Archives of Disease in Childhood, 1988, **63**, 1372–1376

Treatment of renal failure in neonates

A C G MEEKS AND D G SIMS

North Western Regional Perinatal Centre, St Mary's Hospital, Manchester

SUMMARY Thirty neonates with acute renal failure were studied, 27 of whom died (90%) including nine of 12 treated by peritoneal dialysis. Three main aetiological groups were identified. Septicaemia was a principal cause of late onset acute renal failure, with an incidence equal to that of serious perinatal disorders. It is recommended that tolazoline should be used with caution in the treatment of hyperkalaemia as it may have a role in the aetiology of acute renal failure, the incidence of which is increasing.

The incidence of acute renal failure is increasing among neonates. This is partly because of increased awareness of the possibility of renal failure,[1–3] partly because clinicians are better at prolonging survival,[4] and partly from the use of drugs that may have a profound effect on renal function and perfusion. Tolazoline, which is used in the treatment of pulmonary hypertension,[5 6] also has an effect on peripheral vascular resistance causing systemic hypotension. It has already been implicated as cause of acute renal failure in neonates.[7] The use of indomethacin for the closure of a patent ductus arteriosus may be associated with a fall in urine output and a rise in serum urea concentration.[8 9]

Since 1981 acute renal failure among newborn babies has become more common at this hospital; we therefore describe and analyse our experience of a group of 30 patients.

Patients and methods

The study group comprised those babies born between the beginning of 1981 and the end of June 1985 who at some stage during life were diagnosed as having been in acute renal failure, although this had not necessarily contributed directly to their deaths and may have resolved before death. Babies treated by peritoneal dialysis who survived were also included. Data were abstracted retrospectively from the hospital records.

Acute renal failure was defined as anuria (no urine voided for at least 24 hours), or documented concern by the clinician about poor urine output over a 24 hour period together with either a serum urea concentration of more than 10·0 mmol/l (normal ranges 1·5–6·7 mmol/l for premature babies, and 1·6–4·6 mmol/l for babies born at full term)[10] or a serum potassium concentration of more than 7·5 mmol/l (normal ranges 4·5–7·2 mmol/l for premature babies, and 3·6–5·7 mmol/l for babies born at full term).[10]

The onset of renal failure was the day on which poor urine output was first noted or the serum urea concentration first exceeded 10 mmol/l.

Results

Thirty babies were studied; 27 died, and three of the 12 who had been treated by peritoneal dialysis survived. The mean (SD) gestational age of the study group was 30·9 (4·5) weeks and the mean (SD) birth weight 1610 (800) g. Twenty five (83%) were born prematurely, nine at less than 28 weeks' gestation.

In 1981 three babies were recognised as fitting the study criteria, in 1982 there were five; in 1983, six; in 1984, 11; and in the first six months of 1985, there were four. One further baby was included from 1984 whose serum urea concentration rose to 25·1 mmol/l over three days. Although poor urine output was not documented, she received three doses of intravenous frusemide for increasing oedema. Seventeen babies (57%) were anuric.

Analysis showed that the babies could be divided into four aetiological groups: perinatal haemorrhage or asphyxia or both; septicaemia; surgical problems complicated by right to left vascular shunts; and miscellaneous (tables 1 and 2).

The mean age at onset of renal failure was 7·8 days, but if those whose renal failure was due to septicaemia were excluded this fell to only three days.

Peritoneal dialysis was used for a mean of two days, the longest period being six days in a baby who

Table 1 *Numbers of babies each year in each aetiological group*

Year	*Haemorrhage or asphyxia*	*Septicaemia*	*Surgical problems*	*Miscellaneous*	*Total*
1981	0	0	2	1	3
1982	2	1	1	1	5
1983	2	3	1	0	6
1984	6	5	0	1	12
1985	0	0	1	3	4
Total	10	9	5	6	30

Table 2 *Details of the main aetiological groups*

Diagnosis	*No of babies*	*Mean (SD) gestation (weeks)*	*Mean (SD) birth weight (g)*	*Median (range) age at onset of renal failure (days)*	*Median (range) age at death (days)*	*Mean (SD) peak urea concentration (mmol/l)*	*Mean (SD) peak potassium concentration (mmol/l)*
Haemorrhage or asphyxia, or both	10	29·1 (2·0)	1360 (430)	2 (1–3)	3·5 (2–11)	17·6 (6·8)	9·0 (2·2)
Septicaemia	9	28·2 (3·6)	1090 (570)	14 (3–57)	15 (4–60)	11·7 (6·0)	8·8 (2·3)
Surgical problems with right to left shunt	5	38·6 (0·5)	2860 (370)	2 (2–4)	6·5 (3–23)	14·7 (6·1)	6·0 (2·0)
Miscellaneous	6	31·3 (3·1)	1790 (740)	3 (2–8)	5 (2–18)	27·6 (14·6)	7·3 (1·9)

had renal cystic dysplasia. All three survivors were dialysed for two days.

