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The effect of parenteral nitrogen and energy intake on electrolyte balance in the preterm infant.

Running title:

The effect of nutrition on electrolyte balance in the preterm infant.

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Conflict of interest statement

No conflict of interest exists with regard of this study and it was entirely supported by the institution where the study was conducted (University Hospital of Dijon – France).

Abstract

Background: Recent guidelines for preterm parenteral nutrition (PN) recommend an earlier and higher intake of amino acids (AA) and energy to avoid postnatal catabolism and approximate normal foetal growth. Few investigations explored how early PN may affect electrolyte and water homeostasis. We performed a prospective observational trial to assess the effect of nutrient intake on electrolyte homeostasis and balance.

Methods: During 16 months all infants ≤ 32 weeks were eligible. In the first week of life we recorded daily: electrolytes (plasma and 8-hour urine collection), nutritional intake, urine output, body weight and we calculated sodium (Na) and potassium (K) balance. Infants were divided, for analysis, into 3 groups of AA intake: Low < 1.5 g/kg/day (LAA); Medium 1.5-2g/kg/day (MAA) and High > 2 g/kg/day (HAA).

Results: 154 infants were included. HAA group presented lower weight loss. Na balance was influenced by urine output and postnatal age, with little contribution of nutrition. Kalemia and K balance were mainly influenced by AA intake. K balance differed among groups: LAA -2.3 mol/kg/wk, MAA 1.1 mmol/kg/wk and HAA 2.6 mmol/kg/wk ($p < 0.0001$). In the HAA group plasma and urine K were significantly lower and non-oliguric hyperkalemia was reduced.

Discussion: Na homeostasis was very slight modified by early nutrition, suggesting that a negative Na balance is obligatory after birth. We showed that AA intake strongly affects K balance, minimize hyperkalemia and reduces weight loss. As K balance is strictly linked to cellular metabolism, we speculate that early nutrition may inhibit cellular catabolism and reduce the contraction of intracellular water compartment.

Key words: Preterm, Sodium Balance, Potassium Balance, Intracellular Water Compartment, Aggressive Parenteral Nutrition, Amino Acid, Guidelines, Urea, Metabolism, Na/K-ATPase.

Introduction

Transition to the extra-uterine environment is associated with physiological changes of body water composition consisting in isotonic fluid loss, mainly from the extracellular compartment (Sulyok, 2008). In very preterm infants the first days of life are associated with high transcutaneous evaporative water losses and reduced ability of the kidney to concentrate urine, potentially leading to dehydration and hypernatremia (Agren *et al.*, 1998, Wada *et al.*, 2008; Gawlowski *et al.*, 2006). Moreover a particular vulnerability to hyperkalemia exists, especially in extremely low birth weight infants (ELBWI) (Yaseen, 2009). In clinical practice the postnatal adaptation may be assessed by sodium (Na) and potassium (K) plasma determinations and by monitoring urine output and body weight changes. Several perinatal factors such as gestational age (GA), antenatal steroids, respiratory distress or patent ductus arteriosus may influence this adaptation (Omar *et al.*, 2000; Modi, 2003). Also Na and fluid early intake affect changes in body water and salt distribution as several studies have assessed (Modi and Hutton, 1990; Hartnoll *et al.*, 2000).

Furthermore, a study from Heimler *et al.* (1993) conducted in 14 preterm babies showed that the postnatal weight loss was associated with a contraction of the intracellular water compartment and suggested that low energetic intake may increase postnatal weight loss.

Recent nutrition guidelines for the preterm baby recommend early initiation of parenteral nutrition (PN) with relatively high protein and caloric intake, in order to achieve positive nitrogen retention and to prevent extra-uterine growth failure, especially for ELBWI (Koletzko *et al.*, 2005; Rigo and De Curtis, 2004; Van Goudoever *et al.*, 1995; Thureen *et al.*, 2003). Whether this change may influence water and electrolyte balance remains unknown to date.

In June 2006 PN practice in our Neonatal Intensive Care Unit (NICU) has been modified. Amino acids (AA) and energy intake was increased and started immediately after birth when compared to previous regimens of PN. Afterward, standardized PN bags were introduced and AA and caloric intake further increased. Before this change of practice was started, we designed a prospective observational study in order to evaluate how the variations on fluid compartments may be

conditioned by the nutritional approach. Some infants included in this study were also entered in a published report investigating the advantages and the risks of the standardization of PN (Iacobelli *et al.*, 2010).

