Urea and its bioavailability in newborns

EDITOR—Jackson suggests that colonic salvage of urea N—that is, its return to the body N pool and contributing to the effective supply of N—is an important component in the handling of urea N in the newborn.1 Although of interest for nitrogen economy during growth, pregnancy, low protein intake or during hibernation in bears, such an hypothesis at least in the human infant, is not based on compelling evidence.

The estimates of urea N salvage are based on incomplete excretion in urine of the total urea synthesised in the body.2 The discrepancy between the hypothesized amount of urea in the gut but also from excretion of urea in the skin. A significant proportion of N released from hydrolysis of urea in the gut is also known to be recycled into urea or excreted as ammonia in the breath. In healthy adults with a normal protein intake about 20% of synthesised urea is not excreted in urine, and an insignificant amount of urea N is incorporated into protein.3 Whether such a salvage of N occurs in newborns is not known. Data on breast fed infants, both pre-term and full term, have shown that most of the urea ingested is not bioavailable—that is, it is not hydrolysed in the gut.4 So pre-term newborns show that the rate of urea synthesis measured by isotopic tracers ranges between 3 mg and 6 mg N/kg/hour, which is similar to the value in healthy adults.5 In contrast, Wheeler et al observed very high rates of urea N synthesis (about 17-3 mmol N/kg/day or 20 mg N/kg/hour) in six neonates after major abdominal surgery.6 However, the rate of urinary urea N excretion was similar to that reported by others. Thus the discrepancy between synthesis and excretion was astro-nomical (80%). Interestingly, the recycled N was derived from the colonic pool of urea. Several concerns can be raised regarding the validity of measurements in their study —route of tracer administration, the catabolic state of the infant, the accuracy of urine collection, etc. All question the conclusion regarding the salvage of urea N in these infants.

Thus published data on newborn babies do not support the concept that ‘urea production and salvage appear to be normal features of urea in the newborn’.7 It may be important only when protein intake is marginal or only in certain animal species.

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1 Jackson AA. Urea as a nutrient: bioavailability and role in nitrogen economy. Arch Dis Child 1994; 70: 3-4.

Dr Jackson comments:

Dr Kalhan’s comments revisit a longstanding controversy which simply underlines the need for good data in a difficult area of investiga-tion. There are three points of importance: whether salvage of urea-nitrogen has functional importance under any circumstance; whether it is important in infancy; and the nature of the importance. We have formally addressed the methodological criticisms raised.1 Based on an extensive series of investiga-tions we know for adults that normally 25% of daily urea-nitrogen production is salvaged.2 In infants and children the major factors which influence the rate of salvage are the catabolic state and determined in part by energy intake, the absolute protein intake relative to the magnitude of the metabolic demand for protein, and the presence of a functional colonic microflora.3 The data of Wheeler et al4 and the three phases for urea kinetics can be identified: (i) shortly after birth before the microflora are properly established, little or no salvage; (ii) up to 6 weeks of age, with an established flora, salvage is very high in response to the intense metabolic demand; and (iii) after 6 to 8 weeks of age, when salvage is moderate. For each phase there are clear differences in nitrogen metabolism, as identified by catch-up growth. Further investigations are required to adequately explain the different results obtained by different groups. There is no good reason simply to dismiss the data of Wheeler et al4 as we have found considerable salvage in free living infants aged 3 to 6 weeks who were breast fed. These data confirm that at least 50% of the nitrogen salvaged from urea is retained within the system. Although the urea-nitrogen excretion remains an open question at this point in time, we have early evidence which traces the label into essential amino acids.

Given that growth is an important feature of infancy, protein diet they ever take is their mother’s milk, the evidence in favour of the importance of urea-nitrogen salvage need not be compelling to justify full consideration of its potential importance.


Fresh frozen plasma and neonatal sepsis

EDITOR—Acunas and colleagues conclude that fresh frozen plasma (FFP) is less effec-tive than intravenous immunoglobulin as adjunctive treatment for neonatal sepsis.1 They also highlight the possible risk of viral transmission with its use. FFP may also contain viable donor lymphocytes, exposing the recipient to potential alloimmune reactions.2,3 Fatal transfusion associated graft versus host disease (TA-GvHD).2,3 This usually occurs in those with defective cell mediated immunity. However, it may occur in the apparently immunocompetent,1 and transmission of FFP can be also at risk.4 Although TA-GvHD may be prevented by irradiation of blood products,5 FFP is not routinely irradiated on most neonatal units and therefore TA-GvHD may place potential disadvantage of the use of FFP in neonates.

