

Super analgesia of intrathecal morphine may be related to *ABCB1* (*MDR1*) gene polymorphism

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Abstract: Intrathecal morphine provides superior analgesia and minimizes side effects with ~1/300th of the oral dose necessary to achieve this effect. The conversion ratios from oral route to intrathecal route vary greatly among individuals, and this may be related with polymorphisms of the *ATP-binding cassette B1* (*ABCB1*)/*multiple drug resistance 1* (*MDR1*) gene encoding the transporter P-glycoprotein in the blood–brain barrier. In the case presented herein, a patient with cancer pain for over 3 months was treated with oxycodone hydrochloride prolonged-release tablets (Oxycontin) and morphine hydrochloride tablets for breakthrough pain. The patient was admitted due to intolerable adverse effects of Oxycontin. During this admission, he was implanted with an intrathecal morphine pump which can deliver morphine into the cerebrospinal fluid. To our surprise, intrathecal morphine at a dose of ~1/540th of oral morphine equivalent dose produced complete analgesia. Our finding revealed homogenous CC at position 3435 (C3435T) in the *ABCB1/MDR1* gene in this patient, which encodes P-glycoprotein with good efflux pump functionality. As intrathecal morphine bypasses the blood–brain barrier that oral medications have to pass through, the good pump functionality may have contributed to the super analgesia of intrathecal morphine in this case. Genetic analysis of *ABCB1/MDR1* gene polymorphisms can be useful for personalized pain management in patients with intrathecal morphine pump.

Keywords: super analgesia, morphine, intrathecal morphine pump, gene polymorphism, *ABCB1*, *MDR1*

Introduction

The intrathecal morphine pump delivers morphine directly into cerebrospinal fluid to provide analgesia and is becoming increasingly popular for its efficacy and safety in managing cancer-related and noncancer-related chronic pain.^{1–3} As intrathecal morphine can avoid the obstacle of blood–brain barrier (BBB) and target central opioid receptors directly, it can provide strong pain relief and reduce the incidence of the systemic side effects in smaller dosages. The dosage of intrathecal morphine is calculated based on the dose of oral morphine or oral morphine equivalent dose (MED).³ As intrathecal morphine does not undergo metabolism and transportation across BBB before reaching the site of action, the calculation ratios may be influenced by function of organisms involving in pharmacokinetics process of opioids.

The efflux transporter P-glycoprotein (P-gp) is localized in the brain capillary endothelium as a vital component of BBB, which limits the entry of some opioids into the brain.⁴ P-gp is encoded by the *ATP-binding cassette B1* [*ABCB1*, also referred to

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as *multiple drug resistance 1 (MDR1)* gene, and polymorphisms of this gene have been widely described.⁵ One major site of interest, the single-nucleotide polymorphism C3435T (rs1045642), affects the dosages and analgesia of opioids administered by systemic route.⁶

Generally, the dose of intrathecal morphine is calculated as 1/300th of the amount of oral morphine, while other oral opioids are converted to MED before calculation.³ In this report, intrathecal morphine at the dose of 1/540th of the oral MED provided complete pain relief and also eliminated the side effects of systemic opioids, and the relationship between this super analgesia and *ABCB1* gene polymorphism is presented.

Case presentation

A 46-year-old man with a history of left renal carcinoma after surgery presented with a pain syndrome that had lasted over 3 months. The patient complained about a lasting convulsive pain in the left waist, which seriously affected his sleep and mood. He was treated with oxycodone hydrochloride prolonged-release tablets (Oxycontin) (Bard Pharmaceuticals, Cambridge, UK) at a dose of 60 mg every 12 hours, and morphine hydrochloride tablets (Qinghai Pharmaceuticals, Xining, China) at a dose of 10 mg twice daily for breakthrough pain. However, the pain was not relieved completely, as when assessed with the Visual Analog Scale, a score of 4 was observed.

