Opioid plasma concentrations in methadone- and buprenorphine-maintained patients

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Abstract

This is the first trial to compare the relationship of opioid plasma concentrations in methadone- versus buprenorphine-maintained subjects. Sixty subjects (19 females and 41 males) seeking treatment who met Diagnostic and Statistical Manual version IV (DSM-IV) criteria for opioid dependence were recruited and treated at the Drug Addiction Outpatient Clinic at the University of Vienna. Of these, 44 (11 female and 33 male) were included in the analyses of plasma concentrations. Subjects received either daily sublingual buprenorphine (2 mg or 8 mg tablets; maximum daily dose: 8 mg) or oral methadone (racemic R-/S-methadone) and were maintained on a stable dose after an induction period of 2 weeks. Mean dose and mean plasma concentrations were correlated on an individual and collective basis. Correlation was 0.51 for buprenorphine, whereas the score for methadone was 0.69. Intra-individual variation was much higher for buprenorphine (p < 0.0001), while the concentration-to-dose ratio was very small. Based on the differences of the pharmacokinetics of blood plasma of the two agents, we tried to explain the differences in the acceptance of treatment, which was significantly lower in the buprenorphine-maintained group. No such differences could be evaluated between completers and dropouts in buprenorphine-maintained subjects, neither concerning withdrawal scores nor dose, plasma concentration, concentration-to-dose ratios or intra-individual variation.

Introduction

Buprenorphine, a semi-synthetic partial µ-receptor agonist and a κ-receptor antagonist, was first considered in 1978 as a potential agent for opioid-maintenance therapy, due to its long-lasting opioid-agonist effects such as analgesia, euphoria and sedation (Jasinski et al., 1978). In addition, a dose-related plateau effect was observed for buprenorphine on subjective measures and respiratory depression, one of the most common fatal effects of heroin overdose (Walsh et al., 1994). When taken sublingually bioavailability is 35%, with a half-life of approximately 7 hours, and a reported duration of action of up to 72 hours (Bullingham et al., 1982). Peak plasma concentration is reached after about 1 hour and the first effects can be observed after approximately 20 minutes (Chiang & Hawks, 2003). Buprenorphine is considered useful in maintenance therapy due to: (i) a slow increase in plasma concentration, which reduces the risk of respiratory depression; (ii) a relatively low degree of induced euphoria; (iii) a capacity to block the effects of other opioid agonists; and (iv) a low rate of withdrawal symptoms on discontinuation, even if withdrawal is sudden (Nutt, 1997).

In this study, buprenorphine was compared with standard treatment using methadone, the only substance authorized originally when oral opioid maintenance therapy was first introduced in Austria in 1987. In this country, methadone (which was first dispensed for maintenance in the United States in 1965; Dole & Nyswander, 1965) is administered as racemic 50% R- and 50% S-methadone, in the form of an oral sugar solution to avoid intravenous application. However, the use of methadone is limited due to its side effects (especially regarding long-term administration) including weight gain (often in the form of leg oedemas as a sign of water...
intoxication), severe sweating after a short period of intake and mood changes in the form of depression that are associated with lethargy and loss of libido (Kreek, 1973; Gardner-Nix, 2002). Thus, due to the limitations of methadone therapy, alternative maintenance agents were considered for certain subsets of patients (Langrod et al., 1981; O’Conor et al., 1991).

Based on retention rates, compared by means of survival analyses, an average buprenorphine dose of 8.9 mg/day is just as effective as an average methadone dose of 54 mg/day (Strain et al., 1994). Our own comparative study of retention and additional consumption demonstrated that although methadone (average dose 63 mg/day) showed significantly better results in the retention rate than buprenorphine (average dose 7.5 mg/day), those buprenorphine patients who had completed the study after 24 weeks showed a lower rate of positive urine tests (Fischer et al., 1999). Because the demographic and history of drug-dependence variables do not allow for any explanation of the higher dropout rate in the buprenorphine group, the aim of this study was to investigate the relationship of opioid plasma concentrations regarding their relevance to dropout rate and compliance.

