

Determinants of Urea Production and Mineral Retention in Parenterally Fed Preterm Infants

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ABSTRACT

Objective: To determine how weight for gestational age affects urea and mineral excretion by preterm infants receiving total parenteral nutrition (TPN).

Study Design: Daily urine samples were collected from all preterm infants given high calcium TPN, providing 30 kcal/g amino acids, during its first 44 months of use, and from all those given standard TPN, providing 25 kcal/g amino acids, over the previous 24 months. Urine urea and mineral excretion were measured as follows: Urea excretion mmol/kg/day = Urine urea/urine creatinine X creatinine production Creatinine production $\mu\text{mol/kg/day} = -2.07 + 2.34 \times \text{gestational age in weeks}$

Results: High calcium TPN was evaluated in 52 infants. Urea excretion did not rise with increasing TPN intake. During the first week, urea excretion increased with weight for gestational age, with higher rates in above average than below average

weight infants. It also increased with gestational age in above average but not below average weight infants. Below average weight infants had lower potassium and phosphate excretion than those above average.

Standard TPN was evaluated in 20 infants. Urea excretion increased with TPN intake to higher levels than on high calcium, and also increased with weight for gestational age.

Conclusion: Urea excretion was simple to measure, with remarkably consistent daily results in individuals. Below 30 weeks gestation infants on TPN providing 30 kcal/g amino acids had urea excretion $< 0.1 \text{ g urea N/kg/day}$, $< 3.5 \text{ mmol/kg/day}$ if below average weight, and $< 0.12 \text{ g urea N/kg/day}$, $< 4.3 \text{ mmol/kg/day}$ if above average weight. Below average weight infants retained more potassium and phosphate during the first week than those above average, and their greater requirements were provided by the TPN.

Key words: Protein catabolism, Gestational age, Energy protein ratio, Mineral composition

INTRODUCTION

The rate of urea production by the body measures the rate of amino acid catabolism. This determines how well protein is retained from total parenteral nutrition (TPN) for growth. In the 1950s, the rate of protein breakdown during the first 48 hours, measured as change in serum nitrogen plus urine nitrogen excretion, was found to be low in normal term and moderately preterm infants, but much higher in those affected by perinatal asphyxia, respiratory distress syndrome or very low birth weight [1,2]. Without parenteral fluids hyperkalaemia rapidly developed in babies with high rates of protein breakdown [2]. Parenteral glucose infusions reduced protein breakdown [3] and hyperkalaemia [4], with cumulative balance studies showing a close relation between nitrogen and potassium retention [5].

Urea production by sick preterm infants was measured in the 1980s by collecting all urine and correcting change in plasma urea for change in weight [6]. During the first 48 hours while on 10% glucose, small for gestation infants had the lowest rates, with higher rates in ventilated infants and the greatest rates in those with evidence of ischaemic damage on cranial ultrasound, as shown in [Table/Fig-1]. Urea production decreased after 48 hours when TPN providing 28 kcal/g amino acids was started. Once again this study found a close relation between protein and intracellular potassium as well as phosphate metabolism. During the first 48 hours on 10% glucose, around 6 mmol of potassium were produced by cells for each gram of nitrogen incorporated into urea, and from 48 hours to 7 days on TPN, around 5 mmol of potassium and 4 mmol of phosphate were retained in soft tissue with each gram of nitrogen.

The ratio of energy to protein provided by TPN governs the rate of protein catabolism, which increases when low energy to protein ratios are provided, in order to meet the infant's energy needs.

This consumes protein that otherwise could be used for growth. TPN, with an inappropriate amino acid composition for neonatal use, only produced elevated plasma phenylalanine levels when less than 30 kcal/g amino acids were given [7]. This indicates that the lowest energy protein ratio that can be given without increasing protein catabolism is 30 kcal/g amino acids. Ratios above this provide insufficient protein for growth. The previous article confirmed that high calcium TPN providing 30 kcal/g amino

Age		n	Before 48 hours	n	After 48 hours	n	After 48 hours
Fluids			10% Glucose		TPN		10% Glucose
Infants	SGA	10	2.99 \pm 1.74	7	2.32 \pm 0.53		
	AGA/LGA	51	5.03 \pm 1.81	25	4.28 \pm 1.81	4	4.51 \pm 1.44
Not ventilated	SGA	3	0.91 \pm 0.55				
	AGA/LGA	9	3.17 \pm 2.18				
Ventilated	SGA	5	3.97 \pm 1.17				
	AGA/LGA	26	4.94 \pm 1.06				
Ischaemia	SGA	2	2.57, 4.79				
	AGA/LGA	16	6.23 \pm 1.69				

[Table/Fig-1]: Urea production in mmol/kg/day of 24 to 35 weeks gestation preterm infants in 1986 (6)

acids did not increase protein catabolism and produced normal growth, whereas standard TPN, providing 25 kcal/g amino acids increased protein catabolism compromising growth [8]. The purpose of this study was to examine how the growth of babies at birth affects protein catabolism and hence mineral retention from TPN, with the particular aim of clarifying how this affects potassium and phosphate requirements. This information is vital to avoid hypercalcaemia when providing sufficient calcium in TPN for the needs of preterm infants.

