FORENSIC SCIENCE NEWSLETTER
Forensic Pathology and Neuropathology

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www.forensicjournals.com

June 1, 2016

FORENSIC PATHOLOGY

The Safety of Newborn Infants who are Breast Fed by Mothers on Methadone Maintenance Therapy

Before continuing with the safety of newborn infants being breastfed by mothers who are on a methadone maintenance therapy program we need to have some understanding what is methadone and how was it created.

Chemistry

Methadone hydrochloride is chemically described as 6-(dimethylamino)-4,4-diphenyl-3-hepatanone hydrochloride. Its molecular formula is $C_{21}H_{27}NO \cdot HCl$ and has a molecular weight of 345.91.
Methadone exist as a racemic mixture of two enantiomeric optically active forms, R-(-)-methadone, also known as levomethadone and S-(+)-methadone, which is known as dextromethadone. Methadone is described as a mu-agonist (μ-agonist); a synthetic opioid analgesic (pain reliever), with multiple actions qualitatively similar to those of morphine, the most prominent of which involves the central nervous system (CNS) and organs composed of smooth muscle.
As stated, methadone is a racemic mixture of equal amounts of levo (R) and dextro (S) isomers. It is the levo (R) component that accounts for the μ-agonist effect, whereas the dextor (S) component does not effect the opioid receptors (μ-agonist) with the usual dosage, but instead binds to glutamatergic NMDA (N-methyl-D-aspartate) receptors, where it acts as an antagonist. Glutamate is the primary excitatory neurotransmitter in the CNS. NMDA receptors play an important role in modulating longterm excitations and memory formation. NMDA antagonist (dextromethorphan, ketamine, tiletamine, etc.) are being studied for their role in decreasing the development of tolerance to opioids and potentially eliminating addiction/tolerance/withdrawal, through disrupting memory circuitry. Dextro (S) isomer does have analgesic properties in large doses, which some believe may be due to its conversion to minor amounts of alpha-1-methadol and alpha-1-normethadol, both of which are potent analgesics.
Methadone can be detected in the plasma following oral administration within 30 minutes, reaching a peak concentration in ~4 hours (1-7.5 hours). The steady-state plasma concentrations ranges between 65-630 ng/ml and peak concentrations ranges between 124-1255 ng/ml.

Metabolism

Methadone is metabolized in the liver largely by mono-and di-N-demethylation, with spontaneous cyclization of the resulting unstable metabolites principally to form inactive metabolites 2-ethylidene-1,5-di-methyl-3,3-diphenylpyrrolidene (EDDP) and through a second N-demethylation, 2-ethyl-5-methyl-3,3-diphenylpyrroline (EMDP). Cytochrome P450 isoenzymes, primarily CYP3A4, CYP2B6, CYP2C8, and CYP2C19 and to a lesser extent CYP2C9 and CYP2D6, are responsible for the conversion of methadone to EDDP, EMDP and other inactive metabolites.

Another important point to remember is methadone is lipophilic (ability to dissolve in fats, oils, lipids, and non-polar solvents such as hexane or toluene), hence, it can persist in the liver and other tissues. The slow release from the liver and other tissues can prolong the duration of methadone action even though it may have a low plasma concentration. Also, toxic concentrations of methadone can accumulate in patients with liver disease, in geriatric patients with a decreased oxidative metabolism capacity, or in a patient taking an inhibitor of CYP3A4, such as nifedipine, diazepam, and fluvoxamine.

Pregnant patients who are on methadone maintenance therapy present a special set of problems when it comes to the elimination of methadone for it is significantly changed. Total body clearance of methadone is increased in pregnant patients compared to the same patients in postpartum or to non-pregnant opioid-dependent women. The terminal half-life of methadone is decreased during the second and third trimesters. The decrease in plasma half-life and increased clearance of methadone resulting in lower methadone trough levels during pregnancy can lead to withdrawal symptoms in pregnant patients. The dosage may need to be increased or the dosing interval decreased in pregnant patients receiving methadone, all of which will have an affect on the unborn fetus and breastfed newborn.

The metabolism of methadone is also dependent on urinary pH. The typical half-life of methadone is 19 hours. When urinary pH is raised from the normal range of 5.2-7.8 the half-life becomes 42 hours. At the highest pH, a lower percentage of methadone exists in the ionized form, and there is more reabsorption of the drug. Acidification of the urine results in the excretion of 22% of the dose as unchanged methadone resulting in a half-life of less than 19 hours, and only 2% as EDDP. At a normal urinary pH, adult maintenance patients will have a 24 hour urinary methadone concentration of 5-50% of the dose and an EDDP concentration between 3-25%. Again, variation in the pH of the pregnant woman's urine, will not only affect her blood concentration of methadone, but also that of the unborn infant and the breastfed infant.