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EMLA and informed consent in neonates

EDITOR—We were very interested in the account of the use of EMLA cream in 21 neonates, following an earlier trial in seven babies.2 There seem to be few direct reports of the safe use of EMLA in newborns, though Koren suggested that EMLA is in widespread unlicensed use in North America for circumcisions of neonates, without any controlled trials.3 Use of EMLA is not recommended for babies under 1 year of age in the United Kingdom, but the use of EMLA in infants older than 1 month has recently been approved in the United States.

Neonates may be at increased risk of methaemoglobinemia, due to their thin skin, low concentrations of methaemoglobin reductase in their blood, slow metabolism of lignocaine and prilocaine. Fetal haemoglobin is more readily oxidised to methaemoglobin than is adult haemoglobin.

We obtained ethical committee approval for a randomised, double blind trial of EMLA cream in newborn babies. Parents were warned verbally and in writing of the risks of methaemoglobinemia and advised about our methods of ensuring safe use. Fully informed verbal and written consent was obtained. Exclusion criteria were clinically apparent anaemia, oxygen treatment, cyanotic congenital heart disease, weight of less than 1500 g or a baby taking antenatal diabetes medication.

We restricted the dose of EMLA or placebo to 0-1 ml/kg/bodyweight applied once only to an area of skin measuring 2×1 cm for exactly one hour. Each baby was watched closely for 12 hours for signs of temperature change or desaturation, if necessary using a pulse oximeter or other monitors. Blood tests for methaemoglobin, lignocaine, prilocaine and methaemoglobin reductase concentrations
Lipid peroxidation as a measure of oxygen free radical damage in the very low birthweight infant

EDITOR—We read with interest the paper by Inder et al on lipid peroxidation as a measure of oxygen free radical damage in preterm infants.1 They showed a rise in malondialdehyde detected by the thiobarbituric acid (TBA) test over the first week which was significantly greater in those infants developing chronic lung disease. We have also used the TBA test to detect lipid peroxidation in 13 very preterm infants during the first seven days after birth. Concentrations rose from a median of 2-13 μmol/l (1-63-2-77 range) on day 1 to 3-27 μmol/l (2-49-4-48) on day 7 in those not developing chronic lung disease and from 2-07 μmol/l (1-16-2-98) to 3-77 μmol/l (2-6-4-21) in the 40 infants who developed chronic lung disease. No significant difference was observed. It is of interest that our values for the TBA test were about 30 times lower than those of Inder et al, in keeping with other published values for the test.2 We used a fluorimetric method, but the HPLC technique used by Inder et al generally gives lower values than the fluorimetric method.3 Until these differences are explained, we cannot accept the authors’ findings as evidence for lipid peroxidation in very preterm infants.

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Dr Inder and coauthors comment:
We are grateful for the query from Professor Cooke and colleagues which identified an unfortunate calculation error in our malondialdehyde-thiobarbituric acid (MDA-TBA) values that occurred during the conversion of our standard values in ng/ml to μmol/l. Due to this error the published MDA-TBA values were too high by a factor of 60, and should read for cord blood in full term infants (n=48) mean (SD) 1-05 μmol/l (0-16); preterm infants without chronic lung disease (n=6) from cord blood concentrations of 1-19 (0-1) μmol/l to 1-72 (0-1) μmol/l at 7 days and in premature infants with chronic lung disease (n=16) from cord blood concentrations of 1-42 (0-1) μmol/l to 2-66 (0-2) μmol/l at 7 days. These values are approximately half those found by Cooke et al in their premature infants. However, the significance of the raised MDA-TBA values in premature infants with chronic lung disease is unchanged. Why did our assay detect a significant difference in MDA-TBA concentrations? The key issue relates to the specificity of thiobarbituric assays for malondialdehyde as indicators of lipid peroxidation. Both the method we used1 and the method of Wong et al,2 use HPLC to measure MDA-TBA, which eliminates inaccuracies due to interfering chromogens. However, there are several important differences. In our assay, no EDTA is added, plasma lipids are extracted before analysis, and ferric chloride (FeCl3) plus butylated hydroxytoluene are added before heating with TBA. The rationale for adding FeCl3 was to promote efficient breakdown of lipid hydroperoxides to MDA,3 but we are not sure that this is its only mode of action. The Wong method uses whole plasma and is thought to measure primarily protein bound MDA. Thus, although both are considered to be indicators of lipid peroxidation the two methods may clearly be measuring different parameters. Further ongoing research in our premature infants continues to support the findings we have published. However, to understand the true nature of the MDA-TBA product measured, more specific analytical measures of lipid peroxidation products are awaited.

EMLA and informed consent in neonates.

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