Buprenorphine Dose and Dosing Frequency Must Be Increased During Pregnancy

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BACKGROUND

Identification of a clinical issue:

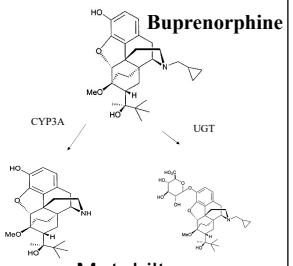
Buprenorphine (BUP) is a treatment option for Substance Use Disorder (SUD).

BUP is superior to methadone in pregnant women.

But, 33% subjects dropped out while on BUP vs 18% dropout while on methadone (1).

Hypothesis:

BUP is metabolized by CYP3A and UGT enzymes. Their activity will be **Increased** and plasma buprenorphine exposure will be **decreased** in pregnant women leading to decreased efficacy (satiety). (2,3).



METHODS

Clinical Study:

BUP exposure: Pharmacokinetic studies performed in the first half (N=14) (first/ second trimester) and second half (N=13) (third trimester) of pregnancy and in postpartum (about two months) (N=13) over a dosing interval of 6, 8 or 12hrs.

Multiple blood samples obtained in one dosing interval. Plasma BUP analyzed by a sensitive and specific liquid chromatography mass spectrometric assay.

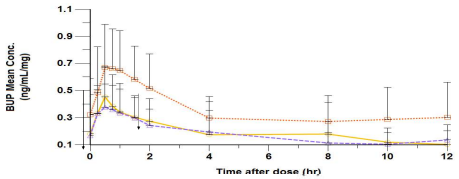
BUP Response: Clinical Opiate Withdrawal Scale (COWS Score) and pupillary diameter were assessed at various time points over one dosing interval.

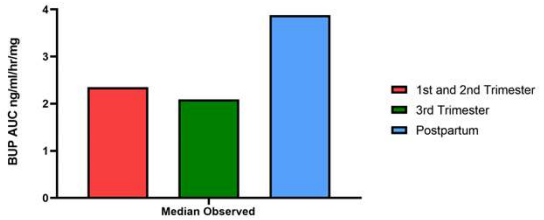
Modeling and Simulation:

Plasma BUP concentrations were simulated to determine duration of time when BUP plasma concentrations are greater than 1 ng/ml (reported as a minimal threshold).

BUP PLASMA EXPOSURE

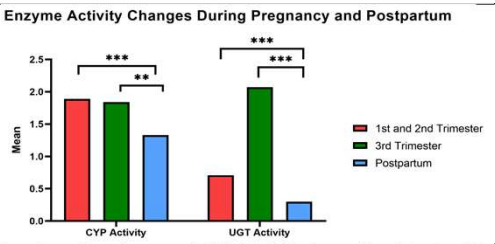
BUP exposure (Dose normalized Area) is decreased significantly in pregnancy





Implications: BUP dose should be increased during pregnancy to get plasma exposure similar to post partum period.

Higher metabolic ratio (Metabilte/BUP) in pregnancy compared to post partum is consistent with increased CYP3A and UGT mediated metabolism of BUP (4).



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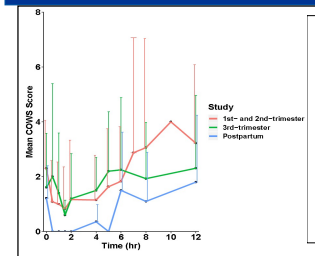
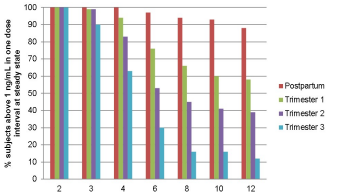
No Conflicts.

RESPONSE / IMPLICATIONS



Lower response as measured by COW Scores/ Changes in pupillary diameter (data not shown) with lower exposure. BUP dose should be increased to get similar exposure and response.

Simulations show BUP levels are above a therapeutic minimum level (1 ng/ml) for fewer number hours in pregnancy. BUP dosing frequency should be increased in pregnancy to keep levels above minimum effective levels (5).



Given the option to select frequency of dosing, given a total daily dose, most patients selected TID. (5)

CONCLUSIONS

BUP exposure decreases in pregnancy.

BUP response is lower in pregnancy corresponding to lower BUP plasma exposure.

BUP dose and dosing frequency must be increased during pregnancy to maintain therapeutic levels.

Increased dosing frequency minimizes, maximum plasma concentration in fetus (Data not shown here).

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