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Case Report

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Olmesartan medoxomil-induced acute renal failure in a premature newborn following maternal exposure during pregnancy: a case report and review of the literature

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Abstract

Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II (AT II) receptor blockers (ARBs) are widely used antihypertensives with well-recognized renoprotective and cardioprotective effects. Although treatment with these agents generally does not result in adverse metabolic consequences, their use during human pregnancy has been associated with negative reactions. Here we report a premature baby with a history of oligohydramnios and maternal exposure to the ARB olmesartan medoxomil who was transferred to our institution with acute renal failure. Conservative treatment with diuretics and meticulous management of fluids and electrolytes resulted in an improvement in renal function in the patient. We conclude that olmesartan medoxomil may cause reversible renal failure in premature neonates.

Keywords: acute renal failure; oligohydramnios; olmesartan medoxomil

Introduction

ACE inhibitors and ARBs, the most potent antihypertensive and renoprotective pharmaceutical agents also recognized for their cardioprotective activity, have been widely applied to a number of illnesses [1]. These agents function by interruption of the production or action of angiotensin II, which is the main end-product of the renin–angiotensin system, causing both vasoconstriction and retention of fluid and sodium. Clinical consequences include (a) reduction of glomerular capillary pressure, (b) reduction of systolic blood pressure and proteinuria and (c) an antiproliferative effect, all of which are considered major actions of these drugs [2]. Their side effects, which have been extensively studied in animals and humans, are classified into three categories: (a) those related to pharmacologic action, (b) those related to chemical structure and (c) those involving hypoperfusion of fetal vasculature, including that of renal tissue. The first category is likely related to women exposed to a pharmaceutical toxic effect during pregnancy and this effect may influence the expression of genes related to the renin–angiotensin system. Side effects related to hypoperfusion of fetal vasculature (or ACE inhibitors ARBs fetopathy) include renal insufficiency, tubular dysplasia, fetal anuria with oligohydramnios, hypocalvaria, pulmonary hypoplasia and intrauterine death [3]. Since the discovery of these agents in 1965, many studies have reported the effects of ACE inhibitors on the fetus and maternal exposure, especially during the second and third trimesters of pregnancy [4–7]. Subsequently, ARBs were manufactured; these powerful antihypertensive drugs are highly selective and specific to the renin–angiotensin system and were developed with the aim of having less adverse effects on the fetus [8]. However, a number of side effects similar to those described in fetuses and newborns of women treated during pregnancy with ACE inhibitors have been reported [9].

The present study describes a pregnant woman who was hypertensive for the last 3 years and treated during the entire pregnancy period with olmesartan medoxomil, the seventh of manufactured ARB agents. Following severe oligohydramnios, diagnosed at 33 gestational weeks, she underwent a caesarean section and gave birth to a female baby. In the first 48 postnatal hours, oligoanuria and acute renal failure were diagnosed.

Case report

The mother was a 40-year-old primigravida with a 3-year history of essential hypertension. She was treated with olmesartan medoxomil (Olmetec® Munich, Germany), a single daily dose of 20 mg, and her hypertension was well controlled with this regimen. Her conception was assisted by IVF. At 33 weeks of gestation, a severe degree of oligohydramnios was diagnosed by ultrasonographic evaluation.

