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Neonatal renal dysfunction and intrauterine exposure to prostaglandin synthesis inhibitors

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Abstract. Three cases of renal dysfunction at birth were observed in premature babies exposed in utero to prostaglandin synthetase inhibitors (PSI) and corticosteroids. Transient water and sodium retention with uraemia occurred in one patient, and severe acute renal failure with marked hyperkalaemia in twins. These findings may be due to impairment of prostaglandin (PG)-mediated renal adaptation to stress conditions after transplacental passage of PSI. Corticosteroids may also have affected PG synthesis inhibition.

Key words: Prostaglandin antagonists – Maternal-fetal exchange – Newborn – Fetus – Kidney failure

Introduction

Indomethacin and prostaglandin-synthetase inhibitors (PSI) (cyclo-oxygenase inhibitors) are increasingly used in the treatment of preterm labour [9, 15, 23, 24]. In utero, ductal closure and persistent fetal circulation are possible effects [2, 14]. In neonates, little is known about the renal consequences of PSI in spite of their well-known nephrotoxicity [8]. We report on three premature babies with renal dysfunction, whose mothers received PSI and corticosteroids at the end of their pregnancy.

Case reports

Case 1

This boy was born by caesarean section 48 h after premature rupture of membranes, in the 31st week of pregnancy. Salbutamol was given on day 3 prior to birth and continued until delivery, and ketoprofen (Profenid, Specia laboratories, Paris, France), a propionic acid derivative PSI, at a dose of 200 mg/day on days 3 and 2 before birth. Betamethasone (12 mg) was administered the day before birth. Apgar scores were 3 at 1 min and 9 at 5 min; birth weight was 1630 g. At birth, cyanosis and respiratory distress required transient mechanical ventilation and oxygen therapy with a maximal FiO_2 of 0.8. Chest X-ray were suggestive of a wet lung syndrome. Striking generalized oedema was associated with oliguria (urine output 30 ml/day). Blood pressure, physical and ultrasonic examination of the kidneys and external genitalia were normal. Laboratory tests showed a moderate elevation of blood urea (from 3 mmol/l at admission up to 7.2 mmol/l at 24 h and 48 h of life), creatininaemia (90 µmol/l) and a moderate metabolic acidosis (pH = 7.20, bicarbonate 14 mmol/l in capillary blood). Potassium, sodium, and calcium were normal.

Urinary analysis gave the following: urea 49 mmol/l, creatinine 2.28 mmol/l, osmolality 239 mmol/kg, urine/plasma urea 6.8; creatinine clearance 7 ml/mn per 1.73 m^2, fractional excretion of sodium 1%; no proteinuria, no haematuria, and no leucocyturia. The urine was sterile. Treatment consisted of restriction of fluid intake, perfusion of bicarbonate and a single dose of frusemide (1 mg/kg). Evolution was characterized by regression of oedema and marked weight loss (300 g i.e. 18% of birth weight in 6 days) accompanied by polyuria and normalization of blood urea together with other parameters. At the age of 18 months, this infant has a normal renal function.

Cases 2 and 3

This monochorial-monoamniotic twin pregnancy was characterized by the occurrence of severe hydramnios in the 26th week, and preterm labour. Salbutamol perfusion was started, and, in order to reduce amniotic fluid volume, repeated amniotic punctures were performed. Ketoprofen (300 mg/day, rectally) and indomethacin (Indocid, Merck, Sharp and Dohme-Chibret, Paris, France) (200 mg/day, orally) were administered, respectively from day 22 to day 20 and from day 19 to day 18 before birth. Corticosteroids (Betamethasone 12 mg) were given on days 13 and 12, with a second course on days 7 and 6 before birth (Fig. 1). Two female infants were delivered by Caesarean section in the 30th week of gestation, after premature membrane rupture and maternal hyperthermia. Fetal heart rate was normal. Initial evaluation of the first twin (case 2) was satisfactory, with an Apgar score of 8 at 1 min, and a birth weight of 1320 g. Haemodynamics were normal (blood pressure 55/28 mm Hg). The second twin (Case 3) needed resuscitation at birth; Apgar scores were 3 and 8, at 1 and 10 min respectively. She exhibited transient arterial hypotension (blood pressure 38/25 mm Hg) rapidly controlled with plasma transfusion. Neonatal disease consisted, in both babies, of *Escherichia coli* infection and respiratory distress syndrome. Treatment included mechanical ventilation, oxygen therapy and antibiotics (mezlocillin and netilmicin). Severe acute oliguric renal failure developed immediately at birth in both babies with a remarkable parallel evolution in the twins (see

