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Case report: quantification of methadone-induced respiratory depression using toxicokinetic/toxicodynamic relationshipsBruno Mégarbane^{1,2}, Xavier Declèves², Vanessa Bloch^{1,2}, Christophe Bardin³, François Chast³ and Frédéric J Baud^{1,2}¹INSERM U705, CNRS, UMR 7157; Université Paris 7; Assistance Publique – Hôpitaux de Paris, Hôpital Lariboisière, Réanimation Médicale et Toxicologique, 2 Rue Ambroise Paré, 75010, Paris, France²INSERM U705, CNRS, UMR 7157; Université Paris 7; Assistance Publique – Hôpitaux de Paris, Hôpital Fernand Widal, 200 Rue du Faubourg Saint Denis, 75018, Paris, France³Assistance Publique – Hôpitaux de Paris, Hôpital Hôtel-Dieu, Laboratoire de Toxicologie, 1 Place Notre-Dame 75004, Paris, FranceCorresponding author: Bruno Mégarbane, bruno-megarbane@wanadoo.fr

Received: 21 Sep 2006 Revisions requested: 26 Oct 2006 Revisions received: 28 Dec 2006 Accepted: 15 Jan 2007 Published: 15 Jan 2007

Critical Care 2007, **11**:R5 (doi:10.1186/cc5150)This article is online at: <http://ccforum.com/content/11/1/R5>© 2007 Mégarbane *et al.*; licensee BioMed Central Ltd.This is an open access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/2.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.**Abstract**

Introduction Methadone, the most widely delivered maintenance therapy for heroin addicts, may be responsible for life-threatening poisonings with respiratory depression. The toxicokinetics and the toxicokinetic/toxicodynamic (TK/TD) relationships of methadone enantiomers have been poorly investigated in acute poisonings. The aim of this study was to describe the relationships between methadone-related respiratory effects and their corresponding concentrations.

Methods We report a 44-year-old methadone-maintained patient who ingested a 240-mg dose of methadone. He was found comatose with pinpoint pupils and respiratory depression. He was successfully treated with intravenous naloxone infusion over the course of 31 hours at a rate adapted to maintain normal consciousness and respiratory rate. We performed a TK/TD analysis of the naloxone infusion rate needed to maintain his respiratory rate at more than 12 breaths per minute (as toxicodynamics parameter) versus plasma *R,S*- and *R*-methadone concentrations (as toxicokinetics parameter), determined using an enantioselective high-performance liquid chromatography assay.

Results Initial plasma *R,S*-methadone concentration was 1,204 ng/ml. Decrease in plasma *R*- and *S*-methadone concentrations was linear and demonstrated a first-order pharmacokinetics (maximal observed concentrations 566 and 637 ng/ml, half-lives 16.1 and 13.2 hours, respectively). TK/TD correlation between naloxone infusion rate and *R,S*- and *R*-methadone concentrations fitted well a sigmoidal E_{max} model (concentration associated with a half-maximum effect [EC_{50}] 334 and 173 ng/ml, Hill coefficient 10.0 and 7.8, respectively). In our chronically treated patient, EC_{50} values were in the range of previously reported values regarding methadone analgesic effects, suggesting that plasma methadone concentrations to prevent withdrawal are lower than those associated with methadone analgesic effects.

Conclusion After the ingestion of a toxic dose of a racemic mixture, plasma *R*- and *S*-enantiomer concentrations decreased in parallel. Despite large inter-individual variability in methadone toxicokinetics and toxicodynamics, TK/TD relationships would be helpful for providing quantitative data regarding the respiratory response to methadone in poisonings. However, further confirmatory TK/TD data are needed.

Introduction

Methadone has been the most widely delivered maintenance therapy for heroin users for almost 50 years. Prescribed with doses adequate to the actual needs of individual addicts, methadone efficiently reduces heroin use, overdose mortality, as well as criminal activities [1-3]. The major pharmacological

activity of methadone, a long-lasting opioid agonist, is related to its binding to the mu-opioid receptors. The available marketed methadone (6-dimethylamino-4,4-diphenyl-3-heptanone) is a racemic mixture of two stereoisomeric forms, the *R*- and *S*-enantiomers [4]. *R*-methadone is the main pharmacologically active isomer, believed to account for most if not all

γ = Hill coefficient; AUC_{inf} = area under the curve from 0 to infinity; Cl/F = total plasma clearance; CYP = cytochrome P450; EC_{50} = concentration associated with a half-maximum effect; EDDP = 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine; E_{max} = maximum effect; ICU = intensive care unit; TK/TD = toxicokinetic/toxicodynamic; V_d/F = distribution volume.

of the therapeutic effects of methadone maintenance treatment. However, although lacking strong opioid effects, *S*-methadone may play a significant role in the adverse responses to *R,S*-methadone [5-7].