Two doses of celestone chronodose were administered, and an emergency caesarean was performed. A premature female baby was delivered, with a weight of 1.980 g, length 45 cm and occipital–frontal circumference 30.5 cm. The Apgar score was 1′/9 and 2′/10. Shortly after the birth, the newborn presented respiratory distress syndrome, and was intubated and ventilated with oxygen supplementation; the newborn received two doses of sulfactant. Unclosed Botal's duct was detected until the second day of life. Oligoanuria was also observed on the first and second postnatal days. On the third day post-birth, renal ultrasonography revealed two kidneys of normal size with increased echogenicity, while on the fifth postnatal day, the plasma creatinine level was 3.1 mg/dl. The neonate was transferred from the maternity hospital to the neonatal intensive care unit at the Children's Hospital for further assessment and management. On admission, the newborn suffered from breathing difficulty and acute renal failure and was on nCPAP 21% O_2. On several occasions, her blood pressure was detected as normal to low (≈70/40 mmHg). Dolichocephaly with cranial and facial asymmetries, light dysplasia of the external ear, equestrian figures of the feet, wide anterior fontanel and dilatation of celebral ventricles were also detected. All of these facial characteristics were likely closely related to the severe degree of oligohydramnios. On brain ultrasonography, IHV of first degree on both sides and increased periventricular echogenicity were recorded, as well as a small asymmetry of lateralis ventricle of brain L>R. Repeated renal ultrasonography confirmed the previously reported findings of increased echogenicity on two otherwise normal kidneys. Muscular tone and neonatal reflexes were normal for the age of gestation, but wide anterior fontanel and sutures were detected. Laboratory findings on admission were as follows: Hb 11.5 g/dl, Ht 35%, WBC 13.3 × 10^3/μl (PMN46%, L32%, M13%), PLT 223 × 10^3 μl, glucose 80 mg/dl, urea 201 mg/dl, creatinine 2.8 mg/dl, uric acid 12.9 mg/dl, urine spot for FENa 13%, SGOT 16 U/l, SGPT 17 U/l, γ-GT 56 U/l, ALP 114 U/l, Ca 9.7 mg/dl, P 7.4 mg/dl, Mg 2.8 mg/dl, K 3.9 mmol/l, Na 134 mmol/l, Cl 88 mmol/l, UA 12.6 mg/dl, total bilirubin 3.1 mg/dl, direct 0.93 mg/dl, CPK 64 IU/l, LDH 342 IU/l, total protein 4.4 g/dl, albumin 2.8 g/dl, CRP 0.43 mg/l, plasma aldosterone 872 ng/dl (normal 19–141 ng/dl) and renin 507 pg/ml (normal 40–220 pg/ml).

During hospitalization, several challenges were observed regarding the treatment and follow-up. CPAP was continued for 3 days post-admission followed by diffuse O_2 for the next 24 h. Following a conservative approach, meticulous fluid and electrolyte adjustment resulted in a gradual improvement of renal function so that by Day 19 after birth, the plasma creatinine level was 0.9%. Plasma creatinine levels during the first 2 weeks of postnatal period and at 1 year of life are displayed in Figure 1. The acute renal failure event and severe degree of oligohydramnios were both attributed to the mother's antihypertensive therapy and are related to the temporarily reduced fetal GFR. One month post-admission, the baby was discharged from the unit in good condition with urea 25 mg/dl, plasma creatinine 0.8 mg/dl and renal trasonographic findings compatible with normal sized kidneys and normal parenchyma echogenicity. At the latest follow-up examination, the baby (1 year old) was well developed and normotensive (BP 105/60 mmHg). Renal function tests showed 35 mg/dl and 0.5 mg/dl plasma urea and creatinine levels, respectively. The eGFR was 65 ml/min/1.73 m^2.

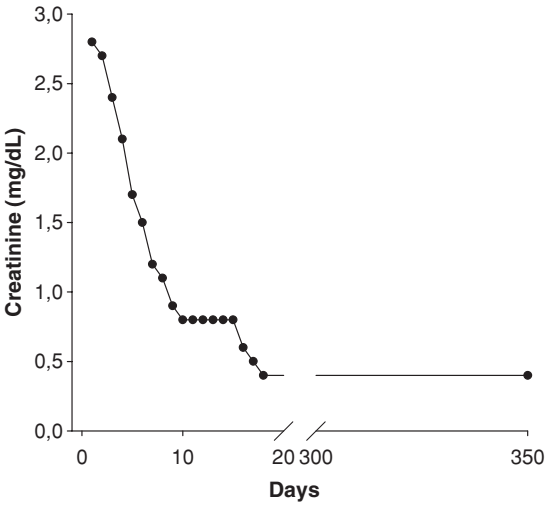

Fig. 1. Creatinine levels over time.