METHODS

High calcium TPN was prospectively evaluated for 44 months following its introduction in 1998 and compared with standard TPN, evaluated over the previous 24 months. During these periods all infants admitted to the neonatal unit at Taranaki Base Hospital, New Zealand, requiring TPN because of respiratory or feeding problems, were studied. The compositions of these TPN regimens are shown in [Table/Fig-2]. Standard TPN provided 25 kcal/g amino acids whereas high calcium TPN provided 30 kcal/g amino acids. Infants given high calcium TPN received low sodium TPN, with the same glucose and amino acid composition, during the first 48 hours.

TPN		Standard	Low sodium	High Calcium
Glucose	g/L	100	125	125
Amino acids	g/L	27.17	24.5	24.5
Nitrogen	g/L	3.84	3.49	3.49
Energy: protein with 17.7% Lipid	kcal/g amino acids	25	30	30
Sodium	mmol/L	25	24	39
Chloride	mmol/L	20.83	24	39
Potassium	mmol/L	25	25	25
Calcium	mmol/L	10	10	17.5
Phosphate	mmol/L	10	12	19.5
Magnesium	mmol/L	2.42	2	2

[Table/Fig-2]: Composition of TPN regimens

Weight centile		Below 10 th		10-50 th		Above 50 th		Above 50 th
Gestation	week					Below 30		30 and above
Infants	n	8		13		11		20
Birth weight	g	1134 ± 436		1258 ± 332		1106 ± 286		2035 ± 264
Gestation	week	31.5 ± 3.5		29.2 ± 2.5		26.5 ± 2.0		31.9 ± 1.0
BW/50 th centile	%	63.97 ± 14.48		91.96 ± 4.34		111.48 ± 9.02		114.47 ± 10.11
Balance studies	n	39		59		62		77
Postnatal age	hour	92.15 ± 42.90		99.30 ± 39.26		94.76 ± 41.09		93.37 ± 37.17
TPN	mL/kg/day	98.5 ± 20.9		105.8 ± 28.3		103.0 ± 23.7		102.3 ± 23.6
17.7% Lipid	mL/kg/day	9.3 ± 2.8		10.0 ± 2.9		9.7 ± 3.0		9.5 ± 2.9
Urine urea nitrogen	g/kg/day	0.063 ± 0.020		0.071 ± 0.028	***	0.098 ± 0.033	**	0.110 ± 0.030
Nitrogen retention	g/kg/day	0.282 ± 0.062		0.298 ± 0.095	*	0.261 ± 0.094		0.248 ± 0.084
Urine potassium	mmol/kg/day	0.777 ± 0.562	*	1.073 ± 0.572	***	1.468 ± 0.507		1.214 ± 0.567
Potassium retention	mmol/kg/day	1.685 ± 0.566		1.571 ± 0.686	***	1.093 ± 0.793		1.343 ± 0.738
Urine phosphate	mmol/kg/day	0.185 ± 0.149	**	0.293 ± 0.189	**	0.400 ± 0.204		0.428 ± 0.241
Phosphate retention	mmol/kg/day	1.804 ± 0.480		1.876 ± 0.669		1.661 ± 0.662		1.607 ± 0.716
Soft tissue P retention	mmol/kg/day	0.844 ± 0.251		0.797 ± 0.368	*	0.654 ± 0.372		0.613 ± 0.423
Urine magnesium	mmol/kg/day	0.039 ± 0.017		0.029 ± 0.013		0.033 ± 0.016		0.038 ± 0.017
Magnesium retention	mmol/kg/day	0.157 ± 0.041		0.180 ± 0.053		0.173 ± 0.051		0.167 ± 0.046
Urine calcium	mmol/kg/day	0.081 ± 0.098	**	0.027 ± 0.018		0.034 ± 0.021		0.035 ± 0.022
Calcium retention	mmol/kg/day	1.598 ± 0.430		1.776 ± 0.534		1.679 ± 0.543		1.650 ± 0.552

[Table/Fig-3]: Mineral balance studies on high calcium TPN during the first week in infants classified according to their weight for gestational age

* p < 0.05 ** p < 0.01 *** p < 0.001

Whenever possible infants below 30 weeks gestation were started on TPN on day 1. In larger babies TPN was sometimes not started until day 2-3, when milk feeds were not tolerated. While receiving TPN, daily urine samples were obtained and analyzed without delay for urea, creatinine, Na, K, Ca, Mg, Cl and PO₄.