Opioid toxicity produces a classic syndrome characterised by a depressed level of consciousness, bradypnea, and miosis. Methadone overdose results in life-threatening respiratory depression, which may be reversed using naloxone, a mu-receptor competitive antagonist [8]. Regardless of whether initial doses of naloxone restore adequate respiration and further therapy is needed, repeated boluses or continuous infusion of naloxone can be used [9,10]. In the setting of close monitoring of neurological and respiratory parameters, naloxone may obviate the need for tracheal intubation and mechanical ventilation.

To our knowledge, toxicokinetic/toxicodynamic (TK/TD) relationships in regard to respiratory depression have not been studied in methadone poisonings. Moreover, the relative kinetics of each methadone enantiomer after the ingestion of a toxic dose remains unclear. Here, we report a case of methadone poisoning with severe respiratory depression treated using naloxone. We performed a toxicokinetics study of both *S*- and *R*-methadone enantiomers and a TK/TD study to understand the relationships between the respiratory effects and the concentrations of the active *R*-enantiomer.

Materials and methods

A 44-year-old man was found unconscious outdoors and admitted to the emergency department of a neighbouring hospital. On presentation, he was comatose (Glasgow Coma Score 3) with a blood pressure of 118/71 mm Hg, a heart rate of 117 beats per minute, a respiratory rate of 10 breaths per minute, and an SpO₂ (percutaneous oxygen saturation) of 75%. His temperature was 36.5°C. Neurological examination showed hypotonic and hyporeflexic coma with pinpoint pupils. Pulmonary auscultation was normal. Arterial blood gas analysis while breathing on room air showed a pH of 7.30, a PaO₂ (arterial oxygen pressure) of 56 mm Hg, PaCO₂ (arterial carbon dioxide pressure) of 48 mm Hg, and a serum bicarbonate concentration of 26 mmol/l. Other routine laboratory tests were unremarkable. Plasma lactate concentration was 2.1 mmol/l. Significant improvement in consciousness level (Glasgow Coma Score 15) without mental confusion was obtained after an intravenous bolus injection of 0.3 mg of naloxone followed by a continuous 0.3-mg/hour infusion. The patient rapidly awoke and declared that he had intentionally ingested 240 mg (3.14 mg/kg) of methadone and 2 mg of flunitrazepam to relax. The delay between ingestion and admission to the hospital was estimated to be 2.7 hours. He had a history of heroin addiction with a maintenance treatment of 70 mg/day of methadone (confirmed by a prescription from his maintenance program centre) and occasional use of 2 mg of flunitrazepam. He suffered from depression, and a recently diagnosed hyperthy-

roidism was treated with neomercazole. He was transferred for monitoring to our intensive care unit (ICU). The attending physicians managed the patient according to the standard treatment guidelines currently used in our department. Naloxone infusion rate was progressively adapted, aiming to keep the patient calm with a normal mental status (Glasgow Coma Score 15) and a respiratory rate of more than 12 breaths per minute. Reduction in naloxone dose was systematically attempted, and when evidence of toxicity occurred, a return to the previous dose was made. Routine toxicological screening of blood and urine, including benzodiazepines, opiates, buprenorphine, cocaine, and tetrahydrocannabinol, was negative, except for methadone. This case outcome was favourable with an uneventful 48-hour ICU stay, except for an aspiration pneumonia treated with amoxicillin-clavulanic acid for six days. The duration of naloxone intravenous infusion was 31 hours with a cumulative dose of 9.1 mg.

