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Interindividual Variability of the Clinical Pharmacokinetics of Methadone

Implications for the Treatment of Opioid Dependence

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Abstract

Methadone is widely used for the treatment of opioid dependence. Although in most countries the drug is administered as a racemic mixture of (*R*)- and (*S*)-methadone, (*R*)-methadone accounts for most, if not all, of the opioid effects. Methadone can be detected in the blood 15–45 minutes after oral administration, with peak plasma concentration at 2.5–4 hours. Methadone has a mean bioavailability of around 75% (range 36–100%). Methadone is highly bound to plasma proteins, in particular to α_1-acid glycoprotein. Its mean free fraction is around

13%, with a 4-fold interindividual variation. Its volume of distribution is about 4 L/kg (range 2–13 L/kg). The elimination of methadone is mediated by biotransformation, followed by renal and faecal excretion. Total body clearance is about 0.095 L/min, with wide interindividual variation (range 0.02–2 L/min). Plasma concentrations of methadone decrease in a biexponential manner, with a mean value of around 22 hours (range 5–130 hours) for elimination half-life. For the active (*R*)-enantiomer, mean values of around 40 hours have been determined.

Cytochrome P450 (CYP) 3A4 and to a lesser extent 2D6 are probably the main isoforms involved in methadone metabolism. Rifampicin (rifampin), phenobarbital, phenytoin, carbamazepine, nevirapine, and efavirenz decrease methadone blood concentrations, probably by induction of CYP3A4 activity, which can result in severe withdrawal symptoms. Inhibitors of CYP3A4, such as fluconazole, and of CYP2D6, such as paroxetine, increase methadone blood concentrations. There is an up to 17-fold interindividual variation of methadone blood concentration for a given dosage, and interindividual variability of CYP enzymes accounts for a large part of this variation.

Since methadone probably also displays large interindividual variability in its pharmacodynamics, methadone treatment must be individually adapted to each patient. Because of the high morbidity and mortality associated with opioid dependence, it is of major importance that methadone is used at an effective dosage in maintenance treatment: at least 60 mg/day, but typically 80–100 mg/day. Recent studies also show that a subset of patients might benefit from methadone dosages larger than 100 mg/day, many of them because of high clearance.

In clinical management, medical evaluation of objective signs and subjective symptoms is sufficient for dosage titration in most patients. However, therapeutic drug monitoring can be useful in particular situations. In the case of non-response trough plasma concentrations of 400 μg/L for (*R*,*S*)-methadone or 250 μg/L for (*R*)-methadone might be used as target values.

Methadone is a synthetic analgesic drug whose mechanism of action, like that of morphine, is mediated by the activation of the opioid receptors, principally of the μ type. It is used in the treatment of pain and as a maintenance treatment for opioid-dependent individuals. Numerous studies, several with double-blind placebo-controlled design, clearly demonstrate that methadone is an effective treatment for opioid dependence, reducing illicit drug use, risk of HIV infection, mortality, crime and unemployment; it improves social stabilisation, retention rate in treatment and patients' contribution to society (for a review, see Bertschy[1], Farrell et al.,[2] and O'Connor and Fiellin[3]). Considering only its effects on the reduction of the risk of HIV infection, methadone has been shown to be a cost-effective treatment.[4] However, since Dole and Nyswander first used methadone in maintenance treatment,[5] this practice has been the topic of much political and professional controversy. Dole's blockade theory of substitution therapy, emphasising the central importance of opioid receptor occupation,[6] is also distinct from another approach, which is to prescribe the lowest dosage that will prevent the onset of withdrawal symptoms.

One of the major sources of disagreement among prescribers is the optimal methadone dosage for methadone maintenance treatment (MMT). In their early work, Dole and Nyswander recommended methadone maintenance dosages of 80–120 mg/day,[7] and several recent studies have consistently shown that an adequate methadone dosage, i.e. at least 60 mg/day but typically 80–100

mg/day, is a major factor in the success of MMT.[8-14] However, many MMT programmes prescribe low dosages of methadone, for political, psychological, philosophical or moral reasons.[15,16] Another point of disagreement among prescribers is the use of dosages over 100 mg/day. Although Dole observed long ago that 100 mg/day of methadone may not be enough to suppress withdrawal symptoms in some patients,[6] in practice this dosage is considered by many prescribers as a limit not to be exceeded. However, recent published case series,[17-19] as well as a an open study on a large number of patients,[20] strongly suggest that methadone dosages higher than, and sometimes greatly in excess of, 100 mg/day may be beneficial to selected patients.

Reviews have been published on the pharmacology, pharmacokinetics and pharmacodynamics of methadone.[21-24] In this paper, we shall outline the clinical pharmacokinetics of methadone and particularly the marked interindividual variations that are found in parameters such as bioavailability and total and metabolic clearances. We shall review the studies showing the involvement of cytochrome P450 (CYP) enzymes in methadone metabolism. Their determinant role in methadone pharmacokinetics also enables us to explain, and possibly avoid, the majority of metabolic interactions involving this drug. The implications of the variability of methadone pharmacokinetics on its use in opioid-dependent patients, in particular with regard to the choice of maintenance dosages, will be discussed, along with the various uses of therapeutic drug monitoring (TDM) of methadone.

1. Chirality and Pharmacodynamics

Methadone has an asymmetrical carbon atom in its structure, which means that it exists in two enantiomeric forms, having the same chemical composition but different spatial arrangements, with one enantiomer being the mirror image of the other. Methadone is marketed in almost all countries as a racemic mixture, i.e. a 50 : 50 mixture of two enantiomers called (*R*)- or *levo*- or *l*-methadone, and (*S*)- or *dextro*- or *d*-methadone. In Germany, until the mid-1990s, only (*R*)-methadone was used, but as (*R*)-methadone is more expensive than (*R*,*S*)-methadone, the racemic form is increasingly prescribed nowadays. The stereospecificity of most opioids for μ receptors is well known, although for methadone the difference between the two isomers is not dramatic, probably owing to a greater conformational mobility of the molecule.[25] Nevertheless, *in vitro* binding experiments have shown that the necessary concentration of (*R*)-methadone to inhibit 50% of [^{3}H]naloxone binding to whole rat brain homogenates is 10 times lower than that of (*S*)-methadone.[25] A 10-fold difference of affinity has also been found between the two enantiomers for the bovine μ_1 receptor, which mediates supraspinal analgesia (50% inhibitory concentration [IC_{50}] of 3.0 and 26.4 nmol/L for (*R*)- and (*S*)-methadone, respectively) and μ_2 receptor, which mediates spinal analgesia [IC_{50} of 6.9 and 88 nmol/L for (*R*)- and (*S*)-methadone, respectively].[26] In human analgesia, (*R*)-methadone is about 50 times as potent as the (*S*)-form.[27]

In one blind study, Dole and Nyswander replaced (*R*)-methadone by (*S*)-methadone in six patients receiving MMT. The patients, not noticing any difference in the taste or immediate effects of the daily dose, gradually began to feel withdrawal symptoms 24–36 hours later, initially attributed to 'flu'.[5,6] After 3 days, they began to suspect the medication and, at this point, they were returned to the usual racemic mixture which cleared all symptoms.[5,6] In another study, neither objective nor subjective morphine-like effects could be observed after administration of 15–90mg of (*S*)-methadone to non-tolerant former dependent subjects, and no significant amelioration of abstinence from morphine could be detected when 30–90mg of (*S*)-methadone were administered subcutaneously to dependent patients after abrupt withdrawal of morphine.[28] It was also shown in healthy male volunteers that the effects of 7.5mg of oral (*S*)-methadone did not significantly differ from the placebo response regarding respiratory and pupillary effects, whereas 7.5mg of (*R*)-methadone and 15mg of (*R*,*S*)- methadone induced

intense and sustained respiratory depression and miosis.[29] However, in the same healthy volunteers, (*S*)-methadone doses between 50 and 100mg slightly depressed ventilation.[29]

In dependent patients, (*S*)-methadone administered at high dosages (650–1000 mg/day) also induced morphine-like subjective effects, partially suppressed abstinence from morphine, and created a mild degree of physical dependence.[30] Although morphine-like effects were observed at such high dosages, patients consistently denied having experienced subjective opioid-like sensations and disliked the effects.[30] Altogether, these results and those of other studies[31-33] show that (*R*)-methadone accounts for the major part, if not all, of the opioid effects of racemic methadone.

Methadone differs from morphine by an additional noncompetitive antagonist activity at the *N*-methyl-D-aspartate (NMDA) receptor. Its inhibition curve and inhibition constant (K_i) value for the displacement of NMDA receptor ligands are very similar to those of dextromethorphan, an established NMDA receptor antagonist.[34,35] This is an interesting feature, as NMDA receptor antagonism attenuates and reverses the development of tolerance to morphine without altering its analgesic properties.[34] Both enantiomers of methadone exhibit fairly similar affinities for the NMDA receptor (K_i of 3.4 and 7.4 μmol/L for (*R*)- and (*S*)-methadone, respectively).[34] As the NMDA receptor plays an important role in pain transmission, this explains why both (*R*)-methadone and (*S*)-methadone have antinociceptive effects as a result of NMDA receptor antagonism.[36] Methadone is also a strong inhibitor of serotonin uptake (K_i of 0.014 and 0.992 μmol/L for (*R*)- and (*S*)-methadone, respectively) and norepinephrine uptake (K_i of 0.702 and 12.7 μmol/L for (*R*)- and (*S*)-methadone, respectively), which might contribute also to its antinociceptive activity.[37]

Although methadone is usually given as a racemic mixture containing the same amounts of (*R*)- and (*S*)-forms, the (*R*)-/(*S*)-methadone ratio varies significantly over the 24-hour administration interval in steady-state conditions,[38] with values significantly lower than 1 up to 4 hours post-dose, as determined in a group of 18 patients receiving MMT.[39] When measuring trough plasma concentrations at 24 hours, large interindividual differences in the (*R*)-/(*S*)-methadone ratio can be observed[33,40-43] (range 0.63–2.4 in one study,[44] see figure 1; 0.7–3.6 in another study[45]). The consequence of such a variability for TDM is discussed in section 7. On the other hand, under steady-state conditions, blood samples drawn on different days for trough plasma concentration reveal that the (*R*)-/(*S*)-methadone ratio remains stable in each patient, provided that compliance is good (see figure 1).[33,44]

2. Pharmacokinetics

Table I summarises pharmacokinetic parameter values for methadone.

2.1 Absorption and Distribution

Methadone is a liposoluble basic drug with a pKa of 9.2. It can be detected in the blood as soon as 15–45 minutes after oral administration.[48,53,60] The peak plasma concentration occurs at 2.5–4 hours after dose intake (t_{max}),[47,48,57,60] with some differences among patients (range 1–5 hours[47]), but independently of the dose.[48] This long t_{max}, as well as a slower absorption of methadone in opioid users compared with healthy subjects, may reflect the pharmacological effect of opioids in slowing gastric emptying.[50] Absorption rates of methadone from tablets and solution appear comparable.[47] A second plasma peak may be detected, probably due to enterohepatic recirculation.[64] Provided that blood samples are drawn at short time intervals, this second plasma peak occurs approximately 4 hours after administration.[48]

It is of interest to mention that patients in MMT are often intolerant to changes in methadone formulations. However, such change in tolerance reflects factors other than the pharmacological properties of the different formulations of methadone.[65] Indeed, as expected, methadone pharmacokinetics are independent of the oral formulation of the drug, as shown by a double-blind

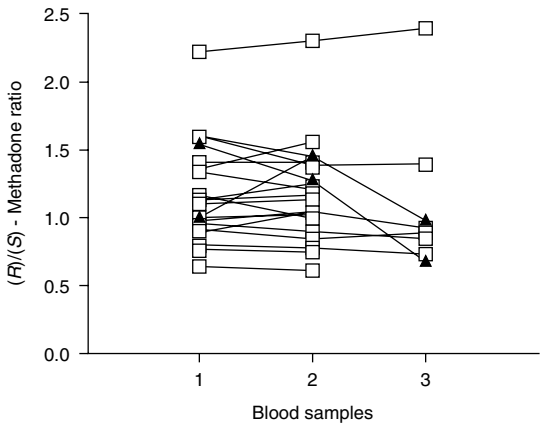

Fig. 1. (*R*)-/(*S*)-Methadone ratios as measured in one, two or three (when available) plasma samples drawn from 22 patients under maintenance treatment with racemic methadone (reproduced from Eap et al.,[44] with permission). The two patients with wide variations in (*R*)-/(*S*)-methadone ratio (possible poor compliance) are indicated by black triangles.

randomised crossover study with 18 patients in MMT.[65] Thus, neither peak plasma concentrations, trough plasma concentrations nor area under the concentration-time curve (AUC) were significantly changed by the administration of methadone in the form of tablets, liquid or diskets.[65]

The oral bioavailability of methadone tablets was found to be around 70–80% for doses between 10 and 60mg,[47,49,53,63] with marked intersubject variation (range 36–100%[47,49,53,63]). A study measured bioavailability values in six patients at the start of MMT and after 25 days of treatment; the patients were receiving 30 mg/day of methadone for 10 days and then 60 mg/day for the remaining period.[49] The results showed a slight but significant ($p < 0.05$) decrease in bioavailability between the two determinations, which might be explained by metabolic induction (mean ± SD: 95 ± 9% versus 81 ± 10% for the first and second determinations, respectively).[49] It should be mentioned that intestinal CYP3A4 significantly contributes to the metabolism of methadone, with a predicted intestinal first-pass extraction around 20%, and significantly influences the oral availability of methadone[66] Similar bioavailability values were determined for both enantiomers of methadone, indicating that the absorption is not stereoselective and consistent with a passive diffusion process across biological membranes.[53]

In vitro studies show that methadone inhibits the activity[67] and is a substrate[68] of the permeability glycoprotein (P-glycoprotein), which is coded by the human multidrug resistance *MDR1* gene, and which is an energy-dependent efflux pump able to export numerous substrates out of the cell. Although the relative contribution of P-glycoprotein in methadone absorption and disposition remains to be determined, a recent study shows that the analgesic efficacy of methadone is increased in mice lacking P-glycoprotein, suggesting that P-glycoprotein plays a role in limiting access of these drugs to the brain.[69]

Methadone is highly bound to plasma proteins,[70,71] including albumin,[72,73] lipoproteins[73] and α_1-acid glycoprotein,[73,74] the role of the latter protein being more important than the two former.[73,75,76] Mean free fractions of around 13, 10 and 14% have been measured for (*R*,*S*)-, (*S*)-, and (*R*)-methadone, respectively.[73,74,77] A lower protein binding of (*R*)-methadone compared to the (*S*)-enantiomer has been confirmed in other studies.[39,56] A 3-fold interindividual variation in these free fractions has been reported in a group of 45 healthy volunteers[74] and in eight healthy female subjects.[56] A 4-fold variation in these free fractions was also observed in studies on 13 cancer patients[77] and 12 MMT patients,[73] whereas a 6-fold variation was measured in a study measuring the percentage of free plasma (*R*,*S*)-methadone from 48 patients in MMT (mean ± SD, 10 ± 3%; range 3–19%).[78] α_1-Acid glycoprotein is an acute phase protein, and its concentration rises in pathological conditions such as cancer,[75] which explains a lower free fraction in cancer patients than in control subjects.[77] Methadone is a low hepatic extraction drug,[51] and changes in the binding of methadone to plasma proteins can alter its total hepatic clearance, but the free methadone concentration is expected to remain unchanged.[51]