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Abbreviations: PSI = prostaglandin-synthetase inhibitors; PG = prostaglandin(s)

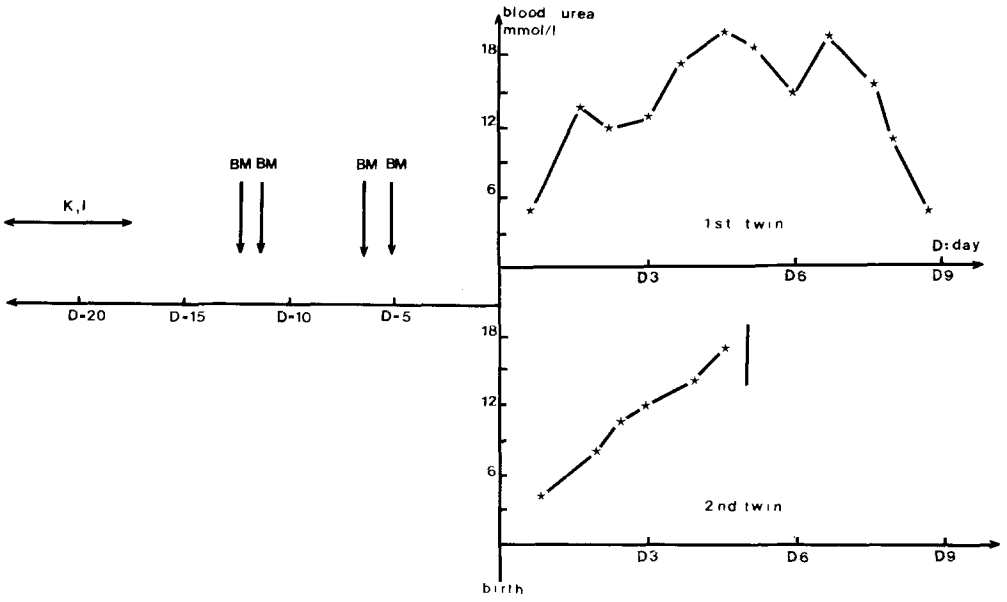

Fig. 1. Chronology of prenatal drug administration and postnatal evolution of blood urea levels in cases 2 and 3 (*K*, ketoprofen; *I*, indomethacin; *BM*, betamethasone)

Fig. 1 for blood urea levels). A marked, precocious hyperkaliaemia (up to 14 mmol/l) with severe consecutive cardiac dysfunction was the revealing and dominant feature in both babies. The following laboratory data were noted in the twins: elevated creatininaemia (160 and 205 μmol/l respectively), metabolic acidosis (pH: 7.15 and 7.18)., hyponatraemia (121 and 123 mmol/l), urine/blood urea ratio: 1.5 and 2; creatinine clearance: 5 and 3.5 ml/mn per 1.73 m^2; fractional excretion of sodium: 7% and 6%; absence of haematuria, leucocyturia, bacteriuria, and proteinuria and no urinary tract obstruction or kidney abnormalities on ultrasonic examination. Treatment consisted of fluid and mineral balance maintenance, dopamine infusion at diuretic rates, intravenous frusemide, and ion exchange resins. The second twin died at age 3 days, as a result of severe hyperkaliaemia. Postmortem examination revealed macroscopically normal kidneys whereas microscopic investigation showed mildly dilated tubules without tubular necrosis. The first twin survived and her renal function normalized at the age of 10 days. Now aged 24 months, she has normal renal function, but is neurologically impaired.

