Urea Production Is Increased in Neonatal Piglets Infused with Alanine at 25, 50, and 75% of Resting Energy Needs$^{1,2}$

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ABSTRACT

To study the ability of neonatal piglets to metabolize a nitrogen load and excrete it as urea, 12 newborn piglets, 6 small (0.95 ± 0.16 kg; expt. 1) and 6 large (1.86 ± 0.16 kg; expt. 2), were infused intravenously with alanine (n = 8; 4 large, 4 small; treatment) or glucose (n = 4; 2 large, 2 small; control) at equal ATP equivalents, supplying 25–75% of the resting energy requirements of the piglet over 18 h. To adjust for differences in the baseline urinary urea nitrogen excretion, blood urea nitrogen (BUN) and estimated urea production between groups, the absolute changes from baseline to maximum value for piglets infused with alanine, and from baseline to the 24-h value for piglets infused with glucose were evaluated statistically. There were no differences (0.1 < P < 0.3) in the absolute changes from baseline to maximum values of urinary urea nitrogen, BUN or estimated urea production between small and large piglets, respectively. Differences in the changes from baseline were detected between alanine and glucose infusions. Small piglets required more time (P < 0.005) for BUN to maximize after initiation of the alanine infusion, suggesting that small piglets require more time to process a nitrogen load. Infusion of alanine resulted in at least a threefold increase from baseline in the rate of calculated urea production, suggesting that neonatal piglets, small or large, have reserve capacity to metabolize nitrogen and excrete it as urea.

KEY WORDS: • piglets • neonate • urea cycle • alanine • nitrogen

The appropriate mixture of energy sources that should be provided to premature, low-birth-weight (LBW)$^4$ human infants in the first few days of life remains a topic of debate (Heird and Gomez 1993). There is evidence that amino acid supplementation initiated within the first 24 h of life results in positive nitrogen balance and increased rates of protein turnover and synthesis (Bauer et al. 1991, Mitton and Garlick 1992, Rivera et al. 1993, Saini et al. 1989, Van Goudoever et al. 1995, Van Lingen et al. 1992). Therefore, withholding amino acids for the first few days of life in premature infants due to suspected immaturity (limited capacity for urea production) metabolic pathways (Batshaw and Brusilow 1978, Hannning and Zlotkin 1989) is a questionable practice. It is difficult to provide adequate nutrients to LBW premature infants to achieve growth rates comparable to those observed in utero because of various limitations, including gastrointestinal immaturity and fluid restriction. Premature infants are born with limited reserves of glycogen and fat. At 31 wk gestation, an infant is born with ~0.5 and 2.3% of body weight as glycogen and fat, respectively, compared with 1 and 16% in the 40-wk term infant (Fomon et al. 1982, Widdowson 1968, Ziegler et al. 1976). Because newborn infants are in a general catabolic state, they must rely on body protein as a source of energy, if not provided with adequate sources of energy to support growth and development in the immediate newborn period.

The benefit of supplementation with nitrogen has been shown by comparing infants consuming equal amounts of energy, with or without added amino acids (Anderson et al. 1979). Results show that infants fed 251 kJ (60 kcal)/(kg • d) as glucose and lipid remain in negative nitrogen balance [−132 mg N/(kg • d)] compared with those fed the same amount of energy, but provided with 2.5 g/(kg • d) of amino acids [+178 mg N/(kg • d)]. On the basis of this information and other studies, Heird and Gomez (1996) suggested that intravenous (IV) amino acid supplementation with at least 2.0 g/(kg • d) appears to be safe and advantageous for premature LBW human infants and should be initiated in the first 24 to 48 h of life.

The ability of neonates to tolerate supplemental amino acids in the first days of life is related directly to the utilization of the amino acids in the synthesis of protein and the disposal of the excess nitrogen via the urea cycle (Brusilow and Hor-
wich 1989, Morris 1992). With an impaired urea cycle, infants may experience an accumulation of ammonium, which can be fatal (Brusilow and Horwich 1989). Information on the capacity of neonates to detoxify and excrete ammonia as urea is essential to decisions regarding the appropriate level of amino acid supplementation at birth.

