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Review Article

Clinical Pharmacology of Methadone in Infants and Children

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Abstract

Methadone is a long-acting μ opioid receptor agonist with pharmacological properties qualitatively similar to those of morphine, is a racemate, consists in R-methadone and S-methadone and the analgesic activity is due to R-methadone. In infants, the initial oral dose of methadone is 100 μg/kg 4 times-daily. In children, methadone is given by sublingual application, orally, intramuscularly, or intravenously and the dose of methadone varies according to the child body-weight. Methadone has been found efficacy and safe in infants and children but may induce toxicity. Methadone is metabolized into inactive metabolites by different cytochromes P450, the main metabolite is 2-ethyl-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP), and females catalyse the formation of EDDP at higher activity than males. The pharmacokinetics of methadone have been studied in infants following oral administration and methadone is rapidly absorbed. The pharmacokinetics of R-methadone and S-methadone have been studied in children in adult patients and in adolescents and the pharmacokinetic parameters of R-methadone are different from those of S-methadone indicating that the disposition of methadone is stereoselective. Methadone interacts with drugs and the treatment and trials with methadone have been reviewed in infants and children. Methadone causes different effects in the human brain, poorly crosses the human placenta, and migrates into the breast-milk in significant amounts. The aim of this study is to review the methadone dosing, efficacy and safely, pharmacokinetics, treatment, and trials in infants and children, and methadone toxicity, metabolism, interaction with drugs, effects on human brain, placental transfer, and migration into breast-milk.

Keywords: syncope; celiac disease; dilated cardiomyopathy; gluten-free diet

Introduction

Mechanism of methadone action Methadone is a long-acting μ opioid receptor agonist with pharmacological properties qualitatively similar to those of morphine. Methadone is a racemate, consisting in R-methadone and S-methadone, and is used clinically as a racemic mixture. R-methadone has a higher μ-opioid receptor affinity and is 50-times more potent as a μ receptor agonist than the S-methadone. S-Methadone binds very poorly to the μ-opioid receptor and so also lacks significant respiratory depressant action and addition liability, although it does possess antitussive activity [1].

Pharmacological effects of methadone

Important proprieties of methadone are its analgesic activity, its efficacy by the oral route, its extended duration of action in suppressing withdrawal symptoms in physically dependent individuals, and its tendency to show persistent effects with repeated administration. Miotic and respiratory-depressant effects can be detected for more than 24 hours after a single dose; on repeated administration, marked sedation is seen in some patients. Effects on cough, bowel motility, biliary tone, and the secretion of pituitary hormones are qualitatively similar to those of morphine [1].

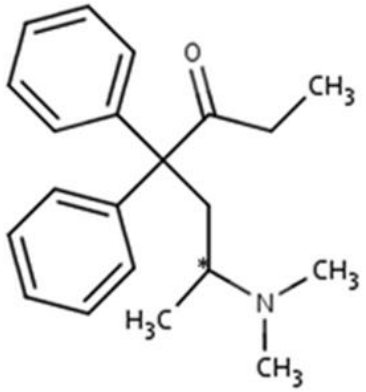
Therapeutic uses of methadone

Although an effective analgesic, the primary use of methadone hydrochloride is detoxification and maintenance therapy treatment for opioid use disorder. Because it is a full agonist with all the properties of morphine, this takes place within certified treatment programs. Outside treatment programs, methadone is used for the management of chronic pain. The onset of analgesia occurs 10 to 20 min after parenteral administration and 30 to 60 min after oral medication. The typical dose is 2.5 to 10 mg repeated every 8 to 12 hours as needed depending on the severity of the pain and the response of the patient. Care must be taken when increasing the dosage because of the prolonged elimination half-life of the drug and its tendency to accumulate over a period of several days with repeated dosing. The peak respiratory-depressant effect of methadone typically occurs later and persists longer than peak analgesia, so it is necessary to exercise vigilance and strongly caution

patients against self-medication with central nervous system depressants, particularly during treatment initiation and dose titration. Methadone should not be used in labour. Despite its longer plasma elimination half-life, the duration of the analgesic action of single doses is essentially the same as that of morphine. With prolonged use, cumulative effects are seen, so either lower doses or longer intervals between doses become possible. Methadone, like other opioids, will produce tolerance and dependence. Development of physical dependence during the long-term administration of methadone can be demonstrated following abrupt drug withdrawal or by administration of an opioid antagonist. Likewise, subcutaneous administration of methadone to those with an opioid use disorder produces euphoria equal in duration to that caused by morphine, and is overall abuse potential is comparable with that of morphine [1]. Methadone is widely used in the management of maternal opioid addiction, and to control the more severe withdrawal symptoms seen in some infants born to mothers with such an addition. The use during lactation results in the newborn receiving about 3% of the weight-adjusted maternal dose, so, breastfeeding should be encouraged as there is some evidence that breastfeed newborns show fewer symptoms of withdrawal, and seems less likely to require medication irrespective of the nature of the mother's addition [2]. Methadone is used in the treatment of neonatal abstinence and opioid dependence. Methadone is a long-acting narcotic analgesic; the oral bioavailability is 50% with peak plasma levels obtained in 2 to 4 hours. Methadone is extensively metabolized via the hepatic N-demethylation and methadone is highly protein bound. In infants, the serum elimination half-life ranges from 16 to 25 hours and it is prolonged in infants with renal failure. Rifampin and phenytoin accelerate the metabolism of methadone and can precipitate withdrawal symptoms [3].