Aim of the present study was to evaluate the influence of early AA and caloric intake on electrolyte homeostasis and balance in a large population of preterm infants on total or partial PN.

Methods

Study population

This study was conducted from the 1st June 2006 to the 30th September 2007. All the infants born below 33 weeks of GA and hospitalized in NICU within 6 hours after birth were eligible.

Exclusion criterion was major congenital anomalies. The study was authorized by the Ethics Committee of the Hospital. Informed, signed parental consent was obtained.

Nutritional prescription

Total or partial PN was administered according to clinical decision. When total PN was prescribed, a central venous line (CVL) was inserted and PN was administered by individualized prescription or by standardized batch-produced bags, as already shown in a previous report (Iacobelli *et al.*, 2010). Minimal enteral feeding by human milk was started on day 1 of life, and maintained at least 4 days. When partial PN was prescribed, a peripheral venous line (PVL) was inserted, enteral nutrition was started on day 1 (20ml/kg/d) and progressively increased during the week. In this case intravenous nutritional complement was limited by the solution osmolarity.

Water and electrolyte intake

We started fluid at 80 ml/kg/d and added electrolytes on day 3, then fluid and electrolyte input was adapted to allow a daily weight loss from 2 to 4% and to maintain natremia and kalemia within 135 to 145 mmol/L and 4 to 6 mmol/L, respectively (Lorenz *et al.*, 1995).

Data collection

Infants were cared for in humidified double-walled incubators, body weight was monitored daily (SECA747 balance, France). Plasma Na, K, calcium, phosphorus, total carbon dioxide (TCO₂), urea and creatinine were determined daily for 7 days. The first blood sample was obtained at 12 hours of life. Daily diuresis was calculated and a consecutive 8-hour urine collection, starting 4 hours before the blood sampling, was performed by using a plastic bag. Urine was analysed for Na, K, calcium, urea and creatinine concentrations. Urine escaping the bag was quantified by weighing nappies (Gouyon *et al.*, 1994). Daily fluid, electrolyte, energy and AA intake was recorded. Oral intakes by human milk were considered in calculating fluid and nutrient intakes. Intravenous flushes and administration by drugs were taken into account when calculating fluid, ion and glucose intake. Plasma and urine electrolytes were measured by an Ortho Clinical Diagnostic analyzer (Rochester, USA), which uses direct potentiometry. Na and K balance were expressed in mmol/kg/d and calculated as the difference between daily intake and daily urinary excretion.

Data analysis

First kalemia, natremia, K and Na balance were associated with perinatal variables and daily water, energy and amino acid intake, using one-factor analysis of variance. Variables significant at a p level <0.20 at the univariate analysis were entered into a backward selection analysis of variance. Then, the infants were divided into 3 groups, according to the mean level of AA intake during the week: Low AA intake: <1.5 g/kg/d (LAA); Medium AA intake: 1.5-2 g/kg/d (MAA); High AA intake: >2 g/kg/d (HAA). Data from continuous variables were expressed as mean ± standard deviation. Differences among groups were analysed using ANOVA test, and results were adjusted for gestational age with ANCOVA test. Statistical tests were performed by SAS software 8.2, results were considered significant at a 5% level.

Results

A total of 1030 plasma determinations and 964 urine collections were carried out from 154 infants.

Univariate and multivariate analysis

Table 1 shows the multivariate analysis. The main independent factor influencing kalemia and K balance was AA intake. Also energy intake and gestational age significantly reduced kalemia. Figure 1 illustrates the linear regression analysis between K balance and AA intake. K balance was positive (94% of cases) when the daily AA intake was more than 2 g/kg/d, and negative (92%) when the infants received less than 1.5 g/kg/d AA. When the daily AA intake ranged between 1.5 to 2 g/kg/h, K balance was positive in about half the cases (55%).

Natremia was mainly influenced by postnatal age (in days). Urine output and postnatal age affected Na balance with a significant contribution of GA and AA intake, albeit of small entity (table 1).

