Analgesic drug dosing requirements to produce satisfactory pain relief with tolerable side-effects are subject to considerable interindividual variability—even in patients with pain of an apparently similar type and intensity. Contributing factors include those of genetic and environmental origin as well as their interaction (Fig. 1). Environmental factors include patient age, sex, status of liver and kidney function, lifestyle variables such as smoking and alcohol consumption, disease comorbidities, and concurrent medications.1,2 Genetic factors include those related to the regulation of analgesic drug pharmacodynamics and pharmacokinetics.2,6

Genotype and Phenotype: Definitions

An individual’s genotype is the inheritable information encoded in a particular set of genes on 23 pairs of chromosomes particular to the individual. Each person has a unique genomic fingerprint comprising two copies of each gene, except for the sex-linked genes. Each gene has a specific locus on a given chromosome, and each gene can have multiple alleles whose relative frequencies may vary markedly among ethnic groups in the general population.5 By contrast, an individual’s phenotype constitutes the observable characteristics or physical manifestations of his or her genotype.

Single-Nucleotide Polymorphisms

A single-nucleotide polymorphism (SNP) is a DNA sequence variation at a single location in the genome resulting in two allelic variants (Fig. 2), with the least common allele occurring at a frequency of at least 1% in the general population.5 The contribution of individual SNPs to observations of drug inefficacy or excessive toxicity in population subgroups (i.e., different patient phenotypes) constitutes the field of pharmacogenetics.5,6

SNPs in genes encoding drug-metabolizing enzymes, efflux transporters in the blood-brain barrier, analgesic drug targets, and neurotransmitter pathways all may contribute to interindividual variability in analgesic drug dosing requirements and adverse event profiles.

Since sequencing of the human genome almost a decade ago,7,8 there have been significant advances in genotyping technologies, which led to predictions that point-of-care devices would become available for genotyping patients to enable
clinicians to individually tailor drug therapy. However, this goal has yet to be achieved in the analgesics field due to the complexity produced by the multiplicity of SNPs in genes encoding drug metabolism enzymes, transporters, receptors, ion channels, and neurotransmitter systems, all of which have the potential to concurrently affect pain relief outcomes in individuals. Hence, it is difficult to predict, a priori, the impact of concurrently occurring SNPs in multiple genes of interest on the pharmacokinetics and pharmacodynamics of analgesic agents in individuals.

Pharmacogenetics Research in Humans

Insight from human pharmacogenetics research in the analgesics field comes from studies designed to examine the possible influence of SNPs in genes of interest on (i) interindividual differences in analgesic drug pharmacokinetics and experimental pain thresholds in healthy subjects and (ii) pharmacodynamic outcomes in patients with clinical pain.

In healthy human volunteers, quantitative sensory testing (QST) is used to determine experimental pain thresholds or stimulus-response curves for sensory processing across a range of pain modalities including thermal, mechanical, electrical, and chemical stimuli.9 More sophisticated designs employing QST involve application of these stimuli to a range of tissue types including skin, muscles, and viscera to produce a mosaic of responses.9 QST has been used in volunteer studies not only to assess the influence of genetic factors on interindividual variability in pain thresholds but also to define pharmacokinetic-pharmacodynamic relationships for analgesic agents of interest.

The following sections present an overview of findings to date on major research themes in the pharmacogenetics field relevant to interindividual variability in analgesic drug dosing requirements.

Genetic Factors and Pharmacokinetics

After oral dosing, analgesic drugs are absorbed across the gastrointestinal mucosa into the portal circulation and delivered directly to the liver (Fig. 3). In the process, absorbed drugs are exposed to an array of metabolic enzymes found in the gastrointestinal mucosa and the liver. The fraction of the dose that escapes first-pass metabolism enters the systemic circulation (Fig. 3). From there, an absorbed analgesic agent may diffuse across the tight junctions of the blood-brain barrier (BBB) to interact with central nervous system (CNS) receptors to produce both analgesia and adverse effects. For centrally acting analgesics that are substrates for drug transporters residing in the BBB, the amount of drug entering the brain is reduced by opposing efflux mechanisms mediated by transporters such as P-glycoprotein that are located in the BBB. Pharmacogenetics research has shown that SNPs in genes encoding drug-metabolizing enzymes, efflux transporters in the BBB, analgesic drug targets, and neurotransmitter pathways all have the potential to contribute concurrently to interindividual variability in analgesic drug dosing requirements and adverse-event profiles.

