Scandinavian Journal of Pain 17 (2017) 193–200

Contents lists available at ScienceDirect

Scandinavian Journal of Pain

journal homepage: www.ScandinavianJournalPain.com

Topical review

Individual variability in clinical effect and tolerability of opioid analgesics – Importance of drug interactions and pharmacogenetics

Vigdis Solhaug[a], Espen Molden[a,b,*]

[a] Center for Psychopharmacology, Diakonhjemmet Hospital, Oslo, Norway
[b] Department of Pharmaceutical Biosciences, School of Pharmacy, University of Oslo, Norway

HIGHLIGHTS

- Interactions and pharmacogenetics cause response variability of opioid analgesics.
- Cytochrome P450 metabolism and/or P-glycoprotein transport regulate opioid exposure.
- Some opioids may induce serotonergic syndrome when combined with antidepressants.
- Genetic variability in CYP2D6 metabolism determines response of many opioids.
- Interaction databases and genetic tests may prevent unfavourable outcomes of opioids.

ARTICLE INFO

Article history:
Received 8 September 2017
Received in revised form
11 September 2017
Accepted 12 September 2017

Keywords:
Opioids
Interactions
Pharmacogenetics
Cytochrome P450
P-glycoprotein
OPRM1

ABSTRACT

Background: As pain is often a comorbid condition, many patients use opioid analgesics in combination with several other drugs. This implies a generally increased risk of drug interactions, which along with inherent pharmacogenetic variability and other factors may cause differences in therapeutic response of opioids.
Aim: To provide an overview of interactions and pharmacogenetic variability of relevance for individual differences in effect and tolerability of opioid analgesics, which physicians and other healthcare professionals should be aware of in clinical practice.
Methods: The article was based on unsystematic searches in PubMed to identify literature highlighting the clinical impact of drug interactions and pharmacogenetics as sources of variable response of opioid analgesics.
Results: Cytochrome P450 (CYP)-mediated metabolism is an important process for both clinically relevant interactions and pharmacogenetic variability of several opioids. Concomitant use of CYP inhibitors (e.g. paroxetine, fluoxetine and bupropion) or inducers (e.g. carbamazepine, phenobarbital and phenytoin) could counteract the clinical effect or trigger side effects of analgesics in the same manner as genetically determined differences in CYP2D6-mediated metabolism of many opioids. Moreover, combination treatment with drugs that inhibit or induce P-glycoprotein (ABCB1), a blood–brain barrier efflux transporter, may alter the amount ('dose') of opioids distributed to the brain. At the pharmacodynamic level, it is crucial to be aware of the potential risk of interaction causing serotonergic syndrome when combining opioids and serotonergic drugs, in particular antidepressants inhibiting serotonin reuptake (SSRIs and SNRIs). Regarding pharmacogenetics at the receptor level of pain treatment, the knowledge is currently scarce, but an allelic variant of the μ1 opioid receptor (OPRM1) gene has been associated with higher dosage requirement to achieve analgesia.
Conclusions and implications: Drug interactions and pharmacogenetic differences may lead to therapeutic failure or serious side effects of opioid analgesics. Many interactions involve combinations with antidepressants and antiepileptics, which are highly relevant drugs in patients suffering from pain. To prevent unfavourable drug interactions it is important that clinicians pay close attention and use electronic drug interaction checkers when treatments are initiated or discontinued. For the management of issues related to pharmacogenetic differences, blood-based CYP genotyping is available as routine test at many laboratories, and provide a valuable tool for proper choice of drugs and doses for treatment of pain and other diseases.

* Corresponding author at: Center for Psychopharmacology, Diakonhjemmet Hospital, PO Box 23 Vinderen, N-0319 Oslo, Norway.
E-mail address: espen.molden@farmasi.uio.no (E. Molden).

http://dx.doi.org/10.1016/j.sjpain.2017.09.009
1877-8860/

Contents

1. Introduction

Pain is a common condition accompanying many different diseases. In the pharmacotherapeutic management of pain, drugs either act peripherally by reducing pain stimuli or centrally by suppressing the perception of pain. Opioids are key drugs used for suppressing pain perception. Although opioids generally are effective drugs, their use is associated with extensive individual differences in clinical effect and tolerability.