R-methadone accounts for most, if not all, of the effect of methadone [5-7]. To this extent, we considered that TK/TD relationships in regard to methadone respiratory effects for *S*-enantiomer would probably just mirror those of *R*-enantiomer. Therefore, we performed a TK/TD analysis of the naloxone infusion rate needed to maintain the respiratory rate of more than 12 breaths per minute (as toxicodynamics parameter) versus plasma *R,S*- and *R*-methadone concentrations (as toxicokinetics parameter). Upon admission to the ICU, verbal informed consent was obtained from the completely awakened and non-confused patient. Venous blood samples were obtained at 2.7, 10.5, 14.5, 18.5, 20.5, 22.5, 26.5, and 30.5 hours after methadone ingestion. Plasma was separated and frozen until methadone concentration measurement. The rate of naloxone infusion was prospectively collected at each blood sampling time, and the nurses in charge were blinded to the results of the toxicological analyses. Both *R*- and *S*-methadone enantiomer concentrations were measured using a validated chiral high-performance liquid chromatography assay as previously described [11]. The plasma kinetics of each enantiomer were analysed using a noncompartmental method. Toxicokinetics parameters and TK/TD relationships were determined using a computerised curve-fitting program (WinNonlin Pro 3.0; Pharsight Corporation, Mountain View, CA, USA). The area under the curve from 0 to infinity (AUC_{inf}) was calculated using the model-independent trapezoidal method.

Results

The maximal observed plasma concentration of *R,S*-methadone was 1,204 ng/ml at 2.7 hours (Table 1). Decrease in plasma *R,S*-, *R*-, and *S*-methadone concentrations was of first-order pharmacokinetics (Figure 1). During the course of overdose after naloxone infusion, the respiratory rate was maintained at more than 12 breaths per minute (therapeutic objective). The Glasgow Coma Score was constantly at 15, and the haemodynamic parameters were within the normal range. TK/TD correlations between naloxone infusion rate (E)

Table 1**Toxicokinetic parameters of the racemic R,S-methadone and both R- and S-methadone forms in a severely poisoned patient**

	$T_{1/2}$	Maximal observed concentration	AUC_{inf}	V_z/F	Cl/F
	(h)	(ng/ml)	(ng-h/ml)	(l)	(l/h)
R-methadone	16.1	566	13,241	211	9.1
S-methadone	13.2	637	13,385	170	9.0
R,S-methadone	14.5	1,204	26,508	189	9.1

AUC_{inf} , area under the curve from 0 to infinity; Cl/F , total plasma clearance; $T_{1/2}$, half-life; V_z/F , distribution volume.

and R,S- and R-methadone concentrations (C) fitted well the sigmoidal E_{max} model, $E = E_{max} C^\gamma / [EC_{50}^\gamma + C^\gamma] + E_0$, where E_0 is the baseline value of the measured rate of naloxone infusion, E_{max} represents the maximum possible infusion rate, EC_{50} represents the concentration associated with the half-maximum infusion rate, and γ (or Hill coefficient) determines the steepness (slope) of the concentration-versus-response curve (Figure 2). Values of EC_{50} and γ are given in Table .

Discussion

Methadone pharmacokinetics and pharmacodynamics are characterised by a high inter-individual variability, even in toxic conditions [7,12,13]. There is up to 17-fold inter-individual variation of blood methadone concentrations for a given dosage [7]. Because methadone is administered as a racemic mixture, our objective was to study the relationships between the respiratory effects and the racemic as well as the active R-enantiomer concentrations.

R-methadone is believed to account for most, if not all, of the therapeutic effects of methadone maintenance treatment [5-7,14]. S-methadone may be a clinically important determinant of adverse responses to racemic methadone and may significantly contribute to the adverse but not the therapeutic effects of racemic methadone during maintenance treatment for opioid dependence. In healthy volunteers, 7.5 mg of oral S-methadone did not significantly differ from the placebo response in respiratory and pupillary effects, whereas 7.5 mg of R-methadone and 15 mg of R,S-methadone induced dramatic and sustained respiratory depression and miosis [15]. In the same volunteers, S-methadone doses between 50 and 100 mg slightly depressed ventilation. In dependent patients, S-methadone administered at dosages of 650 to 1,000 mg/day induced subjective morphine-like effects, partially suppressed abstinence from morphine, and created a mild degree of physical dependence [16].

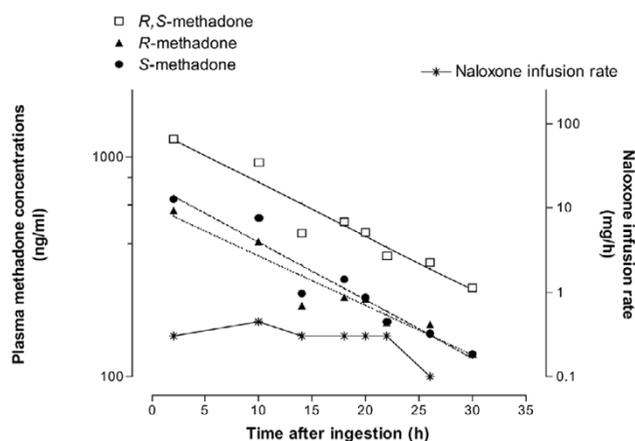
At therapeutic doses, plasma concentrations of R,S-methadone decrease in a bi-exponential manner, with an elimination half-life estimated at 22 ± 7 hours (range 14 to 40) in opioid users after 26 days of methadone [7]. Trough plasma concentrations of 400 ng/ml for R,S-methadone or 250 ng/ml for R-methadone are usual target values when measurement of methadone concentration is performed to investigate a non-