Newborn piglets (1–2 kg) are approximately the same weight and have about the same rate of heat production as LBW (1–1.5 kg) premature infants. The body composition of premature human infants and neonatal piglets is similar in that they both have limited fat and glycogen stores to draw on as energy sources (Widdowson 1968). In addition, neonatal piglets are similar to premature human infants with regard to the physiology of the gastrointestinal system as well as their limited thermal insulation and ability to shiver (Book and Bustad 1974, Cooper 1975, Miller and Ullery 1987). These similarities provide a basis for using piglets as a model with which to study certain elements of nutrition and metabolism that might relate to human preterm infants.

On the basis of V_{O2} comparisons, fetal piglets (Kennan and Cohen 1959) and human fetuses (Raitha and Suikkonen 1968) have a similar ability to synthesize urea in utero. The developmental pattern of the activities of the five urea cycle enzymes is similar in both species, with argininosuccinate synthetase (AS) rate limiting in both cases. However, the in vitro measurement of the activity of an enzyme is carried out in a very controlled, nonphysiologic environment, with pH and substrate concentrations optimal for maximum enzyme activity. Enzyme activities measured in vitro do not represent the cellular setting and cannot be used to forecast substrate flux relationships.

One additional problem must be considered because the urea cycle enzymes carbamoyl phosphate synthetase-1 and ornithine transcarbamylase are in the mitochondrial matrix, whereas the other three urea cycle enzymes are in the cytosol. The production of urea requires transporters, and the activity of ornithine/citrulline, aspartate, malate, and glutamine (a source of ammonium) transporters would have to be measured to estimate a rate of production. For these reasons, we felt that infusion of a nontoxic single amino acid may provide a means whereby we could obtain an estimate of the urea production potential of a newborn animal.

The following study was conducted to determine the ability of intact neonatal piglets to metabolize a nitrogen load given as alanine and to excrete it in the form of urea. On the basis of urinary-N excretion from piglets deprived of food for 60 h (Mickelson et al. 1995), our minimum expected urea-N production rate was 1.2 mmol N/(h · kg^{0.75}). To determine the maximum potential, we infused piglets with alanine at 25, 50 and 75% (this is 1.8, 3.6 and 5.3 times, respectively, the N expected due to protein catabolism during food deprivation) of their resting energy requirement. The use of a single amino acid does not support protein accretion and subjects the animal to a N load that must be metabolized and excreted. We anticipated a capacity that was 3–5 times that required during food deprivation.

MATERIALS AND METHODS

Chemicals and supplies. Liquid phenol (90%) and 98% sulfuric acid were obtained from Fisher Scientific (Pittsburgh, PA). Urease (EC 3.5.1.5) and tyrosine were obtained from Sigma Chemical (St. Louis, MO). L-[U-^{14}C]-Alanine was obtained from New England Nuclear (Boston, MA). Amino acid standards for HPLC analysis were obtained from Pierce Chemical (Rockford, IL). L-Alanine was obtained from U.S. Chemical (Cleveland, OH). Sodium hydroxide, glucose, sodium chloride and 30% hydrogen peroxide were obtained from Mallinckrodt (Chesterfield, MO). Sodium nitroprusside was obtained from Eastman Organic Chemicals (Rochester, NY). Urea was obtained from Amend Drug & Chemical (Irvington, NJ).

Animals. Twelve male piglets, six (3.5 ± 0.16 kg; experiment 1) and six large (1.86 ± 0.16 kg; experiment 2), of Large White and Landrace breeding, were obtained from Pigg Improvement Company (Spring Green, WI). The idea of using small and large piglets is based on the assumption that smaller pigs may not be as mature as larger ones. This assumption is based on the (unproven) belief that the smaller piglets implanted later and are developmentally delayed. Within 3–6 h of birth, piglets were weighed and assigned to treatment (alanine; n = 8) or control (glucose; n = 4) groups. It is not known how many litters were represented or whether the piglets suckled before being removed from the sow. Care and handling of piglets were reviewed and approved by the College of Agricultural and Life Sciences Research Animal Resource Committee.