DIAGNOSES

Haemorrhage or asphyxia or both (n=10)—Asphyxia, defined as an Apgar score of 5 or less at 5 minutes of age, occurred in six babies. Four babies were born after abruptio placentae and another four had severe internal haemorrhages resulting in falls in their haemoglobin concentrations of more than 30%. No patient in this group survived and none was offered peritoneal dialysis.

Septicaemia (n=9)—In eight babies organisms were grown from blood after culture in two different culture media, and one baby was diagnosed as having septicaemia because of his clinical appearance in association with a gut perforation caused by necrotising enterocolitis. No patient in this group survived, although four were treated with peritoneal dialysis.

Surgical problems (n=5)—The clinical courses of these babies were complicated by right to left vascular shunting. Four had diaphragmatic hernias of whom three lived long enough to undergo operations. One baby had an operation for oesophageal atresia with a tracheo-oesophageal fistula associated with a gastric perforation when he was 2 days old. Four patients were treated with peritoneal dialysis. Two survived the immediate crisis, but one of these died 15 days later from respiratory disease.

Miscellaneous (n=6)—Two of these babies had circulatory collapse associated with idiopathic respiratory distress syndrome, one with cardiac tamponade caused by a large haemopericardium. One baby had rhesus hydrops with a cord haemoglobin concentration of only 30 g/l and had had several cardiac arrests during exchange transfusions. One baby had renal cystic dysplasia, and in two the cause of the acute renal failure was not clear although one of them was born at 26 weeks' gestation to a mother who was in end stage chronic renal failure. This baby became anuric when 3 days old. Two of the four babies who were treated with peritoneal dialysis survived.

TREATMENTS

Treatment of hyperkalaemia—Five babies were treated with the ion exchange resin calcium polystyrene sulphonate made up as a slurry and given rectally in a dose of 1 g/kg three or four times daily. The consistency of the slurry made administration difficult and it was poorly retained by most babies. Calcium polystyrene sulphonate can set to become a solid plug, which may cause partial obstruction and bowel distension. Within 24 hours of its use two babies had died, and three were being dialysed.

Acute cardiac arrhythmias were treated with intravenous boluses of 10% calcium gluconate. The babies usually returned to sinus rhythm immediately, but it was not sustained. Three babies were also given soluble insulin 0·1 U/kg as an intravenous bolus while they were having intravenous dextrose infusions. All temporarily reverted to sinus rhythm, but the hypoglycaemia that was caused by this proved difficult to control because of the large volumes of intravenous dextrose that were needed to maintain normal blood glucose concentrations.

Treatment of acidosis—All babies developed metabolic acidosis with base deficits of more than 10 mmol/l. They were treated with intravenous sodium bicarbonate 8·4% unless they also had respiratory acidosis, in which molar concentrations of trometamol were used. In no case were alkalis withheld because of fluid overload. The acid base balances improved of all the babies that were dialysed, although in four the base deficit remained greater than 10 mmol/l. All babies had problems in addition to their renal failure—for example septicaemia and hypotension—so the origin of the acidosis could not be clearly defined.

Control of blood pressure—Eighteen babies had their blood pressure monitored through an indwelling arterial catheter. Twelve of these received continuous dopamine infusions, compared with six of the 12 monitored by Dynamap (Critikon Inc, Tampa, Florida, USA). Analysis by the χ^2 test with Yates' correction showed that the use of direct pressure measurement did not influence the decision to use dopamine. In only two instances was it necessary to exceed an infusion rate of 10 μg/kg/minute. Acute falls in blood pressure were treated with 'walking donor' blood transfusions of 10–20 ml/kg.

Peritoneal dialysis—Table 3 shows a comparison of the 12 babies who were dialysed with those who were not. The significant differences in birth weight ($p<0·02$) and gestational age ($p<0·05$) reflect the fact that most of those dialysed were born at full term with serious surgical problems.

The main indications for peritoneal dialysis were: failure of medical treatment of hyperkalaemia, cardiac arrhythmias, and severe fluid overload with intractable cardiac failure. The two infants who developed resistant hypoglycaemia after intravenous insulin infusions achieved normal blood glucose concentrations as soon as peritoneal dialysis was started.

