

Clinical pharmacology of methadone in neonates and in their mothers. A review

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The outstanding properties of methadone are its analgesic activity, its efficacy by oral route, its extended duration of action in suppressing of withdrawal symptoms in physically dependent individuals, and its tendency to show persistent effects with repeated administration. The analgesic activity of methadone, a racemate, is almost entirely the result of its R-methadone content. Respiratory depression is the chief hazard associated with methadone, and its peak respiratory depressant effects typically occur later, and persist for longer than its peak analgesic effect, particularly in the early dosing period. Methadone undergoes extensive metabolism in the liver and the major metabolic pathway is N-demethylation by CYP3A4 and CYP2B6. There is a remarkable interindividual variability in the rate of methadone metabolism. Mothers with opioid addiction are often placed on methadone before delivery in an attempt to reduce illicit opioid usage. Methadone is useful because it can be taken orally, only requires one or two daily doses and has a long-lasting effect. Weaning should not be attempted during pregnancy and, because of increased clearance, the dose of methadone may need to be increased in the last 3 months of pregnancy. Significant positive correlations were found for umbilical cord methadone concentrations, methadone mean daily dose, mean dose during the third trimester, and methadone cumulative daily dose. In conclusion, umbilical cord methadone concentrations were correlated to methadone dose. A total of 55-94% of infants born to opioid-dependent mothers in US show signs of opioid withdrawal. Methadone is useful to avoid use of opioid illicit drugs.

KEYWORDS: methadone; neonates; metabolism; pharmacokinetic side-effects.

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■ INTRODUCTION

Methadone is a long-acting morphine agonist with pharmacological properties qualitatively similar to those of morphine. Methadone is a racemate, and its analgesic activity is almost entirely the result of its content of R-methadone, which is 8 to 50 times more potent than the S-isomer.¹ The outstanding properties of methadone are its analgesic activity, the extended duration of action in suppressing withdrawal symptoms in physiological dependent individuals, and its tendency to show persistent effects with repeated administration.

Methadone is used in the management of opioid addiction, and to control the more severe abstinence symptoms seen in some infants born to mothers with this addiction.² Methadone hydrochloride is a useful synthetic opioid analgesic, developed in Germany during the 1939-45 war, that is capable of providing sustained pain relief. It is usually taken by mouth, and is less sedating than morphine. Opiate addiction may be associated with reduced fetal growth, but there is no evidence of teratogenicity.²

Mothers with an opiate addiction are often placed on methadone before delivery in an attempt to reduce illicit

opioid usage. Methadone needs to be taken once or twice a day and has a long-lasting effect. Maternal blood levels are therefore more stable, reducing some of the intoxication to which the fetus of an addicted mother is otherwise exposed.² Weaning should not be attempted during pregnancy and, because of an increased clearance of methadone, the dose may need to be increased in the last 3 months of pregnancy. Because of this, infants often start to show some signs of an abstinence syndrome 1 to 3 days after birth, with restlessness, irritability, rapid breathing, vomiting and intestinal hurry, especially where the mother was on a dose of more than 20 mg per day.² The American Academy of Pediatrics (AAP) has a long-standing recommendation against breastfeeding if the maternal methadone dose is above 20 mg/day. In 2001, the AAP lifted the dose restriction of maternal methadone allowing methadone-maintained mothers to breastfeed.³

■ BIBLIOGRAPHIC SEARCH

The bibliographic search was performed electronically using PubMed database as search engine; November 2014 was the cutoff point. The following key words "methadone pharmacokinetics neonate", "methadone effect neonate", "methadone metabolism neonate", were used. In addition,

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the books NEOFAX: a Manual Used in the Neonatal Care by Young and Mangum⁴ and the Neonatal Formulary² were consulted. This review is part of a program of recently published pharmacological reviews (2012 - 2014) covering varied aspects of neonatal pharmacology and toxicology.⁵⁻¹⁴

■ RESULTS

Dose of methadone in neonates

Young and Mangum⁴ state that the initial dose of methadone is 50 to 200 µg/kg per dose Q12 to 24 hours by mouth. Dose should be reduced by 10% to 20% per week over 4 to 6 weeks. The weaning schedule should be adjusted based on signs and symptoms of withdrawal.