Animal preparation. Surgical procedures were performed in an aseptic environment. Piglets were anesthetized with 3% halothane (Halocarbon Laboratories, North Augusta, SC) in oxygen (Liquid Carbonic, Chicago, IL) and maintained with 1% halothane in oxygen throughout the surgery. The umbilical stump was cut close to the body to expose the two umbilical arteries, umbilical vein and urachus. A polyvinyl chloride catheter (3.5 french, Argyle, Sherwood Medi-
cal, St. Louis, MO) was inserted into each artery, one advanced to the level of the kidneys for infusion, and one advanced to several centimeters below the aortic arch for blood sampling. A catheter was also inserted ~4 cm, through the urachus, into the bladder to facilitate continuous urine collection. This was accomplished by puncturing the side wall of the urachus with a 25-gauge needle and using a catheter introducer (Beckton-Dickinson, Rutherford, NJ) to hold the lumen open while inserting a section of PE-50 tubing (i.d. 0.58 mm; o.d. 0.965 mm, Intramedic, Beckton-Dickinson, Sparks, MD) with the tip cut at an angle. Catheters were secured with silk suture (Ethicon, Somerville, NJ) and an antiseptic-germicide (Betadine; Purdue Frederick, Norwalk, CT) applied to reduce infection. Catheter placement has been verified in previous experiments at necropsy. Surgeries required ~1 h; then piglets were bandaged and placed in their experimental chambers for recovery. Experimental chambers were cylindrical (45 cm long × 14 cm i.d.) with space for the piglets to move front to back, and vents at each end for air flow. Piglets recovered from anesthesia within 1–2 h and then were fitted with an orogastric (OG) catheter (12 french, Bard, Covington, LA) for infusion of water. At this time, the IV umbilical and OG oral lines were connected to peristaltic infusion pumps (Rainin Rabbit-Plus, Rainin Instrument, Woburn, MA).

Experimental protocol. All piglets were given water intragastrically (IG) until well hydrated (based on the rate of urine excretion). Once piglets were hydrated (~12 h of age), a time zero blood sample was drawn, and the urine and expired ammonia collections were started. All piglets were infused IG with water (10 mL/h) for the first 6 h of experiment (baseline; Table 1). Piglets were then switched to a 6-h IV infusion of alanine (treatment; n = 8) or glucose (control; n = 4) at 10 mL/h, calculated to meet 25% of their resting energy expenditure (REE), based on ATP equivalents. Piglets were then infused for 6 h with 50% REE as alanine or glucose, followed by a 6-h infusion of 75% REE as alanine or 50% REE as glucose (Table 1). All piglets were then switched back to infusion of water IG for the remaining 12 h of the experiment (washout). After the 12-h washout period, piglets were anesthetized with 3% halothane in oxygen and killed by injection of 10 mL saturated KCl via the indwelling catheters.

The REE, in units of ATP turnover [138 nmol ATP/h · kg^{0.75}], of piglets was calculated on the basis of expired CO_{2} (Tetrick et al. 1995). Infusion rates of alanine or glucose [mmol/h · kg^{0.75}] were based on the expected production of ATP from their catabolism (16 ATP/mol alanine; 38 ATP/mol glucose) and the amount of ATP required to meet the fraction of REE required based on the protocol. All solutions to be infused IV were filtered through sterile 0.2-μm filters (Micron Separations, Westboro, MA) into sterile flasks.

