The importance of individual differences in response to opioid therapy

"…our awareness of the existence of large variability in opioid response, and our increasing knowledge on possible causes, will increase our ability to respond swiftly and adequately to a lack of opioid efficacy despite adequate or high opioid dose, and even more important, to increased and life-threatening opioid toxicity."

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Opioid analgesics are the most commonly used drugs in the treatment of moderate to severe pain, both in the acute (e.g., post-operative) and chronic setting (e.g., treatment of cancer pain). All clinicians involved in prescribing potent opioids for pain relief are aware of the large variable effects of these drugs in the delivery of adequate analgesia, as well as in the development of side effects among individual patients. Both animal and human studies indicate that the variability has multiple origins, ranging from biological (such as related to differences in sex, age, ethnicity and genetic make-up), psychological (such as related to individual differences in coping strategies, social and environmental status, expectation/history and placebo response), co-morbidity and nutritional health status (such as related to individual differences in immune and stress response and antioxidant status) and co-medication (with possible influences on metabolism or related to drug–drug interactions) [1]. While some of these factors are known at the time of treatment (e.g., sex, age and co-medication), others are unknown or require additional testing to become apparent (e.g., the genotyping of genes involved in pain and opioid efficacy). To what extent the individual factors influence the response to pain therapy and how they interact is difficult to know. The practicing pain physician will treat his/her patient based upon weight, age and disease severity. For example, we know that opioid sensitivity is increased in the very young, the very old and the very ill, and consequently adaptation of the dose is required. Recent studies further indicate the importance of sex in opioid efficacy and side effects. Men and women differ in their pain response, with, in general, more severe pain in women [2,3]. In addition, the response to opioids differs between the sexes. Studies on post-operative morphine consumption using patient-controlled analgesia devices suggest reduced opioid consumption in women [4,5]. Whether this is related to a true difference in opioid potency between men and women or is related to a higher incidence of side effects (nausea/vomiting) in the female population and, consequently, a fear of opioid consumption remains unknown. Prospective randomized trials in volunteers do indicate that women have greater morphine potency, causing greater analgesia and coinciding with more intense respiratory depression [6–8].

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The success of the International Human Genome Project resulted in a explosive increase in studies on pharmacogenetics (the genetics of drug responses). Various genes have been identified as modulators of opioid pharmacokinetics and/or pharmacodynamics. The most important genes (so far) being:

- *OPRM1* (μ-opioid receptor gene);
- *COMT* (catechol-*O*-methyl transferase gene involved in the metabolism of catecholamines and also opioid sensitivity);
- *MC1R* (melanocortin 1 receptor gene involved in skin/hair color, but also opioid sensitivity);
- *ABCB1* (the gene coding for P-glycoprotein, which is involved in the efflux of xenobiotics, including opioids, from the brain compartment);
- *CYP2D6* (a cytochrome P450 isoform involved in the metabolism of weaker opioids, such as codeine, tramadol and oxycodone, into more potent hydroxyl metabolites, such as morphine) [9,10].

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Multiple studies examining the variants of single genes were highly successful in observing variations in drug effect, both intended (opioid analgesic efficacy) and side effects (most studied is respiratory depression). This suggests that knowledge on the variants of those earlier mentioned genes will increase our knowledge on individual opioid efficacy, but also on opioid side effects. In a recent multicenter study, Lötsch *et al.* explored all known variants of the *OPRM1*, *COMT*, *MC1R*, *ABCB1* and *CYP2D6* genes in a chronic pain population (n = 352 patients) treated for 1 to 600 months with various opioids (4 to 1750 mg daily oral morphine equivalents) [10]. They observed a rather small (but significant) decrease in a gene dose-dependent manner with the P-glycoprotein variant *ABCB1* 3435C>T, and a tendency towards increased pain in a gene dose-dependent manner with the μ-opioid receptor variant *OPRM1* 118A>G. They concluded that 'the need of outpatient therapy of pain of various causes guided by the presently known functional genetic variants cannot be convincingly concluded from the present data' [10]. This seems somewhat disappointing, and suggests that other factors than those that are genetic, such as those given above, have a much stronger effect on opioid response variability. However, better results may possibly be obtained when focusing on just one opioid, such as has been shown for morphine use in cancer patients. Carriers of the *COMT* 472G>A variant require increased morphine doses for adequate pain relief [11].