Table I. Summary of pharmacokinetic parameter values for methadone. Values are for (*R*,*S*)-methadone, unless specified otherwise

No. of subjects	Mean ± SD	Range	Conditions	Remarks	Reference
Volume of distribution					
5	3.5 ± 0.4 L/kg[a]	2.9–4.0 L/kg	Single dose	Acid urine, healthy subjects	46
5	5.2 ± 0.8 L/kg[a]	4.4–6.5 L/kg	Single dose	Alkaline urine, healthy subjects	46
8	3.9 ± 1.0 L/kg[a]	2.1–5.6 L/kg	Single dose	Opioid users	47
7	2.2 ± 0.4 L/kg[b]	1.8–2.8 L/kg	Single dose	Opioid users	47
5	6.7 ± 2.9 L/kg[c]	5.2–13.4 L/kg	Steady state	Patients in MMT	48
12	3.8 ± 0.6 L/kg[a]	2.6–4.8 L/kg	Single dose	Opioid users (first day of MMT)	49
12	4.7 ± 1.0 L/kg[a]	3.3–7.2 L/kg	Steady state	Opioid users (after 25 days of MMT)	49
13	212 ± 27L[b]		Single dose	Healthy subjects	50
17	239 ± 121L[b]		Single dose	Opioid users	50
8	0.16 ± 0.08 L/kg[b]	0.02–1.3 L/kg	Single dose	Patients with chronic pain	51
8	3.6 ± 1.2 L/kg[d]	1.7–5.3 L/kg	Single dose	Patients with chronic pain	51
7	2.7 ± 1.0 L/kg[c]	1.5–4.1 L/kg	Steady state	Therapeutic failures (patients in MMT)	52
7	1.4 ± 0.3 L/kg[b]	1.0–2.0 L/kg	Steady state	Therapeutic failures (patients in MMT)	52
8	3.1 ± 1.0 L/kg[a]	2.0–4.8 L/kg	Steady state	Therapeutic failures (patients in MMT)	52
6	4.2 ± 0.8 L/kg[c]	3.1–5.3 L/kg	Steady state	Comparison group (patients in MMT)	52
6	2.7 ± 0.4 L/kg[b]	2.0–3.1 L/kg	Steady state	Comparison group (patients in MMT)	52
12	4.6 ± 1.0 L/kg[a]	3.3–7.2 L/kg	Steady state	Comparison group (patients in MMT)	52
7	6.7 ± 1.4 L/kg[c]	4.5–8.5 L/kg	Single dose	Chronic pain patients; (*R*)-methadone	53
7	3.9 ± 0.7 L/kg[c]	2.6–4.3 L/kg	Single dose	Chronic pain patients; (*S*)-methadone	53
20	2.2 ± 1.3 L/kg[b]	1.1–6.3 L/kg	Steady state	Patients in MMT	54
20	4.0 ± 1.9 L/kg[a]	1.9–8.0 L/kg	Steady state	Patients in MMT	54
19	6.1 ± 2.4 L/kg[e]	1.8–12.2 L/kg	Single dose	General surgical or orthopaedic patients	55
8	1.6 ± 1.0 L/kg[a]	0.6–3.8 L/kg	Single dose	Healthy female subjects; (*R*)-methadone	56
8	3.7 ± 3.6 L/kg[a]	0.6–11.3 L/kg	Single dose	Healthy female subjects; (*S*)-methadone	56
Elimination half-life					
8	28 ± 11h	8–47h	Single dose	Opioid users	47
5	25 ± 13h	13–47h	Steady state	Patients in MMT	57
5	27 ± 15h	18–64h	Steady state	Patients in MMT	48
12	54 ± 27h	18–97h	Single dose	Opioid users (after 2 days of methadone)	58
12	22 ± 7h	14–40h	Steady state	Opioid users (after 26 days of methadone)	58
5	20 ± 4h	16–25h	Single dose	Acid urine, healthy subjects	46
5	42 ± 9h	33–55h	Single dose	Alkaline urine, healthy subjects	46
12	35 ± 12h	19–58h	Single dose	Opioid users (first day of MMT)	49
12	34 ± 7h	19–43h	Steady state	Opioid users (after 25 days of MMT)	49
185	32h (mean)	4–130h	Steady state	Patients with pain due to cancer; intravenous injection or infusion	59
13	41 ± 21h		Single dose	Healthy subjects	50
17	207 ± 185h		Single dose	Opioid users	50
8	23 ± 12h	13–51h	Single dose	Patients with chronic pain	51
5	15 ± 4h	12–18h	Single dose	Healthy subjects	60
6	22h (mean)	13–28h	Single dose	Healthy subjects; (*R*,*S*)-methadone	29
6	24h (mean)	19–31h	Single dose	Healthy subjects; (*R*)-methadone	29
6	25h (mean)	21–28h	Single dose	Healthy subjects; (*S*)-methadone	29
8	25 ± 3h	20–28h	Steady state	Therapeutic failures (patients in MMT)	52
12	34 ± 7h	19–43h	Steady state	Comparison group (patients in MMT)	52
7	38 ± 8h	29–47h	Single dose	Chronic pain patients; (*R*)-methadone	53
7	29 ± 11h	19–46h	Single dose	Chronic pain patients; (*S*)-methadone	53

2	48h (mean)	43–53h	Steady state	Patients in MMT; (*R*)-methadone	61
2	40h (mean)	38–41h	Steady state	Patients in MMT; (*S*)-methadone	61
2	48h (mean)	38–59h	Steady state	Patients in MMT; (*R*)-methadone	62
2	31h (mean)	28–35h	Steady state	Patients in MMT; (*S*)-methadone	62
20	31h (mean)	13–53h	Steady state	Patients in MMT	54
19	35 ± 22h	9–87h	Single dose	General surgical or orthopaedic patients	55
9	30 ± 16h	7–65h	Single dose	Patients with pain due to cancer	63
8	43 ± 22h	22–59h	Single dose	Healthy female subjects; (*R*)-methadone	56
8	20 ± 4h	16–29h	Single dose	Healthy female subjects; (*S*)-methadone	56
10	21 ± 13h	7–48h	Steady state	Patients in MMT	64
Plasma clearance					
8	2.08 ± 1.71 ml/min • kg[f]	0.88–6.13 ml/min • kg	Single dose	Opioid users	47
5	3.10 ± 0.45 ml/min • kg[f]	2.46–3.56 ml/min • kg	Steady state	Patients in MMT	48
12	1.40 ± 0.50 ml/min • kg[g]	0.79–2.42 ml/min • kg	Single dose	Opioid users (first day of MMT)	49
12	1.63 ± 0.48 ml/min • kg[g]	0.91–2.51 ml/min • kg	Steady state	Opioid users (after 25 days of MMT)	49
5	2.11 ± 0.23 ml/min • kg[g]	1.86–2.47 ml/min • kg	Single dose	Acid urine, healthy subjects	46
5	1.48 ± 0.38 ml/min • kg[g]	1.15–2.10 ml/min • kg	Single dose	Alkaline urine, healthy subjects	46
185	186 ml/min (mean)	23–2100 ml/min	Steady state	Patients with pain due to cancer; intravenous injection or infusion	59
13	115 ± 25 ml/min[f]		Single dose	Healthy subjects	50
17	53 ± 5 ml/min[f]		Single dose	Opioid users	50
8	142 ± 77 ml/min[g]	57–224 ml/min	Single dose	Patients with chronic pain	51
8	104 ± 36 ml/min[f]	62–166 ml/min	Steady state	Therapeutic failures	52
12	111 ± 36 ml/min[f]	68–179 ml/min	Steady state	Comparison group	52
7	158 ± 35 ml/min[f]	120–228 ml/min	Single dose	Chronic pain patients; (*R*)-methadone	53
7	129 ± 49 ml/min[f]	90–230 ml/min	Single dose	Chronic pain patients; (*S*)-methadone	53
18	161 ± 68 ml/min[f]	103–363 ml/min	Steady state	Patients in MMT; (*R*)-methadone	39
18	159 ± 95 ml/min[f]	79–465 ml/min	Steady state	Patients in MMT; (*S*)-methadone	39
20	1.64 ± 0.8 ml/min • kg[f]	0.76–4.26 ml/min • kg	Steady state	Patients in MMT	54
19	2.7 ± 1.7 ml/min • kg[g]	0.7–7.5 ml/min • kg	Single dose	General surgical or orthopaedic patients	55
9	190 ± 130 ml/min[h]	30–420 ml/min	Single dose	Patients with pain due to cancer	63
8	67 ± 41 ml/min[f]	27–161 ml/min	Single dose	Healthy female subjects; (*R*)-methadone	56
8	345 ± 282 ml/min[f]	52–892 ml/min	Single dose	Healthy female subjects; (*S*)-methadone	56

a Apparent volume of distribution during the β-phase.
b Apparent volume of the central compartment.
c Apparent volume of distribution during steady state.
d Apparent volume of distribution in the body.
e Total volume of distribution during the β-phase.
f Apparent clearance.
g Total clearance.
h Not indicated whether total or apparent clearance.
MMT = methadone maintenance treatment.

The possible consequences of changes of plasma protein binding of methadone, resulting from an increase of α_1-acid glycoprotein, on the pharmacokinetics and on the pharmacological action of methadone have been the subjects of several studies.[24,76,79,80] In two studies, the effects of making rats physically dependent on morphine was examined.[79,80] It was found that such a treatment produced a 2- to 4-fold increase of α_1-acid glycoprotein concentrations.[79,80] After withdrawal from morphine ('abstinent rats'), the pharmacokinetics and pharmacodynamics, i.e. analgesia measured by the tail-flick method, of intravenous methadone were compared between the abstinent rats and control rats. The higher levels of α_1-acid glycoprotein measured in the abstinent rats resulted in a significant increase of plasma protein binding, with unbound fractions of 25 and 17% in the control and the abstinent rats, respectively ($p < 0.05$).[80] Such an increased binding could explain the significant decreases ($p < 0.05$) of total plasma clearance, distribution clearance and volume of distribution at steady-state, with values being 40, 23 and 42%, respectively, in the abstinent rats as compared with the control rats.[80] The extent of distribution of methadone in the brain was also significantly diminished, with values being 49% ($p < 0.05$) in the abstinent rats as compared with the control rats.[80] Finally, analgesia produced by intravenous methadone was significantly lower in the abstinent rats, with values being 45% in the abstinent rats as compared with the control rats ($p < 0.05$).[80] However, such reduced analgesia is observed only when methadone is administered as an intravenous administration, i.e. in the case of a rapid drug input (bolus), but it is not observed when methadone is injected subcutaneously.[81] Also, due to the fact that the abstinent rats had been treated with morphine prior to methadone injection,[80] it cannot be determined whether the lower analgesia produced by methadone in these animals is the consequence of altered methadone pharmacokinetics or the consequences of pharmacodynamic changes induced by the previous morphine treatment, or both.

An influence of methadone binding to plasma proteins on its pharmacological effects was also suggested by another study that assessed the severity of abstinence symptoms in a group of 27 patients hospitalised for a methadone detoxification program. α_1-Acid glycoprotein levels and methadone binding to plasma proteins were also determined in a blood sample collected just prior to the start of the detoxification program.[76] A significant correlation was found between α_1-acid glycoprotein levels and methadone binding ($r = 0.46$, $p < 0.05$) and between α_1-acid glycoprotein and withdrawal symptom scores ($r = 0.48$, $p < 0.005$).[76] However, the calculated coefficient of determination (r^2) between the two latter variables was weak (0.23), and the correlations between α_1-acid glycoprotein and the withdrawal scores were calculated only in a subset of 18 patients due to missing data in 9 patients[76] (R. Calvo, personal communication, November 2001).

In another study in eight healthy female volunteers receiving a single oral dose of (*R*,*S*)-methadone, the percentage of unbound (*R*)- and (*S*)-methadone in plasma was significantly correlated with the plasma half-lives and the renal clearance of both enantiomers.[56] However, the pharmacodynamic effects of methadone assessed by pupillary constriction could be adequately explained neither by (*R*)- or (*S*)-methadone pharmacokinetics nor by variability of methadone binding.[56]

In summary, these results suggest that variations of methadone binding to plasma proteins, such as those produced by marked changes in α_1-acid glycoprotein levels, might significantly alter methadone pharmacokinetics.[56,79,80] However, the consequences of such variations on the pharmacological effects of methadone cannot be precisely determined at the present time, but are probably not major in the case of oral MMT.

Within each individual, there is a genetic polymorphism of α_1-acid glycoprotein. This protein is composed of two slightly different major forms encoded by two separate genes; the ORM1 gene has two major variants, ORM1 F1 and ORM1 S, whereas the ORM2 gene is mainly monomorphic.[82,83]

Methadone has been shown to bind to the ORM2 A variant, but not to the ORM1 F variant.[74,84] In a study in rats, artificially increased plasma ORM2 concentrations significantly reduced the brain concentrations of total methadone injected as a rapid bolus in the common carotid artery.[85] It has also been demonstrated in a study with eight healthy female subjects that, after a single oral dose of 0.2 mg/kg of (*R*,*S*)-methadone, the binding of methadone to α_1-acid glycoprotein, and ORM2 in particular, is important in the disposition of (*R*)-methadone, particularly with regard to its transfer to and from the central to the peripheral compartments, and, by extension, to the site of pharmacological action.[56] However, the pharmacodynamic effects of methadone as assessed by pupillary constriction could be adequately explained neither by (*R*)-methadone pharmacokinetics nor by ORM2 blood concentration variability. Thus, the pharmacological consequence of this genetic polymorphism, and in particular its clinical significance, remains to be elucidated.

Although there are differences in the mean estimates reported in different studies for the apparent volume of distribution at steady-state (between 2 and 5 L/kg for the apparent volume of distribution during the elimination phase; see table I), the values are much higher than the actual physiological volumes, which indicates that methadone is subject to extensive tissue binding, including brain, gut, kidney, liver, muscle and lung,[24,86] a distribution which predominates over binding to plasma proteins. In a population pharmacokinetic study with 35 patients in MMT, it was found that gender and weight of the patients together explained 33% of the variance in the apparent volume of distribution of methadone.[87] The contribution of weight to the variance of the volume of distribution confirms the results of another population pharmacokinetic study.[50] A higher volume of distribution has been reported for (*R*)- than for (*S*)-methadone in a single dose study with ten chronic pain patients (mean ± SD: 497 ± 117 versus 289 ± 78L, $p < 0.001$).[53] This was explained by the lower plasma binding of (*R*)-methadone and/or by differences in the affinity of the enantiomers for various organs, as shown by the higher (*R*)-methadone concentrations measured in the brain, liver and lungs in rats.[53] However, in another recent single dose study with eight healthy female subjects, a nonsignificantly lower volume of distribution was reported for (*R*)- than (*S*)-methadone (mean ± SD: 106 ± 78 versus 227 ± 202L),[56] and studies with a larger number of patients are needed to reach conclusions about possible stereoselectivity in the distribution of methadone.