Discussion

The renin–angiotensin system is very active during fetal organogenesis and plays an important role, particularly in renal development [10]. As early as 1980, well-documented animal studies showed that treatment with ACE inhibitors during pregnancy causes fetal anomalies or fetal loss due to severe hypoperfusion [11]. One year later, the first case report on a human fetus exposed to ACE inhibitors was published [12], and many studies have been reported since then. In 1992, the Food and Drug Administration (FDA) strongly emphasized a warning, especially to the obstetrical community, concerning the use of these agents during pregnancy [13]. In 1995, it was estimated that 50% of neonates born to mothers exposed to ACE inhibitors would be affected by these treatments, while another 25% of the births would be fatal [7]. ARBs were later developed as an alternative treatment, aimed to have less adverse effects on the fetus. Both ACE inhibitors and ARBs, however, are very powerful antihypertensive agents with a similar clinical outcome, and most of the effects in the maternal kidneys have been determined to be due to the dilatation of the efferent arterioles of the glomerulus. It results in hypoperfusion and a decrease in the glomerular filtration rate, which likely affects the development of the fetus. Moreover, these pharmaceutics are excreted by the kidneys and can cross human placenta to be excreted into the amniotic fluid and presumably be swallowed by the fetus [7]. Therefore, fetal hypoperfusion and the consequent anomalies involving the kidneys are not only indirectly related to the mother's hypotensive status, but also directly related to the drugs in the fetal circulation. Additionally, it is possible that exposure to a pharmaceutical toxic agent could also influence the expression of renin–angiotensin system genes.

A number of reports have shown that administration of ARBs in early pregnancy, or at least during the first trimester, is related to 6% of the major abnormalities [14–16]. To our knowledge, 11 reports have been published describing side effects in the fetuses of mothers exposed to ARBs during their second and third trimesters of pregnancy. Nearly all pregnant women treated by these agents gave birth to babies either suffering from fetal abnormalities or born dead. It is of interest that valsartan and losartan were used in four and three of the reported cases, respectively, and all cases of losartan treatments died [3,4,9,17–19]. However, another study reported that three normal babies were born to mothers treated by ARBs during their first trimester of pregnancy [14].

The most recently developed ARB is olmesartan olmetic, and its use during pregnancy, at a dose of 10 mg/day, has only been reported once [17]. According to the authors of this previous study, following oligohydramnios diagnosis at 29 gestation weeks, olmesartan olmetic regimen was withdrawn and rehydration along with a single dose of furosemide was administered to the pregnant woman. The result of this early intrauterine intervention was a healthy baby, born without renal or other abnormalities [17]. It was therefore postulated that fetus renal dysfunction, following olmesartan olmetic maternal exposure, is probably reversible. Our reported findings are, to some extent, consistent with this paper. In our case, the affected newborn was also exposed during his entire fetal life to olmesartan medoxomil at a dose of 20 mg/day. Despite oligohydramnios diagnosis, the medicine was not withdrawn. Apart from various characteristics, mainly craniofacial directly related to oligohydramnios, the neonate suffered from oligoanuric type acute renal failure during the first weeks of life due to olmesartan medoxomil exposure. Renal ultrasonographic findings of increased echogenicity on two otherwise normal kidneys are consistent with acute renal damage. The baby responded very well to the conservative management, and within first 2 weeks of life, recovery of renal function was observed. Thus, one possibility is that fetal renal toxicity following maternal exposure to olmesartan medoxomil is dose related. Another possible explanation is that the adverse reaction of ARBs may be due to genetic polymorphisms in drug-inhibiting enzymes or receptor blockers, which would alter drug concentration, thus affecting drug response [20].

In summary, here we reported a case of a premature female baby born with oligoanuric type of acute renal failure following the mother's exposure to olmesartan medoxomil. We observed a gradual recovery of renal function during the first 2 weeks of life, and therefore, considered that renal impairment was transient. At the latest follow-up 1 year later, renal function was normal, arguing against the presence of irreversible renal damage. Whether this specific antihypertensive agent, olmesartan medoxomil, administered during pregnancy at the dose of 20 mg daily is generally safe with no side effects for the fetus is not yet clear.

Conflict of interest statement. None declared.

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