*CYP2B6*6* or Not *CYP2B6*6*—That Remains a Question for Precision Medicine and Ketamine!

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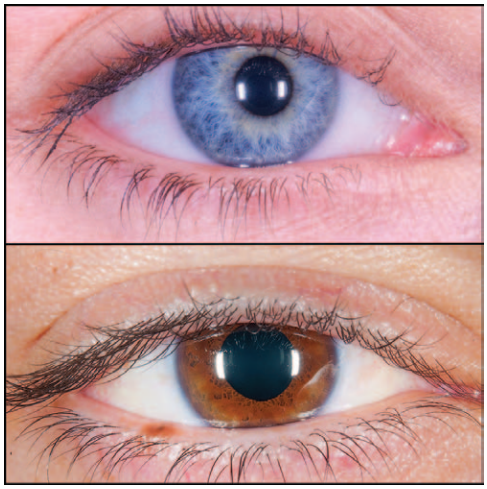
WHILE certainly not the dire existential question posed by Hamlet, could detailed knowledge of variants at *CYP2B6* and other genetic loci bring precision medicine to the clinical dosing of ketamine? We believe that it will, but one nuanced by indication, route of administration, and other factors.

In this issue of Anesthesiology, Rao *et al.*[1] present their work on the pharmacogenetics of ketamine in an attempt to better understand the etiologies of drug response variability, beginning with metabolism and pharmacokinetic differences.[1] Cytochrome P450, family 2, subfamily B, member 6 (CYP2B6) is a high-affinity protein thought to predominate ketamine catabolism. The gene coding for CYP2B6 (*CYP2B6*) is highly polymorphic, with the common *CYP2B6*6* (516G>T and 785A>G) variant, found largely in those of African descent, correlating with diminished hepatic CYP2B6 expression. Functionally, the associated gene product CYP2B6.6 and liver microsomes from *CYP2B6*6* carriers both show reduced ketamine metabolism *in vitro*.[2] Moreover, in chronic pain patients treated with 100 to 500 mg/24-h subcutaneous ketamine infusions, the *CYP2B6*6* allele confers reduced steady-state ketamine clearance with gene dose effect.[3]

From this foundation, Rao *et al.*[1] sought to prove that compared to wild-type *CYP2B6*1/*1* subjects, healthy volunteers heterozygous or homozygous for the **6* minor allele would have reduced ketamine catabolism after low-dose (0.4 mg/kg) oral administration of racemic drug. They chose an accepted-standard primary outcome of ketamine *N*-demethylation as determined by plasma norketamine/ketamine area under the concentration–time curve ratio and then carefully planned validation by complementary methods. With the potential for stereoselective effects seen for other chiral medications, they also queried ketamine enantiomer metabolism and disposition with enantioselective mass spectrometry. Surprisingly, they found no difference in ketamine (*R*-, *S*-, or racemic) metabolism as a function of *CYP2B6*6* genotype.



"Could detailed knowledge of variants at* CYP2B6*... bring precision medicine to the clinical dosing of ketamine?"

How does one reconcile the disparity between these findings and those of the *in vitro*[2] and previous clinical pharmacokinetic studies?[3] The authors offer several plausible explanations invoking dose, route of drug administration, and population characteristics. Apart from ethnic variation, we do not believe methodologic or analytical differences to be contributory. Clearance estimates using single-timepoint specimens obtained at steady state yield equally reliable results to multiple timepoint measurements made after the first dose of drug. Differences in ketamine disposition resulting from low *versus* high dose also seem unlikely as we are not aware of any evidence to suggest dose-dependent pharmacokinetics that would be observed with a readily saturable elimination pathway.

We suspect that the disparity may at least in part relate to the route of administration whereby non–CYP2B6-dependent intestinal metabolic pathways predominate after oral dosing and mask the impact of hepatic CYP2B6 variants. Supportive observations include striking differences in norketamine:ketamine metabolic ratios after oral drug administration, yielding ratios of 4.7 to 7.5,[1] in contrast to 0.4 to 1.1 ratios after parenteral administration.[3] In addition, high circulating concentrations of hydroxynorketamine observed after oral administration are consistent with (but not proof of) significant CYP3A4 metabolism. Could more extensive metabolism of oral ketamine be driven by

Image: J. P. Rathmell.