Individual differences in effect and tolerability of opioids may be the result of many different factors, including age, gender, organ functions, dietary habits, smoking habits, drug interactions and inherent pharmacogenetic differences. These factors may affect concentrations (pharmacokinetics) or receptor/target responsiveness (pharmacodynamics) of opioids. In later years, there has been a growing knowledge on the importance of drug interactions and pharmacogenetics for individual variability in therapeutic response of opioids. The aim of the present topical review was therefore to provide an overview of key drug interactions and pharmacogenetic differences affecting opioids, including possible actions to prevent therapeutic failure or adverse effects, which physicians and other healthcare professionals should be aware of in clinical practice. The review was based on literature identified by unsystematic searches in PubMed.

2. Drug interactions involving opioids

Drug interactions may alter pharmacokinetics (exposure) or pharmacodynamics (sensitivity) when medications are combined. For a drug–drug interaction pair, there will generally be one perpetrator drug creating the interaction and one victim drug being affected by the interaction. Occasionally, however, the drugs may interact mutually and therefore be perpetrators and victims at the same time.

Opioids are usually victims in pharmacokinetic interactions, but may act as perpetrators in pharmacodynamic interactions. The following subsections highlight the most relevant interactions involving opioids, i.e. cytochrome P450, P-glycoprotein and serotonergic interactions. The two former represent pharmacokinetic interactions, while the latter is pharmacodynamic in nature.

2.1. Cytochrome P450 interactions

Enzymes within the cytochrome P450 (CYP) super family are the most important ones in drug metabolism, and many opioids are subject to metabolism via CYP enzymes. The CYP enzymes mainly involved in metabolism of opioids are CYP2D6 and CYP3A4/5 [1]. Methadone, which has been tested in treatment of cancer pain [2], is mainly metabolized by CYP2B6, while CYP3A4/5 play a secondary role [3]. In Table 1, opioids being substrates of the various CYP enzymes are listed along with interacting inhibitors and inducers of the respective enzymes.

Interactions via CYP enzymes occur when a substrate of an enzyme is combined with an inhibitor or inducer of the same enzyme. Generally, combined use of inhibitor–substrate pairs of the same CYP enzyme, results in increased concentration (exposure) and reinforced clinical effect and side effect risk of the substrate. However, in cases where the substrate is a prodrug the opposite scenario will occur.

2.1.1. CYP inhibitors

Two of the most commonly used analgesic opioids, codeine and tramadol, are both prodrugs activated by the enzyme CYP2D6 [1] (Fig. 1). Codeine's analgesics properties are due to its conversion via CYP2D6 to morphine, which has a 200-fold higher affinity for μ-opioid receptors than codeine, and subsequently via glucuronidation to morphine-6-glucuronide, a phase II metabolite with potent analgesic activity. Tramadol is also converted by CYP2D6-mediated oxidation to an active metabolite, *O*-desmethyltramadol. This metabolite is a high-affinity ligand and produce potent analgesia via opioid receptors [4]. Unmetabolized tramadol might have some impact on pain perception by inhibiting reuptake of the neurotransmitters serotonin and noradrenaline, but this mechanism is mainly responsible for adverse effects and unfavourable interactions (see Section 2.3).

In the case of codeine, about 10–15% of the dose is normally converted by CYP2D6 to morphine, which is responsible for the analgesic effect. Thus, if patients are comedicated with CYP2D6 inhibitors, bioactivation of codeine to morphine will be reduced or totally blocked. The degree of interaction mainly depends on the CYP2D6 inhibitor potency, and inhibitors classified as the most potent ones comprise fluoxetine, paroxetine, bupropion and orally administered terbinafine, and antimycotic agent [5–8]. Coadministration of these potent inhibitors will completely block CYP2D6-mediated *O*-desmethylation of codeine to morphine (Fig. 1), while more moderate inhibitors, such as citalopram, escitalopram, methadone and levomepromazine will reduce bioactivation of codeine in a dose-dependent manner [5,9,10].