Patient Presentation

- A 58-year-old Asian male with no significant past medical history presents with acute herpes zoster in the left T4 dermatome.
- Presenting signs and symptoms include severe localized pain and tactile allodynia associated with a vesicular eruption.
- Even after the rash resolves, 3 months later he continues to complain of severe burning pain in addition to allodynia and hyperalgesia in the left T4 dermatomal region, suggesting that he has developed postherpetic neuralgia (PHN).
- 10mg of nortriptyline, a tricyclic antidepressant (TCA), is prescribed for this instance of PHN with a plan to titrate up to a higher dose to achieve effective pain relief if the initial 10mg dose is not helpful enough.
Patient Presentation (2)

- Unfortunately, he is unable to tolerate the initial treatment because he quickly develops intolerable adverse effects: sedation, orthostatic hypotension, and dry mouth shortly after he begins taking it.
- Tramadol and then hydrocodone/acetaminophen are prescribed but these are also poorly tolerated.
- He is then prescribed gabapentin at an initial dose of 300 mg taken at night, which is titrated over several weeks to an effective analgesic dose for PHN: 1800 mg/day in three divided doses.
- Although the burning pain is lessened, it is still not sufficiently controlled and the patient returns for further treatment.
- From the time of presentation for treatment, it has taken over 6 weeks for him achieve any notable degree of pain reduction.

Patient Presentation (3)

- The patient presented was treated according to available evidence-based, current guidelines, yet he did not obtain adequate analgesic benefit from the prescribed medications.
- Clinicians recognize that individual variations in responses to pain itself, as well as in the response to pharmacotherapies for pain relief, are routinely observed.
- Advances in pharmacogenetics may begin to allow us to better understand why patients may have variable responses to various analgesic therapies and may soon allow an opportunity for clinicians to identify the most appropriate pharmacotherapies for a patient BEFORE prescribing and hence improve patient specific outcomes.
- Knowledge of relevant pharmacogenetic information and use of such may indeed help a clinician to truly individualize a patient’s care, an example of personalized health care.

Patient Presentation (4)

- Variability in patient response, including intolerable adverse effects, can be due to non-adherence with the prescribed medication or medication schedule, a drug interaction inhibiting the medication’s effectiveness, mechanisms of pain generation that fail to respond to the prescribed medication’s mechanism of action, or a combination of these, for example.
- It is also possible that the patient’s genetic background has affected his ability to clinically respond to or metabolize the prescribed medications and this is where the emerging field of pharmacogenetics becomes important to recognize.
- This patient example illustrates the variable analgesic response and adverse event profile when analgesics are prescribed.
Patient Presentation (5)

- As noted, clinicians are only too well aware how often individuals may not obtain the expected therapeutic benefit from analgesic medications. The response rates in well-designed studies of various analgesic therapies are approximately 50% to 60%; this "treatment success" rate is similar to trials of therapies used to treat congestive heart failure and epilepsy. Many key areas of medicine are similarly affected by poor responder rates in clinical trials of diverse drug types. Knowledge of relevant pharmacogenetic factors that may influence the effect of a prescribed analgesic should allow clinicians to improve analgesic treatment outcomes.

The Impact of Pharmacogenetic Research on Clinical Medicine

- Pharmacogenetics is the study of the impact of genetics on pharmacotherapeutic responses and tolerability, in an effort to improve drug safety and efficacy through genetically-guided, individually-tailored treatments. One important explanation for this is because each individual's unique genetics provides the genetic blueprint for the generation of singular protein expression profiles, which subsequently leads to functional variations observed as clinical responses. Indeed, taking into account such genetic predisposition and receptor subtype expression has the potential to result in a more satisfactory reduction in symptoms and/or resolution of disease. This approach is certainly at the core of so-called personalized medicine.

Pharmacogenetics Impact

- Single nucleotide polymorphisms (SNPs; pronounced "snips") are the most important contributors to the observed regular variation in the genetic code, which lead to the human population's diversity of appearance, and at a deeper level, to our diversity in physiology. SNPs are defined as deoxyribonucleic acid (DNA) sequence variations resulting from a single nucleotide (adenine [A], thymine [T], cytosine [C], or guanine [G]) change in the genome sequence.
Pharmacogenetics Impact

- Many of these DNA changes do not translate into differences at the protein level.
- However, there are indeed SNPs that in fact do lead to phenotypic differences and some single base pair changes do affect a noticeable, clinically relevant change in phenotype.
- Unique SNPs have been identified that lead to lower activity of various enzymes, red hair color and fair skin, and a lack of/diminished expression of one of the red blood cell antigens.

Pharmacogenetics

- The most commonly observed DNA sequences of a gene are called “wild-type”, and the less common alleles are “variants”, if they are prevalent in more than 1% of the population.
- The even less prevalent alleles have another name; DNA sequences in genes found in less than 1% of the population are called “mutations.”