2.2 Metabolism and Elimination

The elimination of methadone is mediated by biotransformation, followed by renal and faecal excretion. In a study with four subjects receiving radiolabelled methadone, two excreted the major part of the radioactivity in urine, while the other two about equally in urine and faeces.[88] Methadone is extensively metabolised in the body, mainly at the level of the liver, but probably also by intestinal CYP3A4. The main metabolite of methadone (2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine; EDDP) is inactive: it is formed by *N*-demethylation and subsequent spontaneous cyclisation.[89] In addition to methadone, nine metabolites, including EDDP, have been identified in urine, and three metabolites in faeces.[88,90,91] Urinary excretion of methadone plus EDDP accounts for 17–57% of the given dose.[88] When beginning MMT, there were large interindividual variations of the EDDP/methadone urine ratios in six patients (mean ± SD, 0.77 ± 0.38; range 0.40–1.30). The interindividual variation of this ratio was even larger after 4 weeks of treatment, with enhanced metabolism of methadone leading to an increased ratio with very high values in some patients (mean ± SD, 2.90 ± 3.1; range 0.60–9.0).[88]

The elimination of methadone is mostly due to metabolic clearance.[92] The limited amounts of circulating drug that undergo glomerular filtration are partially reabsorbed by the kidney tubules, and this reabsorption is pH-dependent.[57,60,64] In a study in 12 patients in MMT, a 3-fold higher renal clearance was calculated in a group of six patients

with a 24-hour urine pH of 6.1 as compared with a group of six patients with a 24-hour urine pH of 6.6.[64] In five healthy volunteers treated with a large dose of ammonium chloride (26g over 3 days), leading to urine acidification (pH about 5.2), the renal clearance of methadone (mean ± SD, 47 ± 11 ml/min) increased to about 35% of the total body clearance (mean ± SD, 134 ± 21 ml/min), with plasma half-life (mean ± SD) 19.5 ± 3.6 hours and volume of distribution (mean ± SD) 3.51 ± 0.41 L/kg.[46] When the same subjects were treated with sodium hydrogen carbonate, leading to a urine pH of about 7.8, only a small amount of methadone, below 1% of the administered dose for a 96-hour urine collection, was excreted in urine, suggesting almost complete reabsorption by the kidneys. This treatment also resulted in a significant decrease of total body clearance (mean ± SD, 92 ± 9 ml/min, $p < 0.01$), and plasma half-life (mean ± SD, 42.1 ± 8.8 hours) and volume of distribution (mean ± SD, 5.24 ± 0.83 L/kg) increased significantly ($p < 0.01$).[46,92] The unexpected increase in the volume of distribution of methadone when the pretreatment was changed from ammonium chloride to sodium bicarbonate contributes to the increase of half-life values, independently of plasma clearance, and suggests that apparently fewer methadone binding sites are available during acidosis.[46] This is in agreement with the results of another study during which increased volume of distribution was observed in 11 of 12 patients in MMT when urinary pH rose during treatment as a consequence of change in opioid tolerance.[49] Thus, the first dose(s) of MMT may cause acidosis due to respiratory depression, an effect which disappears during development tolerance.[46]

In summary, the published data show that below an urinary pH of 6, renal clearance may become of quantitative importance,[92] but above this value the renal clearance of methadone represents only a minimal part of the total body clearance.[46,51] In two population pharmacokinetic analyses with 35 patients in MMT each, the results indicated that, although clearance was inversely related to urine pH, it explained only 27% of the variance.[87,93] In another population pharmacokinetic study with 13 healthy subjects and 17 opioid users, it was found that urine pH showed no significant relationship to methadone clearance.[50]

In 12 opioid-dependent subjects, urinary pH was lower on days 1–3 of MMT as compared with days 24–26 (mean ± SD, 5.84 ± 0.23 versus 6.36 ± 0.39, $p = 0.004$).[49] This was probably due to respiratory depression induced by methadone at the start of MMT, before tolerance had developed.[49] Accordingly, the contribution of renal clearance, as a percentage of total clearance, decreased significantly from 23.8% (SD, 10.1%; range, 8.0–42.6%) to 13.7% (SD, 10.3%; range, 3.1–38.2%) [$p = 0.047$, Wilcoxon matched pairs test performed by the present authors on the raw data in the original publication]. A small (20%), but not significant, increase in total clearance was noted between the two periods (mean ± SD, 0.095 ± 0.031 L/min versus 0.115 ± 0.036 L/min).[49] On the other hand, a much higher increase (350%) in total clearance was measured between the first dose and steady-state doses of methadone (up to day 30) in a population study with multiple blood samplings in a group of 35 dependent patients.[87] Another population pharmacokinetic study with 35 patients confirmed the auto-induction of methadone metabolism, with a significantly lower clearance of methadone at the start of the MMT (median elimination half-life of 128 hours) than under steady-state conditions (median elimination half-life of 48 hours).[93] Of particular interest, considering the nature of the present review, is the fact that the increase of clearance of methadone during the first weeks of MMT is not observed in all patients [50] and that the parameters describing plasma concentrations of methadone after a single oral dose in healthy subjects cannot be used as a basis for predicting and adjusting dosage in opioid users receiving MMT.[50]

It is important to emphasise that, in a large group of cancer patients, methadone clearance has been reported to vary by a factor of almost 100 (0.023–2.1 L/min, n = 184).[59] Such a large variability can be explained, in part, by metabolic in-

teractions with drugs received by those patients: amitriptyline decreases methadone clearance, whereas phenytoin, spironolactone, verapamil, estrogens and barbiturates increase it. Thus, the highest value of clearance, 2.1 L/min, was measured in a patient receiving barbiturates, which are strong CYP inducers.[59]

With regard to the enantiomers, in a single-dose study in ten patients with chronic pain, a slightly higher mean clearance was measured for (*R*)-methadone as compared with (*S*)-methadone (0.158 versus 0.129 L/min, $p < 0.01$).[53] This result is in discrepancy with those of another recent single dose study that included eight healthy female subjects and that found a much lower mean clearance for (*R*)-methadone than for (*S*)-methadone (0.067 versus 0.345 L/min, $p = 0.024$).[56] In steady-state conditions, in a study with 18 patients in MMT, no difference was found in the apparent plasma clearance between the two enantiomers when considering total methadone concentrations, i.e. free methadone + methadone bound to blood proteins [(*R*)-methadone, 0.161 L/min; (*S*)-methadone, 0.159 L/min)].[39] However, when considering only the unbound fraction, lower mean apparent clearance was calculated for (*R*)- than for (*S*)-methadone (4.611 versus 7.845 L/min, $p = 0.0001$).[39] Although other studies are needed, the results of the two latter studies suggest that the pharmacologically active enantiomer has a lower intrinsic clearance when compared with (*S*)-methadone.[39,56]

After parenteral administration, plasma methadone concentrations decrease in a biexponential manner, with a distribution half-life varying between 1.9 and 4.2 hours.[47] A mean value of 22 hours was found for the terminal half-life in a single-dose study in six healthy male volunteers, which measured methadone concentrations over a 72-hour period.[29] However, there is a very large interindividual variation for the half-life (see table I), and although values between 15 to 60 hours have been reported,[21] values lower than 5 hours and higher than 130 hours have been published.[59,94] A terminal half-life of 6 hours has thus been calculated in a patient taking nevirapine, a strong CYP3A4 inducer.[95-97] It must be mentioned that very different blood sampling time intervals have been used in the different studies listed in table I. Although some studies were performed with extended time intervals (72 hours or more),[29,46,56,61,62] other studies collected blood samples for only 24 hours, due in particular to the requirement of daily methadone administration for patients in MMT,[48,50,54,57-60,64,94] and such a time interval, similar to the half-life, is too short to allow an accurate determination of this parameter.[50]

Besides the intrinsic interindividual variability, induction and inhibition of methadone metabolism by comedications are additional factors explaining this broad range.[59,94] Due to auto-induction of methadone metabolism during the first month of MMT, a shortening of methadone half-life may occur in some patients.[49,93] Following long-term administration of methadone to 12 patients over 26 days, a significant shortening of methadone elimination half-life has been observed (from 55 to 22 hours, $p = 0.006$).[58] In another study in 35 dependent patients, a median elimination half-life of 128 hours was calculated at the start of the treatment and a median value of 48 hours was calculated when the patients had reached steady-state conditions.[93]

With regard to the enantiomers, one single-dose study that measured the blood concentrations of methadone in three different groups of six healthy male volunteers receiving a single oral dose of either 15mg of (*R*,*S*)-methadone, 7.5mg of (*R*)-methadone or 7.5mg of (*S*)-methadone did not find any significant differences in half-lives [24 versus 25 hours for (*R*)- and (*S*)-methadone, respectively].[29] However, when measured in the same subjects, (*R*)-methadone was found to have a significantly longer elimination half-life than (*S*)-methadone in four studies. Thus, mean values of 38 and 43 hours for (*R*)-methadone versus 29 and 20 hours for (*S*)-methadone were measured in two single dose studies on seven patients with chronic pain and on eight healthy female subjects,

respectively,[53,56] whereas mean values of 48 hours versus 40 hours and of 48 hours versus 31 hours for (*R*)- versus (*S*)-methadone, respectively, were measured in two studies under steady-state conditions on two patients each.[61,62]

2.3 Effects of Age, Renal and Hepatic Diseases

Methadone clearance does not appear to be markedly affected by age,[50,55] but over age 65 years a slight decrease was noted.[59] In a study involving three patients with chronic renal failure under MMT, the plasma concentrations of methadone measured (90–680 μg/L) were considered as being within the expected range for the dosage used (40–50 mg/day).[98] A value of 680 μg/L for (*R*,*S*)-methadone can however be considered at the very upper limit of usual values with such dosages.[99] Patients with low renal function increase the fraction of methadone excreted through the faeces, as the elimination of methadone and of its metabolites in anuric patients exclusively occurs through the faecal route.[98] However, until more data are available, some authors have recommended to reduce the normal dosage of methadone by up to 50% in patients with end-stage renal disease.[100] Interestingly, in patients with chronic renal replacement therapy, less than 1% of the daily dose is removed by peritoneal dialysis or haemodialysis,[98,101] due to the high protein binding and extensive volume of distribution of methadone, which means that dialysis is not useful for managing methadone overdose.

In a study assessing methadone pharmacokinetics in 11 MMT patients with severe alcoholic liver disease, compared with nine MMT patients with recent alcohol abuse but no evidence of liver disease, a longer half-life was measured in the former group (mean ± SE, 32 ± 5 versus 20 ± 2 hours, p = 0.04), which could be explained by a higher volume of distribution (mean ± SE, 716 ± 100 versus 438 ± 94L, p = 0.06).[102] On the other hand, the apparent oral clearance was similar between patients and controls (mean ± SE, 0.280 ± 0.023 versus 0.246 ± 0.036 L/min).[102] It has thus been suggested that the usual methadone maintenance dosage could be continued in stable patients with severe alcoholic cirrhosis[102] or liver disease.[103] In two recent studies, it has been suggested that patients infected with hepatitis C require significantly higher dosages of methadone than non-infected patients, possibly due to an induction of CYP enzymes.[104,105] These results need, however, to be confirmed.

Although the abovementioned studies do not suggest a major impact of age, renal or hepatic diseases on methadone pharmacokinetics, clinical experience indicates that some of these patients tend to have an exaggerated response to methadone. Thus, cautious administration is advised, in particular at the start of MMT or when methadone is prescribed as an analgesic to non-tolerant patients.[21,102]

3. Metabolism by Cytochrome P450

In vitro and *in vivo* studies have shown that CYP3A4 and to a lesser extent CYP2D6 are involved in methadone metabolism. Other isoforms, such as CYP1A2, CYP2C9 and CYP2C19, might also be implicated, but their *in vivo* relevance remains to be demonstrated.

Table II summarises reports of CYP-mediated drug interactions with methadone.

3.1 Cytochrome P450 3A4

Several *in vitro* studies measuring the formation of EDDP from methadone, using either human liver microsomes, human intestinal microsomes or microsomes bearing cDNA-expressed CYPs, confirmed the major involvement of CYP3A4 in this metabolic pathway.[66,135-138] Also, the total CYP3A4 content of 20 liver microsomal samples correlated with methadone *N*-demethylation ($r = 0.72$, $p < 0.003$).[135] Moreover, measuring methadone *N*-demethylation activity in different human microsomes heterologously expressing CYPs showed the highest value for CYP3A4.[135,137] Methadone is demethylated to EDDP with an apparent Michaelis constant (K_m) of 545 ± 258 μmol/L (mean ± SD; n = 3)[135] or 165 ± 33 μmol/L

(mean ± SD; n = 6),[137] which indicates a rather low affinity for the enzyme(s) mediating this activity. This suggests that this metabolic pathway can be relatively easily inhibited. Accordingly, chemical inhibitors of CYP3A4 (troleandomycin, gestodene, erythralosamine, ketoconazole, dihydroergotamine, quercetin, diazepam) or monoclonal human anti-CYP3A4 antibodies are able to inhibit the formation of EDDP by up to 80%.[135-137]

The *in vitro* stereoselectivity of methadone *N*-demethylation has also been examined: K_m and intrinsic clearance (CL_{int}) values for (*R*)- and (*S*)-methadone were not significantly different ($p > 0.05$), whereas a slightly lower maximum rate (V_{max}) value (15%) was found for (*S*)-methadone as compared with (*R*)-methadone.[137] These results suggest that a stereoselectivity of this metabolic pathway *in vivo* due to intrinsic metabolic activity alone is unlikely.[137] However, *in vivo*, (*R*)-methadone was found to have a lower intrinsic clearance when compared with (*S*)-methadone,[39,56] with a significantly greater fraction of the dose excreted in the urine as (*S*)-EDDP and (*R*)-methadone than the corresponding enantiomers, suggesting that significantly less (*R*)-methadone than (*S*)-methadone is metabolised to EDDP.[39] Several reasons have been proposed to explain this lack of agreement between the *in vitro* and *in vivo* data, such as stereoselectivity in: (i) metabolic pathways other than EDDP formation;[39] (ii) binding of methadone to proteins in the *in vitro* liver microsomal fraction;[137] (iii) renal clearance; and/or (iv) elimination of EDDP via faeces.[39]

Induction of CYP3A4 at the beginning of MMT probably explains, at least in part, the increased EDDP/methadone ratio, the increased clearance, the decreased elimination half-life and the decreased methadone steady-state plasma concentrations measured in a subset of patients during the first month of treatment,[50,87,93] which could necessitate an adaptation of the dosage.[49,58] Induction of CYP3A4 is also a possible explanation for the decrease of mean (*R*)-methadone concentrations measured in a group of 22 German MMT patients whose (*R*)-methadone dosage was replaced by a double dosage of (*R*,*S*)-methadone.[44] Indeed, in the mid-1990s, many patients in Germany were switched from (*R*)-methadone to (*R*,*S*)-methadone, e.g. 50mg of (*R*)-methadone was replaced by 100mg of (*R*,*S*)-methadone. This change was not popular among dependent subjects, and, despite the bias of such reports due to their unblinded nature, magazines printed for and by drug-dependent patients reported some cases of withdrawal symptoms after the switch.[139] Although the mean decrease of (*R*)-methadone serum concentration/dose ratio measured was small (16%), it might nevertheless explain the withdrawal symptoms reported by some patients and the mean increase of the dose (11%) required by 10 of the 22 patients.[44]

