Official Title: The effect of topiramate on etonogestrel concentrations in contraceptive implant users

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Proposal Narrative

Objective: To evaluate the pharmacokinetic effect of concomitant topiramate therapy on etonogestrel (ENG) contraceptive implant use.

Specific Aims:

1. To evaluate the drug-drug interaction between doses of topiramate used for treatment of migraines (100-200mg per day) and the ENG contraceptive implant.
2. To evaluate the drug-drug interaction between doses of topiramate used for treatment of epilepsy (400mg per day) and the ENG contraceptive implant.
3. To characterize whether any pharmacokinetic reductions in serum ENG concentrations reach below the level needed to maintain ovulation suppression (<90pg/mL).

Rationale:

Topiramate is an anti-epileptic drug initially used for treatment of partial-onset seizures and primary generalized tonic-clonic seizures. However, its main use currently is for migraine prevention: topiramate is considered a first-line treatment for migraine prophylaxis, along with B-blockers and valproate.[1] The majority of patients afflicted by chronic migraines are reproductive age women, most of whom need reliable contraception.[2] Few women with chronic migraines are candidates for estrogen-containing contraceptive methods. We have recently cared for several reproductive age women taking topiramate and have found no evidence supporting or contraindicating the etonogestrel (ENG) contraceptive implant for birth control, and only scant evidence regarding drug-drug interactions between topiramate and norethindrone-containing combined oral contraceptives. As topiramate is a Pregnancy Class D drug, definitive evidence of any potential decreased efficacy of the implant is imperative. Conversely, reassuring evidence of stable ENG levels will broaden the contraceptive options for women using topiramate.

Our recent study on the effect of carbamazepine on ENG concentrations in contraceptive implant users demonstrated clinically significant reductions in serum ENG concentrations with a median decrease of 61% (range 25.4-87.2) and 8/10 participants with concentrations <90pg/mL after the intervention.[3] These findings added to the limited data on the pharmacokinetic interactions between cytochrome P-450 3A4 enzyme inducers (CYP-3A4) and the ENG contraceptive implant, and will likely lead to a change in the US Medical Eligibility Criteria (MEC) for Contraceptive Use. In the MEC, carbamazepine is lumped into a broad category of "Anticonvulsant therapy" that have known CYP-3A4 induction properties.[4] This category also includes medications such as phenytoin, barbiturates, and topiramate. Many of these medications have well documented CYP-3A4 induction properties and

consistent pharmacokinetic effects with hormonal contraceptives.[5] Topiramate is also a CYP-3A4 inducer, but has far less pharmacokinetic data to support that its induction properties have clinical implications. There are only two small published studies that investigated topiramate's pharmacokinetic effect on a combined oral contraceptive pill. Both studies found decreases in serum estrogen concentrations with concomitant topiramate use, but no significant pharmacokinetic effect of topiramate on norethindrone concentrations.[6,7]

The data from the norethindrone studies suggest that topiramate's pharmacokinetic effect on hormonal contraceptives differs significantly from carbamazepine, yet the MEC provides identical recommendations for these medications. Because women with chronic migraines already have limited contraceptive options, differentiating the actual interactions is crucial.

Research design and methods

Outcome Measure: Serum etonogestrel concentrations measured at baseline and then repeated after participants reach three titrated doses of topiramate:

- Visit 2 = 100mg per day
- Visit 3 = 200mg per day
- Visit 4 = 400mg per day

Description of Population to be Enrolled:

We aim to enroll subjects between 18-45 years old based on the following criteria:

Inclusion Criteria: Healthy women, who have had an ENG implant for 12-36 months at the time of enrollment and will maintain their implant during the study without modifications.

Exclusion Criteria: We will exclude women who are taking any known cytochrome P-450 3A4 enzyme inducers or inhibitors. We will also exclude women with a body mass index (BMI) <18.5, as underweight women may have altered metabolism. We will not have an upper BMI cut-off as studies have shown that overweight and obese women have equivalent metabolism and efficacy with the ENG contraceptive implant.[8,9]

We will also exclude women with any hepatic or renal dysfunction as determined by a comprehensive metabolic panel. For purposes of this study, liver function tests will be evaluated and evidence of hepatic dysfunction will be defined as an ALT >52 or AST >39, which are beyond the reference range of normal values used by the University of Colorado clinical laboratory. Renal function will be assessed by a serum creatinine and a value >1.2 will be evidence of renal dysfunction as this is greater than the reference range used by the University of Colorado clinical laboratory.

We will also assess for any history of hepatic or renal disease to screen for diseases such as hepatitis, cirrhosis, kidney transplant, etc.

We will also exclude women with a low serum bicarbonate on screening serum electrolytes due to potential increased risk for side-effects from topiramate. We will use a cut-off of bicarbonate <21 for purposes of this study as this value is outside the reference range for the University of Colorado clinical laboratory.

Study Design

We will conduct a prospective, non-inferiority study to evaluate the pharmacokinetic effect of topiramate on serum ENG levels in contraceptive implant users. We will enroll healthy women using an ENG implant for at least 12 months and no greater than 36 months. Our exclusion and inclusion criteria are detailed as above. Interested women will undergo a phone screening prior to scheduling an enrollment visit. At the enrollment visit, potential participants will have their vital signs checked in the form of a pulse and blood pressure and will have their height and weight measured for purposes of calculating a body mass index. We will review each potential participants past medical history and current medications to ensure study eligibility. If interested participants meet our non-laboratory inclusion and exclusion criteria, then they will undergo informed consent in a private clinic room.