Pharmacogenetics

- Within pain management, an autosomal dominantly inherited peripheral neuropathy, hereditary sensory and autonomic neuropathy (HSAN) type I confers insensitivity to pain mediated through the progressive degeneration of the dorsal root ganglia (DRG) and motor neurons as the result of mutations within a specific location in chromosome 9.
- Individuals with this genetic background cannot sense pain, making them particularly prone to painless but potentially severe injuries, with detrimental complications such as chronic skin ulcers and distal amputations.
Pharmacogenetics

- The clinical integration of genetic information has been increasingly utilized in oncology to guide treatment.
- Other areas of medicine are also beginning to tailor pharmacotherapies based on an individual’s genetic information and as certain biomarkers are now known that can help to guide treatment in many areas of medicine including pain management.
- Pharmacogenetic testing has allowed for benefits for patients and for clinical medicine in general by improving the ability to stratify the risks of various treatments for individual patients by identifying groups of patients with a higher potential for poor efficacy or for treatment side effects.
- The beneficial effects of utilizing information derived from pharmacogenetics in the future of clinical medicine may lead to improved success rates, decreased side effect burdens, and reduced healthcare costs. ³⁸

Pharmacogenetic Research Impact on Pain Medicine

- Individuals have differential responses to pain and different likelihoods for developing chronic pain.
- In 2006 Tegeder and colleagues reported that GTP cyclohydrolase (GCH1), the rate-limiting enzyme for tetrahydrobiopterin (BH4) synthesis, is a key modulator of peripheral neuropathic and inflammatory pain, tracing the predisposition for high pain tolerance to this enzyme cofactor which is upregulated in primary sensory neurons of the dorsal root ganglion following nerve injury.
- This cofactor modulates both inflammatory and neuropathic pain. These investigators identified a “pain protective” polymorphism in 15% of the population within the gene that encodes for this essential cofactor involved in this specific pain pathway, which yields reduced pain sensitivity. Individuals with this “pain protective” genotype could potentially confound analgesic trial results, unless they were identified and randomized. Polymorphisms in other genes have also been linked to pain sensitivity.

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Pharmacogenetic Research Impact on Pain Medicine

- Pharmacogenetic research has the potential to lead to great strides in the optimization of analgesics, as well.
- Genetic variance can impact the therapeutic response of specific pain medications or predispose an individual to adverse effects.
- Differences in clinical response to pain medications, in terms of efficacy, toxicity, pharmacokinetics, metabolism, and drug transport have been linked in part to genetic variations.
- Fishbain and colleagues in 2004 concluded that, "genomic testing for enzymes of drug metabolism has significant potential for improving the efficacy of drug treatment and reducing adverse drug reactions", notably for the pain therapies: tricyclic antidepressants, anti-inflammatory drugs, and opioids among others.

Tricyclic Antidepressants (TCAs)

- Consider the patient example, in which the TCA administered to the patient presenting with PHN led to intolerable adverse effects.
- TCAs are metabolized in the liver by the cytochrome P450 (CYP450) system, which is responsible for the breakdown of 40% to 50% of all commonly prescribed medications.
- CYP450 is the most intensely studied gene family, and polymorphisms within this class of enzymes can lead to reduced or accelerated metabolism of their substrates, including specific medications.
- As such, two individuals having the same weight and given the same drug dosage can have more than a 1000-fold difference in their plasma drug levels.
- This can be extremely important to recognize from a clinical viewpoint. In studies, individuals have been grouped by their phenotype: poor metabolizers, who have two nonfunctional enzyme alleles; intermediate metabolizers, who have at least one reduced functional allele of an enzyme; extensive metabolizers, who have at least one functional allele; and ultra-rapid metabolizers, who have multiple copies of a functional allele and/or an allele with a promoter mutation that confers increased transcription of that gene.

TCAs (2)

- Extensive metabolizers obtain the expected therapeutic benefit from standard doses of a drug, while individuals who are poor metabolizers are at risk of poor efficacy and/or adverse effects if given a prodrug that is incompletely metabolized due to genetic differences in their liver enzyme systems.
- Ultra-rapid metabolizers can be prone to adverse effects due to higher than expected drug concentrations from enhanced metabolism. The plasma drug concentrations in individuals given the same dose of antidepressants have been found to vary—primarily based on the polymorphisms present in the CYP2D6 enzyme (as well as CYP1A2, CYP2C19, and CYP3A4/5).
- The patient presented at the beginning of this chapter, individuals who are poor metabolizers of TCAs (approximately 7% of the Caucasian population) tend to accumulate drug concentrations outside of the drug class’s narrow therapeutic range, leading to adverse TCA effects at lower than expected doses.
- In contrast, patients who are CYP2D6 ultra-rapid metabolizers may require higher doses to achieve analgesia.
- Potentially, the patient presented is a CYP2D6 poor metabolizer.
TCAs (3)

