Ethical Issues Related to Pharmacokinetic (PK) and Pharmacodynamic (PD) Studies in Pregnant and Postpartum Women

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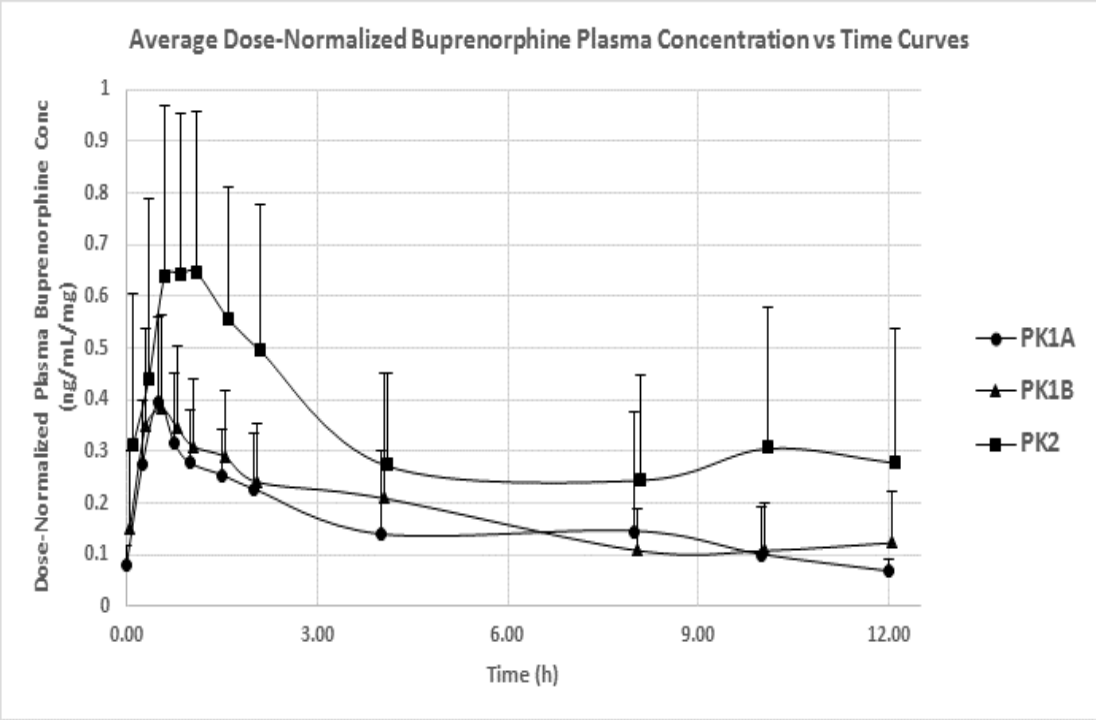
Definitions

- Pharmacokinetics - what the body does to a drug (ADME).
  - studies require measurement of drug in some compartment usually blood or plasma

- Pharmacodynamics - what a drug does to the body.
  - PD studies require measurement of some target organ/tissue response and its relationship to drug concentration either in blood or in tissue.

Ethical Issues with PK Studies

Dose-normalized buprenorphine plasma concentrations during pregnancy and postpartum



Bastian et al. Dose-adjusted plasma concentrations of sublingual buprenorphine are lower during than after pregnancy. AmJ Obstet Gynecol2017;216:64.e1-7.

- Measurement of drug in plasma /blood, saliva, urine poses little risk to mother or baby unless amount of blood withdrawn is excessive.
- Measurement of drug in other biological space may pose risk eg measurement in amniotic fluid or in fetal blood poses risk.
- Performing PK study with drug that mother or fetus do not need clinically poses an ethical challenge.

Why Give a Mother Unneeded Medications

- Pregnancy vs post partum PK studies
- Phase1/2 studies
- Metabolic cocktails – estimate in vivo cytochrome P450 and other metabolic enzyme activities

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Temporal changes in drug metabolism (CYP1A2, CYP2D6 and CYP3A Activity) during pregnancy