After the participant has been consented, we will perform a blood draw to obtain whole blood and serum. Appropriate blood samples will be sent to the University of Colorado Clinical Laboratory for a comprehensive metabolic panel. A blood sample for serum will be centrifuged on location and the serum collected for storage in our -80°F freezer. For participants that meet our laboratory exclusion criteria, we will ultimately measure a serum baseline ENG concentration from the serum collected at the enrollment visit. The research team will then follow-up the comprehensive metabolic panel to determine final eligibility based on the criteria discussed above. Eligible participants will then be given the options of either returning to our clinic to pick up the first course of the study medication or have this first course mailed to them via FedEx.

Participants will then begin a 6 week titration schedule of topiramate to a max dose of 200mg bid by the final week. Women with chronic migraines are typically treated with a dose of 100 or 200mg/day, which will be achieved in the third and fourth week of titration, respectively. The maximum recommended dose of topiramate for treatment of epilepsy is 400mg/day, which will be achieved in the sixth and final week of titration. All participants will return at the end of the third week of the topiramate titration schedule. We will then draw blood from participants at this third week visit. An appropriate blood sample will be sent to the University of Colorado Clinical Laboratory for topiramate

measurement as a measurement of compliance. Serum obtained from this blood draw will be again stored in our -80°F freezer for eventual serum ENG concentration measurement. Participants will also undergo screening for adverse events (AEs) and serious adverse events (SAEs) at this follow-up. Any participant experiencing an SAE will be removed from the study. Participants will then be given the next course of the study medication to continue the titration schedule.

All participants will return at the end of the fourth and sixth weeks to undergo identical study procedures as described for the third week visit. The final course of the study medication will be provided at the fourth week visit to continue the titration schedule through to the conclusion of the study. A topiramate level will again be measured as a measure of study compliance and serum stored for eventual serum ENG concentration measurement. At the conclusion of enrollment, all stored serum samples will be de-identified and assigned a random identification number (three letters) so that the laboratory is blinded to the timing of samples. We will then ship all samples to a Merck® laboratory for serum ENG concentration measurement. Batch analysis will be performed using a liquid chromatography mass-spectrometry method that has been previously validated. Participants will serve as their own controls for this study.

Abrupt cessation of topiramate therapy has been associated with increase in seizures in patients taking the medication for epilepsy. It is unclear if this risk is present in healthy individuals taking topiramate, but we will have participants undergo a gradual withdrawal of topiramate over 1 week after the final blood draw (end of 6 weeks). Participants will be given this withdrawal regimen at the final blood draw visit and undergo down-titration of their topiramate dose over the course of 1 week. Participants who choose to discontinue their participation early will contact the PRA or study physician for a custom down-titration schedule or abrupt discontinuation in the case of serious adverse events.

All participants will be required to use either a back-up non-hormonal method of birth control or abstain from intercourse during the study and for 4 weeks after the last dose of topiramate. Topiramate has a half-life of 21 hours, and thus, will be eliminated within 1 week of the last dose, but we will allow another 3 weeks of buffer to ensure that the ovulation has not occurred and that the contraceptive effect of the implant has reinitiated before recommending resuming unprotected intercourse.

All study visits will occur at the Comprehensive Women's Health Clinic in Lowry. This is our Family Planning site for both clinical and research visits. All consent and enrollment processes will be conducted in a private clinic room and interested participants will be allowed as much time as needed to review the consent and ask any questions regarding the consent and study procedure.

Treatment:

Etonogestrel contraceptive implant - All participants will have had an ENG implant for 12-36 months at the time of enrollment and will maintain their implant during the study without modifications.
Topiramate – Participants will undergo a 6 week titrated regimen of oral topiramate to reach a maximum dose of 400mg per day, followed by a 7-day withdrawal titration schedule, and 4 week abstinence/back-up period:
Week 1: topiramate PO 25mg daily
Week 2: topiramate PO 25mg twice daily
Week 3: topiramate PO 50mg twice daily
Week 4: topiramate PO 100mg twice daily
Week 5: topiramate PO 150mg twice daily
Week 6: topiramate PO 200mg twice daily
Week 7: withdrawal titration schedule – topiramate PO 100mg twice daily for 2 days, 100mg daily for 2 days, 50mg daily for 2 days, 25mg daily for 1 day
Week 8 – 11: abstinence/backup period

Data Analysis Plan

For this study, non-inferiority was defined as a change in serum ENG concentration that would not result in concentrations below the threshold for ovulatory suppression. We chose a non-inferiority limit of 30% because this level of decrease from the median published levels (157-207pg/mL) does not cross the probably threshold for ovulatory suppression (90pg/mL). Based on the variance findings from our carbamazepine study (SD = 67.7), we performed a sample size calculation with an alpha level of 0.05 and a beta of 0.9 for our non-inferiority limit of 30%. We used a higher beta cut-off to account for the use of a statistical sample size calculation based on a normal distribution when serum ENG concentrations has a known non-normal distribution. This calculation resulted in a sample size of 27 women. We will enroll up to 53 women to account for a potential 49% drop-out/non-compliance rate, which accounts for an expected 30% intolerance rate for topiramate doses >200mg/day. Given that this will be a repeated measures study of non-parametric data, we will use a Friedman test for our analysis. We will use a p-value of <0.05 as a cut-off for statistical significance.

Citations

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