In 1992, Loimer & Schmid drew attention to the importance of ‘therapeutic drug monitoring’ within the scope of methadone maintenance programmes and, in a cross-section study, were able to show that plasma concentrations of over 150 ng/ml were favourable for patient compliance. The relationship found between methadone dose and plasma concentration was highly significant ($r^2 = 0.63$; i.e. a correlation of 0.79). Similarly, Wolff et al. (1991a) demonstrated a linear relationship between plasma concentration and dose for the range from 3 to 100 mg methadone ($r = 0.89$) in a sample of 31 methadone patients, whose plasma was analysed over a period of 30 months. The relevant value of the correlation proved to be relatively low at $r = 0.43$ in a Spanish study with a sample of 93 methadone patients (Torrens et al., 1998). However, in this study the majority of participants were taking concurrent medication that interacted with methadone. The adjusted correlation score for a subset of 19 patients without concurrent medication was also $r = 0.89$.

So far, plasma concentration investigations with buprenorphine have focused mainly on dose-ranging studies. In an evaluation of pharmacokinetic data after ingestion of a 40% buprenorphine solution, Walsh et al. (1994) demonstrated a linear relationship between dose and plasma concentration by comparing the blood concentration curves (up to 96 hours after ingestion) of test subjects, whose dose was increased successively from an initial 2 mg up to 32 mg. The peak plasma concentration was reached after 30–60 minutes.

Although many studies have investigated pharmacokinetic aspects in association with individual maintenance agents, the various forms of maintenance therapy with regard to plasma concentrations have rarely been compared. This comparative study investigated the specific pharmacokinetic properties of methadone and buprenorphine, and determined the relationship between the medication retention rate and plasma concentrations. Thereby, the underlying hypothesis is that major intra-individual blood concentration variations, which are atypical for methadone, as found by Chitasombat et al. (1995), are responsible for poorer compliance and, thus, higher dropout rate among buprenorphine patients.

### Materials and methods

#### Subjects and study protocol

A total of 60 patients were randomized to receive either buprenorphine (29 patients) or methadone (31 patients). Sample sizes differed between the two groups due to the protocol-defined requirement that partners in life were assigned to the same maintenance therapy to avoid an exchange or mix of therapeutic substances (see Fischer et al., 1999). Patients were recruited at the drug addiction outpatient clinic of the clinical department of general psychiatry, University Hospital of Vienna.

Patients were between 18 and 45 years of age with a diagnosis of opioid dependence [Diagnostic and Statistical Manual version IV (DSM-IV 304.0)]. Dependence on cannabis (DSM-IV 304.3) and nicotine (DSM-IV 305.1) were permissible, but patients with dependence along the lines of polytoxicomania (DSM-IV 304.9) were excluded. Dependence on opioids was diagnosed by means of toxicological urinalysis and patients with a positive result for methadone were excluded. During an approximately 1-week screening phase, patients were adjusted to oral slow-release morphine and subjected to a comprehensive examination programme that included an internal examination as well as blood tests (differential blood count, liver and kidney function tests and hepatitis and HIV serology). In accordance with the Declaration of Helsinki, patients were included in the study only after approval by the internal specialist and after providing written informed consent.

The study period was defined as 24 weeks. Buprenorphine (2 mg and 8 mg sublingual tablets) was provided by Reckitt & Colman, Slough, Berkshire, UK. The maximum daily dose for buprenorphine was limited to 8 mg due to the lack of incidence-based studies with this substance as a maintenance agent in Europe. Patients were required to attend the drug addiction clinic daily during the 2-week induction phase, during which doses of both maintenance treatments were increased as required. Stable daily doses were then maintained throughout the entire study period.

Abstinence from opioids, cocaine and benzodiazepines, as well as methadone in the buprenorphine group, was monitored by means of supervised urinalysis. Urine was collected from patients twice-weekly during the induction phase and then once-weekly thereafter, and analysed using the Emit$^2$ method (Emit, 1983). The relative rate of opioid-positive urine samples was regarded as the measure for study non-compliance.

Blood was also collected twice-weekly during the induction phase (on days 2, 4, 9 and 11), then once-weekly until week 12 during the maintenance phase, followed once every 2 weeks until the end of the study. Measured plasma concentrations were correlated with the dose of study drug taken 24 hours previously. An additional blood sample was taken during the maintenance phase from patients in the buprenorphine group 1 hour after ingestion to compare these data with previously published blood concentration results (Walsh et al., 1994).

