Pharmacogenetics of analgesics

Opioids

The mu opioid receptor is the major target for all opioids and although there are a large number of variants to its gene OPRM1, the c.118A>G single-nucleotide polymorphism (SNP) in which the G variant allele has a frequency of 10-15% in Caucasians but almost 50% in Asians and results in reduced opioid effects, has been the most widely studied. For example, in healthy subjects administered alfentanil, those with one or two copies of the G variant allele showed a threefold reduced effect to experimentally induced pain from electrical stimulation and 10 fold reduced respiratory depressant effect. It is difficult to quantify analgesic response and the variability in response to opioids in patients with pain. As a consequence, this is often assessed as dosage requirements. In cancer patients on morphine for chronic pain, four patients who had two copies of the G variant gene required a higher dose (mean±SD 225±143 mg/day) compared to 78 with no copy, or 17 with one copy of the variant (97±89 and 66±50 mg/day respectively). However, the small numbers of patients with both alleles variant (homozygous variant), the large interpatient variability in dosage requirements per se and the non gene-dose effect make interpretation difficult.

In a much larger population of 175 cancer patients commencing morphine, while there was no difference in dosage requirements between those with zero, one or
two copies of the G variant allele, those with two copies had a significantly lower change in pain as measured on a numerical rating scale (mean 0.2 unit change), compared to those with one copy (1.8) and those with no copies (3.8), after one week of dosing. When those with one or two copies of the variant allele were combined, the result was significant in that those with the G variant allele had a much lower change in pain rating.3 Thus, the mu opioid receptor gene variant c.118A>G appears to lead to a reduced opioid effect.

This was confirmed in a recent study in postoperative pain conducted in almost 1000 Asian patients in Singapore, noting that the G variant allele has a much higher frequency in this population.4 The authors found a difference in morphine PCA dosage used in that the homozygous variant group required almost double that of the wildtype group, with intermediate use in the heterozygotes (10.9, 5.8, 8.8 dosage units, respectively).

In a recent meta-analysis, Walter and Lötsch (2009) reported that the c.118A>G SNP showed no consistent association with phenotype.5 However, the data were from a combined analysis of postoperative patients, women in labour and patients with chronic cancer pain and chronic non-cancer persistent pain. As mentioned above, one of the major problems in human studies in this area has been low patient numbers in most of the studies included in the analyses.

The COMT (catechol-O-methyltransferase) enzyme system metabolises noradrenaline, adrenaline and dopamine, and can effect morphine dosage requirements. In 207 cancer patients, those with two copies of the COMT A variant at c.474G>A required 95±99 (mean±SD) mg/day, those with one copy required 117±100 mg/day and those with no variant allele (G wildtype) 155±160 mg/day (P=0.025).6 Although the mechanism remains unclear, the A variant causes upregulation of the mu opioid receptor, so that endogenous opioids have a greater effect, resulting in less dosage required of exogenous opioids (eg. morphine).

Opioids must cross the blood-brain barrier for the majority of their effects. P-glycoprotein is an efflux transporter found on the luminal membrane of many organs and tissues. It is located on the apical membrane of the capillary endothelial cells at the blood-brain barrier and functions to limit drug entry into the brain. A lowered function of the transporter allows more drug to be present in the brain. Theoretically, this should lead to an enhanced antinociceptive effect. Some opioids such as fentanyl, morphine and methadone are p-glycoprotein substrates. In acute pain, a variant of the gene ABCB1 (that encodes for p-glycoprotein) causes enhanced respiratory depression following a single intravenous dose of fentanyl.7 Haplotype (multiple SNP) analysis for ABCB1 showed that dosage requirements of methadone used in maintenance treatment for opioid dependence were related to the number of copies of the variant haplotype. Those patients with two wildtype alleles required a higher dose than those with both alleles variant.8 In the study cited above for morphine by Campa and colleagues (2008), those patients with two copies of the most common ABCB1 variant allele c.3435C>T had an increased analgesic effect (increase in pain score of 4.4 units), compared to those with one variant (3.15) and those with wildtype (2.31).9 These findings indicate that several of the opioids that have been tested are p-glycoprotein substrates, and that there will be an enhanced analgesic and adverse effect to standard doses of opioids in patients who have variants in ABCB1.

