Effects of Isotretinoin on CYP2D6 Activity
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Background:
CYP2D6 is a key drug metabolizing enzyme responsible for the metabolism of ~25% of all drugs eliminated by the cytochrome P450 system, including clinically important drugs such as antiarrhythmics, opioids, cough suppressants, antidepressants, antipsychotics, antihypertensives, and antihistamines. As such, understanding CYP2D6 regulation in humans is critical not only for special populations, but also more broadly for patients in general. This study will be the first step towards gaining insight into possible endogenous biomarkers of CYP2D6 regulation and activity in humans, thus moving us closer to individualized drug dosing. In the general population, many of these drugs have been titrated to clinical response, but there has been a desire to individualize therapy. Even after accounting for genotype, CYP2D6 activity varies 4- to 30-fold in extensive metabolizers. If our hypothesis proves to be true, we will continue research in this area, with the goal of developing one or more useful biomarkers to be used in conjunction with genotype to help guide dosing of CYP2D6-metabolized drugs.

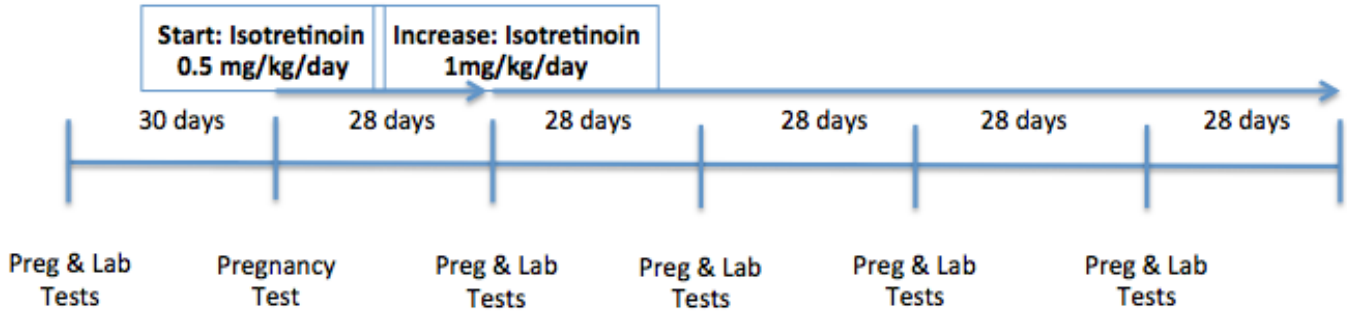
Based on *in vitro* and animal studies as well as preliminary human data*,* ***we hypothesize that retinoic acid concentrations and retinoid signaling in the liver regulates CYP2D6 expression and activity in humans, which in turn contributes to inter-individual pharmacokinetic variability of CYP2D6 substrates***. This study will directly test our hypothesis by evaluating CYP2D6 activity prior to and in the presence of concomitant 13-*cis*-retinoic acid (isotretinoin) in adolescent patients. Higher retinoic acid concentrations should lead to lower CYP2D6 activity. This much needed work will provide foundational mechanistic understanding and translate new basic science research findings into humans. The administration of all-trans-retinoic acid down regulates CYP2D6 in the humanized mouse model. The sum of the data regarding retinoid regulation of CYP2D6 from *in vitro* studies and animal models leads us to believe that administration of retinoic acid will lead to decreased CYP2D6 transcription, expression and activity. Since animal models are not always predictive of the effects in humans, it is now time to translate this work into humans.