To evaluate withdrawal symptoms, the Wang scale was applied daily during the first 2 weeks of the study, followed by an additional two applications during the third week. Severity of withdrawal symptoms during the initial 3 weeks was assessed by comparison of the sum of the scores on the Wang
scale, as a linear curve cannot be drawn for this period (Wang et al., 1974).

**Analysis methods**

Frozen blood samples were sent to the Center for Human Toxicology at the University of Utah in Salt Lake City for toxicological analysis. Blood concentrations of the methadone patients were evaluated using gas chromatography/positive ion chemical ionization mass spectrometry (GC/PICI-MS) analysis (Alburges et al., 1996), whereas those of buprenorphine patients were analysed using liquid chromatography/tandem mass spectrometry (LC/MS/MS; Moody et al., 1997, 2002).

The assay reproducibility of both substances was assessed by analysis of a quality control (QC) sample. For each run for methadone, QC samples were run in duplicates at three concentrations: 1, low (25 ng/ml); 2, medium (250 ng/ml); 3, high (700 ng/ml). The means ± standard deviations (SD) and coefficients of variation (CV) were as follows: QC-1 was 24.5 ± 2.1 ng/ml, CV 8.4%; QC-2 was 248 ± 21 ng/ml, CV 8.4%; and QC-3 was 659 ± 64 ng/ml, CV 9.8%. For each run for buprenorphine, QC samples were run in triplicate at the following concentrations: 1, low (0.25 ng/ml); 2, medium (1 ng/ml); 3, high (5 ng/ml). The results for each QC concentration were: QC-1, 0.259 ± 0.022 ng/ml, CV 8.5%; QC-2, 0.95 ± 0.05 ng/ml, CV 5.3%; and for QC-3, 4.72 ± 0.40 ng/ml, CV 8.5%.

**Data analysis**

Statistical evaluation was performed using the program package SPSS and comprised both descriptive statistics and inference methods. Both absolute and relative rates were determined, and data were described on the interval scale level-to-dose ratio (LDR) was calculated as: LDR = ([plasma]/dose) × weight in kg as described previously by Wolff et al. (1991b). For clarity, the LDR for buprenorphine patients was multiplied by 1000. As a measure for intra-individual variation of the concentration-to-dose ratio, the mean deviation from the LDR was determined for each individual patient.

**Results**

**Patients**

The buprenorphine-maintained study group comprised 29 patients: 19 male (65.5%) and 10 female (34.5%). Average age was 25.92 ± 6.00 years (range 18 – 37 years). The methadone-maintained group comprised 31 patients: 22 male (71.0%) and nine female (29.0%). Average age was 24.97 ± 5.78 years (range 18 – 39 years). The sociodemographic data for these groups has been published previously (Fischer et al., 1999). Age, gender and parameters for history of dependence did not differ between the two groups of subjects.

As published previously, the retention rates of the two study groups showed a significant imbalance. Of the buprenorphine-maintained group, 18 patients (62.1%) withdrew from the study compared with nine (29.0%) of the methadone-maintained group ($\chi^2 = 6.607$, df = 1, $p = 0.010$). The average duration of participation in the study was also shorter with buprenorphine (99.7 days) compared with methadone (133.2 days; $t = -2.157$, df = 58, $p = 0.035$; Fischer et al., 1999).

A total of 17 buprenorphine patients (12 male and five female) and 27 methadone patients (21 male and six female) were available for analysis of plasma concentrations. An insufficient number of blood samples (<7) for statistical evaluation was the reason for exclusion of 11 patients in the buprenorphine-maintained group of the whole sample of the 29 patients. A further patient (patient 3) was excluded as, despite increases in blood concentration in the first week of the study and continued dispensing of a high dose (8 mg), the concentrations at week 2 were sufficiently low to conclude retrospectively that the patient had not taken the medication.

Reasons for excluding the four patients from the methadone group were more diverse. Blood samples could not be taken from one patient (patient 8), due to poor vein status; patient 24 withdrew from the study at her own request in week 2; patient 29 discontinued medication and withdrew from the study shortly after readjustment; the samples of patient 34 had to be excluded from analysis due to poor adherence to the treatment regimen.