Alanine was chosen as the substrate because it is not toxic at the levels used and is involved directly in transamination. Alanine reacts
with α-ketoglutarate via alanine aminotransferase to form glutamate and pyruvate. Glutamate is acted on by glutamate dehydrogenase and yields free ammonium. Ammonium in turn reacts with oxaloacetate via aspartate aminotransferase to form aspartate and pyruvate. Therefore, infusion of alanine presents the animal with transaminated nitrogen (ammonium and aspartate), which can be converted to urea and excreted to prevent hyperammonemia.

The piglets infused with glucose served as an energy control for those infused with alanine by receiving an equal amount of ATP equivalents from a nonnitrogenous source. Thus, changes in the rate of urinary urea nitrogen excretion and BUN may be attributed solely to the infusion of alanine and not to another factor. The rationale for not exceeding 50% REE as glucose to control piglets is based on previous observations in our laboratory that IV infusion of glucose above 50% REE results in the appearance of glucose in the urine above baseline levels, indicating that the reabsorption capacity of the kidneys has been exceeded. It is not known at what blood concentration of alanine the filtering capacity of the kidneys is exceeded because alanine in the urine was not measured.

**Sample collection.** Urine was collected continuously and sampled hourly throughout the experiment from the urachal catheter, which dripped directly into 12-mL tubes stabilized at pH 2 with 100 μL of 6 mol/L HCl. Blood (0.25 mL) was sampled every 2 h over the first 24 h of the experiment and every 3 h during the 12-h washout period. Blood samples were deproteinized by the method of Somogyi (1930) and the supernatants stored at −10°C until analysis. A second blood sample (0.1 mL) was taken at each time for alanine determination by HPLC (Pico-Tag; Waters, Milford, MA; Billingmeyer et al. 1987). The α-amino nitrogen in the water space of the large alanine-infused piglets was determined by the ninhydrin reaction (Rosen 1957) performed on the supernatants of acid-extracted piglet homogenates.

**Calculations.** The equation used for the calculation of the rate of urea production in this study was very similar to that used by Miron et al. (1991):

\[ U_p = U_i + (U_{l2} - U_{b1}) \]

where, \( U_i \) is urea produced, \( U_i \) is urea excreted in urine over a given period of time, and \( U_{l2} \) and \( U_{b1} \) correspond to the estimated total body urea in the water space of the piglet at the beginning and end of the timed urine collection. To estimate the body urea content, it was assumed that the piglet is 80% water, on the basis of our own data (Mickelson, unpublished data from our laboratory, comparable to piglets 12 h old (n = 16, 81% water; piglets infused IV at 50% REE) and 72 h old (n = 7, 82.5% water) and that urea is distributed uniformly in the water space of the piglet (Mitchell and Steele 1987).

**RESULTS**

Complete collection of urine depends on the position of the catheter in the bladder, which can be influenced by the position of the piglet in the chamber. For this reason, the volume of urine collected each hour varies, and may not represent the volume of urine produced. Therefore, results for urea excretion, presented in Figure 1, are 3-h averages, and results for urea production (Fig. 3) are 4-h averages.

The data for expired ammonia gas are not shown over the entire 36-h experiments because they accounted for <0.5% of infused nitrogen and cannot be an important route of nitrogen excretion for neonatal piglets challenged with a nitrogen load.

**Urineal urea nitrogen (UUN).** It is likely, but not known, that the large piglets assigned to receive alanine were from a different litter than the large piglets assigned to receive glucose.
cose; this may explain the significant difference ($P = 0.03$) in baseline UUN excretion rates [mg N/(h $\cdot$ kg$^{0.75}$)]; Fig. 1. The change from the baseline to the maximum average UUN excretion rate [mg N/(h $\cdot$ kg$^{0.75}$)] for piglets infused with alanine ($18.6 \pm 3.2$, small; $23.6 \pm 7.6$, large) was significantly different ($P < 0.001$) from the change from baseline to the 24-h average UUN excretion rate for piglets infused with glucose ($-4.7 \pm 6.6$, small; $1.7 \pm 0.5$, large). However, there was no difference in the change from baseline to maximum when comparing small and large piglets infused with alanine ($P = 0.11$), or from baseline to 24 h when comparing small and large piglets infused with glucose ($P = 0.11$).

