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Clinical Report

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

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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 different 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

Table 1. Time course of the main biochemical and clinical parameters observed in our patient

Parameters	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	At discharge	Normal values
S. creatinine (μmol/L)	77.8	—	85.7	—	—	82.2	93.7	79.6	71.6	—	46.9	50–100
Urine output (mL/kg/h)	Wet diaper[a]	Wet diaper[a]	Wet diaper[a]	∼3	∼2.0	3.0	[b]	2.7	3.0	2.5	4.0	>1–2
S. potassium (mmol/L)	3.9	4.0	3.5	3.9	4.1	5.3	6.2	4.6	4.2	4.6	4.1	3.5–5.0
Morphine dose (mg/kg/24 h)	0.5	0.7	0.6	0.4	0.4	0.3	Interrupted	—	—	—	—	
Finnegan's score	12	11	4	6	6	5	4	8	4	4	2	<8

[a]The patient was not catheterized and no quantitative assessment was performed.
[b]Urinary catheterization performed, residual volume 73 mL.

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 4.1 to 6.2 mmol/L (from 4.1 to 6.2 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 (normal for age 3–4 cm)]. Urinary catheterization drained 73 mL of straw-coloured urine with resolution of the bladder distension. Morphine was discontinued without rebound or adverse effects and over the subsequent 3 days, renal function returned to normal (Table 1). Repeat ultrasound confirmed the resolution of hydronephrosis.

An additional blood sample was collected for pharmacogenetic analyses (after informed consent was obtained from the mother). According to pyrosequencing analysis, the patient was wild type for the most common allelic variants of *UGT2B7*, *OPRM1* and *COMT* genes. However, he was homozygous for the C3435T (rs1045642) polymorphism of the ABCB1 gene that has been previously associated with absent/impaired P-glycoprotein activity [18].

The infant was discharged on Day 33: no further urinary retention was observed during hospitalization. Oral zidovudine therapy was continued for 6 weeks after birth and was well tolerated. The infant was followed during the first 18 months of life to monitor growth and renal development: no sign of renal impairment was reported and the transmission of HIV infection was excluded.

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, vesicoureteral 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.

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Conflict of interest statement. None declared.