Analysis for groups of AA intake

Antenatal, postnatal characteristics and nutritional intake for the 3 groups are summarized in table 2. HAA group was similar to MAA group with regard to birth weight (BW) and GA, but differed for nutritional intake. Infants in the LAA group had higher BW and GA, they received a more restrict amount of all nutrients due to the prevalent use of partial PN by PVL. Figure 2 shows the weight evolution during the week. Weight was significantly different since day 3 among groups. Both blood and urine urea were higher in HAA group, but urea urinary loss did not counterbalance the higher nitrogen intake.

K homeostasis was widely influenced by AA intake. Kalemia was significantly different among groups during the first 5 days (figure 2). Non-oliguric hyperkalemia (NOHK) was observed in day 1 or 2 and it was reduced in the HAA group. Also urinary K losses were reduced in the HAA group. The week K balance was more positive in the HAA group than in the MAA group, while it was globally negative in the LAA group (table 3). In each group a positive balance was obtained by the day when the mean AA intake attained at least 1.5 g/kg/d. (figure 3).

Natremia shows a very similar evolution in the 3 groups (figure 2). Maximal natremia was registered between day 3 and day 5 and the hypernatremia rate was similar among groups. Na

balance was somewhat less negative in the HAA group (table 3). Infants in LAA group were able to limit Na urinary losses especially by the end of the week.

Discussion

This is the first large prospective trial addressing the complex interaction of early nutrition with electrolyte balance in preterm babies. Strength of the study was the large number of ion determinations, the 8-hour urine collections and the exhaustive register of nutritional and electrolyte intake. It was pertinent to involve also infants receiving only partial PN, as they are rarely included in nutrition studies. The main limitation of the study was the lack of randomized allocation of infants to different nutritional regimens, so that disparity in nutrition intake was dependent on clinical judgement and on time of inclusion. The miss of total urinary nitrogen determination for accurate nitrogen-balance was also a weakness of the study.

Our findings indicate that a higher AA intake, immediately after birth, is effective to modify K metabolism, by reducing NOHK and urinary K loss. This appears in contrast with previous data by Rivera *et al.* (1993) who did not find any influence of AA input on kalemia, in a small randomized trial, and by Elstgeest *et al.* (2010) who compared, in a retrospective study, two different PN regimens, but having also a very dissimilar fluid and electrolyte intake, in the first days of life. Na/K-ATPase impairment is often recognized as responsible for NOHK. We speculate that this impairment could be promoted by the disruption, at birth, of the active AA placental uptake and that it could be limited by the early AA supply (Matsuo *et al.*, 1995; Stefano *et al.*, 1993). We observed a reduced weight loss in the HAA group. K is the principal intracellular cation, so its balance may be directly related to cellular growth or catabolism, and to any change in the intracellular water compartment. This suggests that an early AA supply may help to preserve the intracellular water compartment, thus reducing its contribution to postnatal weight loss. In our study, K balance was positive for a level of AA input ranging between 1.5 and 2 grams per kilo and per day. This is consistent with studies assessing cellular metabolism by nitrogen balance.

In these studies nitrogen balance was always positive in the groups with an AA intake more than 2g/kg/d and always negative for less than 1.5g/kg/d (Van Goudoever *et al.*, 1995; Thureen *et al.*, 2003; Wahlig *et al.*, 1994; Rivera *et al.*, 1993; Van Lingen *et al.*, 1992; Mitton *et al.*, 1993).

Moreover the relationship between total body K and protein content is well established in the preterm baby (Spady *et al.*, 1987). Also, recent recommendation to give at least 1.5 g/kg/d of AA intake as soon as possible after birth is confirmed by our results (Koletzko *et al.*, 2005). During the first 2 days of life we observed significant urine K losses in each group, despite no K intake. Since no infant received more than 1.5 g/kg of AA at day 1, we are unable to determine either the K release by the cell is an inevitable birth-related phenomenon or it could be reversible with a high early protein supply.

In the present trial infants with higher BW and GA were often considered not to need total PN, this is a common decision in clinical practice. In these infants we observed more weight loss and a prolonged negative K balance, due to an inadequate nutritional support, regardless of major clinical problems.

Natremia was not influenced by AA intake. Na balance was largely negative in each group during the first days of life. It was strongly associated with postnatal age and urine output, with very little effect of GA and AA intake. Our data confirm that a negative Na balance is a necessary event after birth, closely linked to extracellular water contraction and weight loss, and only little modulated by nutritional approach.