What is important to understand is the metabolism and clearance of methadone is highly variable. There is marked variability between individuals, which is believed to be related to age; genetic polymorphism, which has a marked affect on enzymatic activity and function; and drug interactions, which can enhance or inhibit the isoenzymes. Before continuing we need to have some understanding of what is meant by the term **polymorphism.**

When you examine the sequences in the human genomes, you will find any two individuals will differ in approximately 1 nucleotide pair in every 1000. Most of these variations are common and of no consequence. However, when two sequence variants coexist in the population and are common, the variants are referred to as polymorphic. The majority of polymorphisms are due to the substitution of a single nucleotide called **single-nucleotide polymorphisms** or **SNPs**. Others are due largely to insertions or deletions called **indels** when the change is small, or **copy number variations** when it is large. Although, these common variants can be found throughout the genome, they are not scattered randomly or independently. Rather, they tend to occur in groups called **haplotype blocks**, which are combinations of polymorphisms that are inherited as a unit. Furthermore, like genes that exist in different allelic forms, haplotype blocks also come in a limited number of variants that are common in the human populations, each representing a combination of DNA polymorphisms passed down from a particular ancestor several hundred or thousands of years ago.

Clinical Aspects of Methadone Maintenance Programs

Before 2001, the American Academy of Pediatrics recommended women on methadone maintenance therapy could breast feed their infants as long as the daily dose of methadone did not exceed 20 mg per day. Following several studies, which demonstrated the levels of methadone secreted in human breast milk was relatively low and stable, the drug restriction of no more than 20 mg per day was eliminated. The question that needs to be asked was the lifting of this dose restriction in the best interest of breast fed infants? This is especially of concern since there is general agreement infants born to mothers on methadone maintenance therapy are significantly less mature (premature) and lower in birth weight than control infants. Many believe this fact alone stresses the need for pediatricians and neonatologist to encourage breast feeding in methadone maintained women.

In one study, most women on maintenance therapy typically required 50-150 mg of methadone per day during their pregnancy. The study also showed women who were breast feeding and on a maintenance dose of methadone that varied between 25-180 mg had an average methadone concentration that varied between 27-260 ng/ml, which led to an average daily methadone ingestion of 0.5 mg for the infant. In another study, in 21 neonates with symptoms of withdrawal, the mean maternal methadone level 16 hours after delivery was 183 ± 118 ng/ml, while the mean plasma levels for the neonates was 26 ± 8 ng/ml. Methadone levels decreased in the neonates at the average rate of 0.2 ± 0.3 ng/ml/hr.

What was shown in many of the studies is that half of all infants born to mothers on a maintenance dose of methadone experienced withdrawal symptoms or neonatal abstinence syndrome (NAS). However, other studies demonstrated those infants born to mothers on a maintenance dose of methadone experienced less withdrawal symptoms if they were breastfed. It was believed the reduction of withdrawal symptoms was due to the low concentration of methadone in the breast milk and the beneficial effects of breast feeding itself.

In 2009, a study of methadone-exposed newborns published in *Blog: An International Journal of Obstetrics and Gynecology* reported traces of methadone in the milk of mothers being treated for substance abuse reduced the risk of withdrawal symptoms in their breastfed babies. The likely hood of a baby needing treatment for NAS was reduced by 50% in babies who breastfed for more than three days.

In another study published in December of 2011 in the issue of *Breastfeeding Medicine*, blood tests showed that breastfed infants, including those born to mothers taking 200 mg of methadone per day, received a minute amount of methadone that was well below the 0.3-0.6 mg dose given every 12 hours to treat NAS (withdrawal symptoms in the newborn).

Discussion

When you review the clinical literature, one is given the impression of the relative safety of the present methadone maintenance dosage therapy programs, both for the pregnant woman and her unborn baby, as well as the postpartum woman and her breastfed infant.

When considering the safety of the infant there are certain factors, which you need to be aware of. First, the pharmacokinetics of methadone have not been established in either the unborn fetus, the newborn infant, or for that matter in the pediatric population. Second, the blood concentration for what constitutes a therapeutic range and a toxic range has not been established. Even in adult patients who are on a methadone maintenance schedule, there is often a large overlap between the reported therapeutic (0.03-0.56mg/L) and fatal concentrations (0.16-3.1 mg/L). Third, most pregnant women who are on a methadone maintenance program throughout their pregnancy, as well as in the postpartum period, what the fetus was exposed to *in utero* and what contribution those methadone levels made in the newborn infant are not known. Fourth, the quantity of methadone excreted in the breast milk is determined by the mothers pharmacokinetics, which may either subject the newborn infant to a toxic level or a safe level of methadone. What also needs to be remembered, the infants pharmacokinetics will also play a role in its' ultimate blood level of methadone, however, as pointed out above, the pharmacokinetics for the fetus, infant and the pediatric population has not been established.