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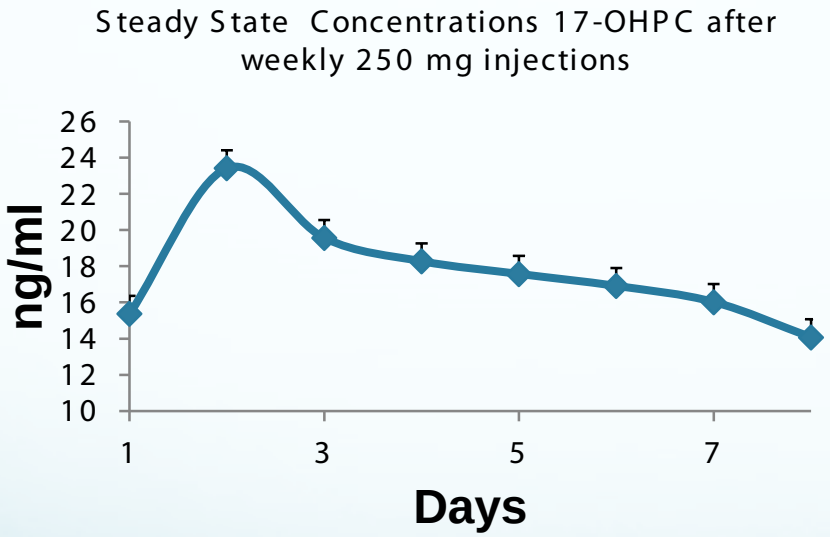
Subjects received 100 mg of caffeine (CYP1A2), 15 mg of dextromethorphan (CYP 2D6 and CYP 3A).

Ethical Issues in PK Studies

- Changing the dose or frequency of dosing to adapt to study design
- Asking mother to fast for an unreasonable time prior to PK study
- Asking mother to delay usual time medication taken

Why Pharmacodynamics?

The PK of a drug allows determination of how the body handles the drug but does not define what concentration achieves the desired effect.

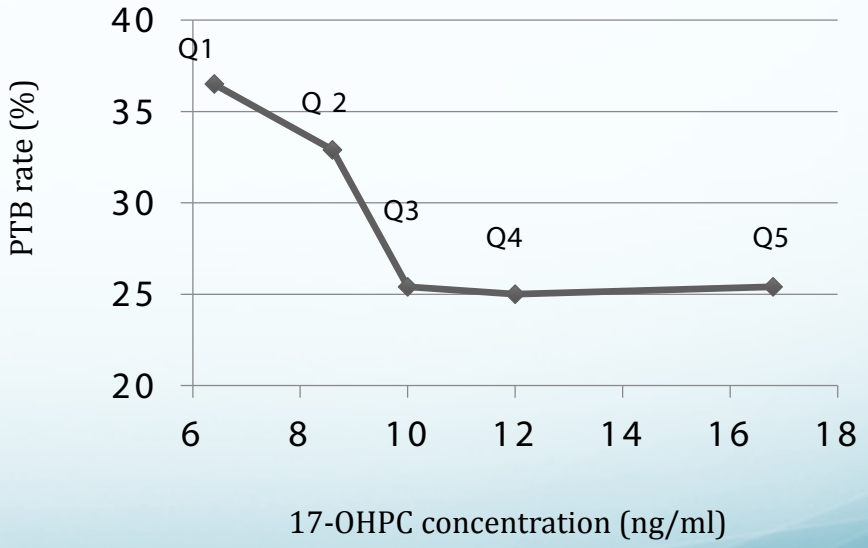


AUC_{t1} (ng/ml/day) (IQR)	Ctrough (ng/ml) (IQR)	Cmax (ng/ml) (IQR)	T max (days) (IQR)
135.6 ± 52.4 (93.1-165.1)	17.0 ± 8.3 (11.5-21.0)	26.4 ± 11.3 (18.0-31.1)	2.3 ± 1.9 (1.0-3.5)

Caritis, Venkataramanan et al for the OPRU

The PD response defines how much drug is required to elicit a desired response.

Relationship between median 17-OHPC concentration within each quintile of 17-OHPC concentration and PTB Rate within each quintile



Caritis, Venkataramanan et al for the MFMU

Why are PD Studies Neded

- Off-label dosing exists for most meds used in pregnancy
- Without PD studies in pregnant women proper dosing hampered – drug may be viewed as ineffective or unsafe (ritodrine)
- Some PD endpoints may be unique to pregnancy – PTB (17-OHPC), tocolytics (nifedipine, Indomethacin), fetal lung maturity (BMX), neuroprotection (MgSO4)

Postpartum PK/PD and Breast Milk Studies

- Postpartum studies

  - Same ethical issues as PK/PD in pregnancy
  - Time commitment of mother
  - Separation of mom and baby

- Breast milk studies – maternal blood, breast milk, neonatal biological fluid usually blood

  - Blood or biological sample from baby
  - Unavailability of breast milk to baby

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