For achieving control, one dose should be given every 6 hours by mouth. The starting dose should be 100 µg/kg, increased by 50 µg/kg each time a further dose is due until symptoms are controlled.² For maintaining control the total dose given in the 24 hours before control was achieved is halved and administered by mouth once every 12 hours. Weaning: once control has been sustained for 48 hours, dosage should be reduced by 10 to 20% once a day. Treatment can usually be stopped after 7 to 10 days although mild symptoms may persist for several weeks.²

Monitoring of methadone in neonates

Respiratory and cardiac status should be monitored closely. A 12-lead ECG should be obtained on methadone-exposed infants experiencing bradycardia or tachycardia. Gastric residues, abdominal distension, and loss of bowel sounds must be assessed.⁴

Metabolism of methadone in neonates and adult subjects

Methadone is difficult to administer as a therapeutic agent because of a wide range of interindividual pharmacokinetics, likely due to genetic variability of the CYP450 enzymes responsible for the metabolism of its main metabolite 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP). CYP3A4 is one of the primary CYP450 isoforms responsible for the metabolism of methadone to EDDP in humans. Richards-Waugh¹⁵ evaluated the role of CYP3A4 genetic polymorphism in accidental methadone fatalities. A study cohort consisting of 136 methadone-only and 92 methadone/benzodiazepine fatalities was selected from cases investigated at the West Virginia and Kentucky Offices of the Chief Medical Examiner. Seven single nucleotide polymorphisms were genotyped within the CYP3A4 gene. Observed allelic and genotypic frequencies were compared with expected frequencies obtained from the National Center for Biotechnology Information dbSNP database. SNPs rs2242480 and rs2740574 exhibited an apparent enrichment within the methadone-only overdose fatalities compared with the control group and the general population. This enrichment was not apparent in the methadone/benzodiazepine cases for these two SNPs. The results of this investigation indicate that there may be two or more SNPs on CYP3A4 gene that cause or contribute to the methadone poorly metabolized phenotype.

There is considerable evidence that pregnancy changes the disposition of drugs in an enzyme- and gestational stage-specific manner.⁶ On the basis of probe drug studies, the activity of CYP3A4 and CYP2D6 increases and CYP1A2 decreases during human pregnancy.¹⁶ However, no studies

of CYP2B6 activity during human pregnancy have been conducted. In rodent models and HepG2 cells, CYP2B enzymes have been shown to be regulated by estradiol.¹⁶ Because estradiol concentrations increase by about 50-fold during human pregnancy, it was hypothesized that the increasing estradiol concentrations during human pregnancy would result in induction of CYP2B6 activity. Hepatocytes from three female donors were treated with estradiol, and the EC(50) and E(max) were measured for CYP2B6 induction during human pregnancy. At 100 nM total estradiol, a concentration achievable during the third trimester of pregnancy, CYP2B6 activity was predicted to increase by 1.5 to 3-fold, based on increased CYP2B6 activity and mRNA. These data suggest that, during human pregnancy, the increasing estradiol concentrations will result in increased clearance of drugs that have CYP2B6-mediated clearance pathways. This could in part explain the observed increase of methadone clearance during gestation.¹⁶

