Clinical Report

Acute kidney injury in a preterm infant homozygous for the C3435T polymorphism in the ABCB1 gene given oral morphine

Laura Pogliani1, Chiara Mameli1, Dario Cattaneo2, Emilio Clementi2,3, Fabio Meneghin1, Sonia Radice2, Simona Bruno4 and Gian Vincenzo Zuccotti1

1Department of Pediatrics, L. Sacco Hospital, University of Milan, Milan, Italy, 2Unit of Clinical Pharmacology, Department of Biomedical and Clinical Sciences, Consiglio Nazionale delle Ricerche Institute of Neuroscience, L. Sacco Hospital, University of Milan, Milan, Italy, 4E. Medea Scientific Institute, Bosio Parini, Italy and 2Castelli Clinic, Bergamo, Italy

Correspondence and offprint requests to: Laura Pogliani; E-mail: laura_pogliani@libero.it

Abstract

A 34-week infant born from a mother with a history of drug abuse developed neonatal abstinence syndrome (NAS) in the first hours of life. Urine drug screening was positive for cocaine and heroin. The infant developed acute kidney injury and bilateral hydronephrosis while receiving oral morphine for control of NAS. Cessation of morphine therapy and urinary catheterization resulted in a rapid and complete resolution of the symptoms. Our patient was homozygous for the C3435T polymorphism in the ABCB1 gene, a polymorphism previously associated with impaired P-glycoprotein activity. We hypothesize that acute renal toxicity was related to accumulation of morphine within urothelial cells due to genetically determined impaired P-glycoprotein activity.

Keywords: acute kidney injury; morphine; pharmacogenetics; preterm infant

Introduction

Morphine is frequently used to relieve pain and achieve sedation in many age groups. In preterm infants, morphine is largely used for pain control in neonatal intensive care units and for the management of the neonatal abstinence syndrome (NAS). Despite its recognized benefits, the use of morphine is associated with adverse effects on the cardiovascular, gastrointestinal and nervous systems such as hypotension, bradycardia, seizures, decreased gastrointestinal motility, intestinal obstruction and respiratory depression [1, 2]. Renal side effects of morphine (urethral spasm, spasm of bladder sphincters, urinary retention or hesitancy, antidiuretic effect and rhabdomyolysis) have been previously reported in adult patients [3, 4]. Little is however known about the adverse kidney effects of morphine on paediatric patients and, in particular, in preterm infants [1, 2, 5, 6].

Studies in adults indicate that peripheral mechanisms may play a role in opioid-induced bladder dysfunction and urinary retention [7, 8]. However, the exact mechanism by which morphine causes urinary retention and renal impairment in premature infants is unknown. Age-related difference in morphine clearance may contribute to the observed difference response to opioid therapy from infancy to adulthood [9–11]. Additionally, the pharmacokinetics and pharmacodynamics of morphine are influenced by several polymorphic genes [12]. Preliminary data suggest that variation in genes coding the drug-metabolizing enzyme (UGT2B7), mu-opioid receptors (OPRM1), the enzyme degrading catecholamines (COMT) and intracellular drug accumulation by P-glycoprotein (ABCB1) can significantly influence the clinical outcome of patients given morphine therapy [13–16]. Despite this, the pharmacogenetics of morphine have not been previously considered in the paediatric population as an explanation for poor drug response and/or for drug side effects.

We report a case of acute kidney injury and bilateral hydronephrosis in a premature infant homozygous for the C3435T polymorphism in the ABCB1 gene treated with oral morphine. We believe that this is the first published report demonstrating a relationship between renal morphine toxicity and genetic background in paediatric patients.

Case report

A 2240 g Caucasian male neonate was born at 34 weeks of gestation by emergency caesarean section performed for premature rupture of membrane. The mother was HIV-positive and had a history of cocaine and heroin abuse throughout her pregnancy. Apgar scores at 1 and 5 min after birth were 6 and 8, respectively. One hour after birth, the infant developed an NAS characterized by central nervous system irritability, tremors, poor feeding, exaggerated Moro reflex, increased muscle tone and uncoordinated sucking. His Finnegan Score (which comprehensively scores all relevant clinical signs of NAS in newborn infants during the first days of life assessing central nervous system hyperirritability, gastrointestinal...
dysfunction, respiratory distress and vague autonomic signs in a semi-quantitative way [17]) yielded a result of >12 (a Finnegan score of 8 or higher is considered severe and requires medical therapy).