Absorption, distribution, metabolism, and elimination of methadone

Methadone is absorbed well from the gastrointestinal tract and can be detected in plasma within 30 min after an oral ingestion; it reaches peak concentrations at about 4 hours. Peak concentrations occur in brain within 1 to 2 hours of subcutaneous or intramuscular administration, and this correlates well with the intensity and duration of analgesia. Methadone also can be absorbed from the buccal mucosa. Methadone undergoes extensive biotransformation in the liver. The major metabolites, pyrrolidine and pyrroline derivatives, result from the N-demethylation and cyclization and are excreted in the urine and in the bile along with small amounts of unchanged drug. The amounts of methadone excreted in the urine are increased when the urine is acidified. In adults, the elimination half-life of methadone is 15 to 40 hours. Methadone appears to be firmly bound to protein in various tissues, including brain. After repeated administration, there is gradual accumulation in tissues. When administration is discontinued, low concentrations are maintained in plasma by slow release from extravascular binding sites. This process may explain why withdrawal symptoms following methadone are less severe than with morphine but longer, resulting in a relatively mild but protracted withdrawal syndrome [1]. Methadone is well absorbed when taken by mouth (90% bioavailability), and largely metabolized by the liver through cytochromes CYP3A4, CYP2B6, and CYP2D6, although these are immature in the newborn and CYP3A7 is also though to play a role in this population. The elimination half-life of methadone shows substantial interindividual variability but in most newborns is about 20 hours [2].



Methadone molecular structure (molecular weight = 309.445 grams/mole)

The asterisk denotes the asymmetric atom

Literature search

The literature search was performed electronically using PubMed database as search engine and the following key words were used: "methadone dosing infants, children", methadone efficacy, safely infants, children", "methadone toxicity", "methadone metabolism, "methadone pharmacokinetics infants, children", "methadone drug interaction", "methadone treatment infants, children", methadone trials infants, children", "methadone human brain", "methadone placental transfer", and "methadone breast-milk". In addition, the books: The Pharmacological Basis of Therapeutics [1], Neonatal Formulary [2], NEOFAX® by Young and Mangum [3], and The British National Formulary for Children [4] have been consulted.

Results

Administration schedules of methadone to infants and children

Administration to infants [2]

Achieving control: Give one dose 4 times-daily by mouth. Start with 100 µg/kg, and increase this by 50 µg/kg each time a further dose is due until symptoms are controlled.

Maintaining control: Calculate the total dose given in the 24 hours before control was achieved, and give half of this amount by mouth twice-daily.

Weaning: Once control has been sustained for 48 hours, try and reduce the dose given by 10% to 20% once each day. Treatment can usually be stopped after 7 to 10 days although mild symptoms may persist for several weeks.

Administration to children [4]

Treatment of moderate to severe pain by sublingual administration

Children with a body-weight of 16 to 25 kg. Give: 100 µg 4 times-daily or 3 times-daily.

Children with body-weight of 25 to 37.5 kg. Give: 100 to 200 µg 4 times-daily or 3 times-daily.

Children with body-weight of 37.5 to 50 kg. Give: 200 to 300 µg 4 times-daily or 3 times-daily.

Children with body-weight of 50 kg and above. Give: 200 to 400 µg 4 times-daily or 3 times-daily.

Treatment of moderate to severe pain by intramuscular injection or by slow intravenous injection

Children aged 6 months to 11 years. Give: 3 to 6 µg/kg 4 times-daily or 3 times-daily.

Children aged 12 to 17 years. Give: 300 to 600 µg 4 times-daily or 3 times-daily.

Efficacy safely of methadone in infants and children

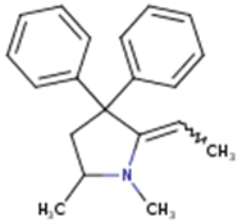
One-hundred-twenty-one infants were born to mothers maintained on methadone and received methadone for the treatment of neonatal abstinence syndrome. The methadone mean oral dose was 3.1 mg/kg daily and this treatment effectively decreases the infant hospital stay and reduces the hospital cost [5]. Methadone oral dose of 0.1 to 3 mg/kg daily effectively treats complex pain in infants and children [6]. In paediatric patients with cancer who are nearing the end-of-life methadone is a valuable adjunctive therapy which effectively treats nociceptive and neuropathic pain and prevents opioid-induced hyperalgesia and opioid tolerance [7]. Methadone is a long-acting opioid which effectively and safely treats pain in children with cancer [8].

Toxicity caused by methadone in children and adult patients

Methadone was administered to children to treat pain and the therapy with methadone caused cardiopulmonary arrest in some children [9]. Methadone was administered to children to treat pain and treatment with methadone causes respiratory-depression, central nervous system depression, and miosis in some children [10]. Methadone serum concentration of > 0.019 ng/ml and particularly > 0.0365 ng/ml causes mortality due to increased cardiac troponin serum concentration in adult patients [11]. A total of 1,511 paediatric patients were treated with methadone to control pain and 154 paediatric patients (10.2%) died because of methadone overdose [12]. A total of 456 of methadone-poisoned patients had been admitted to the toxicology ward. Methadone syrup had been taken by 129 patients (41.4%) while the others had overdosed methadone tablets. The mean ingested dose of methadone was 85.91±82.61 mg (range; 5 to 500), the mean time elapsed between methadone ingestion and admission to the hospital was 9.41±9.87 hours (range; 1 to 72), and some patients died because of respiratory-depression [13]. A total of 1,193 cases of methadone overdose were observed and the overdose causes cardiac disease in 58.9% patients, pulmonary disease in 53.6% patients, hepatic disease in 80.7% patients and renal disease in 25.0% [14]. Oral methadone was co-administered with intravenous benzodiazepines and death was observed in 57 of 87 adult patients (65.5%) who took methadone and benzodiazepines. Death occurs at 5.1 to 6.0 hours after oral ingestion of methadone and intravenous injection of benzodiazepines [15]. Ten adult patients died within few days after receiving a mean dose of 53 mg of methadone and alcohol, or benzodiazepines, or morphine and the mean blood concentration of methadone was 2.1 µmol/L at the time of death [16].