**Blood ammonium nitrogen.** In preliminary background work, we used the method of Rahiala and Kekomäki (1970) to determine whether whole-blood ammonium concentrations varied with treatment. The results from a preliminary study were as follows: fasted piglets, $110 \pm 48$ mmol/L, $n = 6$; piglets infused with Ala at 75% of their REE for 6 h, $278 \pm 48$ mmol/L, $n = 3$; and for piglets infused with glucose at 50% of their REE, $59 \pm 2$ mmol/L, $n = 2$. The values for piglets infused with glucose were probably lower because these piglets were not totally dependent on body protein for meeting their energy needs. Because the assay requires 1 mL of whole blood for duplicate assays, and values were such that they would have no effect on the urea pool and production calculations ($\mu$mol/L vs. mmol/L), we elected not to make further measurements of ammonium concentrations in this experiment.

**Blood urea nitrogen (BUN).** The patterns of BUN concentrations (mmol/L; Fig. 2) throughout the experiment were very similar to the patterns of UUN excretion for all pigs. As was done with UUN excretion, to adjust for the difference in baseline concentrations between treatment groups ($P = 0.01$), a statistical analysis was performed on the absolute change in BUN concentration from the baseline period (mean of h 2, 4 and 6) to the maximum BUN for piglets infused with alanine ($19.1 \pm 2.2$, A; $21.6 \pm 3.3$, B) significantly different from the increases from baseline to the 24-h BUN for piglets infused with glucose ($-1.9 \pm 2.5$, A; $1.8 \pm 0.7$, B), $P < 0.001$. There were no differences between these changes for small and large piglets within treatment groups (alanine or glucose; $P = 0.11$). The time (in hours) that it took to reach maximum BUN following the start of alanine infusion was significantly different between small and large piglets ($P < 0.005$). Abbreviations: IG, intragastric; REE, resting energy expenditure.

**FIGURE 1** Urinary urea nitrogen (UUN) excretion of small pigs (panel A) infused intravenously (IV) with alanine ($n = 3$) or glucose ($n = 2$) and large pigs (panel B) infused IV with alanine ($n = 4$) or glucose ($n = 2$). Each point is the mean ± SD of 2–4 piglets. The absolute changes from baseline to maximum average UUN excretion rate for piglets infused with alanine ($18.6 \pm 3.8$, A; $23.6 \pm 7.6$, B) are significantly different from the changes from baseline to the 24-h average UUN excretion for piglets infused with glucose ($-4.7 \pm 6.6$, A; $1.7 \pm 0.5$, B), $P < 0.001$. There were no differences between the changes from baseline to maximum (alanine) or from baseline to 24 h (glucose) for small and large piglets within treatment groups ($P = 0.11$). Abbreviations: IG, intragastric; REE, resting energy expenditure.

**FIGURE 2** Blood urea nitrogen (BUN) concentrations (mmol N/L) of small pigs (panel A) infused intravenously (IV) with alanine ($n = 3$) or glucose (gluc) ($n = 2$) and large pigs (panel B) infused IV with alanine ($n = 4$) or glucose ($n = 2$). Each point is the mean ± SD of 2–4 piglets. The increases from baseline (mean of h 2, 4 and 6) to maximum BUN for piglets infused with alanine ($19.1 \pm 2.2$, A; $21.6 \pm 3.3$, B) are significantly different from the increases from baseline to the 24-h BUN for piglets infused with glucose ($-1.9 \pm 2.5$, A; $1.8 \pm 0.7$, B), $P < 0.001$. There were no differences between these changes for small and large piglets within treatment groups (alanine or glucose; $P = 0.11$). The time (in hours) that it took to reach maximum BUN following the start of alanine infusion was significantly different between small and large piglets ($P < 0.005$). Abbreviations: IG, intragastric; REE, resting energy expenditure.
glucose, the pattern of BUN differed from those infused with alanine during the substrate-free washout period. Although not analyzed statistically, it appears that after cessation of the glucose infusion, BUN began to rise. This could be due in part to an increased dependence on body protein as a fuel, which could also be the reason for the sustained elevation of BUN in the small piglets after cessation of the alanine infusion.