Conclusion

Early nutrition significantly improves K metabolism after birth, probably by limiting the cellular impairment, and enable to better tolerate K intake. K balance seems to be a good indicator of cellular anabolism and function. However several questions arise from our results on the optimal K intake with the early aggressive parenteral nutrition. Do to limitation of our trial we cannot assess if a further higher AA intake (> 2g/kg/h) immediately after birth could prevent all NOHK, and

allow to introduce sooner any K intake without arm. Similarly, we cannot assess if the progression in AA intake increases K need in a linear relationship.

Our data on Na metabolism confirm previous studies, and the modest influence of nutrition does not authorize amendments to existing guidelines.

Since early nutrition influences postnatal weight loss, we can expect infants to loose less weight than previous admitted. It should be taken into account when prescribing fluid intake.

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Figure legends

Figure 1. K balance association to AA intake at linear regression analysis.

Figure 2. Daily evolution of AA intake, body weight, kalemia and natremia for the three groups during the first week of life. * ANOVA, $p < 0.05$.

Figure 3. Evolution of potassium balance for the three groups.

Table 1. Multivariate analysis for kalemia, natremia, potassium and sodium balance.

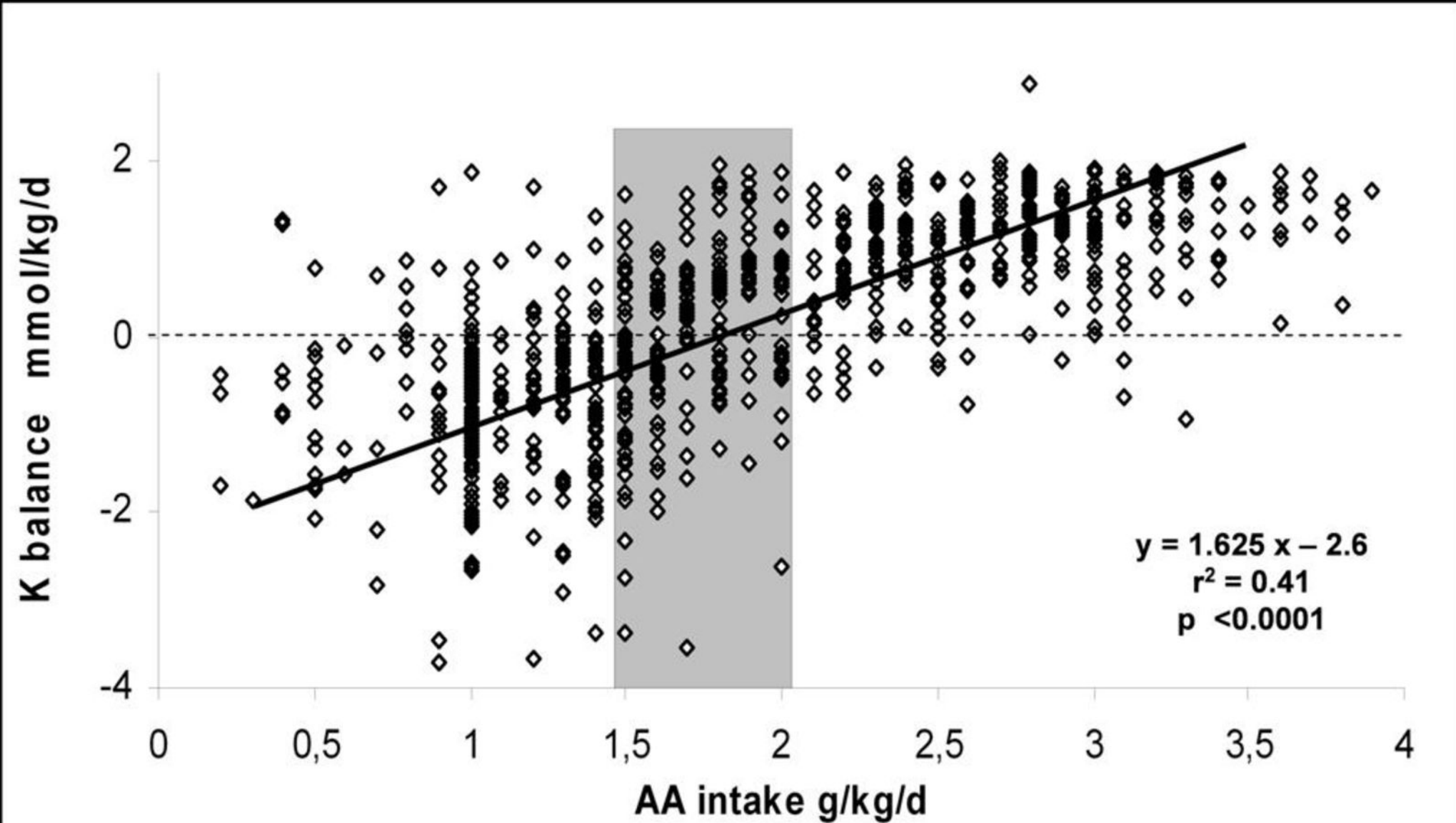
| | β coef. | r^2 Incr. | P |
|----------------------------------------------------|------------------|----------------|----------|
| Kalemia ($r^2 = 0.15$) | | | |
| Amino acid intake | - 0.7 | 0.10 | < 0.001 |
| Caloric intake | - 0.01 | 0.02 | < 0.05 |
| Gestational age | - 0.1 | 0.02 | < 0.05 |
| Potassium balance ($r^2 = 0.53$) | | | |
| Amino acid intake | + 0.8 | 0.40 | < 0.0001 |
| Postnatal age | + 0.3 | 0.08 | < 0.01 |
| Urine output | - 0.2 | 0.04 | < 0.01 |
| Caloric intake | + 0.1 | 0.01 | < 0.05 |
| Gestational age | + 0.1 | 0.01 | < 0.05 |
| Natremia ($r^2 = 0.21$) | | | |
| Postnatal age | + 1.3 | 0.17 | < 0.001 |
| Urine output | + 0.5 | 0.03 | < 0.01 |
| Gestational age | - 0.2 | 0.01 | < 0.05 |
| Sodium balance ($r^2 = 0.49$) | | | |
| Urine output | - 0.9 | 0.27 | < 0.0001 |
| Postnatal age | + 0.4 | 0.19 | < 0.001 |
| Gestational age | + 0.2 | 0.02 | < 0.05 |
| Amino acid intake | + 0.5 | 0.01 | < 0.05 |