Discussion

PSI, such as indomethacin and ketoprofen, are used for the treatment of preterm labour since they reduce prostaglandin (PG)-E and PG-F mediated uterine contractions [23, 24]. They cross the placenta [1, 16, 21], and may thus affect various fetal organs.

Renal effects of PSI have been observed especially in patients with compromised renal perfusion and include water and sodium retention, glomerular filtration impairment, hyperkaliaemia, and acute renal failure [8]. The mechanism is probably via inhibition of the compensatory PG mediated renal vasodilatation in response to a renal perfusion impairment and to the action of vasoconstrictor agents secreted in such circumstances [18]. Water and sodium retention [19], and severe hyperkaliaemia (independent of a glomerular filtration reduction) [8] may be on the other hand secondary to inhibition of probable effects of PG on tubular ion transport and plasma renin and aldosterone activities.

Renal dysfunction in case 1 may be explained by the fetal effects of ketoprofen, a potent propionic acid derivative PSI that reaches significant levels in fetal blood [1]. The clinical course and the absence of another identifiable etiology suggest the role of this agent in the transient reduction of glomerular filtration and in water and sodium retention in this infant. The following characteristics concerning acute renal failure in the 2nd and 3rd cases are remarkable: 1) an early and intense onset at birth in both infants suggestive of prenatal origin; 2) a striking parallelism of clinical course in the twins despite different initial conditions (in particular, clinically satisfactory haemodynamics in the first twin-patient 2); 3) a similar pattern of hyperkaliaemia and myocardial dysfunction as revealing and prevailing features. In the absence of data (including postmortem examination of the second twin) supporting a renal organic pathology or sepsis, we believe that these characteristics are in favour of the implication of a prenatal renal PG synthesis inhibition. In this hypothesis, although drug levels in babies were not assessed, some data may account for the persistence of the effects of prenatal PSI and corticosteroids despite the time lapse until birth. In premature babies indomethacin can induce renal changes lasting for as long as two weeks [11]. Half-life excretion of indomethacin is substantially prolonged in very immature infants, with great intersubject variability [3, 5, 22]. Low levels of the drug are sufficient to inhibit cyclo-oxygenase [10]. Finally, corticosteroids, given repeatedly before birth, may theoretically have added their effects e.g. PG synthesis in the cell requires the availability of arachidonic acid, which has to be released from the phospholipids of the cell-membrane by phospholipases, which are inhibited by corticosteroids [4]. In the literature, oligohydramnios and transient neonatal anuria have been described in an infant whose mother was treated with acetylsalicylate, indomethacin and corticosteroids for juvenile rheumatoid arthritis [7]. Isolated cases of oligohydramnios and fetal death [13] or neonatal lethal anuria [12, 13] have been reported after treatment of premature labour with indomethacin. Effects of PSI on fetal diuresis and amniotic fluid volume [17] have led to their being proposed for the treatment of hydramnios [6]. Data on neonates born to mothers who received indomethacin for treatment of preterm

labour have been recently published [9, 15], showing a favourable outcome when the drug is used for short periods and at a long interval before birth (mean interval = 6.7 weeks in [9]), but renal function was not assessed. It is otherwise remarkable that one of the two deaths mentioned by Dudley and Hardie [9] occurred as a result of pulmonary hypoplasia in a baby whose mother received indomethacin for more than 6 weeks [20].

We conclude that further investigation is needed to establish fetal and neonatal renal effects of tocolysis using PSI. Studies concerning neonatal tolerance of PSI-tocolysis should include renal function. Infants born to mothers treated recently with PSI should be closely monitored for renal function and maintained as strictly as possible in conditions of optimal renal perfusion.

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