complete clinical response [17]. In our overdosed patient, the maximal observed R,S-methadone concentration was approximately three times higher than the reported peak levels in patients treated with a daily therapeutic dosage of more than 80 mg [18].

The almost mono-exponential first-order decline in plasma R- and S-methadone concentrations suggests the absence of any saturation of the distribution and the elimination processes, even at supra-therapeutic concentrations. Methadone toxicokinetics was in close agreement with pharmacokinetics, with an observed half-life in the lower range of the reported pharmacokinetic half-lives [7]. Methadone is metabolised mainly into EDDP (2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine) through cytochrome P450 (CYP) 3A4 and 2B6 pathways, for which genetic polymorphisms and high inter-individual variability of activity were reported, resulting in large inter-individual variability of methadone half-lives. *In vitro* metabolism studies using human liver microsomes showed apparent affinity constants (K_m) regarding CYP-mediated EDDP formation far above the maximal observed methadone concentration in this patient [19], suggesting that saturation of methadone metabolism did not occur in our patient. Moreover, no study of methadone dose-linearity was performed at such elevated concentrations. Thus, we may hypothesise that similar data (first-order kinetics) would have been observed with a larger data set of intoxicated patients presenting similar plasma methadone concentrations. Both enantiomer half-lives were rather short in comparison to previously reported values in eight patients undergoing methadone maintenance treatment (R-methadone 23 to 50 hours and S-methadone 16 to 37 hours) [20]. Thus, although no definitive explanation could be given, we may suggest that our patient was an extensive CYP 3A4 metaboliser, because no CYP 3A-inducing drugs were identified in his treatment. Moreover, as previously reported [7], the half-life of R-methadone was longer than that of S-methadone.

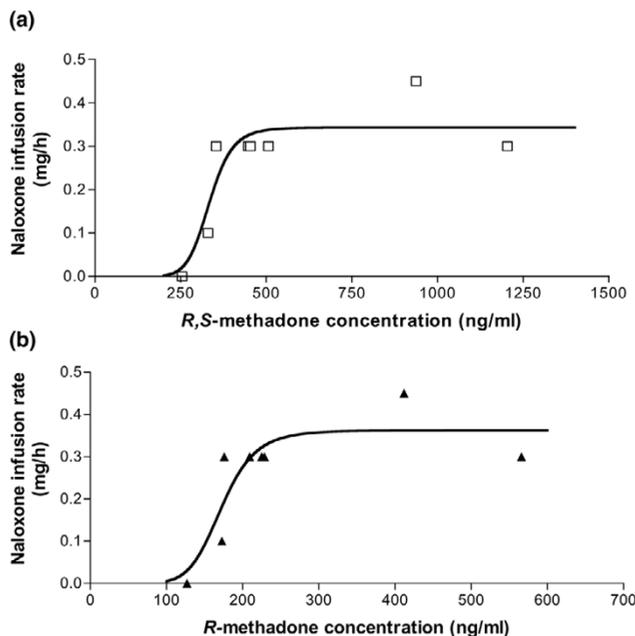
TK/TD relationships allow the descriptive and quantitative characterisation of the time course of the *in vivo* drug effect in relation to its corresponding drug concentrations within an individual [21]. There are several studies dealing with pharmacokinetic/pharmacodynamic relationships for opioids commonly used in anaesthesia or for the treatment of pain [22,23].

Figure 1



Plasma *R,S*-, *R*-, and *S*-methadone concentrations (left y-axis) and naloxone infusion rate (right y-axis) versus time after ingestion of a 3.14-mg/kg single oral dose of the racemic *R,S*-methadone.