The dialysis fluid (Dianeal 137 with 1·36% glucose, Travenol Laboratories Ltd, Norfolk) was first warmed to 37°C. To make it easier to insert the peritoneal catheter, the abdomen was distended with about 50 ml/kg of the dialysis fluid taking care not to compromise ventilation. Cycle volumes were 30 ml/kg, repeated each hour; the fluid was run in rapidly by gravitational flow over five to 15 minutes, allowed to remain for 20–30 minutes, and then drained during the remainder of the hour. Dialysis cycles were repeated less often as urine output resumed. Once the serum potassium had fallen below 5·0 mmol/l, 4·0 mmol potassium chloride were added to each litre of dialysate.

Dialysis catheters were removed after the diuretic phase of recovery from acute renal failure had been completed. Two infants had further rises in serum urea concentrations (to 29·2 and 38·4 mmol/l, respectively) for three and four days after removal of their dialysis catheters. Urine output, however, was maintained and serum potassium concentrations remained below 6·0 mmol/l.

Commercially available catheters (Wallace 14147, Wallace Ltd, Colchester, Essex)) were used for most babies, but they were unsuitable for the smallest (minimum birthweight 620 g) because of the length of catheter needed within the peritoneal cavity. For such cases we found that chest drain catheters (Vygon 625·10, Vygon, Ecouen, France), which we modified by cutting extra holes in the sides, were a satisfactory alternative.

The only complications were minor fluid seepage around the peritoneal catheter, blockage of the catheter, and (in one infant) herniation of omentum through the abdominal wall during removal of a blocked catheter. No infant developed peritonitis. One showed biochemical deterioration during dialysis associated with a second episode of septicaemia;

Table 3 *Comparison of those babies who were dialysed and those who were not*

	No of babies	*Mean (SD) gestation (weeks)*	*Mean (SD) birth weight (g)*	*Median (range) age at onset of renal failure (days)*	*Median (range) age at death (days)*	*Mean (SD) peak urea concentration (mmol/l)*	*Mean (SD) peak potassium concentration (mmol/l)*
Babies dialysed	12	33·0 (5·1)	2070 (860)	4 (2–31)	13 (5–33)	18·3 (10·0)	8·0 (2·0)
Babies not dialysed	18	29·4 (3·5)	1300 (610)	3 (2–57)	4 (2–60)	16·6 (10·5)	8·1 (2·6)

Table 4 *Timing of giving tolazoline and association with onset of renal failure*

	No of babies	*Median (range) at time of use (days)*	*Median (range) age at onset of renal failure (days)*
All babies	15	2 (1–3)	2 (1–14)
Haemorrhage or asphyxia, or both	8	1·5 (1–2)	2 (2–5)
Surgical problems	5	2 (2–3)	2 (2–4)
Others	2	2 (1–3)	8·5 (3–14)

culture of peritoneal dialysis fluid showed no organisms. It was not our practice to add antibiotics to the dialysis solution as a routine.

Despite the technical success of peritoneal dialysis, only three of the 12 treated infants survived. Two others were successfully dialysed but ultimately died: one was dependent on the ventilator, but found to have renal cystic dysplasia on ultrasound examination. After discussion with the parents, ventilation and dialysis were discontinued. One other infant who was dialysed for five days because of postoperative complications died 15 days later from unrelated respiratory disease.

Drugs used before the onset of acute renal failure—Fifteen babies were given tolazoline, all within the first 3 days of life, one having a second course on day 5 (table 4). Doses of 1–4 mg/kg were given as intravenous boluses followed by continuous infusions of 2–5 mg/kg/hour. One baby inadvertently received a 15 mg/kg bolus and an infusion rate of 10 mg/kg/hour. Twelve of the 15 babies were treated with intravenous dopamine infusions at rates sufficient to maintain normal systemic blood pressure (2–15 μg/kg/minute), and 13 were given neuromuscular blocking agents to facilitate mechanical ventilation. Four babies received indomethacin, but this was not associated with their renal failure.

Discussion

The diagnosis of renal failure in the newborn is not straightforward, as it is usually not the baby's only problem. For these reasons we looked at a combination of three criteria associated with acute renal failure: anuria or oliguria, uraemia, and hyperkalaemia.

For the diagnosis of anuria and oliguria we relied on the accuracy of our nursing records in which it is recorded 8 hourly whether the baby has passed urine or not. Oliguria was diagnosed when the nurses expressed concern over the frequency and amount of urine passed.

Other causes for a raised serum urea concentration should be considered. It is unlikely that these babies were dehydrated; all received conventional intravenous fluid regimens during their first days of life and were clinically assessed at least twice a day. Twenty two developed acute renal failure within the first 5 days of life.

Excessive protein loading was also an unlikely explanation for raised serum urea concentrations, only three babies ever received milk feeds, and only seven received intravenous amino acids (Vamin 9 glucose, KabiVitrum Ltd, London) up to a maximum of 2·5 g/kg/day.