Analgesic Drugs and Metabolism

The metabolism of analgesic agents involves enzyme-catalyzed changes in their chemical structure to increase water solubility and facilitate excretion from the body as a key step in terminating drug action. Drug metabolism reactions are subdivided into Phase 1 “functionalization” reactions (e.g. oxidation, reduction, and hydrolysis) and Phase 2 metabolism to form water-soluble glucuronide, sulfate, and/or glutathione conjugates that are readily excreted via the kidney.4 In some instances, metabolism may result in bioactivation to form analgesically active metabolites, such as the metabolism of morphine to morphine-6-glucuronide, the metabolism of codeine to morphine, or the metabolism of tramadol to its M1 metabolite.10 Active metabolites may also contribute to adverse-event profiles such as the metabolism of pethidine (meperidine), morphine, and hydromorphone to their neuroexcitatory metabolites, norpethidine, morphine-3-glucuronide, and hydromorphone-3-glucuronide, respectively.11

The Cytochrome P450 Superfamily of Phase 1 Drug-Metabolizing Enzymes

The cytochrome P450 (CYP) superfamily of enzymes catalyzes Phase 1 metabolism of a wide range of endogenous and exogenous
3 molecules. In the human genome, there are 57 functional CYP genes and 58 CYP pseudogenes within 18 families (i.e., CYP families 1–5, 7, 8, 11, 17, 19–21, 24, 26, 27, 39, 46, and 51), with six CYP isoforms known to have significant roles in the metabolism of clinically used medications, viz CYP1A2, CYP2D6, CYP2C9, CYP3A4, CYP2E1, and CYP2A6. SNPs have been identified in most CYP isoforms, with their allelic variants resulting in altered protein expression and/or enzymatic activity (see www.cypalleles.ki.se). Although CYP2D6 is a minor constituent (2–4%) of hepatic CYP proteins in humans, it has an important role in the metabolism of ~25% of currently used medications, including many agents used to treat pain. Genetic variability in the CYP2D6 gene has been intensively studied in humans.

Functionally, the presence of an allelic variant in a particular CYP isoform will result in one of four drug-metabolizing phenotypes: poor metabolizer (PM), intermediate metabolizer (IM), extensive metabolizer (EM), or ultrarapid metabolizer (UM).

Human Drug Metabolizer Phenotypes

Functionally, the presence of an allelic variant in a particular CYP isoform will result in one of four drug-metabolizing phenotypes: poor metabolizer (PM), intermediate metabolizer (IM), extensive metabolizer (EM), or ultrarapid metabolizer (UM). The corresponding genotypes are: PMs have two nonfunctional (null) alleles, IMs have at least one reduced-functional allele, EMs (normal individuals) have at least one functional allele, and UMs have multiple copies of a functional allele and/or an allele where the mutation confers increased gene transcription. For drugs where CYP2D6-catalyzed metabolism is a major clearance mechanism, individuals with a PM phenotype are at risk of adverse drug reactions or toxicity at regular doses, whereas those with the UM phenotype will require higher doses to achieve therapeutic plasma drug concentrations.

CYP2D6 SNPs

To date, more than 80 distinct allelic variants of the CYP2D6 gene have been identified, resulting in a broad range of phenotypic diversity within populations characterized by marked differences between ethnic groups. In brief, the frequency of the PM phenotype is in the order of Caucasian (7–11%) > African American and Hispanic > Indian > South-Eastern and Eastern Asia > Chinese, Korean, and Japanese (0–1.2%) populations. The frequency of the UM phenotype is in the order of Black Ethiopian and Saudi Arabian (16–20%) > Sicilian, Italian, Spanish, Mediterranean, and Turkish > Caucasian and African American > European Caucasian (1–2%) populations. However, the genotype-phenotype relationship of most CYP2D6 alleles is not yet well established.