However, only a limited number of studies addressed the pharmacokinetic/pharmacodynamic relationships of methadone in healthy volunteers, patients treated for chronic pain, or maintenance patients [5,23-25]. To our knowledge, there is no case of human methadone poisoning with a TK/TD analysis of respiratory effects. In our patient, we found sigmoidal TK/TD relationships. The maximal naloxone infusion rate was associated with an *R*, *S*-methadone concentration ranging from 400 to 1,200 ng/ml, suggesting a saturation of the mu-opioid receptor **Figure 2**



Toxicokinetic/toxicodynamic relationships between the naloxone infusion rate and the plasma concentrations of (a) the racemic *R,S*-methadone and (b) the *R*-methadone enantiomer.

tors at these concentrations. Similarly, a study in healthy volunteers showed a sigmoidal response with minimal hysteresis between the iris/pupil ratio and its corresponding plasma *R*-methadone concentration (EC_{50} 2.3 ng/ml and γ 9.0) [5]. In patients with chronic pain, pain relief was related to the *R*, *S*-methadone concentrations by a sigmoid E_{max} model defined with an EC_{50} of 290 ng/ml and a steepness of 2.03 [25]. In our case, the high value of γ (10.0) clearly indicated that a small decrease in plasma concentrations near the EC_{50} was associated with a dramatic decrease in the rate of naloxone infusion. *R*-methadone exhibited a lower γ than *R,S*-methadone, suggesting that *S*-methadone enantiomer could demonstrate a positive allosteric cooperation with *R*-methadone activity. However, in the present case, the confidence intervals regarding the γ values were largely overlapping, precluding any definitive conclusion. *R,S*-methadone EC_{50} of 334 ng/ml was associated with significant respiratory effects in our patient. This concentration was less elevated than the target concentration of 400 ng/ml in patients treated with elevated doses, suggesting that our patient was probably equilibrated with lower methadone concentrations. However, a relationship if any between EC_{50} and a therapeutic drug monitoring tool, as the trough plasma *R,S*-methadone concentration need to be established.

Moreover, although we may hypothesise that the EC_{50} values regarding methadone respiratory effects in our patient are higher than values that could have been observed in opiate-naïve patients due to a pharmacodynamic tolerance, these EC_{50} values were in the same range as those obtained for pain relief in chronically treated patients [25]. Increase of EC_{50} could also be related in our patient to a pharmacogenetic variant of mu-receptor, as previously reported [26]. Thus, our data clearly support the tight safety index of methadone, previously illustrated by the occurrence of significant respiratory effects after intake at pharmacological dosages [27]. Consistently, during the first months of methadone maintenance, there is a continual alveolar hypoventilation due to the depression of both central and peripheral chemoreception [28]. Interestingly, alteration in ventilatory response to hypoxia persists after a prolonged treatment, although alveolar hypoventilation is abolished after the fully acquired tolerance within two months of the carbon dioxide-sensitive chemoreflex. However, this adaptation of ventilatory response to chronic use of methadone does not prevent the occurrence of alveolar hypoventilation in the case of acute methadone overdose.

Our toxicokinetics study has significant limitations. First, AUC_{inf} could be slightly underestimated due to the absence of any sample before 2.7 hours post-ingestion and between 2.7 and 10.5 hours, as the mean maximal observed concentration has been previously reported between 2.5 and 4.4 hours post-ingestion [29]. The bioavailability of methadone is also unknown in such an overdose situation. In addition, the AUC versus time was calculated between 0 and infinity as if our

Table 2**Parameters of the TK/TD relationships model regarding the naloxone infusion rate versus R,S- and R-methadone concentrations**

	EC_{50} (ng/ml)	γ
R-methadone	173	7.8
R,S-methadone	334	10.0

γ : Hill coefficient; EC_{50} , concentration associated with a half-maximum effect; E_{max} , maximum effect; TK/TD, toxicokinetic/toxicodynamic.

patient ingested a single dose of methadone, regardless of a possible long-term maintenance therapy, which was not certain in the absence of previous therapeutic drug monitoring. Thus, the apparent volume of distribution (V_z/F) and the total plasma clearance (Cl_t/F) values calculated using AUC_{inf} should be interpreted with caution. However, Cl_t/F and V_z/F values for both methadone enantiomers were comparable to those reported in patients undergoing methadone maintenance at therapeutic dosage [20], suggesting the absence of saturation of methadone pharmacokinetics in this case. The V_z/F values of R- and S-methadone (211 versus 170 l, respectively) were lower than those reported in treated patients (470 versus 318 l, respectively [20]) but similar to those reported in healthy volunteers (106 versus 262 l, respectively [7]). We have no definitive explanations for these differences, due to the imprecision of the AUC_{inf} calculation. However, methadone V_z/F is influenced by the acid α -1-glycoprotein levels with regard to its transfer to and from the central to the peripheral compartments and by extension to the site of methadone pharmacological action [7]. The Cl_t/F was similar for both methadone R- and S-enantiomers (9.0 versus 9.1 l/hour, respectively) and close to values reported in treated patients (10.7 versus 9.7 l/hour, respectively [20]). In contrast, in healthy adults, the pharmacologically active R-enantiomer has a lower Cl_t/F when compared with S-methadone (4.0 versus 20.4 l/hour, respectively) [7].