Clearly, at present, no generalized statements are possible regarding specific genotypes and opioid efficacy. Still, when focusing on specific drugs and genes, individual differences in responses to opioids are important and may predict adverse outcome. I will give three examples relevant to an important side effect of opioids – respiratory depression. This side effect remains the main hazard in opioid-naive patients (such as patients treated for acute pain) and opioid-tolerant patients that are overdosed, because of the obvious risk of a fatal outcome.

OPRM1 gene

The most important single nucleotide polymorphism (SNP) of the *OPRM1* gene is the substitution of the nucleotide adenine (A) with guanine (G) at position 118 of exon 1 of the gene (118A>G). The 118G allele frequency is 2–40%, depending on the ethnic population (the frequency is 20–30% in Caucasian and Hispanic populations) [9,12]. The consequence of the substitution is a reduction in opioid analgesic potency. This has now been observed for alfentanil, levomethadone and morphine-6-glucuronide [13–15]. Consequently, homozygous carriers require two- to three-fold greater opioid doses. Of interest is that already heterozygous carriers show a reduced opioid analgesic efficacy, while no reduction is observed in potency for respiratory depression [13,15]. Only the homozygous carriers show a reduction in potency for both end points. Since heterozygous carriers may comprise up to a third of the patient population, these data suggest that a large part of the population may be at risk for opioid-induced respiratory depression. However, the sample sizes of the mentioned studies were limited, and larger association studies are required before definite conclusions may be drawn.

ABCB1 gene

In a Korean patient population, it was observed that three SNPs (3435C>T, 1236C>T and 2677G>T) caused a significant increase in respiratory depression from fentanyl [16]. The most sensitive haplotype was TTT/TTT. The differential effect among haplotypes may indicate a differential ability of P-glycoprotein to evacuate fentanyl from the brain compartment and, consequently, greater brain fentanyl concentrations in the TTT/TTT haplotype.

CYPD26 gene

Various prodrugs are converted in the liver to the more active metabolite via the P450 enzyme system. One such prodrug is codeine, which is converted to morphine by the CYP2D6 enzyme. The gene coding for this enzyme is highly polymorphic, with more than 100 variants identified [9]. Variant allelic expressions relate to copy numbers ranging from nonfunctional alleles (phenotypically poor metabolizers) to multiple functional alleles (ultra-rapid metabolizers). There are large ethnic differences in variant frequencies. For example, 5–10% of Caucasians are poor metabolizers, and 5–10% are ultra-rapid metabolizers. Ultra-rapid metabolizers have greater morphine plasma concentrations in response to codeine treatments relative to the other phenotypes. Koren *et al.* report the case of a breast-fed neonate of a mother on codeine for episiotomy pain [17]. The full-term otherwise healthy child failed to thrive (somnolence and constipation) on day 7 and died on day 13 from opioid toxicity (i.e., respiratory depression). The mother took two to four tablets of codeine 30 mg per day. The post-mortem revealed no

anatomical abnormalities in the baby, but morphine plasma concentrations were 70 ng/ml (the normal range for infants of mothers on codeine is 0.2–2 ng/ml). The mother's milk contained 87 ng/ml morphine (normal values are 2–20 ng/ml at a codeine dose of 60 mg every 6 h). Genotyping classified the mother as an ultra-rapid metabolizer.