Analgesic agents where SNPs in the CYP2D6 gene may influence patient outcomes include tramadol, codeine, tricyclic antidepressants, venlafaxine, and antiarrhythmics, as well as other
agents such as antiemetics (e.g., ondansetron), tamoxifen, and antipsychotics (e.g., risperidone). Several examples are outlined below.

**Tramadol**

After systemic administration, tramadol is metabolized by CYP2D6 to its O-demethylated metabolite, O-desmethyltramadol (M1, Fig. 4A), which is a potent μ-opioid receptor agonist. CYP2D6 PMs are expected to experience less analgesia after standard doses and to have higher tramadol dosing requirements to achieve satisfactory pain relief relative to EM individuals. After oral tramadol dosing in humans, plasma concentrations of M1 are higher in EMs compared with PMs, whereas M1 formation is increased in UMs, who are at higher risk for developing opioid-related side effects.

**Codeine**

Codeine is generally thought to be a prodrug for its O-demethylated metabolite, morphine, with up to 10% of a dose being metabolized to morphine (Fig. 4B) by CYP2D6. In CYP2D6 PMs, morphine levels are virtually undetectable, and codeine reportedly lacks efficacy. By contrast, codeine is extensively metabolized to morphine in UM individuals, raising the risk of respiratory depression after regular doses of codeine. In an extreme case involving a breastfed neonate of a UM mother administered codeine, high levels of morphine were produced in the neonate, resulting in mortality. Subsequently, the authors of a case-controlled study recommended that codeine should not be prescribed to breast-feeding mothers.

**Oxycodone**

Oxycodone is a strong opioid analgesic that is widely used to treat moderate to severe pain. Although ~10% of an oxycodone dose undergoes CYP2D6-catalyzed O-demethylation to oxymorphone (Fig. 4C), a potent μ-opioid receptor agonist, the circulating plasma concentrations of metabolically derived oxymorphone are very low (~1 ng/mL) in EMs and threefold lower (0.3 ng/mL) in PMs. Although animal studies show that oxycodone administered directly into the cerebrospinal fluid of the rat brain produces dose-dependent naloxone-sensitive antinociception, the notion that oxycodone, rather than metabolically derived oxymorphone, is responsible for the analgesic effects of oxycodone in humans has been discounted by some authors. Recent pharmacogenetics research in healthy human subjects as well as in patients with postoperative pain has provided useful insight into this issue. In a study conducted in a group of 10 healthy volunteers comprising six EMs, one IM, one PM, and two UMs, antinociceptive responses to electrical stimulation and tolerance to the cold pressor test appeared to be significantly correlated with CYP2D6 phenotype such that the two UMs experienced superior analgesia relative to EMs and the single PM had lower antinociceptive responses relative to the EMs. However, the relevance of these findings to relief of postoperative pain appears limited, because a recent much larger clinical study involving administration of oxycodone to 270 patients (24 PMs and 246 EMs) for postoperative pain relief showed that analgesic outcomes did not differ significantly between CYP2D6 PM and EM individuals. These findings show unequivocally that oxycodone itself, rather than metabolically derived oxymorphone, underpins oxycodone’s ability to alleviate clinical pain.

**Mexiletine**

Mexiletine undergoes extensive metabolism to largely inactive metabolites, with formation of hydroxymethylmexiletine and parahydroxymexiletine catalyzed predominantly via CYP2D6 (Fig. 4D). Mexiletine has a very narrow therapeutic plasma concentration range (0.5–2 μg/mL), and so downward adjustment of standard doses is required in PMs relative to EMs to avoid toxicity.
Phase 2 Drug–Metabolizing Enzymes: The UGT Superfamily