In the mid-1970s, a double-blind crossover study with 66 patients in MMT comparing adverse effects, drug use, clinic attendance and dosage changes on (*R*)-methadone and (*R*,*S*)-methadone showed no significant differences between the two forms.[31] Two other reports on the switch under double-blind conditions in patients in MMT previously maintained on (*R*)-methadone, to either (*R*,*S*)- or (*R*)-methadone, have been published in Germany.[32,33] In one study, the group of 13 patients who received racemic methadone for 2 weeks did not complain more frequently of withdrawal symptoms.[32] However, in a follow-up period of 9 weeks after replacement of (*R*)-methadone with (*R*,*S*)-methadone, although there was no significant increase in complaints about withdrawal symptoms, six patients needed an increase of their daily dosage by at least 20mg of racemic methadone.[32] In the other study with 40 patients over a 22-day observation period, although the plasma EDDP concentration in the racemic methadone group (n = 20) increased 3-fold after starting treatment with (*R*,*S*)-methadone, which is in agreement with the hypothesis of racemic methadone inducing its own metabolism, there was no significant difference between the two groups in the number of requests for a dosage change.[33] Also, the switch from (*R*)-methadone

Table II. Selected reports of drug interactions with methadone

Agent	Effect	Possible mechanism	Remarks	References
Diazepam	Increased opioid effects	Mechanism unclear, probably not a pharmacokinetic interaction	Clinical relevance unclear	106-108
Rifampicin (rifampin)	Decreased plasma concentrations and opioid effects	Induction of CYP3A	Cases of severe withdrawal symptoms described	109
Phenobarbital	Decreased plasma concentrations and opioid effects	Induction of CYP3A	One case report with a 31% reduction of trough methadone plasma concentrations	110
Amylobarbitone	Increased methadone clearance	Induction of CYP3A	Clearance determined in patients receiving methadone for cancer pain	59
Phenytoin	Decreased plasma concentrations and opioid effects	Induction of CYP3A	Mean 2.4-fold decrease of methadone plasma concentrations with moderately severe opioid withdrawal symptoms	59,111,112
Spironolactone	Increased methadone clearance	Induction of CYP3A	Clearance determined in patients receiving methadone for cancer pain	59
Nevirapine	Decreased plasma concentrations and opioid effects	Induction of CYP3A	Case reports of very marked decrease of methadone plasma concentrations and severe withdrawal symptoms	95-97,113
Efavirenz	Decreased plasma concentrations and opioid effects	Induction of CYP3A	Mean decrease by 57% of AUC in 11 patients. One case report of reduction of both enantiomers of methadone	114,115
Amprenavir	Decreased plasma concentrations, possible decreased opioid effects	Induction of CYP3A	Median decrease by 65% of methadone concentrations in five patients. Association amprenavir + abacavir, amprenavir as the likeliest inducing agent	116
Nelfinavir	Decreased plasma concentrations	Induction of CYP3A, possible induction of P-glycoprotein	Mean decrease by about 55% in two patients	117
Ritonavir	Decreased plasma concentrations and opioid effects	Induction of CYP3A, possible induction of P-glycoprotein; Induction of CYP2C19 and/or CYP2B6 suggested to explain the greater induction of metabolism of (*S*)- than (*R*)-methadone	Mean decrease of AUC by 36% in 11 patients after a 14-day treatment. High interindividual variability of decrease of methadone concentrations	117-120
Fluconazole	Decreased methadone clearance and increased plasma concentrations	Inhibition of CYP3A4	Increased AUC by 35% in 13 patients after fluconazole 200 mg/day for 14 days	121
Fluoxetine	Increased plasma concentrations	Inhibition of CYP2D6 [stereoselectivity for (*R*)-methadone]	Increased plasma concentrations (mean increase 32%) for (*R*)- but not (*S*)-methadone in seven patients	40,122,123
Paroxetine	Increased plasma concentrations	Inhibition of CYP2D6 [stereoselectivity for (*R*)-methadone]	Increased (*R*)-methadone plasma concentrations in eight CYP2C6 extensive metabolisers (32%) but not in poor metabolisers (3%)	124

Sertraline	Increased plasma concentrations	Inhibition of one or several CYP isoenzymes (CYP2D6, CYP3A4, CYP1A2, CYP2C9, CYP2C19)	No adverse effects due to excess dosage recorded	125
Ciprofloxacin	Increased opioid effects	Inhibition of CYP1A2 and/or CYP3A4	One case report of sedation, confusion and respiratory depression	126
Fluvoxamine	Increased plasma concentrations and increased opioid effects	Inhibition of one or several CYP isoenzymes (CYP1A2, CYP2C19, CYP3A4, CYP2C9)	One case report of hypoventilation, severe hypoxaemia and hypercapnia. Two case reports of withdrawal symptoms when fluvoxamine stopped. One case report of fluvoxamine use to decrease methadone metabolism induced by barbiturate	40,127-129
Moclobemide	Increased opioid effects	Inhibition of CYP2D6 and/or CYP1A2	One case report of withdrawal symptoms when moclobemide stopped	130
Fusidic acid	Decreased opioid effects	Induction of CYP3A and CYP2C	Reports of withdrawal symptoms after a 4-week therapy	131
Amitriptyline	Decreased methadone clearance	Inhibition of one or several CYP isoenzymes (CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4)	Clinical relevance unclear	132
Ethanol	Increased opioid effect?	Mechanism unclear	Clinical relevance unclear	133,134

AUC = area under the concentration-time curve; **CYP** = cytochrome P450.

to (*R*,*S*)-methadone did not significantly change the (*R*)-methadone dose/(*R*)-methadone plasma concentration ratios.[33]

In summary, although more studies are needed to draw a firm conclusion, published results on the switch of (*R*)-methadone to a double dose of (*R*,*S*)-methadone suggest that this change might decrease (*R*)-methadone blood concentrations in some but not all patients. This decrease might be explained by an induction of CYP3A4, which might necessitate an increase of methadone dosage.

It is of interest to correlate the *in vivo* activity of CYP3A4 with the pharmacokinetics of methadone, as this allows estimation of the relative importance of this isoenzyme on the disposition of methadone. Three studies tried to do so. In one study in 32 patients in MMT, no significant correlation was found between the 6-hydroxy-cortisol-/17-hydroxy-corticosteroid ratio in urine (used as a marker of CYP3A4 activity) and serum steady-state trough concentrations of methadone corrected for dosage ($r^2 = 0.0015$, nonsignificant).[140] This negative result could be explained by the fact that the cortisol ratio has limited use as a marker of baseline CYP3A4 activity in humans,[140] and does not correlate with established *in vivo* probes for CYP3A4 (e.g. erythromycin *N*-demethylation rate).[141] However, in another study in eight healthy female volunteers receiving a single oral dose of (*R*,*S*)-methadone 0.2 mg/kg, the mean urinary 6-hydroxy-cortisol/cortisol ratio measured over 96 hours significantly correlated with AUC_{96} ($p = 0.023$)[56] and with the amount of EDDP excreted in the urine during 96 hours ($r^2 = 0.78$, $p = 0.005$).[142] Also, the single oral dose of (*R*,*S*)-methadone significantly decreased the 6-hydroxy-cortisol/cortisol ratio in urine for collection periods up to 12 hours ($p < 0.05$).[142] No explanation can at present be given for the discrepancy between the two studies. However, they differed by many points such as steady-state conditions versus single dose, patients in MMT versus healthy volunteers, steady-state trough concentrations versus AUC and 6-hydroxy-cortisol/17-hydroxy-corticosteroid ratio versus 6-hydroxy-cortisol/cortisol ratio.[56,140] Finally, a third *in vivo* study in a group

of 32 patients in MMT confirmed the influence of CYP3A4 activity, measured by the 30-minute plasma 1′-hydroxy-midazolam/midazolam ratio after the oral administration of midazolam 7.5mg, on methadone steady-state plasma concentrations, with (*R*,*S*)-methadone steady-state trough concentrations corrected for dosage significantly correlating with the midazolam ratios ($r^2 = -0.14$, $p = 0.032$).[143]

Methadone metabolism is induced by several classical CYP3A4 inducers, such as rifampicin (rifampin). The administration of rifampicin for the treatment of tuberculosis in dependent patients results in a high incidence of withdrawal symptoms (up to 70%), one-third of these being considered as severe, and with confirmed significantly lower plasma concentrations in the latter patients.[109] In this case, it is recommended to increase the daily methadone dosage, and if necessary split the total dosage into two daily doses, until complete disappearance of the withdrawal symptoms, or until methadone blood concentrations have reached the pre-rifampicin level. However, it should be kept in mind that with strong CYP3A4 inducers, a very large increase of the methadone dosage, and splitting into more than two daily doses, might be necessary. Such an increase is not always possible for several reasons, such as psychological resistance, i.e. fear of the prescriber and/or of the patient, or a policy that prohibits giving higher amounts than a preset ceiling value. An alternative could be, whenever possible, to use another antitubercular drug with a similar spectrum of action. Thus, rifabutin, a semisynthetic antibiotic derived from rifamycin S with a broad spectrum of activity against both Gram-positive and Gram-negative bacteria, induces CYP3A4 less potently than does rifampicin.[144] In a study involving 24 patients under MMT who were prescribed rifabutin 300 mg/day for 15 days, this drug did not influence methadone kinetics, as assessed by peak plasma concentration, time to peak, AUC, systemic clearance or renal clearance.[144] Only mild withdrawal symptoms were reported by three-quarters of the patients, and the three patients requiring a dosage adaptation were clinically stabilised with a modest increase (10 mg/day).[144] Another theoretical therapeutic option, when a strong CYP3A4 inducer is used as a comedication, is to replace methadone by levacetylmethadol (LAAM), another long-acting opioid agonist (see sections 4.3 and 6 for the cardiotoxicity of LAAM).

Other drugs, such as phenobarbital, phenytoin and carbamazepine, are classical CYP3A4 inducers:[145] enhancement of methadone metabolism and withdrawal symptoms triggered by barbiturates[59,110] and phenytoin[59,111,112] represent classical examples. For the treatment of epilepsy, valproic acid can be used instead of the above-mentioned antiepileptics, as it does not appear to require an increase of methadone dosage.[146] Some steroids, such as dexamethasone, a synthetic glucocorticoid, or spironolactone, a semisynthetic antagonist of aldosterone used as a diuretic, are CYP3A4 inducers. This is confirmed by the results of a study showing that steroids and spironolactone increase methadone clearance.[59]

A recent topic, which has prompted many studies, is the interaction between methadone and medications used to treat HIV infection.[147] The nucleoside reverse transcriptase inhibitors do not appear to be inducers or inhibitors of the CYP system, and they do not modify methadone kinetics.[147] Thus, zidovudine, stavudine, didanosine and lamivudine do not modify methadone concentrations.[147] On the other hand, an increase of zidovudine AUC (1.4-fold) by methadone has been reported, most probably by an inhibition of zidovudine glucuronidation.[148,149] Similarly, a recent study did not show any influence of abacavir on time to peak concentration or half-life of methadone.[150] On the other hand, a modest but significant increase of methadone oral clearance was measured (23%, $p = 0.03$).[150] No explanation was given for the increase of methadone oral clearance by abacavir. However, due to the design of the study and the autoinduction of methadone metabolism described by several authors during the first month of MMT,[49,58] it is possible that such an increased

clearance would have been measured even without abacavir.

With regard to the non-nucleoside reverse transcriptase inhibitors, several recent studies have shown that nevirapine and efavirenz enhance methadone metabolism, probably by an induction of CYP3A4, leading to lower blood concentrations and possibly to withdrawal symptoms.[95-97,113-115,151] Thus, in 11 patients receiving stable methadone maintenance therapy, with dosages between 35 and 100 mg/day, administration of efavirenz 600 mg/day for 3 weeks resulted in a marked decrease of the mean maximum plasma concentration of methadone (from 689 to 358 μg/L, $p = 0.007$), and of the mean AUC_{24} (from 12341 to 5309 μg • h/L, $p = 0.012$), which necessitated an average increase of methadone dosage of 22%.[115] In one case report, the switch of nelfinavir 750mg three times daily to efavirenz 600 mg/day resulted in an almost 2-fold decrease of (*R*)-methadone blood concentrations (87% difference) which necessitated a 80% increase of the dosage of methadone.[114] Interestingly, both enantiomers of methadone were decreased by efavirenz.[114] This is in agreement with the *in vitro* study showing a lack of stereoselectivity in the metabolic pathway leading to the formation of EDDP.[137]

Another case report of induction of methadone metabolism by efavirenz illustrates the problems faced by the prescriber when an increase of methadone dosage is needed.[95] Following the successive introduction of nevirapine and efavirenz, severe withdrawal symptoms were identified in a patient under MMT.[95] Methadone dosages were increased accordingly, from 30–40 up to 80–90 mg/day. However, nevirapine therapy (two trials) and efavirenz treatment (one trial) were stopped, not because of adverse effects or lack of efficacy with regard to the antiretroviral activity of the antiretroviral drugs, but because of the recurrence of opioid withdrawal symptoms; the patient did not want to further increase his methadone dosage.[152] Nonadherence to antiretroviral treatment has also been reported following the introduction of nevirapine, a CYP3A4 inducer, which resulted in a 9-fold and a 15-fold decrease of methadone concentrations measured in two patients.[96,97]

Introduction of abacavir, a nucleoside reverse transcriptase inhibitor, and amprenavir, an HIV protease inhibitor, in five dependent patients in MMT resulted in a median decrease to 35% of the original concentration of methadone ($p = 0.043$), with adverse effects compatible with withdrawal reactions in two patients,[116] probably due to an induction of CYP3A4 by amprenavir. Addition of ritonavir and nelfinavir, two HIV protease inhibitors, in patients on steady-state therapy with methadone and nucleoside analogues led to a decrease of methadone steady-state concentrations by 40–50%.[117] In a single oral methadone dose study, 14 days of ritonavir treatment in 11 healthy normal volunteers resulted in a significant decrease of the methadone AUC by 36%, and of the peak plasma concentration by 38%, but without a change of the terminal half-life.[118] In another study in 12 HIV-infected patients in MMT, the administration of ritonavir 400mg/saquinavir 400mg twice daily for 15 days resulted in a significant ($p = 0.001$) decrease of total AUC_{24} for (*S*)-methadone (40% decrease) and (*R*)-methadone (32% decrease).[119] When AUC values were corrected for the changes in protein binding induced by ritonavir/saquinavir, (*R*)-methadone free AUC decreased by 20% whereas (*S*)-methadone free AUC decreased by 25%, neither of these changes being significant ($p = 0.13$ and $p = 0.054$, respectively).[119] It was suggested that the greater induction of metabolism of the (*S*)-enantiomer might be explained by an induction of CYP2C19 and CYP2B6, the two enzymes found to stereoselectively metabolise methadone (data mentioned by Gerber et al.[119] as presented at a workshop, but not available to the present authors). Although no withdrawal symptoms were reported and no modifications of methadone dosage was required during the study, it was acknowledged that some patients might experience withdrawal symptoms given that the variability of decrease of (*R*)-methadone AUC was high.[119] In one case report,

the introduction of ritonavir resulted in withdrawal symptoms which resolved after the increase of methadone dosage from 90 to 130 mg/day.[120]

On the other hand, indinavir or saquinavir did not affect methadone concentrations.[117] Although the exact mechanism by which ritonavir and nelfinavir, which are strong CYP inhibitors,[153,154] decrease methadone concentrations is not known, induction of CYP3A4 and P-glycoprotein,[155] and possibly of other enzymes, by these drugs is probable. A 30% reduction in the AUC of ritonavir has thus been shown after 3–4 weeks of continued therapy with this drug. This suggests enzyme induction following initial enzyme inhibition, which might compensate for, and even overcome, the latter mechanism.[153,156] Finally, methadone has been shown to affect the kinetics of several antiretroviral drugs by mechanisms that do not involve CYP inhibition, such as inhibition of glucuronidation or of absorption, due to methadone-induced reduction in gastric motility (for a review, see Gourevitch and Friedland[147]).