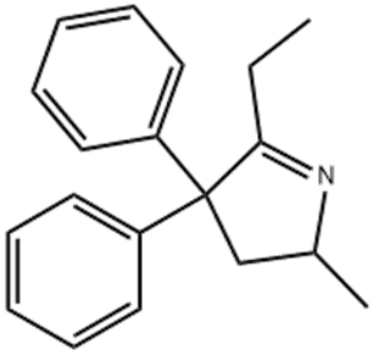
Metabolism of methadone

Gadel et al. [17] studied the metabolism of methadone in-vitro using human liver microsomes. Methadone N-demethylation was evaluated at methadone concentration of 0.25 to 1 µM which is the plasma concentrations of methadone occurring in patients who receive methadone for treatment of pain or substance abuse, respectively. The inactive 2-ethyl-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP) is formed by CYP2B6.4, CYP2B6.1, CYP2B6.5, CYP2B6.9 and by CYP2B6.6 and S-EDDP is formed in higher amounts than R-EDDP. Methadone is also reduced by cytochrome b5, and by CYP2B6.4, CYP2B6.1, CYP2B6.5, CYP2B6.9, and CYP2B6.6.



2-ethyl-1,5-dimethyl-3,3-diphenylpyrrolidine molecular structure (molecular weight = 277.411 grams/mole)

Talal et al. [18] studied the metabolism of methadone in-vivo in 100 adult human patients and 58 were males. Females catalyse the formation of R-EDDP and S-EDDP at significantly higher activity than males (P-value = 0.016 and P-value = 0.044, respectively) thus the metabolic-rate of methadone is lower in males than in females. Dinis-Oliveira et al. [19] studied the metabolism of methadone in-vitro in human liver microsomes. Methadone is first N-demethylated to form inactive EDDP and then is also cyclized to form the inactive 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EMDP). The cytochromes P450 isoenzymes that form EDDP and EMDP are CYP2B6, CYP3A4 and CYP2D6.



2-Ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine molecular structure (molecular weight = 265.4 grams/mole)

Ferrari et al. [20] studied the metabolism of methadone in-vitro using human liver microsomes. Methadone is metabolized is N-demethylated by CYP2D6, CYP3A4 and CYP1A2 to form EDDP. The activity of these cytochromes varies considerably among individual livers and this variability is responsible for the large difference in methadone bioavailability.

Pharmacokinetics of methadone in infants

Wiles et al. [21] studied the pharmacokinetics of methadone in 8 infants with neonatal abstinence syndrome. Infants had a median gestational age of 38.0 weeks (range, 37.4 to 39.5) and a median-body-weight of 3.0 kg (range, 2.6 to 3.2). Methadone was administered orally at a dose of 50 µg/kg 4 times-daily. Infants who respond to this treatment received a methadone oral dose of 40 µg/kg 4 times-daily. Table 1 summarizes the pharmacokinetic parameters of methadone.

			Bootstrap analysis N = 1,000	
Parameter	Estimate	%RSE	Median	95% CI
TBC/F (L/h/70 kg)	8.94	19	8.37	4.73 – 12.8
TBC/F (L/h/kg)	0.37	---	---	---
DV (L/70 kg)	177	40	174	37.4 – 428
DV (L/kg)	2.53	---	---	---
Ka (h^{-1})	0.334	24	0.346	0.140 – 0.659
Lag time (hours)	0.827	33	0.837	0.0956 – 1.14
interindividual variability, %coefficient of variation				
IIV TBC/F	103	14	99.9	50.5 – 132
IIV DV/F	133	19	130	79.1 - 161
Proportional error	15.7	10	15.6	12.4 - 161

%RSE = %relative standard error. CI = confidence interval. TBC = total body clearance extrapolated to 70 kg adult. DV = distribution volume extrapolated to 70 kg adult. F = bioavailability. Ka = absorption-rate constant. IIV TBC/F = interindividual variability of total body clearance. IIV DV = interindividual variability of distribution volume.

Table 1: Pharmacokinetic parameters of methadone which have been obtained in 8 infants with a median gestational age of 38.0 weeks (range, 37.4 to 39.5) and a median body-weight of 3.0 kg (range, 2.6 to 3.2). Methadone was administered orally at a dose of 50 µg/kg 4 times-daily. Infants who respond to this treatment received a methadone oral dose of 40 µg/kg 4 times-daily, by Wiles et al. [21].

This table shows that the distribution volume of methadone is larger than the water volume, methadone is rapidly absorbed as the median absorption-rate constant is 0.334 h^{-1}. In addition, there is a remarkable interindividual variability in the pharmacokinetic parameters of methadone and this variability is caused by the vide variation in infant gestational age and body-weight.

Horst et al. [22] investigated the pharmacokinetics of R-methadone and S-methadone in 24 children aged 15±2 years (range, 7 to 17) and in 23 adult patients aged 25±7 years (range, 18 to 55) and methadone was intravenously administered at a dose of 100 to 125 µg/kg once-daily. Table 2 summarizes the pharmacokinetic parameters of R-methadone and S-methadone.