The patient was admitted due to the adverse effects of Oxycontin, which included dizziness, nausea, urinary retention, and constipation. During this admission, he was implanted with an intrathecal morphine pump (Hospira Inc., Chicago, IL, USA) which can deliver morphine into cerebrospinal fluid. It is widely accepted that intrathecal morphine provides analgesia equal to that of oral morphine alone at 1/300th of the oral dose, and the dose conversion ratio between oral oxycodone and morphine is 2:1. Considering that the patient took 120 mg of oxycodone and 20 mg of morphine each day, the dose of intrathecal morphine should be 0.87 mg/d ($[120 \times 2 + 20] / 300 = 0.87$). To our surprise, when the dose of intrathecal morphine was adjusted to 0.48 mg/d, complete analgesia was observed, with the patient reporting a Visual Analog Scale score of 0. It was amazing that all the previous adverse effects, like nausea, disappeared.

The patient was referred to the Therapeutic Drug Monitoring Laboratory. In the laboratory, the patient was tested for *ABCB1*, *CYP2D6*, and *OPRM1* polymorphisms using an automated BioFilmChip microarray (Sino-era, Beijing, China). The patient had the following polymorphism profiles: *ABCB1/MDR1* (3435C>T) CC; *CYP2D6* *2 (2850C>T) (rs16947) CT, *10 (100C>T) (rs1065852) CC, *14 (1758G>A) (rs5030865) GG; *OPRM1* (118A>G) (rs1799971) AG.

Discussion

Intrathecal morphine analgesia is becoming a substitutive therapeutic option for patients whose current treatments do not meet their specific goals, especially when they suffer from side effects due to opioid intake by the systemic route.³ Usually, the daily dosage of intrathecal morphine is determined as 1/300th of the amount of oral dosage.^{3,7}

In the case of this patient, oral Oxycontin did not provide adequate analgesia. More seriously, the patient was troubled by certain side effects, such as dizziness and nausea, during the oral delivery period. When switched to intrathecal delivery, only ~1/540th the oral MED provided completed pain relief and eliminated the preexisting side effects. Pharmacogenetic analysis was performed, which indicated the presence of a homozygous variant in *ABCB1/MDR1* (3435C>T) gene.

ABCB1/MDR1 3435 C>T polymorphisms alter P-gp conformational status and transportation function.⁵ *ABCB1/MDR1* homozygous CC carriers have good efflux pump functionality and require a higher oral opioid dose to achieve similar analgesia compared with CT or TT carriers.^{6,8} However, this difference could not be expected when the opioids were delivered by intrathecal route, as the drug in this case does not pass through the BBB.³ Thus, a higher conversion ratio of morphine from oral route to intrathecal route is expected in *ABCB1/MDR1* homozygous CC carriers, which is in agreement with the actual calculated conversion ratio in our reported case.

Polymorphisms in genes coding for proteins involved in the metabolism of opioids are also expected to affect the conversion ratio when switching to the intrathecal route.³ *CYP2D6* is one of the major drug-metabolizing enzymes for oxycodone, and the activity of *CYP2D6* caused by genetic variants has a positive relationship with the analgesic response of oxycodone.⁹ However, the high conversion ratio in this case is not due to *CYP2D6* genetic variants as the genotype of this patient is *1/*2, which means he is an extensive metabolizer.¹⁰ An important heterozygous genetic mutation in *OPRM1* was also found in this patient, but not considered to contribute to the difference in conversion ratio as opioids target μ -opioid receptor regardless of the administration route.³

Conclusion

The intrathecal opioid dosages are calculated based on oral MED, and the conversion ratios vary from patient to patient. As the transporter P-gp plays different roles in the oral and intrathecal delivery route of opioids, genetic variants in *ABCB1/MDR1* may be related to the difference in the

conversion ratio. This report first addressed the possible relationship between a higher conversion ratio and *ABCB1/MDR1* (3435C>T) CC genotype. Genetic analysis of *ABCB1/MDR1* gene polymorphisms can be useful in personalizing intrathecal morphine dosing. Further research is warranted to precisely determine conversion ratios from oral route to intrathecal administration route for different genotypes.

Consent and ethics approval

Written informed consent was obtained from the patient for the publication of this case report. The present study was approved by the ethical committee of China-Japan Friendship Hospital (2015-GZR-75).

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Author contributions

All authors contributed toward data analysis, drafting and critically revising the paper, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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