> "*Genetic differences are just one of many causes for the large variation in the observed responses to opioids.*"

These three examples indicate the importance of individual genetic differences in opioid response. Opioid-prescribing physicians need to be aware that these differences exist and that they influence opioid efficacy, as well as the opioid side-effect profile. However, in the general patient population, genetic differences are just one of many causes for the large variation in the observed responses to opioids. At present, opioid responses are hard to predict, even when considering obvious differences among patients, such as age, sex, ethnicity, skin color, weight and so on, or when additional genetic testing is performed. As stated by Lötsch *et al.*, 'genotyping to predefine opioid dose barely merits the laboratory effect' [10]. I agree, and believe that genotyping should be restricted to specific indications and circumstances. However, our awareness of the existence of large variability in opioid response, and our increasing knowledge on possible causes, will increase our ability to respond swiftly and adequately to a lack of opioid efficacy despite adequate or high opioid dose, and even more important, to increased and life-threatening opioid toxicity.

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Bibliography

1 Galley HF, Mahdy A, Lowes DA: Pharmacogenetics and anesthesiologists. *Pharmacogenomics* 6, 849–856 (2005).

2 Wiesenfeld-Hallin Z: Sex differences in pain perception. *Gend. Med.* 2, 137–145 (2005)

3 Chin ML, Rosenquist R: Sex, gender, and pain: 'men are from Mars, women are from Venus …' *Anesth. Analg.* 107, 4–5 (2008).

4 Miaskowski C, Levine JD: Does opioid analgesia show a gender preference for females? *Pain Forum* 8, 34–44 (1999).

5 Chia YY, Chow LH, Hung CC *et al.*: Gender and pain upon movement are associated with the requirements for postoperative patient-controlled i.v. analgesia: a prospective survey of 2298 Chinese patients. *Can. J. Anaesth.* 49, 249–255 (2002).

6 Dahan A, Sarton E, Teppema L, Olievier CN: Sex-related differences in influence of morphine on ventilatory control in humans. *Anesthesiology* 88, 903–913 (1998).

7 Sarton E, Dahan A, Teppema L: Sex differences in morphine-induced ventilatory depression resides within the peripheral chemoreflex loop. *Anesthesiology* 90, 1329–1338 (1999).

8 Sarton E, Olofsen E, Romberg R *et al.*: Sex differences in morphine analgesia: an experimental study in healthy volunteers. *Anesthesiology* 93, 1245–1254 (2000).

9 Searle R, Hopkins PM: Pharmacogenomic variability and anaesthesia. *Br. J. Anaesth.* 103(1), 14–25 (2009).

10 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* 19, 429–436 (2009).

11 Rakvåg TT, Ross JR, Sato H *et al.*: Genetic variation in the catechol-*O*-methyltransferase (*COMT*) gene and morphine requirements in cancer patients with pain. *Mol. Pain* 4, 64–73 (2008).

12 Landau R, Cahana A, Smiley RM *et al.*: Genetic variability of μ-opioid receptor in an obstetric population. *Anesthesiology* 100, 1030–1033 (2004).

13 Oertel BG, Schmidt R, Schneider A *et al.*: The μ-opioid receptor gene polymorphism 118A >G depletes alfentanil-induced analgesia and protects against respiratory depression in homozygous carriers. *Pharmacogenet. Genomics* 16, 625–636 (2006).

14 Lötsch J, Skarke C, Wieting J *et al.*: Modulation of the central nervous effects of levomethadone by genetic polymorphisms potentially affecting its metabolism, distribution, and drug action. *Clin. Pharmacol. Ther.* 79, 72–89 (2006).

15 Romberg R, Olofsen E, Bijl H *et al.*: Polymorphism of μ-opioid receptor gene (*OPRM1:*c.118A>G) does not protect against opioid-induced respiratory depression despite reduced analgesic response. *Anesthesiology* 102, 522–530 (2005).

16 Park HJ, Shinn HK, Ryu SH *et al.*: Genetic polymorphisms in the *ABCB1* gene and the effects of fentanyl in Koreans. *Clin. Pharmacol. Ther.* 81, 1–8 (2007).

17 Koren G, Cairns J, Chitayat D *et al.*: Phramacogenetics of morphine poisoning in a breastfed neonate of a codeine-prescribed mother. *Lancet* 368, 704 (2006).