As discussed earlier in adults, cytochrome P450 isoenzymes, primarily CYP3A4, CYP2B6, CYP2C8, and CYP2C19 and to a lesser extent CYP2C9 and CYP2D6 are responsible for the conversion of methadone to EDDP, EMDP and other inactive metabolites. In adults, it has been noted the *CYP2B6*6* variant, is associated with lower protein expression and is considered a **poor metabolizer phenotype.** In addition, genetic polymorphisms in CYP2B6 leads to a variable methadone clearance. Some studies have shown a high prevalence of *CYP2B6*6* in methadone related adult deaths. To date, 53 haplotypes and 28 alleles have been identified for CYP2B6, with 7 variant alleles occurring at a frequency greater than 1%. Furthermore, there is

considerable ethnic and racial variability in the occurrence of variant alleles. For example, *CYP2B6*6,* whose carriers have up to fourfold lower CYP2B6 expression and activity, occurs in ~ 25% of whites, 33%-40% of Africans and African-Americans, and up to 40% of Chinese. What is also noteworthy, although CYP2B6 is involved in the metabolism of (R)- and (S)-methadone, its role is smaller than that of CYP3A4 and CYP2C8. However, CYP2B6 is the primary isoenzyme for the metabolism of the S-isomer of methadone. Consequently, the *CYP2B6*6* genotype has been associated with specific increases in S-methadone plasma concentrations, which have important clinical consequences.
Increases in S-methadone plasma concentration can cause adverse cardiac events, some of which can lead to sudden death. It is believed this effect is mediated through the ability of S-methadone to bind to human *ether-à-go-go* related gene (hERG) voltage-gated potassium channels in cardiac myocytes resulting in delayed repolarization, and the development of QT prolongation, leading to potentially lethal ventricular arrhythmias.

It has been reported that infant CYP2B6 enzymatic levels can increase by ~twofold in the first 30 days (postnatal period). Thus, if an infant is homozygous for the *CYP2B6*6* haplotype (haplotype is a specific group of genes or alleles the infant inherited from one parent. Being homozygous means the infant has received the same specific group of genes or alleles from both parents), it will greatly increase the risk of methadone toxicity and death, as it has in adults, due to an impaired ability to metabolize methadone. It has also been noted the difference between infants in CYP2B6 protein expression can be as much as 25-fold, which is probably based on the haplotype blocks inherited.

Lastly, there is a protein within the blood brain barrier (BBB) referred to as P-glycoprotein 1 (permeability glycoprotein, multidrug resistance protein 1 [MDR1] or ATP-binding cassette sub-family B member 1 [ABCB1]) whose function is to pump many foreign substances out of cells. Technically, it is an ATP-dependent efflux pump with broad substrate specificity. ATP is an abbreviation for adenosine triphosphate, which is a nucleoside triphosphate used in cells as a coenzyme that transports chemical energy within cells for metabolism. In essence, this ATP-dependent efflux pump allows the capillary endothelial cells (BBB) within the brain to impede the entry of certain drugs into the brain. Thus, polymorphism of the *ABCB1* gene (MDR1gene) can have an affect on the function of this efflux pump. It has been shown that polymorphism in the *ABCB1* gene has been associated with an increased risk of CNS depression from codeine in neonates. It is also believed *ABCB1* polymorphism may play a role in methadone toxicity, as well as other opiates, in infants and adults.

Conclusion

In a recent article in the J. Forensic Science, March 2016, vol. 61, No.2, “Forensic Investigation of Methadone Concentration in Deceased Breastfed Infants,” one of the points they emphasize is the interpretation of postmortem methadone levels in infants should be done with caution.

It also needs to be done with knowledge of the complexity of the various factors involved in the metabolism of methadone. For example, what was the exposure of the infant *in utero* and in the postpartum period? Did either the mother or infant have evidence of polymorphism in the cytochrome P450 (CYP) isoenzymes or in the *ABCB1* gene? Was there impairment in the mother's or infant's liver to metabolize methadone. Did either the mother or infant have evidence of renal insufficiency? What were the sleeping arrangements for the infant?

Lastly, when the Forensic Pathologist interprets the results of the postmortem toxicology they must be cognizant of the postmortem redistribution of methadone, hence, it is important both heart blood and peripheral blood be drawn. It is also essential to compare those values with organ concentrations of methadone, as well as, antimortem values.

Current narcotic treatment program services will, of necessity, need to evolve to provide safer, more effective and integrated care. As discussed above, methadone is a drug that confers significant medical risk, and the ability to assess that risk and provide the best treatment for the pregnant and postpartum woman and her unborn and born infant is essential.