	Children		Adult patients	
Parameter	R-Methadone	S-Methadone	R-Methadone	S-Methadone
Peak conc. (ng/ml)	17±7	28±12	16±7	23±9
Peak conc./D (ng/ml/mg)	6±2	10±5	5±4	7±4
$AUC_{0\text{-}96\ h}$ (ng*h/ml)	429±248	635±424	421±168	601±276
$AUC_{0\text{-}\infty}$ (ng*h/ml)	523±248	716±439	637±324	790±397
$AUC_{0\text{-}\infty}$/D (ng*h/ml/mg)	190±99	262±178	191±94	241±123
TBC (ml/kg/min)	2.1±1.2	1.7±1.0	1.6±0.6	1.3±0.5
*Half-life (h)	34.0±16	24.0±9	52.0±17	38.0±12
DVss (L/kg)	5.9±3.9	3.3±2.2	6.5±1.7	3.9±1.2
Parameter	R-EDDP	S-EDDP	R-EDDP	S-EDDP
Peak conc. (ng/ml)	0.49±0.26	0.90±0.44	0.37±0.20	0.60±0.16
Peak Conc./D (ng/ml/mg)	0.18±0.13	0.33±0.22	0.11±0.06	0.18±0.06
Tmax (h)	6±7	9±8	11±7	11±6
$AUC_{0\text{-}96\ h}$ (ng*h/ml)	19±7	31±12	20±7	32±9
$AUC_{0\text{-}\infty}$ (ng*h/ml)	27±10	41±3	30±10	43±16
$AUC_{0\text{-}\infty}$/D (ng*h/ml/mg)	10±3	14±5	12±8	13±4
*Half-life (h)	42.0±13	31.0±8	54.0±29	41.0±22

Peak conc./D = dose-normalized peak concentration. TBC = total body clearance. DVss = distribution volume at the steady-state. AUC = area under the concentration-time curve. *Elimination half-life. $AUC_{0\text{-}\infty}$/D = $AUC_{0\text{-}\infty}$/dose-normalized. EDDP = 2-ethyl-1,5-dimethyl-3,3-diphenylpyrrolidine. Tmax = time to reach the EDDP peak concentration.

Table 2. Pharmacokinetic parameters of R-methadone and S-methadone which have been obtained in 24 children aged 15±2 years (range, 7 to 17) and in 23 adult patients aged 25±7 years (range, 18 to 55) and methadone was intravenously administered at a dose of 100 to 125 µg/kg once-daily. Values are the mean±SD, by Horst et al. [22].

This table shows that the disposition of methadone and EDDP is stereoselective in children and in adult patients. The peak plasma concentration and the area under the concentration-time curve of R-methadone are lower than those of S-methadone, the elimination half-life of R-methadone is longer than that of S-methadone, the total body clearance of R-methadone is higher than that of S-methadone, and the distribution volume of R-methadone is larger than that of S-methadone. The pharmacokinetic parameters of both R-methadone and S-methadone obtained in children are not significantly different from those obtained in adult patients (Wilcoxon non-parametric test). The peak concentration and the area under the concentration-time curve of R-EDDP are lower than those of S-EDDP. The time to reach the peak concentration of R-EDDP is similar to that of S-EDDP, the elimination half-life of R-EDDP is longer than that of S-EDDP. The pharmacokinetic parameters of both R-EDDP and S-EDDP obtained in children are not significantly different from those obtained in adult patients (Wilcoxon non-parametric test). In addition, there is a remarkable interindividual variability in the pharmacokinetic parameters of R-methadone and S-methadone and of R-EDDP and S-EDDP and this variability is accounted by the wide variation of the age of children and adult patients.

Sharma et al. [23] studied the pharmacokinetics of R-methadone and S-methadone in 61 adolescents aged 14±2 years (range, 5 to 18) undergoing surgery and methadone was administered intravenously at a dose of 100, 200, or 300 µg/kg once-daily. The anaesthesia was induced with propofol and was maintained with sevoflurane or desflurane. Table 3 provides the demographic characteristics of the adolescents included in the study and table 4 summarizes the pharmacokinetic parameters of R-methadone and S-methadone.

	Methadone dose			
Parameter	0	100 µg/kg	200 µg/kg	300 µg/kg
Number of adolescents	30	10	10	11
Age (year)	15±2	14±2	13±2	14±2
Sex (M: F)	9:21	2:8	6:4	2:9
Body-weight (kg)	63±26	61±13	50±8	62±14
Diagnosis				
Scoliosis	26	9	9	10
Kyphosis	2	0	1	1
Operation				
Poster spinal fusion	30	9	10	10
Levels fused	11±3	10±5	11±2	10±3
Anaesthesia duration (h)	5.6±1.5	5.8±1.8	5.4±0.7	5.8±1.3
Estimated blood loss (ml)	448±238	555±269	410±249	405±162
Methadone dose (mg)	0	6.1±1.3	9.9±1.4	17.4±2.3

Table 3: Demographic characteristics of adolescents included in the study. Values are the mean±SD, by Sharma et al. [23].

	Methadone dose							
	100 µg/kg	200 µg/kg	300 µg/kg	All	100 µg/kg	200 µg/kg	300 µg/kg	All
	R-Methadone				S-Methadone			
Peak conc. (ng/ml)	39±35	56±21	78±27*	---	52±50	75±22	106±40*	---
Peak conc./dose (ng/ml/mg)	14±11	13±5	10±4	12±7	19±16	17±6	14±6	17±10**
$AUC_{0-\infty}$ (ng*h/ml)	594±389	837±273	1,588±789*	---	679±375	979±245	1,835±757*	---
$AUC_{0-\infty}$/dose (ng*h/ml/mg)	228±164	189±54	205±102	207±113	256±151	223±58	235±88	238±103**
TBC (ml/kg/min)	1.6±0.7	2.0±0.6	1.6±0.8	1.7±0.7	1.4±0.8	1.6±0.4	1.3±0.5	1.4±0.6**
§Half-life (h)	55.0±38	43.0±16	59.0±37	52.0±31	40.0±25	28.0±11	37.0±17	35.0±18**
DVss (L/kg)	6.4±1.4	6.6±1.7	6.6±1.5	6.5±1.5	4.0±1.0	3.8±1.1	3.8±0.9	3.8±0.9**
R-EDDP					S-EDDP			
Peak conc. (ng/ml)	0.38±1.11	0.88±0.24*	1.14±0.30*	---	0.76±0.18*	1.79±0.52*	2.35±0.54*	---
Peak conc./dose (ng/ml/mg)	0.06±0.01	0.09±0.04	0.07±0.03	0.07±0.03	0.13±0.03	0.16±0.08	0.14±0.54	0.15±0.06**
Tmax (h)	14±14	12±6	11±6	13±9	24±9	17±7	14±6	18±8*

