Urea and its bioavailability in newborns

EDITOR.—Jackson suggests that colonic salvage of urea N— that is, its return to the body—pool and contributing to the effective supply of N—as an important component in the handling of urea N in the newborn. Although of interest for nitrogen economy during growth, pregnancy, low protein intake or during hibernation in bears, such an hypothesis as to what might be the newborn child, 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. The discrepancy between the highest estimate 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.

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 small intestine. Several studies in 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 that of healthy volunteers. Thus the discrepancy between synthesis and excretion was astro-nomical (80%). Interestingly, the recycled N was not shown to be a normal feature of urea synthesis.

Several concerns can be raised regarding the accuracy 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 early infancy’. It may be important only when protein intake is marginal or only in certain animal species.

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Dr Jackson comments:
Dr Kalhan’s comments revisit a longstanding controversy which simply underlines the need for good data in a difficult area of investigation. 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. Based on an extensive series of investigations we know for adults that normally 25% of daily urea-nitrogen production is salvaged. In infants and children the major factors which influence the rate of salvage are the organism’s ability to determine 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.

The data indicate that the major phases for urea kinetics can be identified: (i) shortly after birth when 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 the non-invasive measurement. When these considerations in combination adequately explain the different results obtained by different groups. There is no good reason simply to dismiss the data of Wheeler et al.5, 6 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 long term studies on the natural history of infants remain 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 and that for most people the lowest 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 effective than intravenous immunoglobulin as adjunctive treatment for neonatal sepsis. They also highlight the possible risk of viral transmission with its use.

FFP may also contain viable donor lymphocytes, exposing the recipient to potential risk of fatal transfusion associated graft versus host disease (TA-GVHD). This usually occurs in those with defective cell mediated immunity. However, it may occur in the apparently immunocompetent1, 2 and in the immunosuppressed also at risk.3 Although TA-GVHD may be prevented by irradiation of blood products,4 FFP is not routinely irradiated on most neonatal units and therefore TA-GVHD may be a 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,1 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 circumcision of neonates, with its potential disadvantage of being an agent with the possibility of effecting a return to normal circulatory status. 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 USA.

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 methaemoglobin 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 diuretics.

We restricted the dose of EMLA or placebo to 0.1 ml/kg/bodyweight applied once only to an area of skin measuring 2x1 cm for exactly one hour. Each baby was watched closely for 12 hours for signs of cyanosis, 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 131 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.

Dr McIntosh comments:
In our studies using EMLA cream we were attempting to reduce pain and distress (apparently unsuccessfully) in newborn infants receiving heel pricks. The parents were informed that EMLA cream had not been used other than in our own study on neonates, but that it was commonly used and with no problem in older children. We knew about the possibility of methaemoglobinemia but at the time of starting the study there was only one report of this problem in a child who was also receiving a sulphonamide, so we did not believe that we ought to inform the parents of this specific but theoretical hazard.