Methadone metabolism clinically occurs primarily by CYP2B6.¹⁷ Retrospective studies suggest that the common allele variant CYP2B6*6 may influence methadone plasma concentrations. The catalytic effect of CYP2B6.6, encoded by CYP2B6*6 is highly substrate-dependent. The investigation by Gadel et al.¹⁷ compared methadone N-demethylation by CYP2B6.6 with that by wild-type CYP2B6.1. Methadone enantiomer and racemate N-demethylation by recombinant-expressed CYP2B6.6 and CYP2B6.1 was determined. At substrate concentrations (0.25 to 2 µM) approximating plasma concentrations occurring clinically, rates of methadone enantiomer N-demethylation by CYP2B6.6, incubated individually or as the racemate, were one-third to one-fourth those by CYP2B6.1. For methadone individual enantiomers and metabolism by CYP2B6.6 compared with CYP2B6.1, V_{max} was diminished, K_s was greater and the in vitro intrinsic clearance was diminished 5 to 6-fold. The intrinsic clearance for R- and S-EDDP formation from racemic methadone was diminished approximately 6-fold and 3-fold for R- and S-methadone, respectively. Both CYP2B6.6 and CYP2B6.1 showed similar stereoselectivity (S > R-methadone). Human liver microsomal with diminished CYP2B6 content due to a CYP2B6*6 polymorphism, is catalytically deficient compared with wild-type CYP2B6.1. Diminished methadone N-demethylation by CYP2B6.6 may provide a mechanistic explanation for clinical observations of altered methadone disposition in individuals carrying the CYP2B6*6 polymorphism.¹⁷

Cytochrome P450 2B6 (CYP2B6) belongs to the minor drug metabolizing P450s in human liver. Expression of this cytochrome is highly variable both between individuals and within individuals, owing to non-genetic factors, genetic polymorphism, indelibility, and irreversible inhibition by many compounds.¹⁸ Drugs metabolized mainly by CYP2B6 include methadone. CYP2B6 is one of the most polymorphic CYP genes in humans and variants have been shown to affect transcriptional regulation, splicing, mRNA and protein expression, and catalytic activity. Some variants appear to affect several functional levels simultaneously, thus, combined in haplotypes, leading to complex interactions between substrate-dependent and -independent mechanisms. The most common functionally deficient allele is CYP2B6*6Q172H, K262R, which occurs at frequencies of 15 to over 60% in different populations. The allele leads to lower expression in liver due to erroneous splicing. Recent investigations suggest that the amino acid changes

contribute complex substrate-dependent effects at the activity level, although data from recombinant systems used by different researchers are not well in agreement with each other. Another important variant, CYP2B6*18I328T, occurs predominantly in Africa (4 to 12%) and does not express functional protein. A large number of uncharacterized variants are currently emerging from different ethnicities in the course of the 1000 Genomes Project. The CYP2B6 polymorphism is clinically relevant for HIV-infected patients treated with the reverse transcriptase inhibitor efavirenz, but it is increasingly being recognized for other drug substrates. The present review summarizes recent advances on the functional and clinical significance of CYP2B6 and its genetic polymorphism, with particular emphasis on the comparison of kinetic data obtained with different substrates for variants expressed in different recombinant expression systems.

Disposition of methadone in cord and maternal sera and in the breast milk. de Castro et al.¹⁹ explored whether the umbilical cord disposition of methadone and its metabolite 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidone (EDDP) correlates with maternal methadone dose and neonatal outcomes; they also evaluated the window of drug detection in umbilical cord of in-utero illicit drug exposure. Nineteen opioid-dependent pregnant women derived from 2 studies, one comparing methadone and buprenorphine pharmacotherapy for opioid-dependence treatment and the second examining monetary reinforcement schedules to maintaining drug abstinence. Correlations were calculated for methadone and EDDP umbilical cord concentrations, maternal methadone dose, and neonatal outcomes. Cocaine- and opiate-positive umbilical cord concentrations were compared with those in placenta and meconium, and urine specimens collected throughout gestation. Significant positive correlations were found for umbilical cord methadone concentrations and methadone mean daily dose, mean dose during the third trimester, and methadone cumulative daily dose. Umbilical cord EDDP concentrations and EDDP/methadone concentration ratios were positively correlated to newborn length, peak neonatal abstinence syndrome (NAS) score, and time-to-peak NAS score. Methadone concentrations and EDDP/methadone ratios in umbilical cord and placenta were positively correlated. Many more cocaine- and opiate-positive specimens were identified in meconium than in the umbilical cord. In conclusion, umbilical cord methadone concentrations were correlated to methadone doses. Also, the results by de Castro¹⁹ indicate that methadone and EDDP concentrations might help to predict neonatal abstinence syndrome severity. Meconium proved to be more suitable than umbilical cord to detect in utero exposure to cocaine and opiates; however, umbilical cord could be useful when meconium is unavailable due to in utero or delayed expulsion.