**Urea production (Uₚ).** Urea production [mmol N/(h · kg⁰·⁷⁵)] (Fig. 3) is calculated on the basis of the change in BUN concentration and the UUN excretion as explained previously within treatment groups (alanine or glucose; Fig. 3). The absolute change from the baseline mean Uₚ [mmol N/(h · kg⁰·⁷⁵)] to the maximum mean Uₚ for piglets infused with alanine (2.7 ± 1.2, small; 3.7 ± 1.5, large) was significantly larger (P < 0.004) than the absolute change from baseline to the 24-h average Uₚ for piglets infused with glucose (−0.7 ± 0.9, small; −0.01 ± 0.3, large). There was no difference between the change for small and large piglets within treatment groups (P > 0.20).

**FIGURE 3** Urea production [Uₚ; mmol N/(h · kg⁰·⁷⁵)] of small pigs (panel A) infused intravenously (IV) with alanine (n = 3) or glucose (gluc) (n = 2) and large pigs (panel B) infused IV with alanine (n = 4) or glucose (n = 2). Each bar before 24 h represents the mean ± SD Uₚ over a 4-h period. Due to the blood sampling schedule, each bar after 24 h represents the average Uₚ over a 3-h period. The increases from the baseline average Uₚ to the maximum average Uₚ for piglets infused with alanine (2.7 ± 1.2; 3.7 ± 1.5, B) are significantly different from the differences between the baseline mean Uₚ and the 24-h mean Uₚ for piglets infused with glucose (−0.7 ± 0.9, A; −0.01 ± 0.3, B). There were no differences between these changes for small and large piglets within treatment groups (alanine or glucose; P > 0.3). The bar with the asterisk is representative of only two of the small piglets infused with alanine because one of the piglets had no urine output during the last 2 h of the experiment. Elimination of this data point does not change the statistical outcome. Abbreviations: IG, intragastric; REE, resting energy expenditure.

In Figure 3, the bar with the asterisk over it is representative of only two of the small piglets infused with alanine because no urine could be collected from one of the piglets during the final 2 h of the experiment, making the calculation of production invalid. Elimination of this data point did not change the statistical outcome, only the final calculation of urea production rate for the small piglets infused with alanine.

The patterns of urea production followed during the washout period were similar to the patterns of UUN excretion and BUN concentrations. The urea production rates of large piglets infused with alanine returned to baseline [1.8 ± 0.2 mmol N/(h · kg⁰·⁷⁵)], whereas those of small piglets remained elevated (Fig. 3). This could be due to increased endogenous fuel use after cessation of alanine infusion as well as a slower clearance rate of alanine-derived nitrogen-containing intermediates from the circulation in small compared with large piglets. Uₚ of small and large piglets infused with glucose began to rise after termination of the infusion. This is thought to be due to a return to the use of body protein as a fuel after termination of glucose infusion.

**Blood alanine concentrations.** Blood alanine concentrations (mmol/L) were measured for large piglets only (expt. 2, Fig. 4). The absolute change from baseline concentration to maximum concentration for the piglets infused with alanine (6.9 ± 1.7) was significantly different (P = 0.006) from the absolute change from baseline to the 24-h concentration of piglets given glucose (0.20 ± 0.18). It appears that blood alanine concentrations began to reach a plateau two thirds of the way through each alanine infusion period, and that concentrations fell to baseline within 3–6 h of terminating the alanine infusion, indicating that piglets were adapting to the alanine infusion and that flow through this pool was rapid.

**Recovery of infused nitrogen.** An attempt was made to account for infused alanine-nitrogen by measurement of the expanded body urea pool and a-amino nitrogen (ninhydrin) at the end of the experiment, as well as collection of urine and expired ammonia gas. Calculation of the amount of alanine-N that was recovered showed that the recovery was significantly different from 100% and was significantly greater.