All fluid intakes, blood results and drug therapies were recorded. Urine samples obtained while any infant received dexamethasone were excluded from this study. All samples in this study were obtained while infants were free of infection.

Measurements of creatinine production [6] were used to measure urine urea and mineral excretion as follows:

Urea excretion = [Urea] urine / [Creatinine] urine × Creatinine production

Creatinine production = -2.07 + 2.34 × gestational age (weeks) × μmol/kg/day

Soft tissue phosphate retention = PO₄ retention - 0.6 × Ca retention.

Urea excretion was expressed in g urea nitrogen/kg/day to allow for comparison with TPN amino acid nitrogen intake. Urea nitrogen balance overestimates total nitrogen balance, because it does not include urine losses of non-urea nitrogen. Mineral excretion was expressed in mmol/kg/day.

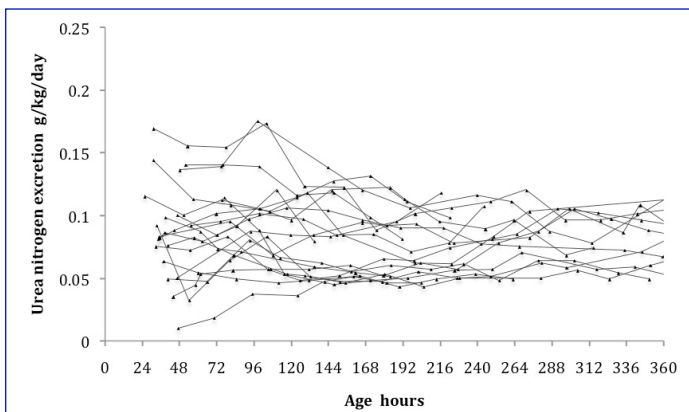
Growth at birth was measured as birth weight expressed as percentage of the 50th centile weight for the gestational age of the infant [9,10]. Results were expressed as mean ± sample standard deviation (SD) and analysis performed with standard parametric tests and linear regression analysis.

RESULTS

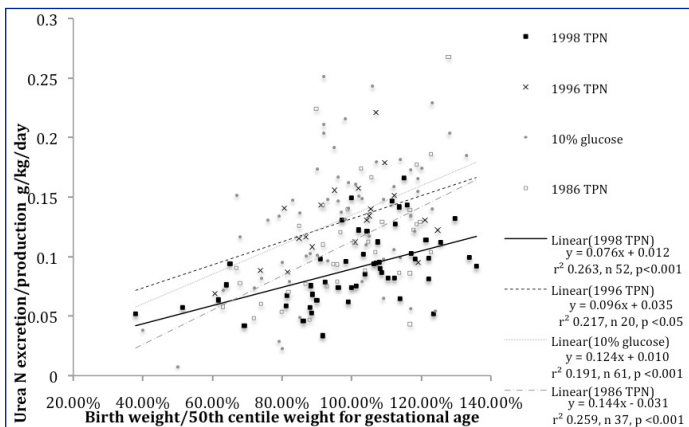
High calcium TPN was evaluated in 52 preterm infants, who were classified according to their weight for gestational age as shown in [Table/Fig-3]. Measurements of urea excretion were remarkably consistent from day to day in individuals, as [Table/Fig-4] shows for below 30 weeks gestation infants. This testifies to the accuracy of this simple method of measuring the rate of protein breakdown in infants receiving TPN.

The mean rate of urea excretion during the first week increased with weight for gestational age, with higher rates in above average

than below average weight infants, as shown in [Table/Fig-5]. It also increased with gestational age in above average but not below average weight infants. Above average weight infants of 30 or more weeks had higher rates than those below 30 weeks gestation, as shown in [Table/Fig-3]. After day 4 less than 30 weeks gestation infants had urea excretion < 0.1 g urea N/kg/day, < 3.5 mmol/kg/day if below average weight, and < 0.12 g urea N/kg/day, < 4.3 mmol/kg/day if above average weight. Urea nitrogen excretion did not rise with increasing TPN nitrogen



[Table/Fig-4]: Urea nitrogen excretion in 20 infants less than 30 weeks gestation on high calcium TPN during the first 15 days



[Table/Fig-5]: Urea nitrogen excretion during the first week increased with weight for gestational age on 1998 high calcium TPN and at higher levels on 1996 standard TPN. Urea nitrogen production also increased with weight for gestational age on 10% glucose during the first 48 hours and on 1986 TPN after 48 hours.

intake in above average weight infants below 30 weeks gestation, r^2 0.026, n 155, and 30 or more weeks gestation, r^2 0.003, n 86. It increased only slightly in below average weight infants as low rates recovered towards normal, $y = 0.072x + 0.035$ g N/kg/day, r^2 0.072, n 203, $p < 0.01$. This confirms that high calcium TPN did not increase protein catabolism.