In a second study de Castro et al.²⁰ calculated the correlations of placental methadone and EDDP concentrations and their correlations with maternal methadone doses and neonatal outcomes. Cocaine- and opiate-positive placenta results were compared with the results for meconium samples and for urine samples collected throughout gestation. Positive correlations were found between placental methadone and EDDP concentrations ($r = 0.685$), and between methadone concentrations and methadone dose at delivery ($r = 0.842$), mean daily dose

($r = 0.554$), mean third-trimester dose ($r = 0.591$), and cumulative daily dose ($r = 0.639$). The EDDP/methadone concentration ratio was negatively correlated with cumulative daily dose ($r = -0.541$) and positively correlated with peak neonatal abstinence syndrome score ($r = 0.513$). Placental EDDP concentration was negatively correlated with newborn head circumference ($r = -0.579$). Cocaine and opiate use was detected in far fewer placenta samples than in thrice-weekly urine and meconium samples, a result suggesting a short detection window for placentas. These authors conclude that quantitative methadone and EDDP measurement may predict neonatal abstinence syndrome severity. The placenta reflects in-utero drug exposure for a shorter time than meconium but may be useful when meconium is unavailable or if documentation of recent exposure is needed.

Bogen et al.²¹ studied 20 women 18 to 38 years old who were treated with racemic methadone doses of 40 to 200 mg/day and (mean, 102 mg/day) provided concomitantly collected plasma and breast milk samples 1 to 6 days after delivery. Most (16 of 20) samples were taken at the time of peak maternal plasma levels; thus infant exposure estimates are for maximum possible exposure. Concentrations of R- and S-methadone were measured in maternal plasma and breast milk. R-methadone concentration was 1.3 to 3.0 times that of S-methadone in all breast milk samples. The mean (\pm SD) milk to plasma for R-, S-, and total ratios of methadone were 0.52 ± 0.28 , 0.28 ± 0.15 , and 0.40 ± 0.21 , respectively. The dose ranges of R-, S-, and total methadone were extremely wide at 4 - 99, 2 - 71, 6 - 170 μ g/kg/day, respectively. R-methadone was found in higher concentrations than S-methadone in breast milk. Thus, even at high methadone doses, breast milk methadone concentrations were relatively lower than plasma methadone concentrations.

Breastfeeding among methadone-maintained women is frequently challenged because of unclear guidelines regarding this practice. Previous research has confirmed that concentrations of methadone in breastmilk in the neonatal period are low. Currently unknown are the concentrations of methadone in breastmilk among women who breastfeed for longer periods of time. Jansson et al.²² examined the concentrations of methadone in the plasma and breastmilk of women who breastfeed their infants beyond the neonatal period. Four methadone-maintained women provided blood and breastmilk samples up to 6 months postpartum. The concentrations of methadone in blood and breastmilk were low, contributing to the recommendation of breastfeeding for some methadone-maintained women.

Jansson et al.²² also evaluated the concentrations of methadone in breast milk among breastfeeding women and the concentrations of methadone in infant plasma. Eight lactating women receiving 50 to 105 mg methadone per day, provided blood and breast milk specimens on days 1, 2, 3, 4, 14 and 30 after delivery, at the times of trough and peak maternal methadone levels. Paired specimens of foremilk and hindmilk were obtained at each sampling time. Eight matched subjects provided blood samples on the same days. Infant blood samples for both groups were obtained on day 14. Urine toxicological screening between 36 weeks of gestation and 30 days after the birth confirmed that subjects were not using illicit substances in the perinatal period. The concentrations of methadone in breast milk were low (range: 21.0 to 462 ng/ml) and not related to maternal dose.