Table 2. Characteristics of 154 infants divided into 3 groups of mean amino acid intake. (LAA) low amino acid intake; (MAA) medium amino acid intake; (HAA) high amino acid intake; (RDS) respiratory distress syndrome; (hsPDA) hemodynamically significant patent ductus arteriosus; (PCA) post conceptional age. ¹ Intraventricular haemorrhage grade 3 or 4 and/or periventricular leukomalacia. ²Infants lost to follow-up: 13 of 154. *p<0.05 versus LAA group; °p<0.05 versus MAA group.

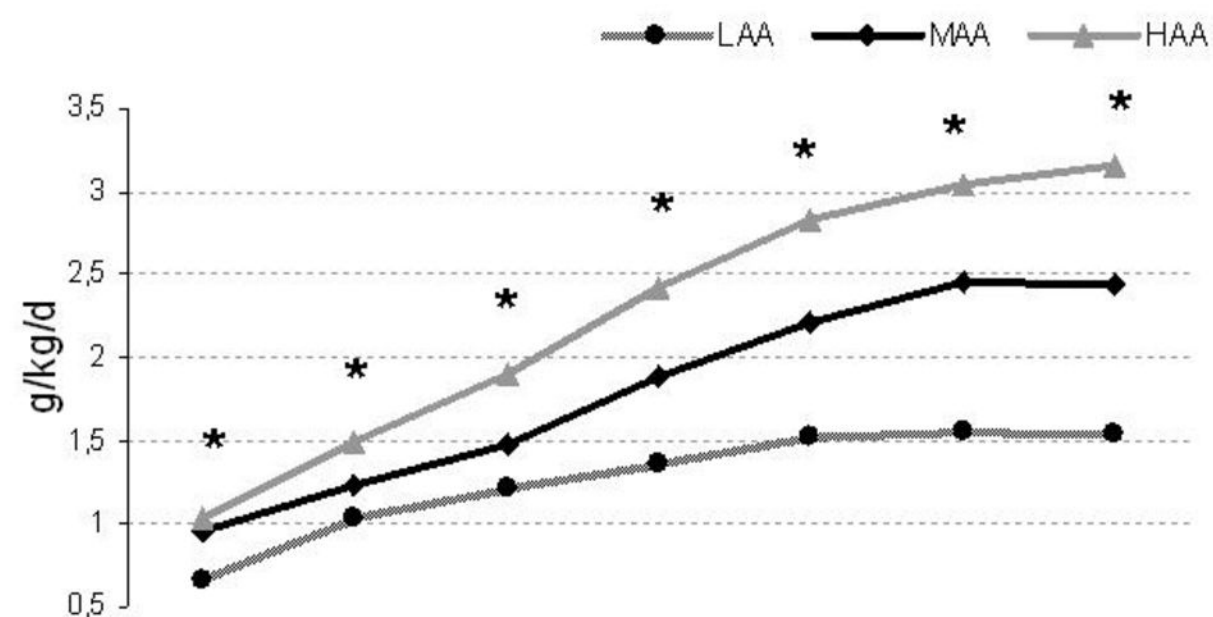
| Groups (number of patients) | LAA (48) <1.50 g/kg/d | MAA (53) 1.5-2.0 g/kg/d | HAA (53) > 2.0 g/kg/d | ANOVA p |
|------------------------------------------------------|---------------------------------|-----------------------------------|---------------------------------|--------------------------|
| Central venous line > 5 days (%) | 21 | 87 * | 100 * ° | < 0.001 |
| Enteral feeding (% tot feed volume) | 32 | 12.8 * | 8.9 * ° | < 0.001 |
| <u>Characteristics at birth</u> | | | | |
| Birth Weight (g) mean ± SD | 1595 ± 284 | 1210 ± 295 * | 1143 ± 332 * | < 0.001 |
| Gestational Age (weeks) mean ± SD | 31.2 ± 1.4 | 29.2 ± 1.9 * | 29.2 ± 1.6 * | < 0.001 |
| <u>Prenatal characteristics</u> | | | | |
| Antenatal steroids (%) | 89 | 74 | 83 | n.s. |
| Caesarean section (%) | 76 | 77 | 85 | n.s. |
| <u>Postnatal characteristics</u> | | | | |
| RDS requiring surfactant (%) | 66 | 83 * | 85 * | < 0.05 |
| Hypotension requiring treatment (%) | 4.3 | 13 | 19 * | n.s. |
| HsPDA requiring treatment (%) | 4.3 | 39 * | 56 * | < 0.001 |
| Oxygen dependency at 36 weeks PCA (%) | 4.3 | 13 | 19 * | n.s. |
| Necrotizing enterocolitis (%) | 2.1 | 1.9 | 1.9 | n.s. |
| Severe abnormal cerebral ultrasound (%) ¹ | 2.1 | 1.9 | 1.9 | n.s. |
| Cerebral palsy at 1 year follow-up ² | 2.3 | 2.1 | 2.0 | n.s. |
| <u>Mean nutritional intakes</u> | | | | |
| Amino acids (g/kg/d) mean ± SD | 1.2 ± 0.6 | 1.8 ± 0.7 * | 2.3 ± 0.8 * ° | < 0.0001 |
| Energy (Kcal/kg/d) mean ± SD | 55 ± 21 | 58 ± 22 * | 65 ± 25 * ° | < 0.0001 |
| Sodium (mmol/kg/d) mean ± SD | 1.8 ± 1.4 | 2.3 ± 1.7 * | 2.9 ± 1.9 * ° | < 0.0001 |
| Potassium (mmol/kg/d) mean ± SD | 0.6 ± 0.6 | 1.0 ± 0.8 * | 1.1 ± 0.8 * ° | < 0.0001 |
| Water (ml/kg/d) mean ± SD | 123 ± 30 | 129 ± 31 * | 125 ± 28 ° | < 0.05 |

Table 3. Potassium (K) and sodium (Na) metabolism in the 3 groups. ¹Hyperkalemia requiring treatment; (UUN) Urine Urea Nitrogen; (TNI) Total Nitrogen Intake; (TCO₂) Total Carbon Dioxide. *p<0.05 versus LAA group; °p<0.05 versus MAA group. Non adjusted probability was estimated by ANOVA test and ANCOVA test was used to adjust probability for gestational age.