Below average weight infants had lower potassium and phosphate excretion and retained more potassium and phosphate during the first week than those of above average weight, as shown in [Table/Fig-3]. High calcium TPN provided enough extra potassium and phosphate to meet the increased needs of small for gestation infants. However these infants had significantly higher urine calcium excretion, compared to the very low levels found in other infants, but not sufficiently high to cause hypercalcaemia in any of them. On the other hand the excess of phosphate in high calcium TPN for appropriate or large for gestational age infants was responsible for causing prolonged early asymptomatic hypocalcaemia with high plasma phosphate in 2 infants.

Standard TPN was evaluated in 20 infants. This TPN increased urea excretion, which again varied with weight for gestational age, as shown in [Table/Fig-5].

DISCUSSION

Urea excretion equals the rate of urea production when plasma urea and creatinine stabilize after delivery and measures the rate of protein catabolism, which is determined by two main factors.

Optimal energy to protein ratio

TPN providing 30 kcal/g amino acids from birth did not increase protein catabolism and provided sufficient protein for normal growth, whereas TPN providing 25 kcal/g amino acids increased

protein catabolism to meet the baby's energy requirements, leaving insufficient for growth [8]. TPN with 10% glucose providing only 1.6 g/kg/day of amino acids produced urea excretion rates mostly above 0.1 g urea N/kg day, indicating that such low energy and protein TPN increases protein catabolism [11].

Weight for gestational age

Growth restricted infants have lower rates of urea production that do not increase with gestational age. Infants with no restriction to their growth have higher rates of urea production as they mature. This is in keeping with higher rates of protein turnover being needed for higher rates of growth, whereas low rates are needed to conserve available resources in growth restricted babies.

Other factors also affect protein catabolism. Dexamethasone was given to 7 infants on high calcium TPN to treat chronic lung disease. It increased urea excretion, but this was offset by greater TPN intake from improved breathing, thereby preventing growth retardation [8]. Previous studies have shown that protein catabolism is increased by perinatal asphyxia, hypoxic ischaemic injury, respiratory distress syndrome and positive pressure ventilation [1,2,6]. Infection should be avoided by meticulous attention to aseptic technique in delivering TPN [8]. However when it occurs protein catabolism increases dramatically and TPN should be stopped.

This study shows that urea excretion is easy and accurate to measure on spot urine samples. Such measurements may be of value in helping to prevent postnatal growth retardation in very premature babies.

Current recommendations are to provide TPN from soon after birth with a high protein content, over 30 g/L amino acids, but with only up to 10% glucose, providing around 22 kcal/g amino acids [12,13]. This high protein content may make up for energy deficiency and still provide sufficient for growth. Infants receiving such TPN developed increases in blood urea in proportion to the amount of protein given, confirming that such regimens increase protein catabolism [14], and fail to prevent early postnatal growth failure in below 28 weeks gestation infants [12].

The rate of protein catabolism determines how much protein from TPN is available for growth after the infant's energy needs have been met. This can now be simply measured on spot urine samples. After day 4, less than 30 weeks gestation infants should have urea excretion below 0.1 g urea N/kg/day, 3.5 mmol/kg/day if below average in weight, and below 0.12 g urea N/kg/day, 4.3 mmol/kg/day if above average in weight. Stable babies with higher urea excretion need more energy to improve protein retention for growth. This can be achieved by increasing the TPN glucose concentration from 10% to 12.5%.

The first formulation of high calcium TPN contained 18 mmol/L of both calcium and phosphate, but it was soon discovered that small for gestation infants given such TPN developed hypercalcaemia. Increasing the phosphate content in the current formulation of high calcium TPN prevented babies with severe growth retardation from developing hypercalcaemia. During the first week on high calcium TPN, small for gestation infants had low urine phosphate and only slightly higher urine calcium than the low rates of excretion found in appropriate and large for gestation infants. Below average weight infants retained more nitrogen, phosphate and potassium in their soft tissues than above average weight infants. Small for gestation infants had the greatest potassium and phosphate requirements, adequately provided by high calcium TPN. However the excess of phosphate in high calcium TPN for appropriate or large for gestation infants may cause prolonged early hypocalcaemia with high plasma phosphate.

In the absence of other sources of information, fetal body composition data has been used as a guide to parenteral mineral requirements [15]. Fetal body composition data estimated nitrogen

and calcium retention rates similar to those achieved on high calcium TPN, but estimated that 0.75 mmol/kg/day of potassium, 0.58 mmol/kg/day of soft tissue phosphate and 0.12 mmol/kg/day of magnesium are retained at 24-29 weeks gestation. These estimates are considerably below those achieved on high calcium TPN, as shown in [Table/Fig-3], possibly because they are based predominately on below average weight infants, who are deficient in these minerals. They should not be used as a guide when designing TPN regimens.

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