$AUC_{0-96\ h}$ (ng*h/ml)	23±10	42±11	55±15	---	42±16	78±22	111±32*	---
$AUC_{0-\infty}$ (ng*h/ml)	46±28	59±20	106±65*	---	60±26	107±49	192±93*	---
$AUC_{0-\infty}$/dose (ng*h/ml/mg)	7.4±4.0	6.0±1.9	6.1±3.7	6.5±3.3	9.8±3.4	11.4±7.1	11.2±5.5	10.8±5.4**
§Half-life (h)	72.0±42	41.0±17	68.0±57	61.0±43	41.0±20	49.0±36	49.0±36	41.0±25**

Peak conc./dose = dose-adjusted peak plasma concentration. AUC = area under the concentration-time curve. $AUC_{0-\infty}$/D = $AUC_{0-\infty}$/dose-normalized. TBC = total body clearance. §Elimination half-life. DVss = distribution volume at the steady-state. EDDP = 2-ethyl-1,5-dimethyl-3,3-diphenylpyrrolidine. Tmax = time to reach the peak plasma concentration of EDDP. *Significantly different compared with 100 µg/kg versus 200 µg/kg and 300 µg/kg (P-value < 0.05). **Significantly different between all cases of R-methadone versus all cases of S-methadone (P-value < 0.05). The dose groups are compared using ANOVA. Difference in EDDP enantiomer pharmacokinetic parameters (all subjects) are compared using Wilcoxon signed rank test.

Table 4. Pharmacokinetic parameters of R-methadone and S-methadone which have been obtained in 61 adolescents undergoing surgery aged 14±2 years (range, 5 to 18) and methadone was administered intravenously at a dose of 100, 200, or 300 µg/kg once-daily. Values are the mean±SD, by Sharma et al. [23].

This table shows that the disposition of methadone and EDDP is stereoselective according to the 3 doses. The peak plasma concentration and the area under the concentration-time curve of R-methadone are lower than those of S-methadone, the total body clearance of R-methadone is higher than that of S-methadone, the elimination half-life of R-methadone is longer than that of S-methadone, and the distribution volume at the steady-state of R-methadone is larger than that of S-methadone. The peak plasma concentration of R-EDDP is smaller than that of R-EDDP, the time to reach the peak plasma concentration of R-EDDP is lower than that of S-EDDP, the area under the concentration-time curve of R-EDDP is lower than that of S-EDDP, and the elimination half-life of R-EDDP is longer than that of S-EDDP.

Interaction of methadone with drugs

Cannabidiol inhibits CYP3A4 and CYP2C19 which are the cytochromes that metabolize methadone thus cannabidiol increases the blood concentration of methadone [24]. Serotonin syndrome is a potentially life-threatening adverse-drug reaction caused by excessive serotonergic agonism in central and peripheral nervous system serotonergic receptors and is caused by the combination of linezolid with methadone [25]. Warfarin inhibits CYP2C19 and CYP3A4 which are the cytochromes that metabolize methadone thus warfarin increases the blood concentration of methadone [26]. Methadone interacts with psychotropic drugs. The co-administration of buprenorphine or tramadol with methadone causes withdrawal symptoms, haloperidol or droperidol co-administered with methadone prolongs the QTc, and the co-administration of chlorpromazine or thioridazine with methadone causes respiratory-depression [27]. Ciprofloxacin inhibits different cytochromes P-450 thus ciprofloxacin increases the blood concentration of methadone [28]. Ciprofloxacin inhibits CYP1A2 and CYP3A4 which are the cytochromes that metabolize methadone thus ciprofloxacin increases the blood concentration of methadone [29]. Methadone was administered for 10 days to a patient to control pain and after 2 days of fluconazole addition the respiratory-depression is achieved [30].

Treatment of infants and children with methadone

A total of 116 full-term infants with neonatal abstinence syndrome were born to mothers maintained on methadone or buprenorphine and were treated with methadone or with morphine. Infants treated with either morphine or methadone developed similar short-term and long-term neurobehavioral outcomes [31]. Infants with neonatal abstinence syndrome were treated with methadone or with morphine. Infants treated with methadone have a significantly shorter hospital stay and a significantly shorter stay in neonatal intensive care unit than infants treated with morphine [32]. It was compared the developmental outcomes in infants with neonatal abstinence syndrome treated with morphine to those treated with methadone. Infants treated with morphine have significantly higher scores in cognitive and gross motor domains compared to infants treated with methadone [33]. It was compared the early growth and developmental outcomes in infants with in-utero exposure to low-dose methadone (< 100 mg daily), to high-dose methadone (≥ 100 mg daily) or to buprenorphine. Infants born to mothers exposed to high-dose of methadone are associated with a reduction of head circumference and have a negative impact on motor skill development during early infancy compared to infants treated with low methadone dose or with buprenorphine [34]. It was assessed the outcomes of infants born to mothers who received methadone for management of pain. Methadone used during pregnancy results in a low incidence of neonatal abstinence syndrome [35]. Ten children received methadone for weaning from continuous opiate infusions for ≥ 7 days and 10 children underwent weaning by standardized protocol. Use of a standardized weaning protocol decreases the time for weaning without increasing the frequency rate of withdrawal symptoms [36].