Demographic characteristics of patients eligible for analysis of plasma concentrations were homogeneous in terms of age ($t = 0.039$, df = 42, $p = 0.969$) (Table 1). The retention rates of the two study groups differed between the two groups. The peak scores among buprenorphine patients were reached on the induction phase differed between the two groups. The peak scores among buprenorphine patients occurred one day earlier (Fig. 1). Mean total Wang score over the 3-week assessment period leaned towards being lower with buprenorphine than with methadone, although this was not statistically significant (Table 1; $t = -1.717$, df = 42, $p = 0.093$).

The mean percentage of opioid-positive urine samples was approximately 50% in both maintenance groups (Table 1; $t = 0.249$, df = 42, $p = 0.805$), although both groups showed variability ranging from 0 to 100%.
Of the 17 buprenorphine-maintained patients available for inclusion in this study, 10 (58.8%) completed the 24-week trial period. The mean duration of trial enrollment for the other seven patients (41.2%) was 91.00 + 23.57 days. On average, 17.30 + 2.98 (minimum 11, maximum 20) plasma samples were available for analysis from patients completing the study compared with 12.43 + 2.94 (minimum seven, maximum 16) samples from patients who withdrew from the trial (t = 7.335, df = 15, p = 0.005).

A total of 23 (85.2%) patients in the methadone-maintained group completed the trial, with four patients (14.8%) withdrawing from the trial after an average of 61.25 ± 43.29 days. The mean number of plasma samples available from the group of completers was 17.17 ± 2.71 (minimum nine, maximum 21), compared with 11.00 ± 3.74 (minimum seven, maximum 16) from patients who withdrew from the trial (t = -3.996, df = 25, p = 0.001).

### Table 1. Characteristics of patients: socio-demographic data, withdrawal scores and opiate-positive urine samples

<table>
<thead>
<tr>
<th>Patients</th>
<th>Age (years)</th>
<th>Weight (kg)</th>
<th>Wang sum</th>
<th>Opiate-positive urine samples (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Buprenorphine-maintained</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Five females, 12 males</td>
<td>25.65</td>
<td>64.88</td>
<td>63.88</td>
<td>49.80</td>
</tr>
<tr>
<td>Mean</td>
<td>6.20</td>
<td>11.39</td>
<td>44.44</td>
<td>29.90</td>
</tr>
<tr>
<td><strong>Methadone-maintained</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Six females, 21 males</td>
<td>25.56</td>
<td>64.76</td>
<td>93.74</td>
<td>47.55</td>
</tr>
<tr>
<td>Mean</td>
<td>5.52</td>
<td>9.24</td>
<td>62.29</td>
<td>8.68</td>
</tr>
</tbody>
</table>

SD: standard deviation.

**Number of plasma samples available for analysis**

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**Correlation of dosage and plasma concentration**

Table 2 shows the dispensed dose and mean plasma levels for the buprenorphine and methadone groups. The mean maintenance dose dispensed to the 17 buprenorphine-maintained patients analysed was 6.11 mg (SD ± 1.55), ranging from a minimum of 1.89 mg to a maximum of 7.60 mg. The mean plasma concentrations varied from 0.226 ng/ml to 1.650 ng/ml, with a mean concentration for all patients of 0.682 ng/ml (SD ± 0.407).

The mean dose dispensed to the 27 methadone patients was 54.05 mg (SD ± 21.75). As in the buprenorphine group, substitution doses required varied greatly between patients, including the need in extreme cases to exceed a previously defined maximum dose of 80 mg (Fischer & Kasper, 1999). The lowest mean dose was 9.00 mg and the maximum mean dose was 85.28 mg. The mean plasma concentration for all methadone patients was 257.41 (SD ± 118.92), ranging from 60.90 ng/ml to 470.86 ng/ml (Table 2).

The correlation coefficient between dose administered and plasma concentration determined 24 hours later for the individual buprenorphine patients ranged from a minimum of 0.168 (patient 27 with a very low dosage) to 0.813, with a mean coefficient of 0.511 for the total patient group. Only nine of the 17 correlations were statistically significant. In contrast, all but one of the correlations were statistically significant in the methadone group. The mean correlation coefficient was 0.692, ranging from 0.461 to 0.903 (Table 2). The difference between the two correlation coefficients could not be verified statistically due to the small sample sizes. The correlation for the buprenorphine group is relatively low (average declared variance $R^2 = 26.11\%$), while the average declared variance in the methadone group is $R^2 = 47.89\%$.