References

1. Sabatino G, Quartulli L, Di Fabio S *et al*. Hemodynamic effects of intravenous morphine infusion in ventilated preterm babies. *Early Hum Dev* 1997; 47: 263–270
2. Koren G, Butt W, Pape K *et al*. Morphine-induced seizures in newborn infants. *Vet Hum Toxicol* 1985; 27: 519–520
3. Popp JE, Sanko WA, Sinha AK *et al*. A comparison of ketorolac tromethamine/oxycodone versus patient-controlled analgesia with morphine in anterior cruciate ligament reconstruction patients. *Arthroscopy* 1998; 14: 816–819
4. Tassinari D, Sartori S, Tamburini E *et al*. Adverse effects of transdermal opiates treating moderate-severe cancer pain in comparison to long-acting morphine: a meta-analysis and systematic review of the literature. *J Palliat Med* 2008; 11: 492–501
5. Bengtsson BO, Wootton-Gorges SL, Poulain FR *et al*. Urinary effects of morphine in preterm infants. *Acta Paediatr* 2003; 92: 251–253
6. Khassawneh M, Al-Balas H. Renal impairment and hydronephrosis in a premature infant following morphine infusion: case report. *Pediatr Nephrol* 2008; 23: 1887–1888
7. Petersen TK, Husted SE, Rybro L *et al*. Urinary retention during i.m. and extradural morphine analgesia. *Br J Anaesth* 1982; 54: 1175–1178
8. Rosow CE, Gomery P, Chen TY *et al*. Reversal of opioid-induced bladder dysfunction by intravenous naloxone and methylnaltrexone. *Clin Pharmacol Ther* 2007; 82: 48–53
9. Fabiano V, Mameli C, Zuccotti GV. Adverse drug reactions in newborns, infants and toddlers: pediatric pharmacovigilance between present and future. *Expert Opin Drug Saf* 2012; 11: 95–105
10. Knibbe CA, Krekels EH, van den Anker JN *et al*. Morphine glucuronidation in preterm neonates, infants and children younger than 3 years. *Clin Pharmacokinet* 2009; 48: 371–385
11. Saarenmaa E, Neuvonen PJ, Rosenberg P *et al*. Morphine clearance and effects in newborn infants in relation to gestational age. *Clin Pharmacol Ther* 2000; 68: 160–166
12. Darbari DS, Minniti CP, Rana S *et al*. Pharmacogenetics of morphine: Potential implications in sickle cell disease. *Am J Hematol* 2008; 83: 233–236
13. Klepstad P, Dale O, Skorpen F *et al*. Genetic variability and clinical efficacy of morphine. *Acta Anaesthesiol Scand* 2005; 49: 902–908
14. Klepstad P, Rakvåg TT, Kaasa S *et al*. The 118 A > G polymorphism in the human mu-opioid receptor gene may increase morphine requirements in patients with pain caused by malignant disease. *Acta Anaesthesiol Scand.* 2004; 48: 1232–1239
15. Fujita K, Ando Y, Yamamoto W *et al*. Association of UGT2B7 and ABCB1 genotypes with morphine-induced adverse drug reactions in Japanese patients with cancer. *Cancer Chemother Pharmacol* 2010; 65: 251–258
16. Ross JR, Riley J, Taegetmeyer AB *et al*. Genetic variation and response to morphine in cancer patients: catechol-O-methyltransferase and multidrug resistance-1 gene polymorphisms are associated with central side effects. *Cancer* 2008; 112: 1390–1403
17. Zimmermann-Baer U, Nötzli U, Rentsch K *et al*. Finnegan neonatal abstinence scoring system: normal values for first 3 days and weeks 5–6 in non-addicted infants. *Addiction* 2010; 105: 524–528
18. Cascorbi I. P-glycoprotein: tissue distribution, substrates, and functional consequences of genetic variations. *Handb Exp Pharmacol* 2011; 201: 261–283
19. Hayes MC, Birch BR, Cooper AJ *et al*. Cellular resistance to mitomycin C is associated with overexpression of MDR-1 in a urothelial cancer cell line (MGH-U1). *BJU Int* 2001; 87: 245–250
20. Kubo H, Sumizawa T, Koga K *et al*. Expression of the multidrug resistance-associated protein (MRP) gene in urothelial carcinomas. *Int J Cancer* 1996; 69: 488–494
21. Kakehi Y, Wu WJ, Kim WJ *et al*. Comparison of multidrug resistance gene expression levels with malignant potentials and influence of chemotherapy in urothelial cancers. *Int J Urol* 1995; 2: 309–315
22. Petrylak DP, Scher HI, Reuter V *et al*. P-glycoprotein expression in primary and metastatic transitional cell carcinoma of the bladder. *Ann Oncol* 1994; 5: 835–840
23. Cattaneo D, Ruggenenti P, Baldelli S *et al*. Mycophenolate Steroids Sparing (MYSS) Genetics Study Group.: ABCB1 genotypes predict cyclosporine-related adverse events and kidney allograft outcome. *J Am Soc Nephrol* 2009; 20: 1404–1415
24. Sia AT, Sng BL, Lim EC *et al*. The influence of ATP-binding cassette sub-family B member -1 (ABCB1) genetic polymorphisms on acute and chronic pain after intrathecal morphine for caesarean section: a prospective cohort study. *Int J Obstet Anesth* 2010; 19: 254–260
25. Lötsch J, von Hentig N, Freynhagen R *et al*. Cross-sectional analysis of the influence of currently known pharmacogenetic modulators on opioid therapy in outpatient pain centers. *Pharmacogenet Genomics* 2009; 19: 429–436
26. Coulbault L, Beaussier M, Verstuyft C *et al*. Environmental and genetic factors associated with morphine response in the postoperative period. *Clin Pharmacol Ther* 2006; 79: 316–324
27. Evans WE, Relling MV. Pharmacogenomics: translating functional genomics into rational therapeutics. *Science* 1999; 286: 487–491
28. Evans WE, McLeod HL. Pharmacogenomics-drug disposition, drug targets, and side effects. *N Engl J Med* 2003; 348: 538–549
29. Evans WE, Relling MV. Moving towards individualized medicine with pharmacogenomics. *Nature* 2004; 429: 464–468

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