.
2. urine potassium excretion increased.
3. urine sodium and sodium fractional excretion (S vs C $p < 0.01$) reduced.
4. free water clearance significantly decreased ($p < 0.05$).

Furthermore, the A + S group had the lower ($p < 0.05$ vs S) potassium excretion, along with a reduced fractional sodium excretion ($p < 0.01$ vs C).

4 Discussion

Our results support the view that antenatal exposure of the fetus to steroids is followed by enhanced renal tubular reabsorption of sodium immediately after birth, preventing salt wasting [1, 2. 4].

There is, in fact, vast experimental documentation, supported by recent neonatal clinical data underlining how prenatal steroid administration induces differential renal tubular maturation, earlier than that of the glomerulus, according to the hypothesis of steroid tubule induction of the Na^+-K^+ ATPase enzymatic system in the preterm newborn [2, 19].

In our study, furthermore, as AL-DAHAN et al. showed with administration of dexamethasone, the preterm newborn who undergoes prenatal steroid therapy has a reduced fractional sodium excretion when compared with controls [2]. The above authors also observed early high levels of the urinary ratio of K^+/Na^+ and a later increase of the GFR [2, 8].

We also found in the steroid group a high urinary osmolality and a lowered natriuria with respect to controls, possibly because the site of greatest tubular cation exchange and of glucocorticoid receptor is the collecting ducts [3, 19].

The prenatal administration of aminophylline, that crosses the utero-placental barrier and reaches comparable blood levels in mother and by its tocolytic and platelet antiaggregating effect, may improve utero-placental blood flow and of the intervillous microcirculation, and also enhances pulmonary maturity [7, 9, 10, 15, 18]. In our neonatal population it did not play an important part in the renal maturation process. The therapeutic effects, however could be obviously more evident in later life, since the drug has a longer half-life in the premature [5].

Our data do not show that aminophylline, associated or not with steroids, could interfere with hydrosaline equilibrium, nor with plasma osmolality of the preterm at birth, nor accelerate maturation of renal function in immature infants. However, later on, in the treatment of apnea, aminophylline induces an increase in the GFR, and others have descibed dehydration and hyponatremia that persisted until the drug's discontinuation [16, 21]. In the current study specific investigations were not undertaken in these aspects, and will be the subject of future study. In fact, the coupling of tubular and glomerular function is imperfect in the preterm, in which the aminophylline half-life is prolonged [12]. Moreover, studies in the first 24 hours of life, using creatinine, sodium and potassium reflect to some extent the maternal plasma values [4].

In conclusion, our results support the view that endogenous glucocorticoid hormones play an important part in the normal renal maturation process and tubular Na^+-K^+ ATPase enzymatic system. However, it seems reasonable to verify, in the days after birth, the possible tubular and glomerular effects of the prenatal administration of aminophylline and steroids.

Table II. Comparison between aminophylline (A), steroid (S), aminophylline and steroid-treated (A + S) and controls (C) of plasma (P_{cr}) and Urine (U_{cr}) creatinine and creatinine clearance (C_{cr}), plasma (P_{na}) and urine (U_{na}) sodium, fractional sodium excretion (FE_{na}), plasma (P_{osm}) and urine (U_{usm}) osmolality, urine: Plasma osmolality ratio ($Osm_{u:p}$), ratio and free water clearance (FW_{cr}) at birth. Values are expressed as mean ± 1 SD, the tabulated P values were calculated by Student's t-test or x^2 as appropriate.

	C	A	S	A + S	Difference P
Pcr (mg%)	1.22 ± 0.23	1.19 ± 0.34	1.05 ± 0.39	1.09 ± 0.31	NS
Ucr (mg%)	12.9 ± 6.96	14.6 ± 5.36	16.9 ± 12.6	11.6 ± 3.29	NS
Ccr ml/min	0.87 ± 0.42	0.9 ± 0.38	1.07 ± 0.38	1.03 ± 0.50	NS
P_{Na} mEq/l	137 ± 6.84	139 ± 4.92	140 ± 4.54	139 ± 4.2	NS
U_{Na} mEq/l	40 ± 18	42 ± 30	36 ± 15	33 ± 15	NS
FE_{Na} %	4.26 ± 2.6	3.09 ± 1.7	1.69 ± 0.7	1.9 ± 1.1	(S VS C >.01) (A + S VS C <.01)
P_{osm} mOm/kg H_2O	292 ± 18.3	295 ± 12.5	296 ± 11.9	292 ± 8.7	
U_{osm} mOsm/kg H_2O	147 ± 28	173 ± 44	201 ± 45	146 ± 34	(S VS C <.005) (S VT A <.005) (S VS A + S <.005)
$Osm_{U:P\ ratio}$	0.49 ± 0.07	0.55 ± 0.15	0.66 ± 0.14	0.49 ± 0.10	
P_K µmol/l	5.05 ± 0.84	4.8 ± 0.48	4.9 ± 0.61	4.9 ± 0.46	
U_K µmol/l	20 ± 11	22.9 ± 11	28 ± 11	19.3 ± 11	(S VS A + S <.05)
$U_{K:Na\ ratio}$	0.68 ± 0.32	0.71 ± 0.39	0.94 ± 0.55	0.89 ± 0.74	
FW_{CR} ml/dl VFG	4.42 ± 2.3	3.59 ± 1.9	2.39 ± 1.3	4.41 ± 2.2	(S VS A <.05) (S VS A + S <.05) (S VS C <.05)