Concentrations of methadone in maternal plasma were unrelated to maternal dose. The concentrations of methadone in infant plasma were low (range: 2.2 to 8.1 ng/ml) in all samples. Infants in both groups underwent neurobehavioral assessments on days 3, 14, and 30; there were no significant effects of breastfeeding on neurobehavioral outcomes. Fewer infants in the breastfed group required pharmacotherapy for neonatal abstinence syndrome, but this was not a statistically significant finding.²²

Limited pharmacokinetic and pharmacodynamic data are available to use methadone-dosing recommendation in pediatric patients for either opioid abstinence or analgesia. Considering the extreme inter-individual variability of absorption and metabolism of methadone, population-based pharmacokinetics would be useful to provide insight into the relationship between dose, blood concentrations, and clinical effects of methadone. To address this need, an age-dependent physiologically based pharmacokinetics model has been constructed to systematically study methadone metabolism and pharmacokinetics.²³ This model, which includes whole-body multi-organ distribution, plasma protein binding, metabolism, and clearance, is parameterized based on a database of pediatric pharmacokinetic parameters and data collected from clinical experiments. Based on measured variability in CYP3A enzyme expression levels and plasma orosomucoid (ORM2) concentrations, a Monte-Carlo-based simulation of methadone kinetics in a pediatric population was performed. The simulation predicts extreme variability in plasma concentrations and clearance kinetics for methadone in the pediatric population, based on standard dosing protocols. In addition, it is shown that when doses are designed for individuals based on prior protein expression information, inter-individual variability in methadone kinetics may be greatly reduced.

Johnson et al.²⁴ reported that 55 to 94% of infants born to opioid-dependent mothers in US will show signs of opioid withdrawal. Of approximately 309 infants exposed, a neonatal abstinence syndrome has been reported in 62% infants with 48% requiring treatment; apparently more than 40% of these cases are confounded by illicit drug abuse. The neonatal abstinence syndrome associated with buprenorphine generally appears within 12-48 hours, peaks at approximately 72 to 96 hours, and lasts for 120 to 168 hours. These results appear similar to or less than those observed following in utero exposure to methadone.

Wojnar-Horton et al.²⁵ quantified the distribution and excretion of methadone in human milk during the early postnatal period and investigated the exposure of breast feed to the drug. Blood and milk samples were obtained from 12 breast-feeding women who were taking methadone in daily doses ranging from 20 to 80 mg (0.3 to 1.14 mg/kg). The infants were observed for withdrawal symptoms. The mean (95% CI) milk/plasma ratio was 0.44 (0.20 to 0.64). Exposure of the infants, calculated assuming an average milk intake of 0.151/kg per day and a bioavailability of 100% was 17.4 (10.8 to 24) µg/kg per day. The mean infant dose expressed as a percentage of the maternal dose was 2.79 (2.07 to 3.51%). Methadone concentrations in seven infants were below the limit of detection for the hplc assay procedure, while one infant had a plasma methadone concentration of 6.5 µg/l. Infant exposure to methadone via human milk was insufficient to prevent the development of a neonatal abstinence syndrome which was seen in seven (64%) infants.

No adverse effects attributable to methadone in milk were seen. Wojnar-Horton et al.²⁵ conclude that exposure of breast fed infants to methadone taken by their mothers is minimal and that women in methadone maintenance programs should not be discouraged from breast feeding because of this exposure.

Gordon et al.²⁶ compared the transfer of buprenorphine and methadone between maternal and cord blood in women under chronic dosing conditions to determine if differences exist in the transfer of the two methadone enantiomers. Maternal and cord blood samples were collected at delivery from women maintained on methadone (25 to 149 mg/day), median and range were 6.00 and 1 to 20 mg/kg, respectively, during pregnancy. Plasma concentrations are presented as an indicator of fetal exposure relative to mother. Methadone was quantified in all samples, cord:maternal plasma methadone concentration ratios (n = 15 mother-infant pairs) being significantly higher (p < 0.0001) for the active R-methadone enantiomer compared with S-methadone. Thus, the transfer of the individual methadone enantiomers to the fetal circulation is stereoselective. The R- to S-methadone concentrations ratios were also significantly higher (p < 0.001) in maternal plasma. Half of the infant buprenorphine samples were below the assay lower limit of quantification (LLOQ) (0.125 ng/ml). The cord:maternal plasma buprenorphine concentrations ratio (n = 9 mother-infants pairs) was 0.35 and for norbuprenorphine it was 0.49.

