Letter to the Editor

Integrating Clinical Pharmacokinetics, Pharmacogenetics, and Quantitative Cytochrome P450 Polymorphic Gene Drug-Drug Interactions (DDIs)

To the Editor:

We read the article by Deer and Gunn [March-April issue] (1) with substantial interest, and felt it might be helpful to provide readers with a quantitative viewpoint. A methodology for rational opioid dose regimen design and modification based on clinical pharmacokinetics for therapeutic drug monitoring is available (2). This methodology has been integrated with pharmacogenetics for precision medicine dosing of oxycodone (3). Precision medicine is an emerging approach for the treatment of disease that accounts for patient-specific pharmacogenetic variability (4). In the US, The White House announced President Obama's Precision Medicine Initiative (5). In France, efforts are underway to extend clinical pharmacokinetics integrated with pharmacogenetics for quantitative prediction of the effect induced by cytochrome P450 gene polymorphisms on opioid dose regimen design and modification (6;7). Such a precision medicine approach is crucial in view of the large number of deaths from multiple drug ingestion (8), medication errors (9), and drug-drug interactions (DDIs).

Clinical Example

A 58-year-old, 80.7 kg Caucasian man (10) with a history of depression develops acute low back pain caused by lumbar spinal osteoarthritis. The patient underwent genotyping prior to antidepressant selection (11). His genotype is CYP2D6 *1*3-8; that is, CYP2D6 intermediate metabolizer category (IM). His clinician wants to start him on oxycodone immediate-release (IR) 10 mg orally every 6 hours. The patient has been taking paroxetine 20 mg daily for 6 months. First, however, his clinician checks for a drug-drug interaction (DDI) between oxycodone and paroxetine using DDI Predictor (www.ddi-predictor.org/). DDI Predictor is a website constructed by the Genophar II Working Group under Professor M. Tod (Lyon, France). This website is dedicated to quantitative prediction of DDIs moderated by P450 polymorphic cytochromes.

The formula for quantifying the oxycodone-paroxetine interaction is (6;7):

$$\frac{AUC^{*}_{XM}}{AUC_{EM}} = \frac{1}{\left[CR_{2D6} \cdot FA \cdot \left(1 - IR_{2D6}\right) + \left(1 - CR_{2D6}\right)\right]},$$

where CR_{2D6} (contribution ratio) represents the fraction of oxycodone's clearance rate due to CYP2D6 in wild-type *1*1 extensive metabolizer category (EM) patients. FA is CYP2D6's genotype-specific fractional activity, i.e., CYP2D6's fraction of activity resulting from the sum of the activities of a combination of its mutated alleles, relative to the FA of the reference wild-type *1*1 genotype. CR_{2D6} is the time-averaged CYP2D6 inhibitor ratio for paroxetine. These unknowns are automatically provided by DDI Predictor for the oxycodone-paroxetine interaction:

CR_{2D6} = 0.20; FA = 0.47; and IR_{2D6} = 0.99.

Hence, $AUC^{*}_{XM} / AUC_{EM} = 1.25.$

Estimates of the CRs, IRs and FAs of the internal DDI Predictor database were obtained using Bayesian orthogonal regression.

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Oxycodone's steady-state analgesic plasma concentration range is 20–50 µg/L (12). Hence, an analgesic target therapeutic concentration (TTC) for oxycodone can be calculated as (3):

$$TTC = \frac{50 - 20}{\ln(50/20)} = 32.74 \ \mu g/L.$$

Then, the phenotype-specific dose rate assuming EM phenotype is,

$$DR_{EM} = \frac{TTC{=}32.74\ \mu g/L \times Cl_{EM} = 0.51\ L/h/kg \times 80.7\ kg}{F = 0.74} \times 0.001 = 1.82\ mg/h$$

where Cl_{EM} is oxycodone's phenotype-specific clearance rate for EM (wild-type *1*1) and F is oxycodone's average bioavailability of 74% [range: 60–87%] (13). Now, the phenotype-specific maintenance dose assuming EM phenotype equals

$$DM_{EM} = DR_{EM} \times \tau = 10.9\ mg, \text{ where } \tau = 6\ h \text{ is the dosing interval.}$$

This dose is rounded to a practical dose of 10 mg. Finally, the genotype-specific adjusted maintenance dose to account for this patient's IM phenotype is given by

$$D_{ADJUM} = \frac{DM_{EM}}{AUC^{*}_{XM}/AUC_{EM}} = 8.0\ mg$$

D_{ADJUM} is the dose of oxycodone, for a patient in whom D_{ADJUM} would be obtained, by prescribing oxycodone 10 mg per dosing interval τ. In other words, D_{ADJUM} is the steady-state dose required to obtain the same exposure of oxycodone that an EM patient not taking paroxetine would have.

At first glance, a 2 mg reduction in dose to account for IM phenotype may not seem like allot, but over a 24 h dosing period, that can represent 12 mg of oxycodone, or a little over 10 mg (2 × 5 mg tablets) daily. Over the span of one week, this represents 84 mg, or a little over 16 × 5 mg tablets. These findings are particularly relevant for oxycodone dosing in patients with liver and kidney dysfunction. They are also relevant in the treatment of complex pain such as that in obese obstructive sleep apnea patients (14), where a clinician may treat complex pain at the boundary between oxycodone's maximum safe concentration (MSC) and its toxic level (15).

Therefore, measurement of plasma opioid concentrations combined with simplified web-based methodology that integrates clinical pharmacokinetics, pharmacogenetics, and quantitative cytochrome P450 polymorphic gene DDIs is a new approach for opioid dose regimen design and adjustment. This precision medicine approach inherently promotes patient safety in opioid prescribing. We are optimistic that its practical use will become more important as electronic programmable tools become routinely embedded as part of the e-chart.

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In Response

We thank Dr. Linares and his colleagues for their thoughtful insights regarding our article. It is important for the reader to understand the clinical relevance of this new conceptual thinking of personalized medicine. Dr. Linares points out the quantitative methods in which these concepts may be applied and in doing so has added a great deal to the discussion.

We feel that the combination of clinical necessity, technical quantitative abilities, and a commitment to patient safety and compliance will eventually change the clinical environment of practice both in the United States and abroad. At present the ability to have access to these methods are limited in most settings by reimbursement and we encourage further prospective studies to validate the clinical necessity of these important parameters. The collaboration of physicians, toxicology, and laboratory acumen will all be needed to accomplish this goal.

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