Abstract

Creatinine clearance and renal sodium excretion were measured consecutively in three groups of 12 premature infants (gestational age ≤ 35 weeks) whose mothers had received either steroids or aminophylline, or steroids and aminophylline before delivery.
We found no significant differences for plasma and urine creatinine and its clearance in the groups considered.
The steroid group presented urine osmolality and urine/plasma osmolality ratio significantly higher than among the other groups. Furthermore, urine potassium excretion increased, and urine sodium and sodium fractional excretion were reduced.
Aminophylline exposure did not interfere with the hydrosaline equilibrium nor with renal function of the preterms at birth.
Our results reconfirm that corticosteroid hormones play an important part in the fetal renal maturation process, inducing a precocious maturation of the tubular Na^+-K^+ ATPase enzymatic system, that is substantially unmodified by aminophylline exposure. However, due to the prolonged half-life of aminophylline in prematures, it seems reasonable to verify the coupling of tubular and glomerular functions also in the following days of life.

Keywords: Aminophylline, glomerular filtration rate, premature, renal function, sodium excretion, steroids.

Zusammenfassung

Antenatale Aminophyllin- und Steroidgabe und ihr Einfluß auf die glomeruläre Filtrationsrate und NaCl-Ausscheidung bei Frühgeborenen
Bei 12 Frühgeborenen (Gestationsalter ≤ 35 Wochen) bestimmten wir die Kreatinin-Clearance und die renale NaCl-Exkretion. Es wurden 3 Gruppen gebildet: die Mütter hatten entweder Steroide oder Aminophyllin bzw. Steroide und Aminophyllin vor der Entbindung erhalten. Wir wollten mögliche Effekte auf die Nierenfunktion zum Zeitpunkt der Geburt erfassen.
In den 3 Gruppen fanden sich keine signifikanten Unterschiede hinsichtlich der Kreatininwerte im Plasma und Urin bzw. der Clearance.
In der Steroidgruppe waren die die Osmolalität im Urin und der Quotient aus Urin/Plasma-Osmolalität signifikant höher als in den beiden anderen Gruppen. Darüberhinaus zeigte sich eine erhöhte Kaliumausscheidung sowie eine erniedrigte NaCl-Ausscheidung im Urin und erniedrigte fraktionierte NaCl-Ausscheidung.
Die Gabe von Aminophyllin beeinflußte weder den Wasserhaushalt noch die renale Funktion der Frühgeborenen bei der Geburt.
Unsere Ergebnisse zeigen erneut, daß die Corticosteroide beim Reifungsprozeß der fetalen Niere eine wichtige Rolle spielen, indem sie eine frühzeitige Stimulierung der Enzyme, hier der tubulären Na^+-K^+-ATPase, induzieren. Dieser Enzymapparat wird durch Aminophyllin grundsätzlich nicht tangiert. Da jedoch bei Frühgeborenen die Halbwertszeit von Aminophyllin verlängert ist, sollte man in den ersten Lebenstagen wegen der Kopplung von tubulärer und glomerulärer Funktion weitere Untersuchungen durchführen.

Schlüsselwörter: Aminophyllin, Frühgeburt, glomeruläre Filtrationsrate, NaCl-Ausscheidung, renale Funktion, Steroide.

Résumé

Exposition anténatale à l'aminophylline et aux stéroïdes: effets sur le taux de filtration glomérulaire et l'excretion rénale de sodium chez les nouveaux-nés prématurés
On a mesuré de façon consécutive la cléarance de la créatinine et l'excrétion rénale de sodium dans trois groupes de 12 prématurés (âge gestationnel ⩽ 35 semaines) dont les mères avaient reçu soit des stéroïdes soit de l'aminophylline soit des stéroïdes et de l'aminophylline avant l'accouchement afin d'évaluer leurs possibles effets rénaux à la naissance.
Nous n'avons pas trouvé de différences significatives au niveau de la créatinine plasmatique et urinaire ainsi que pour la clearance dans les différents groupes.
Le groupe stéroïde présente une osmolalité urinaire et un ratio osmolaire urine/plasma significativement plus élevés que dans les autres groupes. De plus, l'excretion potassique urinaire est augmentée, et le sodium urinaire ainsi que l'excrétion fractionnée du sodium sont diminués.
L'exposition à l'aminophylline n'interfère pas avec l'équilibre hydrosalin ni avec la fonction rénale des prématurés à la naissance.
Nos résultats reconfirment que les hormones corticostéroïdes jouent un rôle important dans les processus de maturation rénale du fœtus, en induisant une maturation précoce du système enzymatique tubulaire Na^+, K^+, ATP ase, système qui n'est pas modifié par l'exposition à l'aminophylline. Toutefois, du fait de la demie vie prolongée de l'aminophylline chez les prématurés, il semble raisonable de vérifier le couple des fonctions tubulaires et glomérulaires également au cours des jours de vie suivant.

Mots-clés: Aminophylline, excrétion de sodium, fonction rénale, prématurés, stéroïdes, taux de filtration glomérulaire.

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