Jansson et al.²⁷ evaluated the concentrations of methadone in breast milk and plasma among a sample of methadone-maintained women in the immediate perinatal period. Twelve methadone-maintained, lactating women provided blood and breast milk specimens 1, 2, 3 and 4 days after delivery. Specimens were collected at the time of trough (just before the next methadone dose) and peak (3 hours after dosing) maternal methadone levels. Paired specimens of foremilk (prefeed) and hindmilk (postfeed) were obtained at each sampling time. There was a significant increase in methadone concentration in breast milk over time. The methadone concentrations in breast milk were small, ranging from 21 to 314 ng/ml, and were unrelated to maternal methadone dose. Results obtained from this study contribute to the recommendation of breastfeeding for methadone-maintained women regardless of methadone dose.

Berghella et al.²⁸ determined whether maternal methadone dosage correlates with neonatal withdrawal in a large heroin-addicted pregnant population. Neonatal withdrawal was assessed objectively by the neonatal abstinence score. The average of methadone dose in the last 12 weeks of pregnancy and the last methadone dose before delivery (cutoffs of 40, 60 or 80 mg) were correlated to various objective measures of neonatal withdrawal. One hundred mother/neonate pairs on methadone therapy were identified. Women who received an average methadone dose <80 mg (n = 50 women) had a trend toward a higher incidence of illicit drug abuse before delivery than women who received doses of ≥80 mg (n = 50 women; 48% versus 32% NS).

Doberczak et al.²⁹ defined the relationships between neonatal opiate withdrawal and drug-related factors such as maternal methadone dosage, maternal and neonatal plasma levels, and rate of decline of methadone in neonatal plasma. Twenty-one methadone-dependent women and their newborn infants were studied. Fourteen of the women used

other illicit drugs. The severity of neonatal withdrawal was assessed with a standardized scoring system. Venous blood samples for methadone levels were collected from the mothers within 24 hours of delivery and from their newborns within 24 hours of birth and on day 3 to 4 of life. The maternal methadone dosage at delivery correlated significantly with the maternal plasma level drawn at 16 hours postpartum ($r = 0.512$, $p < 0.05$), and the maternal methadone level in turn correlated significantly with the neonatal plasma methadone level on day 1 of life ($r = 0.545$, $p < 0.05$). A positive correlation was found between the severity of central nervous system signs of withdrawal and the rate of decline of the neonatal plasma methadone level from day 1 to day 4 of life ($r = 0.55$, $p < 0.05$). Doberczak et al.²⁹ conclude that this spectrum of relationships supports the concept that careful reduction of the maternal methadone dosage during pregnancy under intensive medical and psychosocial surveillance may benefit the drug-exposed new-born infant clinically.

Mack et al.³⁰ observed the effects of methadone exposure in utero, with special reference to maternal and neonatal methadone concentrations and neonatal withdrawal. Two groups of mother-infant pairs were studied. In the first group serum methadone concentrations were determined in infants at 1, 6 and 24 h after delivery. In the second group, blood was obtained at 24, 48, 72 and 96 hours after birth. There was no correlation between neonatal serum levels and the intensity of withdrawal symptoms. There was no relationship between maternal methadone dose at delivery or maternal serum levels and methadone levels. The results of this study may be complicated by the prenatal exposure of the neonate to other drugs of abuse apart from methadone.

■ DISCUSSION

Methadone is used in the treatment of neonatal abstinence syndrome and opioid dependence. This drug is a long-acting narcotic analgesic. It has an oral bioavailability of 50%, with peak plasma levels obtained in 2 to 4 hours. Methadone is a racemate and the analgesic activity is almost entirely due to R-methadone. Methadone is extensively metabolised by the action of CYP3A4 and CYP2B6, the main metabolic pathway is the N-demethylation to give 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP). There is a remarkable interindividual variability in the rate of formation of EDDP because of the activity of CYP2B6 varies considerably among individuals.