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intestinal and/or hepatic CYP3A4? Although CYP2B6 exhibits greater ketamine *N*-demethylation activity per picomole of CYP450 protein, CYP3A4 is 30-fold more abundant in hepatic microsomes such that, at ketamine concentrations corresponding to analgesic plasma levels, CYP3A4 contribution to ketamine catabolism per microsome mass is double that of CYP2B6.[4] CYP3A4 is also abundant in intestinal tissue, and by sequential action in the gut and then by mass effect in the liver, it could easily dominate ketamine *N*-demethylation overall. Several clinical studies support this theory: CYP3A4 inhibitors clarithromycin[5] and grapefruit juice[6] increase *S*-ketamine plasma concentrations and decrease metabolic ratios, while St. John's Wort, a potent CYP3A4 inducer, does the opposite.[7] Although a conflicting study suggested a stronger influence of CYP2B6 as inhibited by ticlopidine and a lesser role for CYP3A4 as inhibited by itraconazole,[8] we believe that the cumulative evidence points to a route-dependent effect favoring one of the competing catabolic pathways.

What might be done to resolve this? Difference resulting from first-pass metabolism is a testable hypothesis: in subjects stratified by genotype, evaluate metabolite/parent plasma concentrations after both enteral and parenteral drug administration. Intravenous administration bypasses intestinal metabolism and hepatic first-pass effects and would potentially allow *CYP2B6* variant influences to manifest. The conservative 0.4 mg/kg oral ketamine dose studied was principally chosen for safety reasons; however, larger intravenous doses (0.5 to 1 mg/kg) are safely used in clinical practice and could be studied with appropriate precautions. Might there be additional important variants to examine? Does the less common *CYP2B6*4* (785A>G) allele increase ketamine metabolism as it did for methadone?[9] More well-defined clinical phenotypes should be evaluated for associations with serum ketamine levels and genotype. Validated tools for assessment of experimental pain, sedation, and cognitive and motor impairment should be used. With regard to the self-assessment questions, it is possible that ketamine effects may have gone underreported in the current study. If one is mildly impaired, can one reliably recognize and report it?

Pharmacogenetics/genomics is moving from discovery to validation to early preemptive clinical diagnostics.[10,11] Efforts through the Pharmacogenomics Knowledgebase, a partner of the National Institutes of Health Pharmacogenomics Research Network, and the Clinical Pharmacogenetics Implementation Consortium have published guidelines on multiple actionable variants, many of which apply to clinical anesthesiology and pain management.[12–18] Further, the U.S. Food and Drug Administration has issued a list of pharmacogenomic biomarkers used in labeling 165 medications of which 31 relate to our discipline.[19] Although *CYP2C9*, *CYP2C19*, and *CYP2D6* have prominent, documented roles in drug response variability, increased attention has been directed toward *CYP2B6*, which may contribute to as much as 10% of total hepatic CYP content and is associated with 20- to 250-fold interindividual variation in protein expression.[20] *CYP2B6* has been classified by Pharmacogenomics Knowledgebase as an important pharmacogene[21] and is included among the 82 pharmacogenes captured and studied in the Pharmacogenomics Research Network sequence data from the Electronic Medical Records and Genomics Network.[22]

Ketamine has many clinical applications, and although its pharmacokinetics and pharmacodynamics are better understood,[23] pharmacogenetic dosing remains in early validation stages. Drugs with strong single-locus genetic effects such as codeine with common *CYP2D6* variants resulting in poor, rapid, or ultrarapid metabolism have well-validated, unequivocal pharmacogenetic dosing guidelines, offering proof of concept for precision medicine relevant worldwide.[14,15,24,25] Methadone is in midstage validation, with *CYP2B6* variant metabolism effects that must next be tested for utility in larger clinical trials.[9] Could there be actionable *CYP2B6* variants for ketamine? Although the answer would appear to be no for *CYP2B6*6* and low-dose oral ketamine, this does not preclude *CYP2B6*6* or other variants at this locus, affecting intravenous or even higher oral dose pharmacokinetics. We believe that ketamine will eventually have pharmacogenetic dosing guidelines, perhaps specific to administration route, that include actionable *CYP2B6* and *CYP3A4* variants. Finally, beyond these candidate genes, novel common variants identified by genome-wide association studies[26] and rare variants found through whole-genome sequencing will likely add to the test array that brings precision medicine to clinical ketamine use.

We applaud the investigators for having conducted this study and also Anesthesiology's commitment to publish informative, negative results that help establish application boundaries. We maintain our continuing awe of the complexity and elegance of the processes studied. With substrate-specific gene effects, variability associated with drug administration route, polygenic traits, gene–gene and gene–environment interactions, posttranscriptional changes, and other variables that may alter phenotype and medical care requirements, clinicians can expect complicated, arduous journeys in the development of specific pharmacogenomic guidelines. However, precision medicine is part of our future, and the detailed information required to advance it is rapidly growing.

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Competing Interests

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