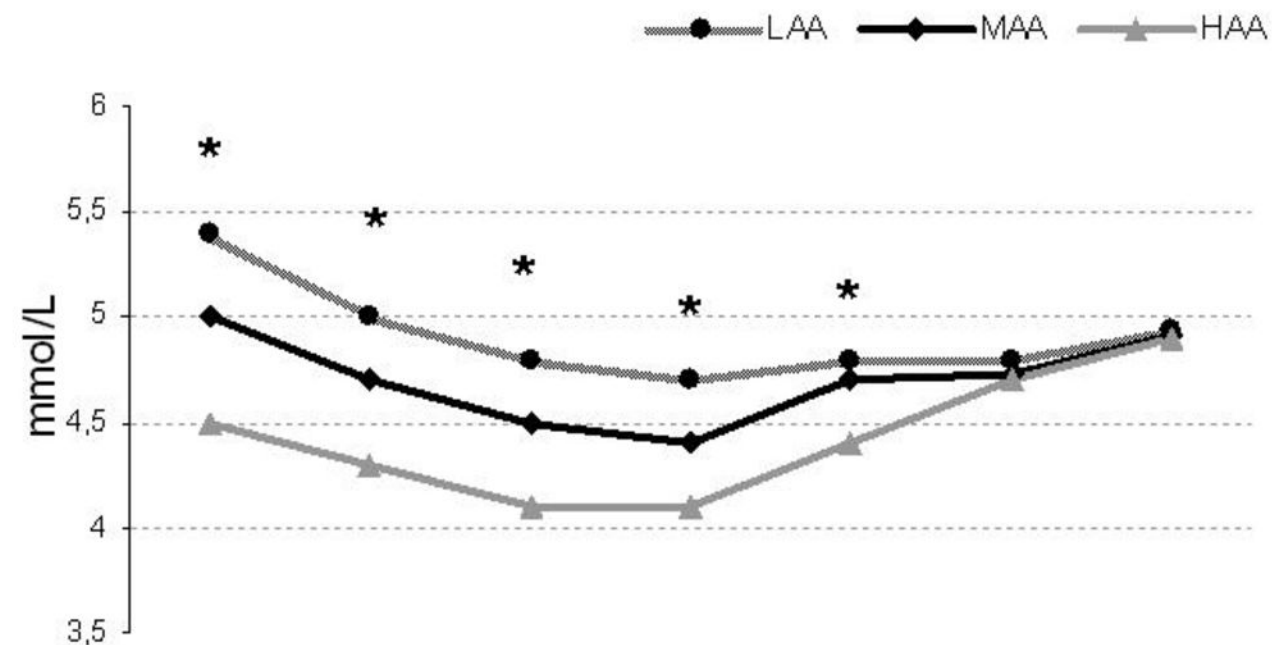
| Groups (number of patients) | LAA (48) <1.50 g/kg/d | | MAA (53) 1.5-2.0 g/kg/d | | HAA (53) > 2.0 g/kg/d | | Non Adjusted | Adjusted for GA |
|-------------------------------------|--------------------------|-------|----------------------------|-------|--------------------------|-------|-----------------|--------------------|
| | | | | | | | p | p |
| HyperKalemia > 6.0 (%) | 15/48 | 31 % | 10/53 | 19 % | 4/53* | 7.5 % | < 0.01 | < 0.01 |
| HyperKalemia ≥ 7.0 (%) ¹ | 4/48 | 8.3 % | 3/53 | 5.7 % | 0/53* | 0.0 % | n.s. | < 0.05 |
| Maximal Kalemia (mmol/L) mean ± SD | 5.7 ± 0.8 | | 5.3 ± 0.8 * | | 4.9 ± 0.8 * | | < 0.0001 | < 0.0001 |
| Mean Kalemia (mmol/L) mean ± SD | 4.9 ± 0.8 | | 4.7 ± 0.8 * | | 4.4 ± 0.7 * | | < 0.0001 | < 0.0001 |
| Urine K (mmol/kg/d) mean ± SD | 0.96 ± 0.5 | | 0.84 ± 0.6 * | | 0.75 ± 0.6 * ° | | < 0.01 | < 0.01 |
| K Balance (mmol/kg/wk) mean ± SD | -2.3 ± 1.5 | | 1.1 ± 1.7 * | | 2.6 ± 1.6 * ° | | < 0.0001 | < 0.0001 |
| HyperNatremia ≥ 150 (%) | 0/48 | 0.0 % | 3/53 | 5.7 % | 2/53 | 3.7 % | n.s. | n.s. |
| Maximal Natremia (mmol/L) mean ±SD | 142.8 ± 3.0 | | 144.2 ± 3.6 | | 143.9 ± 3.0 | | n.s. | n.s. |
| Mean Natremia (mmol/L) mean ± SD | 138.2 ± 4.1 | | 138.9 ± 4.4 | | 139.2 ± 4.3 | | n.s. | n.s. |
| Urine Na (mmol/kg/d) mean ± SD | 3.1 ± 1.8 | | 3.8 ± 2.2 * | | 3.6 ± 1.9 * | | < 0.01 | n.s. |
| Na Balance (mmol/kg/wk) mean ± SD | -9.3 ± 4.8 | | -10.2 ± 8.2 | | -6.9 ± 7.1 * ° | | < 0.05 | < 0.05 |
| Plasma Urea (mmol/L) mean ± SD | 4.3 ± 2.3 | | 5.5 ± 2.8 * | | 6.1 ± 3.4 * ° | | < 0.0001 | < 0.05 |
| UUN (mg/kg/d) mean ± SD | 110 ± 65 | | 135 ± 80 * | | 135 ± 66 * | | < 0.001 | < 0.05 |
| TNI - UUN (mg/kg/d) mean ± SD | 88 ± 89 | | 158 ± 133* | | 227 ± 128* ° | | < 0.0001 | < 0.001 |
| Urine output (ml/kg/d) mean ± SD | 3.2 ± 1.4 | | 3.5 ± 1.5 * | | 3.3 ± 1.5 | | < 0.05 | n.s. |
| TCO ₂ (mmol/L) mean ± SD | 22.4 ± 2.8 | | 21.4 ± 2.9 * | | 21.5 ± 1.5 * | | < 0.01 | n.s. |