It is intriguing that the combination of variants in OPRM1 and ABCB1 can have opposite effects on response, with the former lowering analgesic response while the latter enhances analgesia. Thus, overall response will depend on which combination of these two gene variants a patient has. For example, Campa et al (2008) showed that the best response to morphine in their cancer patients was in those with a combination of wildtype OPRM1 plus ABCB1 variant (4.8 unit change in pain score) and the worst response was in those with a combination of OPRM1 variant and wildtype ABCB1 (1.3).10

Opioids such as codeine, tramadol and oxycodone that are O-demethylated to more potent opioid metabolites such as morphine, O-desmethyltramadol and oxymorphone, respectively, by the highly polymorphic cytochrome P450 CYP2D6 enzyme, show reduced effects to the parent drug in subjects with mutations in the CYP2D6 gene, resulting in the poor metaboliser (PM) phenotype. For example, CYP2D6 PMs given codeine show a substantially reduced response to cold pressor pain and reduced respiratory depression and lower psychomotor performance.8 However, there have been no large clinical pain studies to test this premise. Similarly with oxycodone, in a small study in palliative care, the one PM patient required the highest dose of oxycodone and greatest number of breakthrough analgesic doses.10 Finally, for tramadol in postoperative patients following abdominal surgery, there was a significantly higher number of non-responders in PMs (81%) compared to extensive metabolisers (EMs 17%).11 In addition to PMs, who comprise about 7% of the Caucasian population, about 2% of Caucasians are ultrarapid metabolisers (UMs) mainly through having multiple copies (up to 13) of the CYP2D6 gene. In such people, enhanced adverse effects such as euphoria and dizziness have been reported due to increased conversion of codeine to morphine.12 Adverse psychiatric reactions have been reported to oxycodone and hydrocodone in patients with the UM phenotype.13

In summary, people with variants in the mu opioid receptor gene OPRM1 have a reduced response, those with variants in the p-glycoprotein efflux transporter gene ABCB1 an enhanced response and those with poor metaboliser variants in the CYP2D6 gene have a reduced response to some opioids that produce metabolites with substantially enhanced mu opioid activity.14

**Non Steroidal Anti-inflammatory Drugs (NSAIDs)**

The major polymorphic enzymes involved in the metabolism of NSAIDs are CYP2C9 (primarily) and CYP2C8 (less so). Plasma concentrations of flurbiprofen, ibuprofen, diclofenac (minor effect), lornoxicam, piroxicam and celecoxib are increased in subjects with the CYP2C9*3 variant (loss of function) allele, however the magnitude is less than two fold in most cases.15 For celecoxib, those who were homozygous for CYP2C9*3 had a seven fold increase in drug exposure,16 but this has not been confirmed. For the
active S-ibuprofen and piroxicam, such increased exposure results in greater thromboxane A2 concentrations, raising the potential that the CYP2C9 polymorphisms might reduce its COX-2 selectivity. In terms of NSAID induced gut toxicity, NSAID induced bleeding is higher in those with the CYP2C9*3 variant allele.

Some NSAIDs are also UGT substrates for glucuronidation, with diclofenac induced hepatotoxicity being more common in those with UGT2B7*2 variant alleles compared with controls.

In regard to genetic polymorphisms in the COX1 and COX2 enzymes and NSAID effects, in patients following dental surgery given rofecoxib, ibuprofen or placebo, those homozygous for the G allele of c.-765G>C of COX2 had a significantly lower pain intensity score from rofecoxib at 48 hours compared with those on ibuprofen, whereas those homozygous or heterozygous for the minor allele variant had a significantly higher pain intensity score compared to the wildtype. The mechanisms underpinning these findings and their clinical importance remain to be established.

Tricyclic antidepressants

Amiriptiline, nortriptyline and doxepin are metabolised by CYP enzymes. CYP2D6 contributes about 50% to the overall metabolism of amitriptyline and its active metabolite nortriptyline. Loss of function of CYP2D6 alleles result in an approximate doubling in plasma concentrations of the drug. It is uncertain to what extent the CYP2D6 phenotype contributes to enhanced efficacy, especially in neuropathic pain. It is generally considered that dose reductions are unnecessary in these patients, and the practice has not been adopted in the psychiatric and pain palliative care communities. Nortriptyline CYP2D6 ultrarapid metabolisers have plasma concentrations of only 20-50% of those with two functioning alleles and this could lead to drug resistance; a higher incidence (25%) of postural hypotension was reported in ultrarapid metabolisers (25%) compared to extensive metabolisers (0%).

Conclusion

Pain response to analgesia remains unsatisfactory in 10-30% of patients. Dose requirements required in order to obtain adequate pain relief vary considerably, especially with opioid therapy, where the inter-patient variation can be as high as 40%. There are many pharmacogenetics factors that can contribute to the efficacy and adverse effects of analgesics, especially the opioids. It is as yet unclear however, how significant these factors are in routine clinical practice. The number of patients included in many of the studies has been low, and some studies have shown no, or only borderline value in pharmacogenetic testing for predicting the response to opioids. It seems likely however, that genetic testing will in the future at least contribute to inter-individualised pain management.

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References