The maximum cross-correlation in the buprenorphine group was 0.689 at lag 0, the maximum cross-correlation in the methadone group was higher at 0.925, also at lag 0. The difference between the two correlations was statistically significant ($z = 2.3095$, df = 0.021).

The level-to-dose ratios determined similarly to the method of Wolff et al. (1991b) and the mean intra-individual variation of the LDRs both for buprenorphine and methadone are shown in Table 2. Comparison between groups of the mean intra-individual variation shows a significantly greater variation in the buprenorphine group ($t = 4.448$, df = 19.226, $p < 0.0001$).

An additional blood sample was collected 1 hour after ingestion of the study medication from 10 buprenorphine patients to further investigate plasma absorption. Eight patients received 8 mg, one patient received a dose of 2 mg...
and one patient received 6 mg. These plasma concentrations were correlated with the concentrations measured after 24 hours. For the patients given 8 mg, the average ratio of concentration at 1 hour : concentration at 24 hours was 5.81 (4.354 ng/ml after 1 hour compared with 0.750 ng/ml after 24 hours), with a range from 2.10 to 23.42. For the patient with a dose of 2 mg the ratio was 3.32, and for the patient with a dose of 6 mg it was 5.51.

**Intragroup comparisons**

Within each group of patients providing sufficient numbers of blood samples for the current analysis, the subset of patients who completed the study according to the protocol were compared with the subset of patients who did not complete the study. There were no significant differences between mean values for the 10 completers and the seven non-completers in the buprenorphine group for the socio-demographic variables age, weight and gender (Table 3); neither were there any significant differences between the two subgroups in terms of withdrawal scores (Wang sum) during the induction phase, dose, plasma concentration or concentration-to-dose ratios (Table 3). Marginal differences were found in the intra-individual variation (p = 0.059) although, unexpectedly, the completers showed higher variation (50.75%) than non-completers (34.05%). The average correlation between dose and plasma concentration of 0.63 (declared variance 39.69%) for the non-completers was higher than that for the completers (0.43, R² = 18.49%). However, the mean percentage of opioid-positive urine samples in non-completers suggested that non-completers tended to have a higher relapse rate compared with completers (64% versus 40%, respectively; p = 0.100).

In the methadone group, only four patients did not complete the study compared with 23 completers, making comparisons difficult (Table 4). Two socio-demographic variables showed a significant difference between subgroups, namely gender (only one of the four non-completers was male; p = 0.025) and weight (p = 0.037). However, no differences were found for clinical variables.

**Discussion**

After completion of this comparative study of the maintenance substances buprenorphine and methadone in opioid-dependent patients, differences were observed in acceptance of treatment. While only one-third of patients who received methadone discontinued prematurely in the 24-week study, the dropout rate in the buprenorphine group was approximately two-thirds (Fischer et al., 1999). The relationship of plasma concentrations was analysed with regard to demographic variables to determine whether they had any influence on the issue of premature termination.

This study analysed the subgroup of patients who were maintained in the trial long enough to obtain sufficient blood samples for analysis. The sample comprised 17 patients in the buprenorphine group and 27 patients in the methadone group, without differences between groups with regard to age, gender distribution or weight. With exception to the induction phase, at all time-points individual patients coped with the demand for opioid abstinence very differently. All variations between the extremes of total abstinence and non-abstinence were observed within each group, but there were no significant differences between the groups. The average additional opioid consumption rate of about 50% was comparable with (or even better than) that found in outpatient studies conducted in the United States. Schottenfeld et al. (1997), for example, reported rates of 45% after 24 study weeks for a patient group receiving a dose of 65 mg methadone and 58% in a group receiving 12 mg buprenorphine. Ling et al. (1998) reported rates of 61% opioid-positive urine samples in a 12 mg buprenorphine group, 67% in an 8 mg group, 71% at 4 mg, and 81% at a buprenorphine dose of 1 mg/day during a 16-week dose-ranging study. The initial stage of withdrawal, referred to as dysphoria or ‘clarity’, which has also been observed in other studies (Bickel et al., 1988; Kouri et al., 1996) and which lasts a few days, may account for the increased number of patients discontinuing the study after only a short time in the buprenorphine group compared with the methadone group. In concordance with this, a significant time course in the reduction of the Beck Depression Scale was reported in a recently published study by Seifert et al. (2005) for patients detoxified with buprenorphine within 14 days, while for patients detoxified with methadone no such effect could be found. Patients that cannot handle the critical first period of the induction phase and drop out may not reach this state of mood balance. However, the more rapid development of withdrawal symptoms according to the results on the Wang scale suggests that the induction phase is more difficult for the methadone patients.