A urine test performed soon after birth was positive for cocaine and heroin. Treatment with oral morphine was immediately started (0.5 mg/kg/24 h in four divided doses given every 6 h and then decreased to 0.4 mg/kg/24 h in three divided doses given every 8 h). To reduce the risk of vertical HIV transmission, oral zidovudine was started at 6 h of life. On Day 5, urine output decreased gradually and the serum creatinine level increased from 77.8 to 93.7 μmol/L (from 0.88 to 1.06 mg/dL) on Day 7 (Table 1). The potassium level rose concomitantly from 77.8 to 93.7 μmol/L (from 0.88 to 1.06 meq/L), whereas sodium remained normal without the development of metabolic acidosis. Physical examination revealed hypotonia, lethargy, distended abdomen and a vesical globe.

A renal ultrasound showed bladder distension with bilateral hydronephrotic kidneys [bipolar length 4.5 cm]. Urinary catheterization drained 73 mL of straw-coloured urine with resolution of the bladder distension. Morphine was discontinued without urinary retention was observed during hospitalization. Oral zidovudine therapy was continued for 6 weeks after birth and was well tolerated. The infant was followed up and was discharged home.

**Discussion**

A few cases of acute kidney injury and hydronephrosis have been reported in the literature after opioid administration in preterm infants [5, 6]. To our knowledge, this is the first case in which a possible pharmacogenetic cause has been identified. Other important causes of acute kidney injury bladder distension and hydronephrosis, such as urological malformations, neoplasia, vescicoureteral reflux and neurogenic bladder, were excluded in this case. The renal impairment was also reversible and improved soon after discontinuation of morphine. The clinical evidence thus suggests a pathophysiological mechanism related to morphine. Nevertheless, the possibility that other as yet unknown factors may be involved cannot be excluded.

Our patient was homozygous for a polymorphic variant in position 3435 of the ABCB1 gene. This gene encodes for P-glycoprotein, a protein that belongs to the ABC transporter family and is expressed in leucocytes, hepatocytes, blood–brain barrier and mainly on the brush border of enterocytes and renal tubular cells [18]. Importantly, P-glycoprotein is also expressed in urothelial cells [19–22], playing a key role in the disposition of chemotherapy in urothelial cancers [19, 21]. Our patient experienced acute kidney injury and bilateral hydronephrosis while receiving oral morphine for the control of NAS. This resolved after urinary catheterization, suggesting that the site of the obstruction was the bladder neck. We hypothesize that acute renal toxicity was related to accumulation of morphine and its metabolite within urothelial cells due to genetically determined, impaired P-glycoprotein activity.

A potential limitation is that we did not measure the plasma concentrations of morphine and its main glucuronide metabolite. However, studies showing the impact of C3435T polymorphism in the ABCB1 gene on clinical outcomes have consistently failed to demonstrate an association with blood drug concentrations, suggesting a local (rather than systemic) effect on drug disposition [15, 23]. P-glycoprotein is an efflux transporter that actively transports lipophilic drugs from the intracellular to the extracellular domain. Consequently, reduced expression and/or altered activity of P-glycoprotein can increase the intracellular and tissue drug concentrations, ultimately resulting in local drug toxicity.

Studies aimed at investigating the role of ABCB1 polymorphisms on morphine efficacy and/or safety have provided conflicting results. Some studies have reported significant associations between allelic T variants of ABCB1 with morphine-induced adverse gastrointestinal and central drug reactions in adults patients with cancer [14, 15], whereas other investigators have failed to document a role of genetic factors with morphine response [24–26]. No clinical studies have previously addressed the role of ABCB1 polymorphisms on morphine-related
kidney injury and our single case report does not provide a definitive conclusion on this topic. Nevertheless, we believe that it provides an intriguing mechanistic hypothesis that needs further investigation.

Conclusion

Pain and NAS in newborns are therapeutically managed by the administration of opioids. Morphine is one of the most important and widely used opioids in neonatology; but, large variability in its efficacy and/or safety represents a major clinical challenge. Clinical pharmacology studies in adults have demonstrated the importance of pharmacogenetics in determining the response to drug therapy [27–29]. Our observation is in line with these data and suggests that pharmacogenetics can aid our understanding of morphine-induced adverse effects in neonates as in other age groups.

Acknowledgements. Funding. The financial support by Regione Lombardia (MEAP project, Monitoraggio degli eventi aversi in pediatria) is gratefully acknowledged.

Conflict of interest statement. None declared.

References


Received for publication: 23.4.12; Accepted in revised form: 13.7.12