In humans, Phase 2 metabolism of endogenous molecules such as bilirubin, bile acids, fatty acids, and steroid hormones, as well as that of many commonly prescribed medications, is characterized by considerable interindividual variability. Phase 2 metabolism is catalyzed by members of the uridinediphosphoglucuronosyltransferase (UGT) superfamily of enzymes to form water-soluble glucuronide conjugates.50,51 There are two major UGT enzyme classes in humans—UGT1A and UGT2—with at least eight isoforms of UGT1A (UGT1A1, 1A3, 1A4, 1A6, 1A7, 1A8, 1A9, and 1A10) and seven isoforms of UGT2 (UGT2A1, 2B4, 2B7, 2B10, 2B11, 2B15, and 2B17) having been identified.52 Of these, UGT2B7 has a key role in the metabolism of opioid analogues such as morphine and hydromorphone, nonsteroidal anti-inflammatory drugs, and anticonvulsants with this isoform being abundantly expressed in the gastrointestinal mucosa and the liver.53,54 Although pharmacogenetic research on variants in UGT genes to date has revealed considerable complexity, interpretation is difficult and ongoing research is required.51

Drug Transporters in the Blood–Brain Barrier

Efflux drug transporters such as P-glycoprotein that are located in the BBB have evolved to protect the brain from toxins of environmental and dietary origin. Most efflux transporters belong to the adenosine triphosphate (ATP)-binding cassette (ABC) superfamily of membrane proteins that influence the intracellular concentration of a broad array of compounds in cells and tissues.55 To date, 49 members of the ABC-transporter family, subdivided into seven subfamilies, A–G, have been identified (http://nutrigene.4t.com/humanabc.htm).55,56 The ABC transporter P-glycoprotein (ABCB1) is the best-characterized human drug transporter, with reports of more than 50 SNPs and several insertion/deletion polymorphisms in the ABCB1 gene.55 P-glycoprotein plays an important role in the BBB efflux transport of a range of clinically used drugs, including antidepressants, steroids, digoxin, and cyto-statics.55,57 Pharmacogenetic studies show considerable between-study variability with regard to the influence of a particular SNP in the ABCB1 gene on pharmacokinetic and pharmacodynamic outcomes, making it difficult to draw conclusions.55,57

The mechanism through which lower COMT activity appears to reduce opioid analgesic dosing requirements is multifactorial, with potential effects at multiple levels of the neuraxis.

SNPs and Analgesic Drug Pharmacodynamic Outcomes

In the pharmacogenetics field, considerable research efforts in the last decade have focused on assessing the influence of SNPs in the genes encoding the μ-opioid receptor and to a lesser extent, the enzyme catechol-O-methyl-transferase (COMT), on inter-individual differences in opioid dosing requirements as well as reported levels of pain.

Receptor/Ion Channel Polymorphisms: OPRM1 (Mu–Opioid Receptor)

Many strong opioid analgesics produce analgesia by activating the μ-opioid receptor in a manner similar to morphine.58 To date, ~1800 variants in OPRM1, the gene encoding the μ-opioid receptor, have been identified, with more than 20 of these variants being SNPs producing amino-acid changes.29 One OPRM1 SNP that occurs at the A118G position (N40D variant) is relatively common, with the rare allele occurring in approximately 20–30% of the population.60 Although initial genetic association studies suggested its functional importance,61 subsequent studies either did not replicate or only partially replicated the earlier findings. Recently, the relevance of the OPRM1 A118G genetic variant for the management of clinical pain has been seriously questioned because a meta-analysis found no consistent association between OPRM1 A118G genotypes and most of the phenotypes (opioid dosing, pain, and side effects) across the studies reviewed.52 Although there appeared to be an association between less nausea and increased opioid dosing requirements for homozygous carriers of the N40D variant, the correlation was weak.52 Hence, OPRM1 genotyping of patients to facilitate individual tailoring of opioid analgesic dosing requirements is not supported by research findings to date.63