![FIGURE 4](https://academic.oup.com/jn/article-abstract/130/8/1971/4686364)}
DISCUSSION

This study was designed to test the capacity of neonatal piglets to synthesize urea and excrete it in urine. The results from this study could be used also to calculate the proportion of infused nitrogen that was recovered in urine, expired ammonia and the expanded α-amino nitrogen pool. Our results support the notion of an existing alternate route of nitrogen excretion because only 50–75% of infused nitrogen was recovered. These data precede related studies in our laboratory exploring this difference (Rasch et al. 1999).

Few studies have focused on the ability of the newborn to convert amino acid nitrogen into urea nitrogen. In one such study (Kalhan 1993), based on tracer dilution of [15N-15N]-urea, it was found that soon after birth, normal fasting human term infants synthesize urea at a rate of 5.9 ± 2.0 mg N/(h · kg). This rate is slightly lower than the average baseline urea production rates of neonates present experiments [9.1 ± 9.8 mg N/(h · kg); range 0.63–25.8 mg N/(h · kg)]. The large variation among piglets has been observed routinely in work carried out in our laboratory.

Measurements of urea excretion rates in preterm LBW infants should approximate urea production, assuming constant hydration status and no change in the body urea pool over the urine collection period. Premature LBW human infants, 28.5–29.5 wk gestational age, receiving solely glucose and small piglets infused with glucose. If due to litter, then the differences observed in baseline values for UUN and BUN may be due to developmental differences resulting from genotype.

As evidenced by the blood alanine concentrations for the large pigs, alanine is cleared rapidly from the circulation (Fig. 4). Because blood samples were limited, alanine was not measured in blood obtained from small piglets. However, on the basis of the prolonged rise in the BUN concentration (Fig. 2) and the urea production rate (Fig. 3) during the washout of small piglets infused with alanine, one could speculate that alanine was cleared more slowly in small than in larger piglets.

Two of the small piglets infused with alanine experienced clinical symptoms of hyperammonemia during the highest level of alanine infusion and during part of the washout period; one of these piglets presumably had kidney failure and was not included in calculations. In the preliminary study, large piglets infused at the highest alanine level had whole-blood ammonia concentrations of 270 μmol/L, a value expected to result in altered behavior. Brusilow et al. (1982) reported that ammonia concentrations of 100–300 μmol/L result in vomiting, 300 in coma and 500 in death. In summary, these results support the hypothesis that the small piglets infused with alanine may have experienced more difficulty metabolizing the infused nitrogen than the larger piglets in these experiments. Due to the differences in baseline levels of urea excretion, BUN and urea production, the fold-increase from baseline for small piglets was greater than for large piglets infused with alanine, although, on a per kg basis, the large pigs clearly had more capacity to produce urea (Fig. 3). Adjusting for baseline (by analyzing the difference from baseline to maximum), the increases due to alanine infusion were not different for small and large piglets for any of the variables calculated.

On the basis of the results of this study, which involved infusion of alanine IV at rates equivalent to 25, 50 and 75% of the piglets’ REE, newborn piglets have the capacity to detoxify and excrete ammonium-N as urea-N at a rate that is at least three times that required under starvation conditions. These observations support the idea that amino acids can be added to total parenteral nutrition solutions of premature infants on the first day of life. We speculate that such infants have the metabolic capacity to "manage" the increased nitrogen infusion.

ACKNOWLEDGMENTS

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LITERATURE CITED


Mitton, S. G., Calder, A. G. & Garlick, P. J. (1991) Protein turnover rates in sick, prematurity LBW human infants, 28.5–29.5 wk gestational age, receiving solely glucose and altered hydration status and no change in the body urea pool

P < 0.02) in small pigs 73.8 ± 6.7 (n = 3) vs. 53.7 ± 2.6 (n = 4) than in large piglets.