In only one instance was a raised urea concentration the only feature of renal failure. The baby was born at 27 weeks' gestation weighing 800 g, and had severe perinatal asphyxia (Apgar score 1 at 5 minutes). Because of increasing oedema she was treated with frusemide on day 3. The serum urea first rose above 10 mmol/l on day 5, reaching a maximum of 25·1 mmol/l on day 8.

The cases reported are a highly selected group. All were extremely ill, and those who survived were unlikely to have done so without dialysis. The exact cause of death could not be determined in most cases; the contribution of acute cardiac arrhythmias caused by hyperkalaemia in a baby with overwhelming septicaemia, for example, makes it difficult to assess.

As far as we are aware no other babies developed acute renal failure during the study period. Other babies may have had transient renal insufficiency as part of the idiopathic respiratory distress syndrome,[11 12] but this required nothing more than a period of fluid restriction. Others might possibly have developed acute renal failure if they had survived long enough.

Treatment of hyperkalaemia with drugs was disappointing. Intravenous calcium gluconate and insulin were almost immediately effective in stopping cardiac arrhythmias but only in the short term. Calcium polystyrene sulphonate was difficult to use and seemed to give little benefit.

We have found peritoneal dialysis to be a safe procedure without serious complications. It was technically successful in all cases, the 25% survival rate being a reflection of the babies' conditions before dialysis rather than a problem with the dialysis itself. In babies with cardiac arrhythmias dialysis was successful after conventional treatment had failed to maintain sinus rhythm. It is possible, therefore, that earlier use of dialysis as prophylaxis against hyperkalaemic arrhythmias could have increased the rate of survival. This raises the ethical dilemmas of offering dialysis to sick neonates; most babies already had a poor prognosis before the onset

of their renal failure and dialysis would only have delayed their deaths. We suggest that those babies who have had severe perinatal asphyxia or who develop a large intraventricular haemorrhage with cortical extension and severe neurological abnormality should not be offered dialysis if they develop acute renal failure shortly after birth.

Tolazoline is an α adrenergic blocking agent that also has a direct action on vascular smooth muscle to produce dilatation. It is used in infants with severe hypoxaemia associated with pulmonary hypertension and right to left vascular shunting.[5 6] Tolazoline also has an excitatory action on the myocardium and may cause cardiac arrhythmias.[13] Because it is excreted largely unchanged by the renal tubules[14] modification of the dose may be necessary when renal function is impaired.

The association between the use of tolazoline and the onset of renal failure appeared close, but it was used only in extremely sick infants who already had other reasons to develop acute renal failure. It is impossible to say whether the use of tolazoline was responsible for any of these babies developing acute renal failure, but its hypotensive effect may have further compromised their already impaired renal function. It is also possible that tolazoline may have precipitated some of the cardiac arrhythmias. It should be stated, however, that many more babies received tolazoline during the study period and did not go on to develop acute renal failure.

Since 1981 most babies were treated with tolazoline and also received intravenous infusions of dopamine. The dose was titrated against blood pressure, aiming to raise the systolic pressure above 50 mm Hg. At low infusion rates (2–5 μg/kg/minute), dopamine stimulates dopamine receptors in the renal arteries causing them to dilate and so increase renal blood flow.[15] At higher rates of infusion (>10 μg/kg/minute), however, stimulation of α adrenoreceptors causes an increase in vascular resistance and thus a fall in renal blood flow.[16] In the study group, there were wide variations in dopamine infusion rates (2–15 μg/kg/minute). It seems that dopamine did not have a beneficial effect on renal function in this group of babies.

In conclusion, there has been an increase in the number of babies developing acute renal failure during the past few years reflecting improved resuscitation of extremely sick infants and increased survival from the idiopathic respiratory distress syndrome,[4] although increased awareness of the possibility of renal complications may also play a part.

Peritoneal dialysis is a safe and effective way to manage acute renal failure in the newborn. We suggest that if the baby is thought to be a suitable candidate, dialysis should be started before cardiac arrhythmias develop or immediately after any emergency treatment for hyperkalaemia.

Tolazoline should be used with caution in infants with renal impairment as it is excreted by the kidneys, compromises renal circulation, and may precipitate cardiac arrhythmias. The use of dopamine to maintain blood pressure after giving tolazoline needs to be studied more critically and compared with the effects of plasma and other drugs.

We thank Dr AJ Barson for his help with this paper and colleagues at the neonatal medical and surgical units, St Mary's Hospital, Manchester, for allowing us to report their patients. The practical help of Dr RJ Postlethwaite in the management of some patients is acknowledged.

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Correspondence to Dr ACG Meeks, The Jessop Hospital for Women, Leavygrove Road, Sheffield S3 7RE.

Accepted 5 July 1988