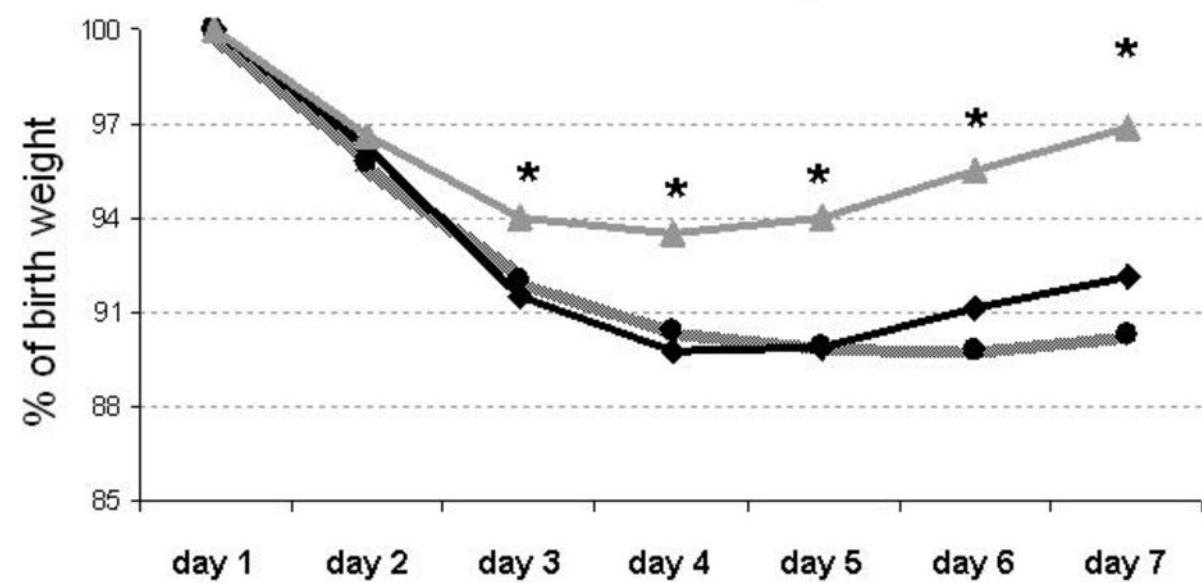
amino acid intake



kalemia



weight evolution



natremia