Trials conducted with methadone in infants and children

A meta-analysis was performed to study the neurodevelopmental outcome of infants born to mothers prescribed methadone in pregnancy. Infants born to mothers who received methadone in pregnancy are at risk of neurodevelopmental problems [37]. It was tested the hypothesis that brain development is altered among infants whose mothers' received methadone during pregnancy. Prenatal exposure to methadone is associated with microstructural alteration in major white matter tracts which is present at birth [38]. Methadone was administered to 46 children with cancer to treat and methadone significantly improves neuropathic pain [39]. Methadone was administered to 40 children with cancer to treat pain and methadone significantly improves neuropathic pain through a targeted effect of allodynia and its pressure/squeezing component [40]. Methadone is an effective and inexpensive alternative in treating pain in cancer children but the incidence of serious toxicity suggests that methadone should only be initiated in an adequately monitored setting by pain management experts [41]. It was assessed the early executive functioning of children born to mothers receiving methadone during pregnancy and these children have difficulties in controlling the attention and learning [42]. Methadone should be administered at low dose to children to avoid complications such as over-

sedation [43]. Infants with neonatal abstinence syndrome were treated with methadone or with morphine and the length of hospital stay is similar in infants treated with methadone and in infants treated with morphine [44].

Effects of methadone on the human brain and methadone concentration in the human brain

Exposition to 10 μM methadone increases I_{Na} (4.5-fold) and I_{KD} (10.8-fold), and reduces the shift of Na^+ channel gating properties [45]. Methadone decreases the frequency and amplitude of excitatory postsynaptic currents in neurons indicating a critical role of methadone in weakening synaptic transmission in neural networks in human brain cortical organoid. In addition, methadone significantly attenuates the voltage-dependent Na^+ current in human brain cortical organoids. Thus, methadone interrupts the neural growth and function in human brain [46]. Methadone maintenance treatment induces impairments in human brain function and structure despite its clinical effectiveness [47]. The medial prefrontal cortex and the extended limbic system in methadone maintenance patients with a history of heroin dependence remains responsive to salient drug cues which suggests a continued vulnerability to relapse [48]. The concentration of R-methadone and S-methadone was measured in human brain. The concentration of R-methadone and S-methadone ranges from 0.03 to 13 mg/kg and from 0.6 to 6.8 mg/kg, respectively. The median unbound fraction of R-methadone and S-methadone in human brain is 3.9% (range, 3.0 to 5.3) and 3.7 % (range, 2.9 to 4.9) [49].

Transfer of methadone across the human placenta

In literature there is only one study on the transfer of methadone across the human placenta and it has been reported by Nanovskaya et al. [50]. These authors studied the transfer of methadone across the human placenta using the perfusion of the preterm and term placenta. The transfer-rate methadone across the preterm placentas is $19\pm5.8\%$, and that across the term placentas is $31\pm9.7\%$ (P-value < 0.01). The clearance index of methadone in preterm placenta (0.57 ± 0.2) is lower than that in term placenta (0.95 ± 0.3, P-value < 0.01). The transfer of methadone across the perfused placenta is lower in preterm than in term placenta. These results are consistent with the view that methadone poorly crosses the human placenta.

Migration of methadone into the breast-milk

Methadone was administered orally at a dose ranging from 25 to 180 mg daily to 10 lactating women and methadone concentration in the milk ranges from 27 to 260 ng/ml [51]. Methadone was administered to 8 lactating women at an oral dose ranging from 50 to 105 mg daily and methadone concentration in the milk ranges from 21 to 460 ng/ml [52]. Twelve lactating women were treated with methadone orally for 4 days after delivery. The concentration of methadone in the milk ranges from 21 to 314 ng/ml and increases with the time after dosing (P-value = 0.0255) [53]. Eight lactating women were treated with methadone at an oral dose ranging from 25 to 180 mg daily and methadone concentration in the milk ranges from 27 to 260 ng/ml with a mean concentration of 95 ng/ml [54]. Methadone was administered at an oral dose ranging from 20 to 80 mg daily to 12 lactating women and the mean (95% confidence interval) of milk to maternal plasma ratio is 0.44 (0.24 to 0.64) suggesting that methadone migrates into the breast-milk in significant amounts [55]. Ten lactating women were treated with methadone at an oral dose ≥ 40 mg daily. In immature milk (N = 8) the mean milk to maternal plasma ratio of the area under the concentration-time curve is 0.68 (95% confidence interval = 0.48 to 0.89) for R-methadone and is 0.38 (95% confidence interval = 0.26 to 0.50) for S-methadone. In mature milk (N = 2) the milk to maternal plasma ratio of the area under the concentration-time curve is 0.39 to 0.54 for R-methadone and is 0.24 to 0.30 for S-methadone. These results show that R-methadone migrates into the milk in higher amounts that S-methadone [56].