- The value of genotyping before prescribing antidepressants was considered in a large population-based study of 1,198 elderly Dutch patients.
- Poor metabolizers of TCAs more than extensive metabolizers required either lower maintenance doses or discontinuation of TCAs altogether.
- Although current research does not provide clear evidence to support the routine clinical use of liver enzyme genotyping before analgesic treatment, there have been an increasing number of commercial entities which have developed the capabilities to perform these assays and thus they are now increasingly available for the clinician to consider using.
- Clinically, the recognition that an individual patient could be a poor metabolizer, with or without confirmatory testing, can assist the prescriber to consider medication changes (dose adjustment or frank discontinuation) when poor efficacy and/or adverse events are observed.

Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

- Pharmacogenetic research in pain management has identified wide inter-individual variation in the analgesic efficacy of both nonspecific NSAIDs and selective inhibitors of cyclooxygenase-2 (COX-2) due to SNPs within the COX genes.
- A SNP in the promoter for the gene encoding COX-2 (the -1195G to A change) has a prevalence of greater than 10% and has been associated with mild asthmatic reactions.
- Another functional effect of the increased expression of COX-2 potentially mediated by several SNPs is the enhanced susceptibility to hypersensitivity in response to standard doses of aspirin and other NSAIDs that inhibit COX-2, otherwise known as aspirin-intolerant asthma (AIA).

NSAIDS (2)

- Additionally, a large genotyping study has determined that individuals with specific variants of the COX-1 and COX-2 genes have an increased risk of cardiovascular disease when taking aspirin.
- Other studies have investigated an association between genotypes of the cytochrome P450 enzyme CYP2C9 and taking NSAIDs metabolized by that enzyme. In patients with this co-occurrence, an increased risk of developing gastroduodenal bleeding was noted.
Opioid Analgesics

• In properly selected patients, opioids can be effective treatments for acute moderate to severe pain, as well as chronic moderate to severe pain. Similar to tricyclic antidepressants, most opioids are metabolized by the CYP450 enzyme class. Hence, SNPs in CYP450s can have an impact on clinical analgesic and adverse effect responses.

Opioid Analgesics (2)

• In particular, codeine has been associated with variable individual clinical responses.
• Codeine itself is a prodrug: a medication that is inactive until it is enzymatically converted to its active metabolite.
• Codeine must be converted to morphine via CYP2D6 to provide analgesia.
• In addition to codeine, CYP2D6 poor metabolizers may experience suboptimal analgesic efficacy when prescribed “routine” doses of tramadol. This is because the analgesic benefit attributed to its opioid related mechanism of action requires that tramadol first be metabolized via a CYP2D6 based mechanism to an active metabolite.

Opioid Analgesics (3)

• The metabolism of many currently available opioids can be affected by SNPs with the CYP450 system.
• There are 3 opioid analgesic medications that are not metabolized through this system at prescribed doses including hydromorphone, morphine and oxymorphone.
• Therefore, if it has been identified, perhaps by noting poor analgesic efficacy and/or intolerable adverse effects (or even possibly actual pharmacogenetic testing), that an individual has a SNP that alters the enzymatic activity of one or more of the CYP450 isoenzymes, an opioid analgesic (if otherwise appropriate for that patient) might be considered that is not metabolized through this mechanism in order to increase the likelihood of a successful treatment outcome.
Clinical Value of Pharmacogenetics

- The current clinical value of pharmacogenetic research illustrates that pharmacogenetic data may play a role in risk stratification and may help guide prescribers in their decision making.
- Relevant to the patient presented above, 41% to 51% of individuals of Asian origin express an unstable CYP2D6 enzyme, while 12% to 21% of Caucasian people express an inactive CYP2D6 enzyme.
- However, in clear contrast, 10% to 29% of people of Ethiopian or Saudi Arabian descent have heightened CYP2D6 activity.
- When considered for the purposes of clinical decision making, this pharmacogenetic information can provide clues about how a specific patient may respond to codeine and other opioids metabolized by CYP2D6 and thereby, offer prescribing guidance.

Clinical Value (2)

- The patient presented above may be genetically predisposed to low CYP2D6 activity, and his inherent enzymatic capacity may be not be sufficient to obtain analgesia from the prodrug codeine as well as other opioids such as hydrocodone - hydrocodone is metabolized to hydromorphone through a CYP450 dependent process.
- Pharmacogenetic information may provide the connection between the opioid prescribed and the lack of expected clinical response or the presence of unexpected adverse effects.