Fluconazole, an antimycotic able to inhibit several CYP enzymes including CYP3A4, has been shown to modify methadone kinetics in 13 patients under MMT.[121] After 14 days of fluconazole 200 mg/day, serum methadone AUC and mean peak and trough concentrations increased by 35% ($p = 0.0008$), 27% ($p = 0.008$) and 48% ($p = 0.002$) respectively, while oral clearance was reduced by 24% ($p = 0.0007$).[121] Although exposed to increased concentrations of methadone, patients did not exhibit signs of opioid overdose;[121] this is not surprising, considering the relatively modest increase of methadone concentrations and the tolerance to opioid effects which develops during MMT. A case report of slow metabolism and long half-life of methadone in a patient with lung cancer and cirrhosis receiving fluconazole has also been recently described.[157] It is expected that other strong CYP3A4 inhibitors, such as ketoconazole or erythromycin, would also increase methadone concentrations, although, to our knowledge, no studies have been published on such interactions.

Diazepam, a CYP3A4 substrate,[158] inhibits methadone *N*-demethylation in supernatant fractions of rat hepatic homogenates and in human liver microsomes, with K_i values of 170[159] and 50[135] μmol/L, respectively. By modelling *in vitro* data, it was suggested that coadministration of diazepam with methadone would inhibit the metabolism of methadone by 10–20%.[160] However, the diazepam interaction potential, both at the pharmacokinetic and pharmacodynamic levels, remains controversial. Indeed, another study using human liver microsomes ($n = 3$) found that diazepam at a concentration of 100 μmol/L did not significantly inhibit the formation of EDDP.[137] An *in vivo* study showed that diazepam increases some physiological and subjective opioid effects of methadone, and the authors suggested that the relatively great use/abuse of diazepam among patients under MMT could be related to the enhancing effect of diazepam on methadone.[106] Although the plasma time-course or AUC of methadone were not significantly changed by diazepam administration,[107,108] a pharmacokinetic interaction in other organs cannot be ruled out, as in rats and mice a significant increase in brain and liver but not in plasma concentrations of methadone was produced by diazepam administered 1 hour before methadone.[107]

Finally, it should be mentioned that, up to now, no data are available on the possible interaction of grapefruit juice and methadone, but based on the known inhibitory effect of grapefruit juice on CYP3A4[161] and P-glycoprotein,[162] such an interaction is likely.

3.2 Cytochrome P450 2D6

In vitro studies measuring the formation of EDDP from methadone only showed a minor role of CYP2D6 in this metabolic pathway.[135-137] Although in two studies[135,136] cDNA-expressed human CYP2D6 has been found to be able to demethylate methadone, a third study did not find such an activity.[137] The hepatic activity, calculated from the activity of microsomal preparations of human heterologously expressed CYPs and from the total CYP liver content of each isoform, was four times

lower for CYP2D6 than for CYP3A4 (63 versus 242 pmol/min per mg of protein).[135] Although in one study 10 μmol/L quinidine, which is a strong CYP2D6 inhibitor,[163] was found to inhibit methadone *N*-demethylation in human liver microsomes by up to 25%,[135] two other studies did not find a significant inhibition of this metabolic pathway by quinidine.[136,137] It should however be mentioned that the high quinidine concentration (10 μmol/L) used in the former study[135] as compared to that used in the two latter studies (1 μmol/L)[136,137] might lead to inhibition of both CYP2D6 and other isoforms. One can thus consider that CYP2D6 contributes only to a small extent, if at all, to the formation of EDDP. On the other hand, several *in vivo* studies measuring methadone concentrations in the presence of CYP2D6 inhibitors or in poor metabolisers of CYP2D6 showed that CYP2D6 significantly contributes to methadone disposition (see below). It is very likely that CYP2D6 is involved in another metabolic pathway than the *N*-demethylation step leading to the formation of EDDP. Although EDDP is considered to be the major metabolite of methadone, nine metabolites were isolated and identified in the urine of six dependent subjects treated with increasing dosages of methadone for 1 month.[88]

To our knowledge, with the exception of EDDP, other methadone metabolites produced by other metabolic pathways are not available for analytical work. In an elegant study using human lymphoblast-expressed CYP2D6 microsomes and pooled human liver microsomes, the metabolism of methadone was examined by measuring the loss of methadone enantiomers in the incubation mixture by chiral high performance liquid chromatography (personal communication, D.W. Boulton, C.L. DeVane, P. Arnaud, Medical University of South Carolina, December 2000). Loss of methadone in a time-dependent fashion was observed in both CYP2D6 and human liver microsome incubations. On the other hand, the same experiment without the cofactor NADP+ resulted in no change of methadone concentration, showing that the disappearance of methadone was the result of an enzymatic activity and not of a binding and/or chemical degradation. During human liver microsome incubation, the loss of methadone was associated with the appearance of EDDP over time, whereas no EDDP peaks were observed during CYP2D6 incubation, confirming that CYP2D6 does not participate in the formation of EDDP.

In two other *in vitro* studies using rat and human liver microsomes, it was found that methadone strongly inhibits two typical CYP2D6 metabolic pathways, namely codeine *O*-demethylation (with a K_i of 0.3 μmol/L)[164] and dextromethorphan *O*-demethylation (with a mean K_i between 3 and 8 μmol/L),[165,166] which suggests that methadone definitely interacts with this enzyme.

Desipramine metabolism to 2-hydroxydesipramine is another specific marker of CYP2D6 activity.[167] *In vivo*, an interaction of methadone with CYP2D6 is also suggested by the 73–169% increase of desipramine blood concentrations in five patients following the introduction of methadone 0.5 mg/kg/day over 2 weeks.[168]

The interaction of fluoxetine with methadone is an interesting problem. Based on the K_m of methadone (545 μmol/L) and the K_i of fluoxetine (55 μmol/L), on the mixed type of inhibition, and on the typical plasma concentration during treatment which is around 1 μmol/L for both substances, it was estimated that fluoxetine and its metabolite, norfluoxetine, would inhibit to a limited extent (1.7 and 7%, respectively)[138] methadone *N*-demethylation, the metabolic pathway catalysed by CYP3A4 and possibly by CYP2C9 and CYP2C19.[137] These *in vitro* data seem to be confirmed by two *in vivo* studies that did not find any significant increase of blood concentrations of (*R*,*S*)-methadone after introduction of fluoxetine in patients under MMT.[122,123] On the other hand, when measuring the two enantiomers separately, fluoxetine 20 mg/day was found to significantly increase the concentration-to-dose ratio of (*R*)-methadone (mean increase 32%, range 4–52%), but not (*S*)-methadone, in seven patients under MMT.[40] As fluoxetine is a strong CYP2D6 inhib-

itor, this suggests that CYP2D6 preferentially metabolises (*R*)-methadone.

A very recent *in vivo* interaction study with paroxetine, another selective serotonin reuptake inhibitor, brings another argument for the involvement of CYP2D6 in methadone metabolism, with a preferential stereoselectivity towards the (*R*)-enantiomer. Paroxetine is a strong CYP2D6 inhibitor but a mild inhibitor of CYP1A2, CYP2C9, CYP2C19 and CYP3A4.[169] Thus, paroxetine, at a dosage of 20 mg/day, significantly increased (*R*)-methadone concentrations in a group of eight CYP2D6 extensive metabolisers by a mean value of 32%, while in two CYP2D6 poor metabolisers, (*R*)-methadone concentrations were not modified by the introduction of paroxetine (mean increase 3%).[124]

Stereoselectivity of CYP2D6 is also suggested by a panel study measuring the disposition of a 5–10mg single oral dose of racemic methadone in four extensive and four poor metabolisers, showing a significantly lower partial metabolic clearance of (*R*)-methadone in the poor metabolisers.[170] This study has however only been presented as a conference abstract. The involvement of CYP2D6 in methadone metabolism was also demonstrated in another recent study, where significant differences in the weight-adjusted steady-state concentration-to-dose ratios of methadone were found between CYP2D6 poor (n = 18), extensive (n = 228) and ultrarapid (n = 10) metabolisers.[171] The mean value of (*R*)-methadone concentration-to-dose ratio in the ultrarapid metabolisers group was only 54% of the value in the poor metabolisers ($p = 0.009$).[171] Interestingly, although the difference was nonsignificant ($p = 0.103$), 72% of the poor metabolisers and only 40% of the ultrarapid metabolisers were considered successful in their treatment.[171]

3.3 Other Cytochromes P450

An *in vivo* study examined the effect of sertraline, at dosages between 50 and 200 mg/day, on the steady-state trough plasma concentrations of methadone in 12 patients.[125] After 6 weeks, patients on sertraline showed a mean increase in methadone plasma concentration-to-dose ratios of 26% (SD 43%, range –32 to 118%). This increase was statistically significant when compared with another group of 19 patients on placebo for the same period of time ($p < 0.02$). On the other hand, the two groups did not differ with regard to adverse effects, i.e. the increase of methadone blood concentrations in the sertraline group apparently did not lead to patients experiencing effects of excess dosage. As sertraline is a mild inhibitor of CYP2D6, CYP3A4, CYP1A2, CYP2C9, and a mild to moderate inhibitor of CYP2C19,[169] and as the demethylation pathway of methadone leading to the formation of EDDP can be relatively easily inhibited (see section 3.1), an inhibition of one or of several of these isoenzymes could explain this result. It should be mentioned that after 12 weeks the plasma concentration-to-dose ratios tended to return toward baseline in the sertraline group, and the difference was no longer significant when compared with the placebo group.[125] An induction of methadone metabolism was proposed as a possible explanation for the results at week 12.[125] However, as sertraline plasma concentrations were not measured, and as it is known that compliance with antidepressants decreases over time,[172] it is also possible that decreased compliance at week 12 compared with week 6 might explain this result.

An *in vitro* study measuring the formation of EDDP from methadone using human liver microsomes suggested that, besides CYP3A4, CYP2C9 and CYP2C19 (but not CYP1A2) might also be involved in this metabolic pathway.[137] As a higher plasma clearance of (*R*)- and (*S*)-methadone was measured in four smokers as compared with four nonsmokers (see comments in section 3.2 on this study),[170] and as CYP1A2 is induced by smoke tar, it is possible that, like CYP2D6, CYP1A2 is involved in another metabolic pathway than the *N*-demethylation step. With regard to the induction of CYP1A2 by tobacco tar, it is of interest that patients who smoke more are significantly more likely to report problems of not feeling 'held' by their methadone dosage.[173] Although no

methadone blood concentrations were measured in that study,[173] one might speculate that induction of CYP1A2 in such patients might explain in part this result.

Ciprofloxacin, a quinolone antibacterial and a strong competitive inhibitor of CYP1A2, caused profound sedation, confusion and respiratory depression in a patient successfully treated with methadone for more than 6 years.[126] It has to be mentioned that the activity of CYP3A4 is also depressed by this drug.[126] Fluvoxamine, another selective serotonin reuptake inhibitor, is a strong CYP1A2 and CYP2C19 inhibitor and a moderate CYP2C9 and CYP3A4 inhibitor.[169] Fluvoxamine has been shown to increase the plasma concentrations of both enantiomers of methadone in six dependent subjects under MMT.[40,127] Interestingly, among the six patients who received fluvoxamine, two cases of withdrawal symptoms were reported when fluvoxamine was stopped, whereas no such cases were found in patients receiving fluoxetine, although this latter drug increases (*R*)-methadone plasma concentrations.[40,123,127] This can probably be explained by the very long elimination half-lives of fluoxetine and its metabolite, norfluoxetine (1–4 days and 7–15 days, respectively) as compared with fluvoxamine (17–22 hours).[174] Strong withdrawal symptoms were also described in patients receiving methadone and the antidepressant moclobemide after the interruption of the latter drug.[23] This could be due to the short elimination half-life of moclobemide (1–4 hours) and to the inhibition of CYP2D6 and CYP1A2 by this drug.[130]

In one patient receiving a stable drug regimen including methadone 70 mg/day, the addition of fluvoxamine resulted in hypoventilation, severe hypoxaemia and hypercapnia.[128] This case should however be interpreted with caution, considering the multiple comedications received by the patient, including diazepam, which may interact with methadone (see section 3.1), and spironolactone, which may increase methadone clearance.[59] In another case report, fluvoxamine was intentionally, and successfully, used as a blocking agent of methadone metabolism to eliminate opioid withdrawal symptoms in a patient enrolled in MMT who already received methadone 200 mg/day split in two daily doses and who exhibited rapid metabolism of methadone due to the intake of butalbital, a barbiturate and an inducer of the CYP3 and the CYP2 families.[129]

Fusidic acid is a steroidal drug used for the treatment of staphylococcal infections. HIV-1-infected patients, under treatment with (*R*)-methadone, developed clinical signs of methadone underdosage after 4-week therapy with fusidic acid, which might induce the CYP3A and CYP2C isoenzymes.[131] On the other hand, amitriptyline, a tricyclic antidepressant, decreases methadone clearance,[59] probably by an inhibition of the various CYP enzymes, including CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4.[132]

In rats, acute administration of ethanol elevates the concentration of methadone in the brain, probably by decreasing liver metabolism of methadone.[133] Using rat liver microsomes, ethanol has been found to inhibit the *N*-demethylation of methadone with a K_i of 32 mol/L (146 mg/dl), a value achievable after the acute ingestion of ethanol.[133] On the other hand, in the rat, chronic administration of ethanol induces liver metabolism and decreases brain and plasma concentrations of methadone.[134] This could be explained by an interaction of ethanol with CYP2E1, the ethanol-inducible form of CYP.[175] However, results from *in vitro* studies are not conclusive: although EDDP has been measured in supernatants of cDNA-expressed CYP2E1 following incubation with methadone in one study,[136] it has also been found that CYP2E1-specific antibodies did not inhibit the formation of EDDP,[137] whereas inconclusive results were found when testing with diethyldithiocarbamate, a chemical inhibitor of CYP2E1. A significant inhibition of EDDP formation was thus found in one study with 100 μmol/L diethyldithiocarbamate but not with 10 μmol/L,[137] while in another study no significant inhibition was measured with 100 μmol/L of the same inhibitor.[136] In a clinical study with five well-stabilised MMT

patients without evidence of liver disease and without history of alcohol abuse, the acute administration of 90ml of a 50% solution of ethanol did not modify the plasma concentrations of methadone.[134] Finally, disulfiram, a CYP2E1 inhibitor, does not significantly interact with methadone disposition,[134,176] which suggests that CYP2E1 does not significantly contribute to methadone metabolism.