Discussion

Methadone is a long-acting μ opioid receptor agonist with pharmacological properties qualitatively similar to those of morphine. Methadone has a chiral center and is used clinically as the racemate although the analgesic activity is almost enterally due to R-methadone. The primary use of methadone is detoxification and maintenance therapy treatment for opioid use disorder. Methadone may be administered orally or intravenously and following oral dosing methadone is well absorbed and is detected in plasma 30 min after an oral ingestion and reaches the peak concentration at about 4 hours. The onset of analgesia occurs 10 to 20 min after parenteral administration and 30 to 60 min after oral administration. The peak concentration of methadone in brain occurs 1 to 2 hours of subcutaneous or intramuscular administration and methadone concentration in brain correlates well with the intensity and duration of analgesia [1]. In infants, the initial oral dose of methadone is 100 μg/kg 4 times-daily [2]. and in children, the treatment of moderate to severe pain may be treated with sublingual, intramuscular, or intravenous methadone and the methadone dose varies according to the child body-weight [4]. The efficacy and safely of methadone has been reviewed in infants and children. Infants born to mothers maintained on methadone had neonatal abstinence syndrome and received methadone orally at a mean dose of 3.1 mg/kg daily. This treatment effectively decreases the infant hospital stay and reduces the hospital cost [5]. oral dose of 0.1 to 3 mg/kg daily of methadone effectively treats complex pain in infants and children [6]. methadone effectively treats nociceptive and neuropathic pain in paediatric patients with cancer and prevents opioid-induced hyperalgesia and opioid tolerance [7]. and methadone effectively and safely treats pain in children with cancer [8]. These results indicate that methadone effectively treats neonatal abstinence syndrome in infants and treats pain in infants and children. The toxicity induced by methadone has been reviewed in children and in adult patients. Methadone was administered to children to treat pain and methadone causes cardiopulmonary arrest in some children [9]. and methadone causes respiratory-depression, central nervous system depression, and miosis in some children [10]. Methadone serum concentration of > 0.019 ng/ml and particularly > 0.0365 ng/ml causes mortality due to increased cardiac troponin serum concentration in adult patients [11]. methadone was administered to paediatric patients to control pain and an overdose of methadone causes mortality in about 10% of paediatric patients [12]. a mean overdose of about 86 mg (range, 5 to 500) of oral methadone causes mortality due to respiratory-depression in some patients [13]. an overdose of methadone causes cardiac disease, pulmonary disease, hepatic disease and renal disease in some patients [14]. the co-administration of oral methadone with intravenous benzodiazepines causes mortality in about 65% patients and the death occurs 5.1 to 6.0 hours after the administration of methadone and benzodiazepines [15]. and methadone administered at an initial dose of 53 mg causes death in patients who also received alcohol, or benzodiazepines, or morphine and the mean blood concentration of methadone at the time of death is 2.1 μmol/L [16]. Methadone is extensively metabolized into inactive metabolites by different cytochromes P-450 in-vitro in human liver and in-vivo in humans. Methadone is N-demethylated to form 2-ethyl-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP) by different variants of CYP2B6 and methadone is also reduced by cytochrome b5 and by different variants of CYP2B6. The formation of EDDP is stereoselective; S-EDDP is formed in higher amounts than R-EDDP [17]. Females catalyse the formation of R-EDDP and S-EDDP at significantly higher activity than males [18].

Methadone is first N-demethylated to form EDDP and is also cyclized by CYP2B6, CYP3A4, and by CYP2D6 to form the inactive 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine [19]. The activity of CYP2D6, CYP3A4, and CYP1A2 was measured in-vitro using human liver microsomes and the activity of these cytochromes varies among livers and such variability is responsible for the large difference in methadone bioavailability [20]. The pharmacokinetics of methadone have been studied in infants. Following oral administration, methadone is rapidly absorbed as the absorption-rate constant is 0.334 h^{-1} and the distribution volume of methadone is larger than the water volume [21]. The pharmacokinetics of R-methadone and S-methadone have been studied in children and in adult patients and methadone was intravenously administered [22]. The mean elimination half-life of R-methadone and S-methadone is 34.0 and 24.0 hours, respectively, in children and 52.0 and 38.0 hours, respectively, in adult patients. The mean elimination half-life of R-EDDP and S-EDDP is 42.0 and 31.0 hours, respectively, in children and 54.0 and 41.0 hours, respectively, in adult patients. The time to reach the peak plasma concentration of R-EDDP is shorter than that of S-EDDP thus the former metabolite is formed faster than the latter metabolite. The disposition of methadone and EDDP is stereoselective in children and in adult patients. The pharmacokinetic parameters of R-methadone and S-methadone and those of R-EDDP and S-EDDP are not different in children and in adult patients. The pharmacokinetics of R-methadone and S-methadone have been studied in adolescents and methadone was administered intravenously at the dose of 100, 200, and 300 µg/kg [23]. The peak concentration and the area under the concentration-time curve of R-methadone and S-methadone increase with the dose whereas the elimination half-life and the distribution volume of R-methadone and S-methadone are independent by the dose. The disposition of methadone and EDDP is stereoselective in adolescents. The time to reach the peak plasma concentration of R-EDDP is shorter than that of S-EDDP suggesting that the former metabolite is formed faster than the latter metabolite. The interaction of methadone with drugs has been reviewed. Cannabidiol inhibits CYP3A4 and CYP2C19 which are the cytochromes that metabolize methadone thus cannabidiol increases the methadone blood concentration [24], linezolid combined with methadone causes serotonin syndrome which is a life-threatening adverse-drug reaction caused by excessive serotonergic agonism in central and peripheral nervous system serotonergic receptors [25], warfarin inhibits CYP2C19 and CYP3A4 which are the cytochromes that metabolize methadone thus warfarin increases methadone blood concentration [26]. Methadone interacts with psychotropic drugs. The co-administration of buprenorphine or tramadol with methadone causes withdrawal symptoms, haloperidol or droperidol co-administered with methadone prolongs QTc, and the co-administration of chlorpromazine or thioridazine with methadone causes respiratory-depression [27]. Ciprofloxacin inhibits different cytochromes P-450 thus ciprofloxacin increases the blood concentration of methadone [28], ciprofloxacin inhibits CYP1A2 and CYP3A4 which are the cytochromes that metabolize methadone thus ciprofloxacin increases the blood concentration of methadone [29], and methadone co-administered with fluconazole causes respiratory-depression [30]. These results indicate that methadone interacts with drugs. The treatment of infants and children with methadone has been reviewed. Infants with neonatal abstinence syndrome were treated with either morphine or methadone and both drugs develop similar short-term and long-term neurobehavioral outcomes [31], infants with neonatal abstinence syndrome were treated with methadone or with morphine and infants treated with methadone have a shorter hospital stay and a shorter stay in neonatal intensive care unit than infants treated with morphine [32], infants with neonatal abstinence syndrome treated with morphine have higher scores in cognitive and gross motor domains than infants treated with methadone [33], infants were exposed in-utero to low-dose of methadone (< 100 mg daily), or to high-dose of methadone (≥ 100 mg daily), or to buprenorphine. Infants exposed to high-dose of methadone have reduced head circumference and have a negative impact on motor skill development during early infancy than infants exposed to low-dose of methadone or to buprenorphine [34], the maternal exposition to methadone causes a low incidence of neonatal abstinence syndrome [35], 10 children received methadone for weaning from continuous opiate infusion for ≥ 7 days and 10 children underwent weaning by standardized protocol. The use of a standard weaning protocol decreases the time for weaning without increasing the frequency-rate of withdrawal symptoms [36]. Trials with methadone have been reviewed in infants and children. Infants born to mothers treated with methadone are at risk of neurodevelopment problems [37], prenatal exposure to methadone is associated with microstructural alteration in major white matter tracts which is present at birth [38], methadone treats neuropathic pain in children with cancer [39], methadone was administered to cancer children to treat pain and methadone improves neuropathic pain through a target effect of allodynia and its pressure/squeezing component [40], methadone treats pain in cancer children but the incidence of serious toxicity suggests that the treatment with methadone should be monitored by pain management experts [41], children born to mothers treated with methadone during pregnancy have difficulties in controlling the attention and learning [42], treatment of children with methadone should be initiated with the lowest dose possible to avoid over-sedation [43], infants with neonatal abstinence syndrome were treated with methadone or with morphine and infants treated with methadone have similar length of hospital stay as infants treated with morphine [44]. The effects caused by methadone in human brain and the concentration on methadone in human brain have been reviewed. Exposition to 10 µM methadone increase I_{Na} and I_{KD} and reduces the shift of Na^+ channels gating properties [45], methadone decreases the frequency and amplitude of excitatory postsynaptic currents in neurons thus is weakening synaptic transmission in neural networks and attenuates the voltage-dependent Na^+ current in human brain cortical organoids. Thus, methadone interrupts the neural growth and function in human brain [46], methadone maintenance treatment impairs human brain function and structure despite its clinical effectiveness [47], the medial prefrontal cortex and the extended limbic system in methadone maintenance patients with heroin history dependence remains responsive to salient drug cues which suggests a continued vulnerability to relapse [48]. The concentration of R-methadone and S-methadone was measured in human brain [49]. The concentration of R-methadone ranges from 0.03 to 13 mg/kg and that of S-methadone ranges from 0.6 to 6.8 mg/kg. The median unbound fraction of R-methadone and S-methadone in human brain is 3.9% and 3.7%, respectively. These results indicate that the concentration of R-methadone and S-methadone varies in human brain and this variability causes variable effect of methadone. The transfer of methadone across the human placenta has been studied using the perfusion of the preterm and term placenta [50]. The transfer-rate of methadone across the preterm and term placenta is 19±5.8% and 31±9.7%, respectively (P-value < 0.01) thus the transfer-rate of methadone is higher in the term than in preterm placenta but methadone is poorly transferred across the human placenta. This finding is consistent with the work performed by Sharpe et al. [35] who stated that infants born to mothers who received methadone during pregnancy have low incidence of neonatal abstinence syndrome. The migration of methadone into the breast-milk has been investigated in 5 studies [51-55] and methadone migrates into the milk in