SNPs and Neurotransmitter Pathways: COMT

Catechol-O-methyl transferase (COMT) is an enzyme that catalyzes the metabolism of endogenous catecholamine neurotransmitters such as epinephrine, norepinephrine, and dopamine that have important roles in nociceptive signal transduction and analgesia.64 A functional valine-to-methionine SNP at position 158 (V158M) in COMT (called rs4680) is associated with a three- to fourfold reduction in COMT activity and appears to be linked to a requirement for lower doses of morphine to attain satisfactory relief of cancer pain.65,66 In one study, this SNP appeared to be associated with an increased sensitivity to painful stimuli, but subsequent studies failed to show a genetic association with postsurgical pain, chronic widespread pain, or experimental pain.67–69 The mechanism through which lower COMT activity appears to reduce opioid analgesic dosing requirements is multifactorial, with potential effects at multiple levels of the neuraxis.66,70 These effects include enhanced descending noradrenergic inhibition, as well as enhanced dopaminergic signaling, resulting in reduced neuronal enkephalin concentrations, followed by an upregulation of opioid receptors.66,70

Sodium Channel Mutations and Pain Sensitivity

Local anesthetics such as lidocaine and antiarrhythmics such as mexiletine produce their pain-relieving effects via blockade of voltage-gated sodium channels in sensory nerves. However,
they may also produce a range of unwanted effects, including motor block, cardiac conduction block, and neurotoxicity, through inhibition of sodium channels in motor nerves, cardiac tissue, and the brain. Of the nine sodium channel subtypes identified to date, Na\textsubscript{v}1.3, Na\textsubscript{v}1.7, Na\textsubscript{v}1.8, and Na\textsubscript{v}1.9 appear to be mainly expressed in sensory nerves, and so novel analgesics targeted to these sodium channel subtypes have the potential to have more favorable adverse-event profiles while retaining analgesic efficacy.\textsuperscript{71–73} Support for this approach comes from human pharmacogenetics research, whereby individuals with rare loss-of-function or gain-of-function mutations in the SCN9A gene that encodes the Na\textsubscript{v}1.7 sodium channel subtype,\textsuperscript{74} present with one of two extreme pain phenotypes—an inability to sense pain or a familial chronic pain syndrome, respectively.\textsuperscript{75} These observations raised the possibility that SNPs in the SCN9A gene may correlate with levels of clinical pain reported by patients. In support of this notion, a recent genetic study involving 1,277 individuals across five different patient cohorts with a variety of pain conditions (osteoarthritis, sciatica, pancreatitis, post-diskectomy pain, and phantom limb pain) found a significant association between the SCN9A SNP, rs6746030 (G/A substitution), and pain perception.\textsuperscript{74} Individuals with the rarer A allele reported higher pain scores compared with individuals with the more common G allele.\textsuperscript{74} Collectively, human pharmacogenetics research points to an important role for the Na\textsubscript{v}1.7 sodium channel subtype in the modulation of clinical pain, which validates drug discovery programs targeted to the development of Na\textsubscript{v}1.7 blockers as future analgesic agents.

Collectively, human pharmacogenetics research points to an important role for the Na\textsubscript{v}1.7 sodium channel subtype in the modulation of clinical pain, which validates drug discovery programs targeted to the development of Na\textsubscript{v}1.7 blockers as future analgesic agents

Conclusions

Pharmacogenetics research conducted in humans over the past decade has provided important insight into the multiplicity of genetic factors that contribute to the often marked interindividual differences in analgesic dosing requirements for patients with clinical pain of apparently similar type and intensity. These genetic factors include those affecting analgesic drug metabolism, transport of analgesic agents across the BBB, and their activity at target receptors and ion channels and in the modulation of neurotransmitter pathways.

Extrapolation from the findings of genetics research conducted in very large numbers of subjects for other complex disorders, such as diabetes,\textsuperscript{76} suggests that the genetic component to interindividual variability in analgesic dosing requirements and reported levels of clinical pain is probably underpinned by concurrent small differences in a very large number of genes. Although the technology to routinely genotype patients and identify a large number of genetic variants is within reach, clinical application of the data so generated to enable tailoring of analgesic dosing regimens in individual patients is still some way off. Progress in this area will require cost reduction as well as development and validation of robust methods not only for producing an integrated interpretation of an individual’s pharmacogenetic profile but also for determining its susceptibility to modulation by environmental factors.

References


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