4. Interindividual Variability

4.1 Pharmacokinetic and Pharmacodynamic Variabilities

The variability of CYP enzyme activities, which are genetically and environmentally determined, probably accounts for a substantial part of the interindividual variability in clearance and plasma half-life of methadone. The possible interindividual variability of P-glycoprotein activity on methadone disposition should also be considered.[68] Sequence variations in the P-glycoprotein gene have been recently described, with a significant correlation between a polymorphism in exon 26 and the expression and function levels of this transporter. Thus, individuals homozygous for this polymorphism had significantly lower duodenal P-glycoprotein expression and higher digoxin plasma concentrations after a standard dose.[177] CYP3A4 has been shown to be present both at the level of the liver and of the intestinal mucosa, with up to 30-fold variability of its activity in liver and up to 11-fold in gut.[158] Thus, in an *in vitro* study using 20 different human liver microsomes, the *N*-demethylation of methadone leading to EDDP formation, mainly mediated by this enzyme, presented a 20-fold interindividual variation.[135] With regard to CYP2D6, a more than 100-fold difference in activity has been found, with the existence of poor, extensive and ultrarapid metabolisers[178] (see section 3.2 for the consequence of this genotype on methadone blood concentrations). Large interindividual variabilities of the activities of CYP2C19, CYP2C9 and CYP1A2 have also been described, with the existence of genetically determined poor and extensive metabolisers for CYP2C9 and CYP2C19.[178,179] Recent research has shown that a very rapid activity of various isoforms of CYP (such as CYP2D6, CYP3A4 and CYP1A2) may lead to low blood concentrations of drugs metabolised by these isoforms and to therapeutic failures.[158,180-183] Finally, it should be mentioned that during MMT a production of antibodies against methadone has been demonstrated in some patients. Although binding of methadone to antibodies in such patients might change its pharmacokinetics, the clinical significance of this finding still remains to be demonstrated.[184]

The fact that methadone has several mechanisms of action (see section 1) probably contributes to the marked interindividual variability in the relationship between the concentration of methadone and its pharmacological effect when measuring outcomes such as pain relief,[24,51,55,63,185-187] rated well-being, mood states or withdrawal symptoms.[45,188,189] Genetic polymorphisms of various receptors, including the μ opioid receptor[190] or the dopamine D_2 receptor,[191] could also contribute to this variability. With regard to the latter receptor, it is known that opioids and other drugs of abuse increase brain dopamine concentrations and enhance neurotransmission in the nucleus accumbens of animals.[191] Considering the extensive connections of the nucleus accumbens with limbic areas involved in emotion, the activation of dopaminergic neurotransmission in the nucleus accumbens is thought to be involved in the motivational and reward properties of opioids and other drugs of abuse.[191] Interestingly, mice lacking D_2 dopamine receptors show an absence of opioid rewarding effects.[192]

A study examined recently the frequency of the *Taq*I A1 allele, an allele which is associated with a reduced central dopaminergic function of the *DRD2* gene, in a total of 95 Caucasian opioid-dependent patients who were followed over a 1-year period in MMT.[191] Twenty-two of these patients discontinued the methadone programme (group A), 54 had successful treatment (group B) and 19 had a poor treatment outcome, which was

assessed in particular by a continued abuse of heroin (group C). The frequency of the A1 allele was the highest in group C (42.1%), followed by group A (22.7%) and was the lowest in group B (9.3%); the more than 4-fold higher frequency of the A1 allele in the poor treatment outcome group compared with the successful treatment outcome group was highly significant ($p = 0.00002$). These results suggest that, in opioid-dependent patients who are engaged in MMT, a poor prognosis is expected for carriers of the DRD2 A1 allele. Another interesting finding was that the average use of heroin (g/day) during the year prior to study entry was more than twice as great in patients with the A1+ allele (A1/A1 or A1/A2 genotype) than in those with the A1– allele (A2/A2 genotype) [$p = 0.003$]. This could explain why the carriers of the DRD2 A1 allele are more likely to fail in their treatment, if one assumes that opioid-dependent patients who, prior to treatment, had consumed high amounts of heroin, are more likely to fail in a MMT than those who had consumed low amounts of this opioid, particularly when the administered daily dosages of methadone during MMT are low.[191]

4.2 Interindividual Variability of Blood Concentrations

The administered dosage is an important determinant of methadone blood concentrations. In a study including 31 patients under MMT, a significant correlation was observed between (*R*,*S*)-methadone plasma concentration and methadone dosage corrected for bodyweight, with an r^2 of 0.67 ($p < 0.001$).[193] When measuring (*R*)- and (*S*)-methadone concentrations over a 24-hour period in 18 patients under MMT, (*R*)- and (*S*)-methadone dosages were significantly correlated with the AUC during the administration interval, with r^2 values of 0.68 and 0.47, respectively.[39] In another study during which most of the patients stayed at the clinic for a couple of days prior to the investigation to ensure compliance, r^2 values of 0.29 and 0.19 were calculated between (*R*)- and (*S*)-methadone trough concentrations and methadone dosages in a group of 25 patients who complained of low dosages.[45] Significant correlations were also calculated when relating (*R*)- and (*S*)-methadone plasma trough concentrations to the drug dosage corrected for bodyweight in two studies with 50 ($r^2 = 0.48$, $p < 0.001$; $r^2 = 0.12$, $p < 0.05$, respectively)[194] and with 211 ($r^2 = 0.33$, $p < 0.001$; $r^2 = 0.12$, $p < 0.0001$, respectively) MMT patients.[99] In the latter study, when incorporating only the data from patients without any comedications, a higher r^2 value was calculated [$r^2 = 0.42$, $p < 0.001$; $r^2 = 0.23$, $p < 0.0001$; (*R*)- and (*S*)-methadone, respectively],[99] as comedications are able to introduce a further variability by inhibition or induction of methadone clearance.[99] A factor that could contribute to the higher r^2 value found in one study[39] was that methadone dosages were correlated with the AUC during the administration interval[39] instead of the trough plasma concentrations.[45,99,193,194] Another factor that could contribute to the lower r^2 value calculated in the two latter studies,[99,194] as compared with the two former,[39,193] could be the larger number of patients, which increases the probability of including subjects with very high or very low metabolic clearance. In the two latter studies,[99,194] the range of methadone dosages was broader, ranging from 30 to 230 mg/day[194] and from 5 to 350 mg/day,[99] as compared with 3–100 mg/day[193] and 7.5–130 mg/day.[39] This represents another possible source of variability, as autoinduction of methadone metabolism[49,58] might be dose-dependent.[99]

Thus, although methadone blood concentrations are significantly correlated with dosage,[39,99,193,194] when considering a large number of patients the dosage explains less than 50% of the variability of the concentrations of (*R*)-methadone, even in patients without comedications.[99] When measuring (*R*) and (*S*)-methadone steady-state concentrations in 18 patients under MMT, there was a 4- to 6-fold interindividual variability after the values were normalised to a 70mg dose of racemic methadone.[39] A recent study in 18 patients in MMT with controlled administration of methadone during 3 weeks showed up to a 5-

fold interindividual variability in the trough plasma concentrations of (*R*,*S*)-methadone for the same dosage.[65] Although significant, a poor correlation ($r^2 = 0.04$, $p = 0.048$) was found between methadone dosages and methadone serum concentrations in a study with 32 patients in MMT.[140] In another study with 211 patients, for a given dosage, (*R*)-methadone trough blood concentrations corrected for bodyweight varied up to 17-fold in patients without comedications (mean ± SD, 112 ± 54; range, 19–316 μg • kg/L • mg), whereas they varied up to 41-fold in patients with comedications (mean ± SD, 111 ± 64; range, 10–407 μg • kg/L • mg).[99] It has been stated that, when compliance is good, plasma concentrations and methadone dosages are highly correlated.[195,196] Although the problem of compliance must not be neglected, it is important that this statement not be understood as an indication that only noncompliance or poor compliance can explain unexpectedly high or low blood concentrations. Indeed, methadone, like many other drugs, displays a wide dose–plasma concentration relationship, typical of drugs that are metabolised by CYP3A4 and/or a polymorphic enzyme such as CYP2D6.

Studies performed in conditions where compliance problems can be excluded also show large interindividual variabilities in methadone concentrations. A trial performed in a closed metabolic ward with a group of 12 patients showed a 3-fold variation of (*R*,*S*)-methadone trough steady-state concentrations corrected for bodyweight after 26 days, with a fixed oral dosage of either 40 (six patients) or 80 (six patients) mg/day.[58] In another study, also performed in a closed metabolic ward, (*R*,*S*)-methadone trough steady-state concentrations showed a 7- (with 30 mg/day) and > 10-fold (with 60 mg/day) difference in a group of 17 patients under MMT.[197] Interindividual variabilities of methadone pharmacokinetics have also been demonstrated in single-dose studies involving methadone-free subjects in whom compliance problems can be excluded. In one study, after oral administration of methadone 20mg to a group of eight volunteers, a 7-fold difference was found for AUC_{48}.[47] Another study demonstrated a large variability in AUC_{24} normalised to a 10mg dose of methadone in 17 methadone-free opioid users (see figure 2).[50] Finally, it must be mentioned that, despite this large interindividual variability, there is a good relationship between dose and plasma concentrations within an individual,[48,198] provided that no inducing or inhibiting comedications are introduced or removed (see also section 7).

4.3 Blood Concentration, Elimination Half-Life and Treatment Success

Because of the large variability of methadone concentrations, several studies have aimed to find the optimum methadone blood concentration for effective methadone maintenance therapy.[6,189,197,199-207] In some studies, such a threshold could not be found,[189,203-205,207] whereas various values ranging from 50 to 600 μg/L of (*R*,*S*)-methadone have been proposed by other investigators.[6,197,199,201,202,206] A concentration of 400 μg/L is now often considered as necessary to provide stabilised maintenance, and is used as a reference value when performing TDM of methadone.[15,207] However, to our knowledge, studies to validate such a threshold are lacking.

As the opioid effect of (*R*,*S*)-methadone resides mainly in the (*R*)-enantiomer, and considering the wide interindividual variability of the (*R*)-/(*S*)-methadone ratio measured in blood,[33,40-45] it could be more reliable to measure the concentration of (*R*)-methadone than (*R*,*S*)-methadone to correlate blood concentrations with therapeutic outcome. This hypothesis is supported by a study which showed that (*R*)-, but not (*S*)-methadone, trough concentrations were significantly correlated with several items of the Subjective Opiate Withdrawal Scale in a group of 25 patients who complained of low dosages.[45] In a recent study, trough plasma concentrations were measured in 180 patients in MMT.[99] The mean ± SD methadone dosage received by the patients was 100 ± 58 mg/day (range 5–350 mg/day) and the therapeutic response was defined by the absence of illicit opioids in urine samples collected during a 2-month

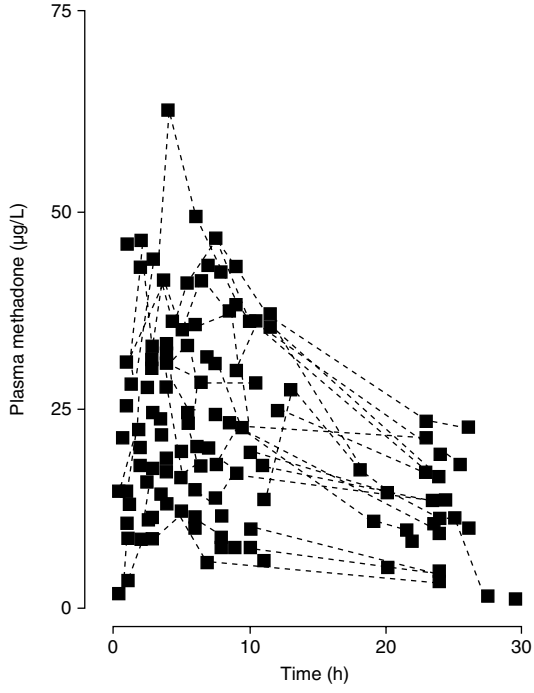

Fig. 2. Plasma methadone concentrations in 17 opioid users after oral administration of a single dose of methadone. Data are normalised to a 10mg dose of methadone HCl (reproduced from Wolff et al.,[50] with permission from Blackwell Science Ltd).

period. (*R*)-Methadone (at 250 µg/L, $p < 0.002$) and (*R*,*S*)-methadone (at 400 µg/L, $p < 0.05$), but not (*S*)-methadone, concentrations were associated with therapeutic response. Interestingly, the specificity of the threshold was found to be higher for (*R*)-methadone (93%) than for (*R*,*S*)-methadone (81%). In other words, only 7% of the nonresponders had plasma concentrations of (*R*)-methadone above 250 µg/L, whereas this proportion was 19% at the cutoff value of 400 µg/L of (*R*,*S*)-methadone.[99] On the other hand, this study also showed that a majority of patients already responded to their treatment, i.e. stopped taking illicit opioids, with (*R*)- and (*R*,*S*)-methadone blood concentrations lower than these threshold values: 75 and 68% of responders, respectively, had plasma concentrations below these values. Thus, if a patient responds well to methadone, there is really no need to increase his/her trough blood concentration if it is low. It is well known that, besides pharmacokinetic factors, pharmacodynamic parameters, such as variability in receptors[191] and psychological or social factors,[1,22] are very important for the success of MMT.

Altogether, these results suggest that TDM of methadone is not necessary for every patient. However, in case of nonresponse, i.e. continued use of illicit opioids, trough plasma concentrations of 400 µg/L for (*R*,*S*)-methadone, or preferably of 250 µg/L for (*R*)-methadone, might be used as target values.[99] Interestingly, due to the high interindividual variability of methadone blood concentrations for a given dosage, obtaining concentrations of 250 µg/L of (*R*)-methadone theoretically requires dosages of racemic methadone as low as 55 mg/day or as high as 921 mg/day in a 70kg patient without any comedication.[99]

These results are in agreement with a report on a group of 56 patients who were still using illicit opioids despite being prescribed up to 80 mg/day of methadone and despite supervised administration. Trough blood (*R*,*S*)-methadone concentrations were determined in these patients, and when below 300 µg/L (45 of the 66 tests), dosage increases of 15 mg/day were allowed each week, with total dosages reaching up to 330 mg/day.[19] This resulted in a marked reduction of heroin use, as shown by random urine testing, and in improvement in self-reported use of benzodiazepines, alcohol and stimulants.[19]

Besides the intrinsic value of assuring adequate trough blood concentrations of methadone, it is very likely that the elimination half-life of methadone is also important for determining the appearance of withdrawal symptoms.[188] In a study that examined concentration-effect relationships in patients with and without withdrawal symptoms, a significant correlation ($r^2 = 0.36$, $p < 0.001$) was found between the maximum rate of decline in plasma concentrations of (*R*,*S*)-methadone and the mean number of withdrawal symp-

toms during one administration interval.[188] Differences in the degree of mood change between subjects who do or do not experience significant withdrawal symptoms might also be due to variations in the rate of decline of plasma concentration from peak to trough.[189] These results are in agreement with those of another study that found significantly lower elimination half-lives in eight patients reported as therapeutic failures in MMT as compared with an unselected group of 12 patients stabilised on methadone for 25 days (mean ± SD, 24.5 ± 2.6 versus 34.0 ± 7.0 hours, $p < 0.001$). This might also be explained by a smaller volume of distribution in the former group.[52]

For patients with a very short half-life (values lower than 5 hours have been reported when a strong inducer was given as comedication[59]), besides the necessary increase of methadone total daily dosage, a splitting into several doses is also necessary. Alternatively, another opioid agonist with a longer elimination half-life, such as levacetylmethadol, might be considered. Levacetylmethadol is interesting in that it is a prodrug, with a relatively short half-life (7 hours), and its long duration of action is attributed to its metabolites norlevacetylmethadol and dinorlevacetylmethadol (half-lives of greater than 48 hours). As the biotransformation of levacetylmethadol to its metabolites is mediated by CYP3A4,[136] it appears to be a particularly suitable drug in patients with an increased drug clearance due to high CYP3A4 activity (but see section 6 for the cardiotoxicity of levacetylmethadol).