significant amounts. The migration of R-methadone and S-methadone into the immature milk (N = 8) and mature milk (N = 2) has been studied [56]. In immature milk, the mean milk to maternal plasma ratio of the area under the concentration-time curve is 0.68 and 0.38 for R-methadone and for S-methadone, respectively, and in mature milk this ratio is 0.39 to 0.54 for R-methadone and 0.24 to 0.30 for S-methadone thus R-methadone migrates into the breast-milk in higher amounts than S-methadone. Infants breast-feed from mothers maintained on methadone may develop dependence.

In conclusion, methadone is a long-acting μ opioid receptor agonist with pharmacological properties qualitatively similar to those of morphine. Methadone is a racemate, consists in R-methadone and S-methadone, and the analgesic activity is due to R-methadone. Methadone may be administered by sublingual application, orally, intramuscularly or intravenously. In infants, the initial oral dose of methadone is 100 μg/kg 4 times-daily. In children, moderate to severe pain is treated with methadone administered by sublingual application, orally, intramuscularly or intravenously and the dose of methadone varies according to the child body-weight. Methadone has been found efficacy and safe in infants and children but it may induce toxicity. Methadone is extensively metabolized in human liver by different cytochromes P-450. The pharmacokinetics of methadone have been studied in infants following oral dosing and methadone is rapidly absorbed. The pharmacokinetics of R-methadone and S-methadone have been studied in children in adult patients and in adolescents and the pharmacokinetic parameters of R-methadone are different from those of S-methadone indicating that the disposition of methadone is stereoselective. The pharmacokinetics of R-methadone and S-methadone have been studied in adolescents using 3 doses of methadone and the peak plasma concentration and the area under the concentration-time curve of R-methadone and S-methadone increase with the dose whereas the elimination half-life and the distribution volume of methadone enantiomers are independent by the dose. Methadone interacts with drugs and the treatment and trials with methadone have been reviewed in infants and children. Methadone causes different effects in the human brain, is poorly transferred across the human placenta, migrates into the breast-milk in significant amounts, and R-methadone migrates into the breast-milk in higher concentrations than S-methadone. The aim of this study is to review the clinical pharmacology of methadone in infants and children.

Conflict of interests

The authors declare no conflicts of financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employments, gifts, and honoraria.

This article is a review and drugs have not been administered to men or animals.

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