### Table 2. Characteristics of patients: mean dose, mean plasma level, Pearson correlation of dose and plasma level, LDR and intra-individual variation of blood plasma levels

<table>
<thead>
<tr>
<th></th>
<th>Buprenorphine-maintained Patients</th>
<th>Methadone-maintained Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean dose (mg/day)</td>
<td>Mean plasma level (ng/ml)</td>
</tr>
<tr>
<td>Mean</td>
<td>6.11</td>
<td>0.682</td>
</tr>
<tr>
<td>SD</td>
<td>1.55</td>
<td>0.407</td>
</tr>
<tr>
<td>Mean</td>
<td>54.05</td>
<td>257.41</td>
</tr>
<tr>
<td>SD</td>
<td>21.75</td>
<td>118.92</td>
</tr>
</tbody>
</table>

LDR: level-to-dose ratio; SD: standard deviation.
The comparison between the two dose–concentration correlations showed a low ratio of 0.51 for buprenorphine, while the ratio for methadone was almost 0.70. This suggests that even at a steady dose, the plasma–concentration variations in a patient receiving buprenorphine are greater than in a patient receiving methadone. In terms of correlations for individuals within the groups, the total average for the methadone group was exceeded by only three of the 17 patients in the buprenorphine group (17.65%), whereas only one of the 27 patients in the methadone group (3.70%) was below the average ratio for the buprenorphine group. In addition, compared with the buprenorphine group, LDRs for methadone patients were higher and the intra-individual variation was significantly lower. Only three of the buprenorphine patients (17.65%) had an average variation that was lower than the average variation for all methadone patients, while all the average variations for methadone patients were considerably lower than the average score for the buprenorphine group.

These results may be due to the different properties of the maintenance agents. The opioid agonist, methadone, is taken as a solution with syrup in liquid form, whereas buprenorphine is a partial opioid agonist/antagonist that was taken in sublingual form during this study. Previous experience of the pharmacokinetics of buprenorphine suggests that the plasma concentration peaked 30–60 minutes after ingestion, depending on the dosage, whereas the peak concentration of methadone is usually reached later (approximately after 90–120 minutes) due to the oral presentation form (Walsh et al., 1994). Our data show considerable concordance with the results of Walsh et al. (1994) that demonstrated plasma concentrations of patients receiving 8 mg buprenorphine (40% solution) to peak at approximately 8.5 ng/ml after 60 minutes and that diminish after 24 hours to approximately 1.5 ng/ml. The ratio calculated for these two time-points (5.67) is similar to the ratio for the eight patients in our study (5.81), who also received 8 mg buprenorphine (sublingual), and demonstrated an average plasma concentration of 4.35 mg/ml after 60 minutes and an average of 0.75 ng/ml after 24 hours. It should be noted, however, that the individual ratios cover a range from 2.1 to 23.4. The small sample of patients available for this examination also has to be seen as a limitation. Lower doses appear to be associated with lower ratios, as the patient receiving 2 mg buprenorphine showed a relatively low ratio of 3.3. The characteristics resulting from the different properties of these two maintenance agents are a useful starting point for interpreting the differences in the rates of study completion. Rapid onset of symptoms during the induction phase, which eliminates the long-lasting central sedation caused by heroin abuse within a short time, and the relatively low correlation between the steady dose of the maintenance agent and plasma concentrations, which are subject to relatively long variations over time, form the basis of the hypothesis to explain the high dropout rate.

Because the key ratios of the two maintenance agents differ, the main question in verifying this hypothesis was: does the buprenorphine group show any difference in parameters between completers and non-completers—particularly with regard to the toxicological analysis? Are there any indications for acceptance of buprenorphine that could be explained by dose, plasma concentration, concentration–dose ratio or variations in plasma concentration?