5. Optimal Dosage

Several studies, most of them with randomised double-blind design, have consistently shown that patients receiving methadone dosages in the range of 60–100 mg/day performed significantly better on measures of retention, opioid use and opioid craving than those receiving 20–50 mg/day.[8-14] In one study on 238 heroin-dependent subjects, a clear inverse correlation was found between dosage increase and risk of leaving treatment; the relative risk of leaving treatment was halved in the group of patients receiving 60–79 mg/day as compared with those receiving less than 60 mg/day, and halved again for those who received at least 80 mg/day.[14] A study with patients in MMT over an 18-month period showed significantly ($p < 0.05$) higher daily methadone dosage (mean ± SD, 67 ± 2 mg/day) in the 103 patients still in the treatment at the end of the study than in the 11 patients who left treatment (mean ± SD, 56 ± 9 mg/day).[208] Also, during the study, significantly more patients stopped regular cocaine abuse (69%) than started using cocaine (10%, $p = 0.02$).[208]

A 52-week randomised double-blind clinical trial with 75 patients receiving 80 mg/day of methadone, and 75 patients receiving 30 mg/day of methadone, showed that the former performed significantly better than the latter on measures of retention over the entire period of the study (retention at 52 weeks of 31 and 19%, respectively), opioid use and opioid craving.[12] Another 28-week double-blind study with 28 patients on 65 mg/day, and 30 patients on 20 mg/day, showed a significant difference between the two dosages on the rates of opioid-positive urinary test (45 versus 72%, $p < 0.005$).[13] Although the rate of completion of the 24-week trial for the methadone 65 mg/day group was 64.3%, and only 46.7% for the 20 mg/day group, this difference fell short of statistical significance ($p = 0.09$).[13] This might be explained, at least in part, by the low number of subjects included in each group and by the relatively low methadone dosage in the high-dosage group. A 40-week randomised double-blind trial in 192 patients showed that dosages in the range of 80–100 mg/day resulted in a significantly larger decrease of illicit opioid use than dosages ranging from 40 to 50 mg/day (53.0% of opioid-positive urine samples versus 61.9%, respectively, $p = 0.05$).[11] Another 17-week study, also with a double-blind randomised design, showed a higher number of treatment days (mean ± SE, 105 ± 4 versus 70 ± 4, $p < 0.001$), a higher percentage of patients with 12 or more consecutive opioid-negative urine specimens (28 versus 8%, $p = 0.005$), and a lower self-evaluation of the severity of the drug

problem at the time of the last report (38 versus 53, scale 0–100, p = 0.002) for patients receiving dosages of methadone between 60 and 100 mg/day (n = 55) than for patients receiving 20 mg/day (n = 55).[8]

Despite this compelling evidence of the necessity to use effective dosages of methadone, it is a real public health problem that low dosages are still prescribed in many places, not for pharmacological but for political, psychological, philosophical or moral reasons.[15,16] Thus, in a national survey in the US published in 1992, 21% of patients were found to receive dosages of methadone of less than 40 mg/day, 25% of all included centres had an upper dosage limit between 20 and 60 mg/day, whereas only 45% of the centres had an upper dosage limit between 61 and 80 mg/day.[16] The situation seems to have slowly improved, as the US average methadone daily dosage was 45, 46, 57, 59 and 69mg in 1988, 1990, 1993, 1995 and 1998, respectively.[209,210] The most recent survey found that the percentage of patients receiving methadone dosage levels less than the recommended 60 mg/day decreased from 79.5% in 1988 to 35.5% in 2000, and concluded that although efforts to improve methadone treatment practices appear to be making progress, many patients are still receiving substandard care.[211]

Another dramatic consequence of the use of too low methadone dosages is the fact that it may lead to the misperception that methadone is not an effective treatment, thus decreasing the number of patients enrolled in a treatment of lifesaving importance. Dose policy may vary between countries, states and clinics, and prescription of low dosages of methadone is sometimes based on the assumption that prescribing high dosages would be too permissive.[16] Without entering into moral considerations, it can however be argued that, besides the irrationality of prescribing dosages that are marginally adequate, the policy of using low methadone dosages creates inequality between patients, whose metabolic clearance is genetically and environmentally determined. Some prescribers and some patients also believe that the detoxification phase from methadone is easier, and/or more successful, with continued low-dosage methadone throughout MMT. This assumption is not supported by a recent study showing that, following a 30-week period of MMT with a daily dosage of 40–50mg or of 80–100mg, the lower proportion of positive urine samples measured in the high-dosage group during the MMT persisted during the subsequent period of methadone withdrawal (46.4 versus 66.9%, p = 0.002).[11] Nineteen (33%) out of 57 patients in the high-dosage group, and only 11 (20%) out of 54 patients in the moderate-dosage group, completed detoxification. Thus, an even higher proportion of patients in the high-dosage group completed detoxification. Although this difference was not significant (p = 0.12), one can speculate that the success of detoxification is not hampered by high dosages of methadone, but favoured by a MMT period during which the consumption of illicit opioids is either suppressed or at least kept to a minimum. High dosages may be required for an appropriate stabilisation period, minimising the contacts between the patient and the drugs scene and allowing a progressive alleviation of conditioned stimuli assumed to favour relapses.

Although the above-mentioned studies demonstrate that methadone dosages ranging from 60 to 100 mg/day are effective for the majority of patients, it is now increasingly acknowledged that dosages in excess of 100 mg/day are required for optimal benefit in some patients.[11,20,209] Thus, although the introduction of MMT at dosages between 60 and 100 mg/day results in a strong decrease of opioid use in most opioid-dependent patients, with many individuals completely stopping their use of illicit opioids, some of them still complain about withdrawal symptoms, and their illicit use of opioids remains significant. For example, a 17-week study in 55 patients receiving methadone dosages between 60 and 100 mg/day revealed a mean self-report of opioid use of four times a week, and 62% of the urine samples were still positive for opioids.[8] A 30-week study in 95 patients receiving methadone dosages between 80

and 100 mg/day showed 53% of opioid-positive urine samples,[11] a lower proportion that can be attributed to the higher dosage in the latter study, and possibly to the longer duration of treatment, allowing more significant changes in lifestyle. Dole observed long ago that 100 mg/day of methadone is not sufficient for some patients,[6] and his original study, establishing the efficacy of methadone for decreasing heroin use, was conducted with daily dosages ranging from 50 to 150mg.[7] However, in practice, 100 mg/day is considered by many practitioners as a maximum dosage, and no controlled studies have been carried out exploring the use of methadone dosages higher than 100mg. Nevertheless, methadone dosages in excess of, and sometimes largely in excess of, 100 mg/day are currently used in an increasing number of centres, and some papers have already been published on this topic.

Byrne reported that, in his practice, patients on MMT who continue to crave or use heroin are permitted gradual dosage increases, without an arbitrary maximum.[17] Among 121 patients under treatment over a 6-month period, 10 were taking dosages between 150 and 350 mg/day, whereas the remaining 111 were taking between 2.5 and 145 mg/day.[17] Although no data on the urine tests for the low-dosage group are available over that period, which would allow a meaningful interpretation, it was reported that 79 urine tests were available on a random basis in eight of the ten patients receiving high dosages and that only one of those urine samples was tested positive for opioids.[17]

In the Addiction Psychiatry Unit of Sienna, Pisa and Cagliari (Italy), where there are no limits regarding treatment dosage or duration, patients with psychiatric comorbidity require higher methadone dosages for clinical stabilisation than do those without such a condition.[18] Thus, 19 patients with bipolar psychiatric comorbidity required an average stabilisation dosage of 146 ± 80 mg/day (mean ± SD) compared with 99 ± 49 mg/day for 52 patients whose main diagnosis was opioid dependence.[18]

In an open study, Shinderman and Maxwell identified a group of 164 patients who, despite methadone dosages up to 100 mg/day, had high rates (87%) of continuing illicit opioid use.[20] These patients, assigned to high dosages, received clinically guided dosage increases, resulting in a mean dosage of 211 mg/day (range 120–780 mg/day) without signs of toxicity. This cohort was compared with a randomly selected control group receiving an average dosage of 69 mg/day (range 10–100 mg/day) drawn from the clinic population. The fraction of urine samples tested positive for illicit drugs decreased from 87 to 3% in the high-dosage group and from 55 to 36% in the control group. The 1-year retention in treatment rate was much higher for the high-dosage group (86%) than for the general clinic population (35%). In agreement with the above-mentioned study,[18] the proportion of patients with comorbid psychiatric diagnoses was higher (63%) in the high-dosage group than in the control group (32%).[20] Finally, it was also reported that titration of methadone dosage against benzodiazepine and alcohol abuse was very useful in motivated patients, a result which is in agreement with the abovementioned report of Byrne, where an improvement in self-reported use of benzodiazepines, alcohol and stimulants was noted following adequate titration of methadone dosage.[19] Such an effect might tentatively be explained by the use of benzodiazepines and alcohol to compensate for an inadequate dosage of methadone.[20] A 152-week follow-up study of the abovementioned patients[20] confirmed the better retention (61 vs 46%) and lower rates of positive urine toxicologies (16 vs 37%) in the group of patients receiving high doses of methadone (≥100 mg/day, mean dose: 211 mg/day of methadone, n = 144; after 152 weeks, mean dose: 285 mg/day; range: 13–1100 mg/day) as compared to a control group (<100 mg/day, mean dose: 65 mg/day, n = 101; after 152 weeks, mean dose: 94 mg/day; range: 10–500 mg/day). Of importance is the fact that mortality was not statistically different in the high-dose group (2/144, 1.4%) as compared to the control group (2/101, 1.9%).[212]

Thus, in the absence of prospective randomised studies examining the efficacy of methadone dosages above 100 mg/day, these observations suggest that such studies are needed. Based on the data presently available and on the interindividual variability of methadone kinetics and blood concentrations for a given dosage, our opinion is that no convincing data argue against the use of methadone dosages higher than 100 mg/day, provided that all necessary steps are taken to ensure the safety of treatment.

6. Adverse Effects and Toxicity

The adverse effects and toxicity of methadone are similar to those described for morphine, another full opioid agonist. These include respiratory depression, nausea, vomiting, dizziness, mental clouding, dysphoria, pruritus, constipation, increased pressure in the biliary tract, urinary retention and hypotension.[213] Long-term treatment with methadone results in tolerance to its analgesic, sedative and euphoric effects, with minimal toxicity. Two important problems are discussed in the present review: the first is related to the respiratory depression caused by opioid agonists in overdose, and the second to cardiac rhythm disorders.

6.1 Respiratory Depression

Respiratory depression can be a serious problem, particularly in patients initiating MMT, who are only partially tolerant to opioid agonist effects. The risk of overdose is highest during the induction period.[214] Then, although MMT significantly reduces the risk of sudden death from all causes including heroin abuse, compared with subjects not included in programmes, the risks in the first stages of MMT are higher than those outside treatment, since some clients are not opioid-dependent, are prescribed too high a dosage, misuse other drugs during treatment or have some form of natural disease increasing the sensitivity to methadone.[214] The risk factors to be identified are the starting dosage, the use of other drugs, e.g. alcohol, benzodiazepines and heroin, and general health.[214] For example, ten deaths were reported for heroin-dependent subjects starting MMT.[215] These deaths could be due, in part, to a reduced clearance of methadone and/or to illicit intake of supplementary methadone doses, as suggested by a high methadone blood concentration (mean, 710 μg/L; range, 300–2520 μg/L), and/or to the high dosage used on starting MMT (mean 60 mg/day).[215] For a nontolerant adult, a toxic dose of methadone is in the vicinity of 40–60mg.[22] When beginning MMT, the initial dose should be between 20 and 40mg (20mg for patients with a history of dependence but who have not used opioids recently).[22] A further dose of up to 20mg may be safely administered on the first day, but only after it has been verified that no signs of intoxication occurred in the first 4–6 hours and that signs of withdrawal are present.[22] Dosages may be increased daily, in the induction period, by up to 10 mg/day in the presence of withdrawal signs and the absence of intoxication, for the first 2 weeks, usually not to exceed 60 mg/day in the first 7 days and not to exceed 100 mg/day in the following week.

In tolerant subjects, after the first weeks of induction, the rate of dosage increase is probably the most important factor in overdose risk. Even with high dosages, problems related to respiratory depression are not expected when the dosage is increased stepwise, in response to clinical signs and symptoms, at intervals sufficient to reach steady-state conditions prior to another increase (typically, dosage increase up to 20% per week). In the study of Shinderman and Maxwell, no adverse events occurred in the 164 patients treated with high dosages.[20] By the middle of 2000, the number of patients prescribed methadone dosages in the range of 110–1400 mg/day in Shinderman's practice had increased to 600 (M. Shinderman, personal communication, August 2000).

It is important to mention that full tolerance to the opioid effects of methadone may never fully develop, even after long-term MMT. Thus, even in tolerant patients, a too rapid methadone dosage increase or the introduction of strong inhibitor(s) of methadone metabolism might be a serious prob-

lem, in particular when several CYP isoenzymes are simultaneously inhibited. A recent case report describes heavy sedation, confusion and respiratory depression (antagonised by naloxone) in a patient treated for pain with methadone 140 mg/day for more than 6 years after the introduction of ciprofloxacin, a CYP1A2 and CYP3A4 inhibitor.[126] The adverse opioid effect was even more severe when she simultaneously received ciprofloxacin and fluoxetine, the latter being a CYP-2D6, CYP3A4, CYP2C9 and CYP2C19 inhibitor.[126,169]

6.2 Cardiac Rhythm Disorders

It is known that many drugs, including psychotropic agents[216] and drugs of abuse such as cocaine, can induce ventricular arrhythmia. Thus, antipsychotics and antidepressants are associated with an increased risk of sudden death.[216,217] It has recently been shown that the administration of levacetylmethadol, a drug with a chemical structure very close to that of methadone, also given as a maintenance treatment for opioids, may result in rare cases (less than 1%) of life-threatening cardiac rhythm disorders. Principally, prolongation of the QT interval has, in some cases, resulted in severe arrhythmia (torsade de pointes).[218] The European Medicines Evaluation Agency (EMEA) recommended, in December 1999, that levacetylmethadol should not be administered to patients with known or suspected QT prolongation (corrected QT, QT_c, >440 msec).[218,219] A more recent statement (EMEA, December 2000) recommended that prescribers should not introduce any new patients to levacetylmethadol therapy, and in 2001 (EMEA, April 2001) it was recommended to suspend the marketing authorisation for levacetylmethadol in the European Union.[218,220] However, the American Methadone Treatment Association advised that concern with the prolonged QT_c interval phenomenon 'should not deter the use of LAAM in individuals who would prefer LAAM and do benefit from its use' in conjunction with the necessary precautions.[221] It is very likely that these recommended procedures will be subject to change in the future as more is learned about the risks associated with use of levacetylmethadol.