In non-pregnant adolescents, there is more than 2-fold variation in retinol concentrations. **Isotretinoin has been a commonly used medication in adolescent patients for decades as it is uniquely effective at improving severe acne.** However, we are unable to locate any published studies evaluating the effects of isotretinoin on CYP2D6 activity in humans. Some degree of acne affects almost all adolescents 15-17 years of age, with approximately 15–20% of teenagers developing moderate to severe acne. In 2000, approximately 2 million prescriptions were written for isotretinoin in the United States. If our hypothesis holds true, given the frequency of isotretinoin use in the adolescent population and the potential for interaction with CYP2D6 substrates, it is essential that we evaluate isotretinoin's effect on CYP2D6 activity and simultaneously directly test the hypothesis that retinoids play a role in CYP2D6 regulation in humans. **The therapeutic administration of isotretinoin provides us with a unique opportunity to directly explore the mechanism of CYP2D6 regulation by retinoic acid in humans.**

In summary, adolescent patients commonly experience medical conditions that require treatment with CYP2D6 substrates. Although genetics play an important role in CYP2D6 variability, even after accounting for genetic variation, there is still a great deal of unaccounted variability in CYP2D6 activity. High variability makes the utilization of CYP2D6 substrates challenging in this special population. With strong basic science data suggesting that retinoids play a key role in regulation of CYP2D6, exploring the relationship between CYP2D6 activity and retinoid concentrations in humans will provide mechanistic understanding of the variability in drug therapy, which is critical to the provision of individualized pharmacotherapy and the first step toward development of an endogenous biomarker that potentially could be used in combination with genetics to predict CYP2D6 activity.

Objective:
To investigate if isotretinoin (13-*cis*-retinoic acid) administration decreases CYP2D6 activity in adolescent patients

Design:
Routinely at the UW Dermatology clinic, female patients with severe cystic acne who will be receiving isotretinoin undergo an initial evaluation, which includes laboratory tests (including a pregnancy test). Thirty days later, the pregnancy test is repeated and isotretinoin is initiated at 0.5 mg/kg/day. Twenty-eight days later, the pregnancy and laboratory tests are repeated and isotretinoin is increased to 1 mg/kg/day and continued for 3-4 months. Pregnancy and laboratory tests are repeated every 28 days. A similar protocol is followed for the male patients, excluding the pregnancy tests. The timing of our proposed study will fit into routine clinical visits and enhance the ease and success of study conduct.



Study Design
This is a prospective, pharmacokinetic study of oral dextromethophan in adolescent patients. The study will be divided into 2 phases. Phase 1 will occur prior to initiation of isotretinoin and involve a single dose of oral dextromethorphan. Phase 2 will occur ≥ 1 week after initiation of steady-state isotretinoin and will repeat the single oral dose of dextromethorphan. Each subject will serve as his or her own control. All studies will be performed at the University of Washington.

Experimental Methods:
4.3.3. Study Design Summary:

Test	Phase 1 Pre-isotretinoin	Phase 2 Concomitant Isotretinoin
CYP2D6 genotype (pre-DM study)	**X**	

Dextromethorphan single 30 mg oral dose	**X**	**X**
Concomitant steady state isotretinoin administration		**X**
4-hour urinary DM/DX MR	**X**	**X**
Total plasma all-trans retinoic acid, 13-*cis*-retinoic acid, retinol (all-trans and 13-*cis*), retinyl palmitate, 4-oxo-all-trans retinoic acid, 4-oxo-13-*cis*-retinoic acid and retinol binding protein concentrations	**X**	**X**
Serum creatinine, BUN, ALT, bilirubin, albumin	**X**	**X**
Urine creatinine and pH	**X**	**X**

4.3.4. Dextromethorphan administration: Following a ≥4 hour fast, subjects will receive DM (alcohol free) 30 mg orally on each study day. DM was selected as our CYP2D6 probe because it is a standard probe for CYP2D6 activity and has a well-established safety record in adolescent patients and children.(4,131-134)

4.3.5. Isotretinoin administration: Isotretinoin administration will follow routine clinical practice. Isotretinoin administration will not be altered for research purposes. The Phase 2 study with concomitant isotretinoin will take place once patients have been taking oral isotretinoin 1 mg/kg/day for ≥ 1 week. If the patient does not tolerate 1 mg/kg/day and is reduced to 0.5 mg/kg/day as their final isotretinoin dose, then ≥ 1 week after starting that dose, subjects will complete their Phase 2 study. Subjects receiving higher doses will also be included. We will attempt to study all subjects while receiving ~1 mg/kg/day, but recognize that some patients might require higher or lower doses and will be studied on their clinically indicated dose.