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The comparison between the two dose–concentration correlations showed a low ratio of 0.51 for buprenorphine, while the ratio for methadone was almost 0.70. This suggests that even at a steady dose, the plasma–concentration variations in a patient receiving buprenorphine are greater than in a patient receiving methadone. In terms of correlations for individuals within the groups, the total average for the methadone group was exceeded by only three of the 17 patients in the buprenorphine group (17.65%), whereas only one of the 27 patients in the methadone group (3.70%) was below the average ratio for the buprenorphine group. In addition, compared with the buprenorphine group, LDRs for methadone patients were higher and the intra-individual variation was significantly lower. Only three of the buprenorphine patients (17.65%) had an average variation that was lower than the average variation for all methadone patients, while all the average variations for methadone patients were considerably lower than the average score for the buprenorphine group.

These results may be due to the different properties of the maintenance agents. The opioid agonist, methadone, is taken as a solution with syrup in liquid form, whereas buprenorphine is a partial opioid agonist/antagonist that was taken in sublingual form during this study. Previous experience of the pharmacokinetics of buprenorphine suggests that the plasma concentration peaked 30–60 minutes after ingestion, depending on the dosage, whereas the peak concentration of methadone is usually reached later (approximately after 90–120 minutes) due to the oral presentation form (Walsh et al., 1994). Our data show considerable concordance with the results of Walsh et al. (1994) that demonstrated plasma concentrations of patients receiving 8 mg buprenorphine (40% solution) to peak at approximately 8.5 ng/ml after 60 minutes and that diminish after 24 hours to approximately 1.5 ng/ml. The ratio calculated for these two time-points (5.67) is similar to the ratio for the eight patients in our study (5.81), who also received 8 mg buprenorphine (sublingual), and demonstrated an average plasma concentration of 4.35 mg/ml after 60 minutes and an average of 0.75 ng/ml after 24 hours. It should be noted, however, that the individual ratios cover a range from 2.1 to 23.4. The small sample of patients available for this examination also has to be seen as a limitation. Lower doses appear to be associated with lower ratios, as the patient receiving 2 mg buprenorphine showed a relatively low ratio of 3.3. The characteristics resulting from the different properties of these two maintenance agents are a useful starting point for interpreting the differences in the rates of study completion. Rapid onset of symptoms during the induction phase, which eliminates the long-lasting central sedation caused by heroin abuse within a short time, and the relatively low correlation between the steady dose of the maintenance agent and plasma concentrations, which are subject to relatively long variations over time, form the basis of the hypothesis to explain the high dropout rate.

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As both subgroups of 10 completers and seven non-completers in the buprenorphine group were the same with regard to the socio-demographic characteristics of gender, age and weight, the verification of the hypothesis showed a surprising result (Table 3). Although there were no differences between the two groups with respect to dose, plasma concentration or LDR, the average intra-individual variation for the non-completers was marginally lower ($p = 0.059$). This apparently eliminates a high degree of plasma concentration variation as a possible reason for premature discontinuation of the study by the buprenorphine-maintained patients. However, it should be noted that there were fewer blood samples available for analysis from the non-completers (mean of 12.4 versus 17.3).

The repeated relapses in the buprenorphine-maintained group may also be associated with the protocol-defined dose limit of 8 mg for buprenorphine. Johnson et al. (1992) report that the daily administration of 8 mg sublingual buprenorphine is comparable with about 60 mg oral methadone in terms of retention and additional consumption (ratio 7.5). Within the scope of a flexible regimen, Strain et al. (1994) found that the average effective dose of 8.9 mg/day buprenorphine is comparable with an average effective methadone dose of 54 mg/day for opioid-dependent patients (ratio 6.07). With regard to the dosage received by the patients in our study, an average methadone dose of 54.05 mg/day is compared with an average daily buprenorphine dose of 6.11 mg (ratio 8.85). It may be speculated that, at least in part, this high dosage ratio is due to the limitation of the buprenorphine dose, even for patients with repeated non-compliance. Because recent studies are already working with dosage regimens of 16 or even 32 mg buprenorphine per day, new findings with regard to the efficiency and compliance of high-dosed buprenorphine patients may well be expected.

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References