In an *in vitro* test with isolated guinea-pig heart, high concentrations of (*R*,*S*)-methadone were found to affect several parameters of cardiac conduction through unspecific mechanisms different from the stimulation of opioid receptors.[222] Dextropropoxyphene, an analgesic with low opioid potency and also with a chemical structure related to methadone, may cause fatal poisoning when taken in overdose because of its membrane stabilising activity.[223] With a test measuring protozoan motility as an indirect marker of drug-induced conduction disorders, methadone can block nerve conduction because of its membrane stabilising activity, potentially causing cardiac arrhythmia or cardiovascular collapse.[223] In the abovementioned cases of deaths reported at the start of MMT, cocaine, dextropropoxyphene or alcohol may have interacted with the effects of methadone, potentiating its activity.[215,223]

In human cardiomyocytes, the HERG potassium current represents the rapid component of the delayed rectifier potassium current and is the target for many drugs that cause slowing of cardiac repolarisation, an effect that is often associated with the development of torsade de pointes.[224] It has been reported very recently that (*R*,*S*)-methadone blocks HERG current in transfected HEK cells with an IC_{50} value of 9.8 μmol/L (3032 μg/L), suggesting that methadone could contribute to cardiac complications when high-dosage methadone is prescribed.[224] In another recent study, ECG recordings in an inpatient setting were compared for age, sex and drug treatment.[217] Among the 260 subjects with a QT_c above 420 msec, 78 (38%) were methadone users, compared with the expected proportion of 20%, with an average QT_c of 446 msec.[217] However, all methadone users received one (22%) or more (78%) antipsychotics, which may themselves prolong QT.[217]

In Shinderman's clinics, three very high-dosage patients (600 mg/day or more) had documented torsade de pointes in the last 2 years, and since November 2000 an ECG has been required for ev-

ery patient with a methadone dosage higher than 500 mg/day. Presently, this practice has not demonstrated that administration of very high methadone dosages alone is associated with clinically significant QT prolongation. Other factors, such as familial or personal history of cardiac problems, comedications that prolong the QT interval and methadone-comedication interactions that result in supratherapeutic concentrations of either or both drugs, appeared to be more important than methadone dosage itself in these three cases of torsade de pointes (M. Shinderman, personal communication, February 2001).

Recently, a case report of methadone-induced long QTc and "torsade de pointe" has been described.[225] A retrospective case series on 17 methadone-treated patients who developed torsade de pointes has also been published very recently.[226] High (>100 mg/day, two subjects) or very high doses (>200 mg/day, 11 subjects) of methadone were given to a majority of patients in that group, resulting in a high mean daily dose (mean ± SD, 397 ± 283 mg/day; range, 85–1000 mg/day). However, it has to be mentioned that four patients were prescribed doses between 65 and 97 mg/day. The mean QTc interval was 615 msec, and 14 patients had known risk factors for arrhythmia, such as hypokalaemia (seven subjects), or were taking other drugs that could prolong the QT interval. On the other hand, no methadone blood levels were available.[226]

More studies are clearly needed. However, until such results are available, it seems judicious to consider that methadone can, at presumably high blood concentrations, alone or with concomitant use of other drugs and/or with the existence of other factors such as congenital long QT syndromes,[227] alter QT and induce life-threatening arrhythmia.

From a practical point of view, major cardiotoxicity of methadone when used up to 100 mg/day seems unlikely, as it has been administered for over 30 years to several hundreds of thousands of patients at such dosages without evidence of an increased incidence of arrhythmia. However, an under-reporting bias might exist in the methadone treatment population where it may be assumed that sudden death is the result of narcotic overdose.[226] At present, the administration of methadone is not considered to require a preliminary ECG check, and it does not seem justified to recommend it on a general basis unless the drug is given to patients with known or suspected QT prolongation. Moreover, a potential cardiotoxicity of methadone would be more likely to be related to blood concentrations than to dosages. Many patients requiring dosages higher than 100 mg/day, because of high clearance,[143] would have (*R*,*S*)-methadone blood concentrations in the same range as those measured in patients stabilised at 100 mg/day or less, typically up to 800 μg/L of (*R*,*S*)-methadone.[98,99] One could thus consider that patients on high dosages but with usual blood concentrations do not present higher risks of cardiotoxicity induced by methadone. This, however, does not take into account possible cardiotoxicity induced by one of the various methadone metabolites. In such a case, low or normal methadone concentrations may be detected in patients with high metabolic clearance, yet high and toxic metabolite concentrations may be formed and accumulate. However, at this stage and in the absence of studies examining the possible cardiotoxicity of methadone metabolites, no conclusions can be drawn on this point.

Presently, based on the assumption of cardiotoxicity mainly mediated by methadone and not by its metabolite(s), it does not seem justified to recommend an ECG with usual blood concentrations, up to 800 μg/L, except again for patients with known or suspected QT prolongation. On the other hand, it was reported in some studies that very high methadone dosages, resulting in increased concentrations of (*R*,*S*)-methadone (from 800 to 1800 μg/L), were necessary for a few patients to reach stabilisation, i.e. before withdrawal symptoms disappeared and/or before they stopped the intake of illicit drugs.[20,209] In these patients, pharmacokinetic factors, i.e. high clearance resulting in low methadone blood concentrations, clearly cannot

explain continued use of illicit opioids, but other factors, such as variabilities of receptors,[190,191] can be tentatively proposed (see section 4.1). We believe that patients with definitely high methadone blood concentrations should be carefully monitored with regard to their cardiac function, until more studies on possible cardiotoxicity at such concentrations are available. An alternative strategy would be that, in such cases, an ECG is performed in every patient for whom an increase of methadone dosage is planned beyond a particular threshold. A value of 500 mg/day was chosen in Shinderman's clinics, but a more conservative (lower) cutoff value could also be used, in particular when comedications with a potential for cardiotoxicity or for dramatically increasing methadone concentrations are administered. In any case, when such ECGs are performed, it is advisable to record them in steady-state conditions at the peak plasma concentration, i.e. about 4 hours after methadone intake.

It is important to state that methadone, like any other drug, may induce adverse effects and/or toxicity. This has to be taken into account and adequately handled. However, this argument should not be used to deny patients an effective dosage, provided that steps are taken to ensure treatment safety. Adverse effects and concerns about potential toxicity induced by methadone have to be balanced against the fact that, for example in the US, illicit drug use is responsible for more than 25 000 deaths annually and for $US100 billion in total economic costs, heroin emerging as the major contributor to this societal problem.[3]

7. Therapeutic Drug Monitoring

TDM of methadone does not represent a necessity in the management of patients, since a careful clinical follow-up of objective signs and subjective symptoms is sufficient for dosage titration.[6,20] However, the prescriber might find it useful in selected situations, for example, when dosages largely in excess of 100 mg/day are given to patients, and it is feared that such dosages might lead to very high methadone concentrations and potential cardiotoxicity.

Based on the results of the abovementioned study showing significant associations between therapeutic response (i.e. no consumption of illicit opioids) and plasma concentrations of (*R*)-methadone or (*R*,*S*)-methadone,[99] TDM of methadone could be also useful in cases of treatment failure, i.e. persistence of withdrawal symptoms or intake of illicit opioids. Target values of 250 μg/L or 400 μg/L can be recommended for (*R*)- or (*R*,*S*)-methadone, respectively (see section 4.3). In this indication, TDM should only be performed after a sufficient period of adequate dosages (at least 60 mg/day, but preferably 80–100 mg/day). In our experience, the demonstration in patients of low methadone blood concentrations, presumably due to high clearance, can be of value for overcoming the fear of the prescriber and/or of the patient to increase the dosage.

TDM of methadone can also be of considerable help in situations where blood concentrations are expected to change markedly, such as upon introduction of a comedication or during pregnancy.[228] On introducing a drug known to induce methadone clearance, a simple TDM of methadone before and after the introduction of the inducing agent can be helpful for adapting the dosage.[152] This helps to diminish the patient's discomfort due to severe withdrawal symptoms. In particular, when it is known that the comedication is a strong inducer and if there is no other choice (e.g. one antiviral drug chosen because of a particular profile), TDM allows a quicker adaptation of the dosage. Without TDM, adaptation could take months because of the necessary slow dosage increase for fear of overmedication. TDM may also be useful for convincing patients to increase their methadone dosage and for avoiding that he/she stops comedication for withdrawal symptoms, as it has been described with antiviral drugs.[96,97,152] TDM can also be used for dosage decrease. Thus, in a stabilised patient, upon introduction of a comedication which is known to be an inhibitor of methadone clearance, TDM helps to decrease the

dosage and to make the patient accept the decrease. It is important to stress that the extent of a drug interaction is difficult to predict. Thus, on prescribing a drug that inhibits a particular isoform of the CYP family, it is expected that a patient with a low CYP activity will not be affected to the same extent as another with a high CYP activity.

It has also been suggested that TDM could be helpful for the problem of methadone diversion.[196] Some patients are assumed to take advantage of their take-home dose privilege to divert methadone and sell it. Although, in our opinion, these patients represent only a small minority, in some centres the fear of such diversion may prevent access to take-home doses in patients entirely trustworthy and eligible for such a privilege. TDM of methadone can thus be used for checking compliance. Although methadone blood concentrations differ markedly between individuals, they tend to remain stable within the same individual provided that the drug is taken in steady-state conditions and that the samples are drawn at similar timepoints during the elimination phase, preferably just prior to intake of the next dose. Concentrations of methadone can be measured after a period during which the intake of methadone is controlled, i.e. with daily attendance at the centre and supervised intake during 4–7 consecutive days. If necessary, this reference value can then be used to assess a change in compliance during take-home periods, with the possible help of published nomograms to assess compliance.[229] However, the patient serves as his/her own control, and methadone blood concentrations cannot easily be used to determine a theoretical dosage. Any changes in methadone concentrations could reflect a modification of compliance (such as reduced consumption and selling parts of doses, or increased consumption from illicitly obtained drug). But such changes could also result from a changed methadone clearance due, for example, to the intake of comedications. These factors need to be checked before concluding the existence of poor compliance.

8. Intravenous Use

The prescription of injectable methadone to opioid-dependent subjects is a practice mainly limited to Great Britain.[230] In a survey of community pharmacies in England and Wales, 11 and 9.3% of all prescriptions were for tablets, which are covertly injectable, and for injectable ampoules, respectively.[230] This proportion reached 33% for both forms of prescriptions from physicians in private practice.[230] The few studies that have examined the prevalence of methadone injection in patients under MMT have shown a high proportion (up to 50%) of methadone injecting in Sydney, Australia,[231,232] and in Fribourg, Switzerland.[233] Other surveys report a very low proportion of methadone injecting (1%) due to a strict take-away policy and to the mandatory dilution of methadone take-aways in a large amount of liquid (Melbourne, Australia[232]). Intravenous administration of methadone is associated with poorer general health, higher levels of emotional, psychosocial or psychiatric disturbances, higher use of illicit drugs, and a higher number of problems related to employment and support. Current methadone injectors were more likely to have recently shared injection equipment, involving a risk of HIV or hepatitis contamination, and to have committed criminal acts.[231,234]

Among other reasons for preferring injection of methadone, the 'flush' experience or the injection ritual have been evoked. However, the injection of methadone differs from oral intake by the fact that it avoids CYP-mediated metabolism and P-glycoprotein efflux activity in both the gut wall and the liver. As mentioned earlier, there is a large interindividual variability in the bioavailability of methadone, ranging from 36 to 100%.[47,49,53,63] For subjects with a low bioavailability, i.e. presumably with high P-glycoprotein and/or CYP activity, methadone injection instead of oral intake results in an increase in blood concentrations by more than 2-fold. The highest plasma concentration attained after intravenous administration of methadone 20mg, compared with the values reached after oral administration of the same dose,

is shown in figure 3.[47] Quinn and collaborators stated in a review on the pharmacokinetics and pharmacodynamics of illicit drug use that 'Drug users adapt the method and route of drug administration to optimise the delivery of the drug to the brain while attempting to maximise the bioavailability of the drug. Intravenous injection maximises the bioavailability of an administered drug'.[235]

Based on the hypothesis that higher effects could be preferred by some intravenous methadone users, an open pilot trial proposed a dosage increase to 25 methadone injectors in an attempt to reduce or stop this mode of intake. Thirteen patients decreased their use of injectable methadone, whereas five others completely ceased injecting methadone.[236] This small pilot study needs to be replicated under controlled conditions in a larger number of patients. It is possible that some patients will not accept an increase of their dosage, which would prevent them from experiencing the effects of intravenous use (such effects would probably not be felt if the dosage is adequate). However, considering the high frequency of methadone injection in some locations and the problems associated with this route of administration, the therapeutic option of increasing methadone dosages should be further examined.

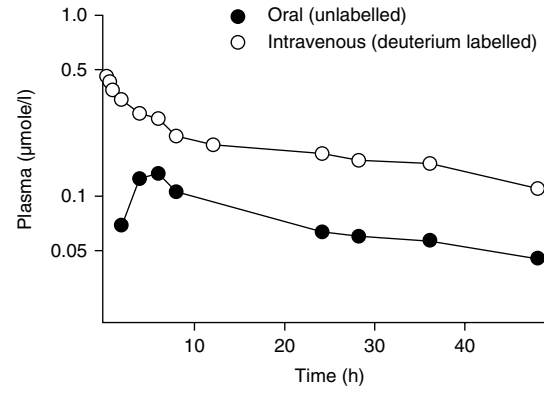

Fig. 3. Plasma concentrations of unlabelled methadone and deuterium-labelled methadone in one subject after simultaneous oral and intravenous administration of unlabelled methadone HCl 20mg as tablets and intravenous deuterium-labelled methadone HCl 20mg (reproduced from Meresaar et al.,[47] with permission).

9. Conclusions

Methadone displays a large interindividual variability in its pharmacokinetics and probably also in its pharmacodynamics, a variability which is both genetically and environmentally determined. It is thus of major importance that methadone treatment is individually adapted to each patient, in particular with regard to the dosage and to the choice of comedications administered. Several prospective double-blind randomised clinical studies have shown that methadone must be used at an effective dosage, i.e. at least 60 mg/day, but typically between 80 and 100 mg/day. However, a subset of patients might benefit from methadone dosages larger than 100 mg/day, many of them because of high clearance. Provided that all necessary steps are taken to ensure treatment safety, in particular with regard to respiratory depression and potential cardiotoxicity, there are presently no convincing data that would argue against the use of such high dosages. Illicit opioid dependence is associated with a high morbidity and mortality. Besides essential aspects such as counselling, familial, social, psychological or psychiatric support, the pharmacological treatment of opioid dependence, like any other medicinal treatment, must be conducted with the necessary quality standards.

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