Estradiol concentrations increase by about 50-fold during pregnancy, resulting in induction of CYP2B6 activity with consequent increase in the rate of EDDP. Consequently the dose of methadone should be increased in the last 3 months of pregnancy. The catalytic of CYP2B6, encoded by CYP2B6*6 is highly substrate dependent and the allele variant CYP2B6*6 may influence methadone plasma concentrations.

Toxicity of methadone consists in a respiratory depression. In some cases, deaths appear to have occurred due to respiratory or cardiac effects of methadone and too-rapid titration without appreciation of the accumulation of methadone over time. Respiratory depression is the chief hazard associated with methadone, and its peak respiratory depressant effects typically occur later, and persist longer than its peak analgesic effects, particularly in the early dosing period.

de Castro et al.¹⁹ found significant correlations for umbilical cord methadone concentrations and methadone mean daily dose. Thus the methadone maternal dose influences the infant serum concentrations of this drug. The cord EDDP concentrations and the EDDP/methadone concentration ratios were positively correlated with newborn length and the placental EDDP concentration was negatively correlated with newborn head circumference.²⁰ These findings suggest that methadone and/or its metabolite EDDP influence the fetal development. de Castro et al.²⁰ observed positive correlations between placental methadone and EDDP concentrations and between placental methadone concentrations and methadone dose at delivery. These data suggest that the placental, and thus the serum umbilical cord concentrations, correlate with the methadone dose.

Methadone is secreted in the breast milk but the concentration of this drug in the milk is lower than in the maternal plasma. R-methadone, the active enantiomer, was found in higher concentrations than S-methadone in breast milk.³¹ The concentrations of methadone in breast milk ranged from 21 to 462 ng/ml and were not related to the maternal dose. In infant plasma, the concentrations of methadone ranged from 2.2 to 8.1 ng/ml²² and thus were lower than those in breast milk and in maternal plasma.

Johnson et al.²⁴ found that 55 to 94% of infants born to opioid-dependent mothers in US will show signs of opioid withdrawal and will require treatment with methadone.

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■ FARMACOLOGIA CLÍNICA DA METADONA EM NEONATOS E SUAS MÃES. REVISÃO

■ RESUMO

As mais importantes propriedades da metadona são sua atividade analgésica, a sua eficácia por via oral, a sua prolongada ação supressora de sintomas de abstinência em indivíduos fisicamente dependentes e a persistência de seus efeitos com administração repetida. A atividade analgésica de metadona, um racemato, é quase inteiramente o resultado do seu teor de R-metadona. A depressão respiratória é o principal risco associado a seu uso, e o pico de depressão respiratória normalmente ocorre tardiamente e persiste após o fim de seu efeito analgésico especialmente durante as fases iniciais de seu uso terapêutico. A metadona é metabolizada no fígado e a principal via metabólica é a N-desmetilação por CYP3A4 e CYP2B6. Há uma variabilidade interindividual notável em relação à sua taxa de metabolização. Mães com dependência de opiáceos são frequentemente colocadas em terapêutica com metadona antes do parto, na tentativa de reduzir o uso de opiáceos ilícitos. A metadona é útil porque pode ser tomada por via oral, só precisa de uma ou duas doses diárias e tem efeito de longa duração. O desmame não deve ser executado durante a gravidez; por causa do aumento da depuração, a dose de metadona pode precisar ser aumentada nos últimos três meses de gravidez. Correlações positivas significativas foram encontradas para a metadona entre os seguintes parâmetros: concentrações no cordão umbilical, dose média diária, dose durante o terceiro trimestre, e dose diária média cumulativa. Em conclusão, as

concentrações de cordão umbilical de metadona foram correlacionados com a dose de metadona. Entre 55% e 94% dos recém-nascidos de mães dependentes de opiáceos nos Estados Unidos mostram sinais de abstinência a opiáceos. A metadona é útil para evitar o uso de drogas ilícitas opióides.

UNITERMOS: metadona; neonatos; metabolismo; efeitos colaterais farmacocinéticos.

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