

Host: This is the podcast from *Clinical Chemistry*. I am Bob Barrett. Buprenorphine, or BUP, has made the news recently as it is increasingly used to treat pain and as an alternative to methadone in cases of opioid-dependency.

A study published in the June issue of *Clinical Chemistry* analyzed BUP as a medication therapy for pregnant women who are dependent on opioids. Dr. Marilyn Huestis is the Chief of Chemistry and Drug Metabolism Intramural Research Program at the National Institute of Drug Abuse at the National Institutes of Health Bio-medical Research Center.

Her team investigated urinary BUP and metabolites in women undergoing supervised BUP maintenance therapy during the second and third trimesters of pregnancy and postpartum, and she's our guest in this podcast.

Dr. Huestis, tell us, what sparked your interest in this research?

Dr. Marilyn Huestis: We are very interested in knowing about drug exposure of infants whose mothers abuse drugs during pregnancy. We are the National Institute on Drug Abuse, and we are very interested in all aspects of drug abuse.

This study gave us the opportunity to look at the disposition of buprenorphine in urine of pregnant women. For ethical and safety reasons we, of course, would not do controlled dosing studies in this vulnerable population as we do with many other drugs in other populations, but the use of the pharmacotherapy buprenorphine gave us the opportunity to study this exposure to the fetus and the metabolism in the mother throughout gestation.

Host: How exactly do your results differ compared with other recently published studies?

Dr. Marilyn Huestis: Well, this particular study is the first one ever performed in pregnant women, that's one big difference. The other thing is that we have multiple samples collected throughout the different stages of the gestation and postpartum.

So, it gave us the opportunity to be able to see differences in metabolism at different stages of pregnancy, and these data, hopefully, will be able to provide evidence-based information for treatment providers and also policymakers on the best dosing strategies for pregnant opioid-dependent patients.

Host: So, does buprenorphine offer advantages compared with methadone for treating pregnant women who are dependent opioids?

Dr. Marilyn Huestis: Well, addiction is just like any other disease, whether it be hypertension or diabetics, certain medications work better for individuals, and until just recently we've only had methadone as the primary pharmacotherapy for opioid dependence, and now buprenorphine that is approved for use in the general population, is under investigation for use in pregnant women.

And so this drug offers an alternative therapy that may work better in certain individuals. We have clearly seen that buprenorphine works as effectively as methadone in preventing heroin relapse. Some of the side effects of buprenorphine are less difficult for the women and also we know although both buprenorphine and methadone produce neonatal abstinence syndrome in the infant who's been exposed throughout pregnancy, there was no more or more severe NAS with buprenorphine and methadone.

And we also found that baby tended to need less treatment than when they were exposed in utero to methadone, the severity was less, they required less treatment for recovering from that syndrome, and we found significantly shorter hospital stays for the infants who are exposed to buprenorphine as compared to methadone.

So, that was an economic affect as well.

Host: How exactly do our bodies metabolize buprenorphine?

Dr. Marilyn Huestis: Well in the body we have buprenorphine N-dealkylated to norbuprenorphine by the cytochrome P450 3A4 enzyme and this is the Phase I metabolic function, and then we also have a strong Phase II metabolism of glucuronide analytes to form both glucuronide and sulfate conjugates and this Phase II metabolism is accomplished by uridine diphosphate glucuronosyltransferase or UGT activity, and we know in pregnant women that the activities of both of these enzymes increase during pregnancy.

Host: So, why is urinary monitoring of buprenorphine important?

Dr. Marilyn Huestis: As for methadone, it's required that heroin-dependent individuals that are on pharmacotherapy that they have urine testing to monitor compliance with the treatment program, so that's one important reason.

Second of all, buprenorphine is abused in many countries of the world and in the United States we are very fortunate that the form of buprenorphine available to us also contains

naloxone. And naloxone as you realizes, is an opioid antagonist, but the bioavailability of that drug is very low when it's taken orally or sublingually as prescribed. But if the drug is diverted for illicit use then they can inject the drug and in that case you have good bioavailability of naloxone, and it would block the effects of buprenorphine.

But in other areas of the world, buprenorphine is given alone, and it is a drug that can be abused, and so it's important both for detection, exposure, and abuse as well as compliance during treatment.

Host: What are important attributes when immunoassays screen for urinary buprenorphine biomarkers?

Dr. Marilyn Huestis: It's very interesting because as you know in drug test monitoring because of the cost and the labor-intensive processes of conformation and almost always we have a screening procedure that occurs first, and usually that's done with immunoassays.

What's very, very important about monitoring buprenorphine in urine is that the antibodies in the immunoassays be directed against metabolites, rather than the parent, so there is significantly more norbuprenorphine-glucuronide that's the primary analyte that is present in urine and then the next most common one is buprenorphine-glucuronide and norbuprenorphine itself.

So, all three of these metabolites of buprenorphine, and many of the immunoassays that are available are directed against the parent drug buprenorphine, which is present in very low concentrations. In fact, we only found free buprenorphine in a very small number of samples in these samples that were collected across gestation.

So, having an immunoassay that's directed against the parent rather than the metabolites might cause individuals to be missed or to have false-negative drug tests.

Another really important aspect of our study is the fact that we had urine samples collected three times a week throughout gestation. Most other studies that are published have single urine value.

So, we are able to actually look at the total disposition in urine. We did several 24-hour collections in order to do this study of disposition of buprenorphine in urine.

Host: So, is it necessary to monitor all four analytes?

Dr. Marilyn Huestis: Well, it is necessary from the point of view of research, for instance the data that we are presenting because you need

to see the variation in metabolism and to see the disposition of the different analytes.

So, until this study was done we may not know what that disposition is. So, from that point of view, for research purposes it's important to do that, and also it might aid clinicians if you have the concentrations of all four analytes in better understanding and adjusting the buprenorphine dose.

But for routine monitoring purposes, if you were able to monitor the norbuprenorphine-glucuronide effectively you would have a good assay for screening for buprenorphine in urine.

Host: What factors might change buprenorphine's pharmacokinetics during pregnancy that might impact bioavailability and drug clearance.

Dr. Marilyn Huestis: Well, we know that during gestation that the enzymes responsible for buprenorphine metabolism are actually increased during pregnancy, and this will, obviously, affect the disposition of the drugs and the excretion of the drugs. We also know that renal clearance also increases. This is the first data that have shown us the variable metabolism in excretion at different stages of pregnancy and during postpartum period of time while the mother is returning to their normal hormone and metabolism.

Host: Dr. Marilyn Huestis is the Chief of Chemistry and Drug Metabolism Intramural Research Program at the National Institute of Drug Abuse at the National Institutes of Health Biomedical Research Center.

She is our guest in this podcast from *Clinical Chemistry*. I am Bob Barrett. Thank you for listening.

Total Duration: 10 Minutes.