Clinical Value (3)

- Opioid responsiveness is widely recognized as a highly individualized phenomenon, depending upon many factors, including pain etiology, prior exposure to opioids and opioid tolerance level, other psychophysiological determinants.
- Consequently, pharmacogenetics can have a significant impact on the clinical response to opioid therapy.
Clinical Value (4)

- Genetic determinants beyond metabolic enzymes (such as the CYP450 family) also affect an individual’s responses to opioid analgesics.
- These include drug transporters and drug targets such as the µ-opioid receptor gene OPRM1.
- A common polymorphism of OPRM1 is the substitution of a single nucleotide at position 118, with an adenine substitution by a guanine.
- The reported allelic frequencies for this are estimated at 10-30% among Caucasians, lower among African-Americans and higher among Asians.

Clinical Value (5)

- There is great interest in this polymorphism because it has been associated with pharmacological and physiological consequences affecting not only experimental pain models but also with impact on neuraxial opioid use for labor analgesia, postoperative analgesia and cancer related pain.

Clinical Value (6)

- The different combination of these SNPs within genes that code for the targets of opioid analgesics, e.g. OPRM1, may result in different clinical effects and thus knowledge of these for a specific patient could one day allow for improved outcomes for opioid prescribing.
- In addition to the CYP450 family of enzymes, the µ-receptor gene (OPRM1, p.118A/G), the catechol-O-methyltransferase (COMT Val158Met), several types of the ATP-binding cassette and subfamily B member 1 gene (ABCB1) have been extensively studied.
- At the same time it has been determined that interaction of several polymorphisms likely influence the pharmacokinetics and pharmacodynamics of medications, e.g. inherited differences in drug targets (receptors), as well as drug metabolism and drug transport.
Clinical Value (7)

- Recognizing that morphine and most clinically used opioids act via the μ-opioid receptor, the concept of μ-receptor multiplicity has been studied with recognition that various different splice variants of the MOR-1 gene exist with the potential to clinically affect the benefits or lack thereof of morphine as well as other opioid analgesics.
- This kind of information will likely increasingly affect the manner in which clinicians prescribe opioids in the future.

Clinical Value (8)

- Alternative splice variants of the mu opioid receptor have been identified and have been correlated with the clinical phenomenon of incomplete cross-tolerance by which tolerance to one opioid does not translate to tolerance to other opioids.
- In addition, although most clinically used opioids are selective for the mu opioid receptor, their ability to activate the receptor can vary, leading to widely different efficacies and side effect profiles between individual patients.
- In fact, the minimal effective analgesic concentration for morphine can vary among patients by as much as 10-fold.
- Further response variation within an individual is related to changing gene expression patterns over time and even diverging across organ systems and tissues, based on an individual’s state of health, and degrees or type of physiologic or emotional stress present.

Clinical Value (9)

- Chronic opioid therapy treatment guidelines developed by the American Pain Society and the American Academy of Pain Medicine recommended considering “opioid rotation” e.g. switching from one opioid to another if the initially prescribed opioid is neither well tolerated or clinically effective after a reasonable trial.
- Grilo and colleagues completed a study of 67 patients with difficult to treat rheumatologic pain, and in most of the patients rotated the patients from morphine to either transdermal fentanyl or hydromorphone.
- Those patients who underwent such opioid rotation experienced a mean reduction of 30mm on a visual analogue scale, indicating a clinically meaningful reduction in pain intensity.
Clinical Value (10)

• In a study of opioids for treatment of chronic non-cancer pain, Quang-Cantagrel and colleagues reported that the first long-acting opioid prescribed was effective for 36% of patients.
• However, the initially prescribed opioid had to be discontinued due to adverse effects in 30% or ineffectiveness in 34% of those studied.
• Eventually, a clinical response was obtained by changing to a second (31% responded), third (40% of the remainder responded), fourth (56% of the remainder responded), and fifth (14% of the remainder responded) opioid.

Clinical Value (11)

• These data however do not indicate that eventually a patient will respond to a particular opioid and thus it is important to note that the failure of one opioid does not predict the patient’s response to another opioid analgesic.
• The concept of opioid rotation is based not only upon empirical clinical observations but also would be predicted based upon pharmacogenetic considerations discussed earlier.
• Safe and effective opioid rotation requires specific clinical knowledge; if opioid rotation is believed to be an appropriate approach to managing the care of an individual patient, guidelines are available for the calculation of equianalgesic dosing and other important steps in this process.

Conclusions

• Advances in pharmacogenetics will hopefully allow clinicians to more precisely individualize optimal pharmacologic care for their patients with acute and chronic pain.
• Commercial pharmacogenetic testing is currently available; however, it is not yet clear how practical and helpful this is in a real world setting.
• The potential benefits of such testing are attractive enough given the potential for more effective and safer management of patients with acute and chronic pain to warrant further study to improve their clinical applicability.
References


References (4)


References (5)


References (6)


Questions?

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