We considered the naloxone infusion rate as a surrogate marker of methadone-induced respiratory depression. However, because the elimination rate of naloxone varies with a half-life of 45 to 90 minutes, a continuous infusion runs the risk of naloxone accumulation, complicating the pharmacodynamic interactions. Otherwise, such a toxicodynamics surrogate marker requires a close concordance between real effects on respiration and the titrated infusion rate of naloxone. Moreover, serum and urine specimens were not tested for flunitrazepam in our patient. Consistently, one unusual feature in this case is the rapidity with which the patient appears to have suffered unconsciousness. Given that the peak effects of methadone usually occur approximately four to six hours after ingestion [7] and that flunitrazepam is a short-acting agent with respect to methadone, we think the initial presentation may have been influenced by the co-ingestion of flunitrazepam. However, several studies suggest that methadone peak plasma concentrations and effects may occur much earlier [30,31], supporting

(as in our patient) methadone-related steep concentration-effect relationships. Otherwise, we cannot rule out potential interactions between flunitrazepam and methadone that contributed to the respiratory depression. Both molecules are metabolised by the CYP 3A4, which may lead to clinically significant drug-drug interactions. However, the relatively short half-life of R, S-methadone does not support any inhibition of CYP 3A4-mediated methadone metabolism by flunitrazepam.

Sources of inter-individual variability of the response to methadone are numerous, including demographic and physiological characteristics of the methadone-maintained subjects [23,32]. Thus, analysis of the TK/TD relationships in one patient precludes any definitive conclusion regarding the various possible situations of exposures to methadone in other patients. In addition, because plasma is not the effect site of methadone and time is needed before the drug distributes into the central nervous system, another significant concern in our study is the absence of characterisation of the plasma-versus-biophase distribution. For some opioids, there may be a delay between the time course of the plasma concentrations and the time course of the effects [5,22,25]. Moreover, the rate of plasma protein binding was not determined in this patient. However, because methadone is a highly lipophilic drug, the rate of cerebral distribution of the pharmacologically active molecules should not be a limiting step in this study of TK/TD relationships at toxic concentrations. Here, we described TK/TD relationships during the methadone elimination phase.

Conclusion

Plasma toxicokinetics of R- and S-methadone enantiomers were parallel. The study of TK/TD relationships appears to be helpful for quantifying the respiratory response to methadone during poisonings. Despite a possible pharmacodynamic tolerance in our patient, the EC_{50} values regarding the methadone respiratory effects were in the same range as those previously reported for the analgesic effects in chronically treated patients, thus suggesting a limited safety index for methadone. A better understanding of the toxicokinetics and toxicodynamics of methadone and its enantiomers will be possible as more data accumulate in this regard.

Competing interests

The authors declare that they have no competing interests.

Key messages

- Methadone may be responsible for life-threatening poisonings with respiratory depression.
- The pharmacokinetics of plasma R- and S-methadone enantiomers is of first order, with elimination half-lives of 16.1 and 13.2 hours, respectively.
- The TK/TD correlation between the naloxone infusion rate needed to maintain a respiratory rate of more than 12 breaths per minute and R,S- and R-methadone concentrations fits well a sigmoidal E_{max} model (EC_{50} 334 and 173 ng/ml, γ 10.0 and 7.8, respectively).
- Despite large inter-individual variability, TK/TD relationships would be helpful for providing quantitative data on the respiratory response to methadone in poisonings.
- In the reported chronically treated patient, EC_{50} values are in the range of the previously described values for methadone analgesic effects.

Authors' contributions

BM and FJB were in charge of the patient, coordinated the data analysis, and drafted the manuscript. XD and VB performed the TK analysis and the study of TK/TD relationships. CB and FC contributed to the measurements of methadone concentrations. All authors read and approved the final manuscript.

Acknowledgements

The authors would like to acknowledge Dr. Rebeca Gracia, PharmD, DABAT, from the North Texas Poison Center, Dallas, TX, USA, for her helpful review of this manuscript.

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