High-Dose Methadone and the Need for Drug Measurements in Plasma

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We report a case of high-dose methadone prescribed to a heroin addict for pain control. The patient was prescribed methadone during convalescence from surgery and subsequently for maintenance treatment. Dosing was started at 360 mg of methadone per day and reduced over 12 days to an 80 mg/day maintenance dose. Although the patient was drowsy on the initial dose, his recovery was uneventful. However, there were complaints of pain and withdrawal discomfort when the plasma concentration decreased to <1 mg/L. Measurements of methadone in plasma were helpful for monitoring the recovery of this patient after surgery and are likely to prove useful in similar cases.

Additional Keyphrases: abused drugs • monitoring therapy

Methadone, a synthetic opioid, has been used to treat heroin addiction in the U.K. for the past 20 years. Methadone is usually given orally, once daily, and only in sufficient quantity to prevent the onset of opioid withdrawal symptoms. Doses >80 mg of methadone per day are rare. Prescribing doses lower than this is based on the premise that it would not be safe to prescribe high doses to patients because of possible ill effects (e.g., sedation or respiratory distress) (1) and also because of the fear of the drug's being diverted into the black market (2). However, addicts prescribed methadone often complain that their dose is inadequate and that the drug does not sustain them for the whole dosing interval (3).

In addition to treatment of opioid dependence, methadone is used in other clinical situations as a narcotic analgesic, for the treatment of acute (intra-postoperative surgery) (4) and chronic (progressive cancer) pain (5). Because of the patient's development of tolerance to the drug, treatment has to be adjusted often to provide satisfactory pain relief. However, there is little published information on the proper procedures for ensuring pain relief for opioid-dependent patients with acute or chronic pain.

It has been well established (3, 6) that dose, provided it is sufficient, is only a crude indication of the efficacy of methadone treatment; no other tool is currently available to the clinician for patient management. Plasma methadone is not routinely measured, but if it were, the information could be helpful to clinicians in monitoring drug therapy.

We report here the case of a patient who was prescribed 360 mg of methadone per day for the relief of acute postoperative pain, and the concentration of plasma methadone measured by high-performance liquid chromatography (HPLC) during his treatment. The aim of this paper is to demonstrate the possible usefulness of laboratory measurements when managing drug addicts prescribed methadone for pain relief.

Case Report

A 25-year-old man with an eight-year history of intravenous drug use (heroin and opioid-based pharmaceutical drugs) presented for treatment at the Leeds Addiction Unit and was initially prescribed 60 mg of methadone per day.

After complaints of multiple bruising, investigation revealed a thrombocytopenia. This was thought to be related to the status of the patient, who had been positive for human immunodeficiency virus (HIV) antibody for about a year. The patient was treated for one month with a high dose of prednisolone (60 mg/day), but some months later, clinical evidence of bruising occurred again, at which time the patient's platelet count was very low (19 × 10^9/L). Prednisolone was again prescribed (60 mg/day) for 21 days and continued as a maintenance dose (7.5 mg/day). However, this schedule still failed to prevent the recrudescence of clinical bruising and thrombocytopenia with the platelet count at 21 × 10^9/L. A splenectomy was recommended, which was performed 16 months after the patient had first presented for treatment at the Leeds Addiction Unit.

The postoperative course was complicated by the difficulty in achieving adequate pain relief. Immediately after the operation, 100 mg of morphine was prescribed. The patient's tolerance to opioids was such that for the next 24 h, a 2 mL/h infusion of 150 mg of morphine in 50 mL of isotonic saline was required, more than fourfold the normal morphine requirement. Because the patient continued to complain of pain, morphine was replaced with an infusion of diamorphine in isotonic saline (40 mg/h). A postoperative chest infection may have contributed to the patient's discomfort.

Four days after the operation, the patient complained that the diamorphine infusion was not effective; he requested, and was given, oral methadone (180 mg of methadone twice daily, or 360 mg of methadone per day). The daily dose of methadone was rapidly reduced.

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over the next 72 h (by 30 mg, 90 mg, and 60 mg of methadone per day, respectively). While receiving 180 mg of methadone per day, the patient was moved to another hospital for convalescence. After four days, and against hospital advice, the patient discharged himself, complaining that his dose (now 140 mg of methadone per day) was insufficient to stop pain or withdrawal symptoms. The patient was subsequently persuaded to attend the Addiction Unit, and the dose was reduced to 80 mg of methadone per day. Maintenance dosing with 80 mg of methadone per day continued for the next five weeks.

Materials and Methods

Blood (10 mL) was collected regularly from the patient by venipuncture before the consumption of the early morning dose of methadone linctus. Concentrations of plasma methadone were measured from the onset of the high-dose prescription and throughout maintenance treatment as previously described (7).

Results

Figure 1 shows the relationship between the methadone dose and the concentration of methadone in plasma. The plasma concentration of methadone decreased precipitously after the dose reduction from 360 to 80 mg of methadone per day. At concentrations of plasma methadone >2.8 mg/L, our patient was drowsy but had no other untoward effects; recovery on a dose of 360 mg/day was uneventful. When the concentration of plasma methadone decreased to <1.0 mg/L (while on 140 mg of methadone per day), the patient complained of pain because his dose was inadequate.

Figure 2 shows the concentrations of plasma methadone during reduction from 360 to 80 mg of methadone per day. We found the relationship between plasma concentration and methadone dose (the least-squares method) to be $y = -0.152 + 0.009x$. The correlation coefficient ($r = 0.95, P < 0.004$) shows a linear relationship, even though our patient was not at steady state until he was maintained on 80 mg of methadone daily; steady-state conditions are achieved after five to six days on the same dose (the half-life of methadone is about 24 h) (8).

We obtained weekly blood samples from our patient when he was prescribed 80 mg of methadone per day. During this period, the patient complained neither of pain nor of withdrawal discomfort, and good compliance was indicated by the concentrations of methadone in plasma, which showed little variation (mean 0.66, SD 0.05 mg/L), ranging from 0.73 to 0.61 mg/L.

Discussion

Patients prescribed methadone will at times supplement their dose with illicitly obtained methadone (9). Patients are also considered to be able to tolerate doses much higher than those prescribed without having any adverse side effects (10). However, little of the literature deals with the effect of treating opioid-tolerant patients with high doses of methadone. We found only one study documenting the prescription of high doses of methadone (180 and 260 mg/day) to heroin addicts; the authors did not report any adverse health effects as a consequence of these doses (11).

We have measured concentrations of plasma methadone successfully in our patient, who showed tolerance to the gastrointestinal effects of methadone at very high doses. Our opioid-tolerant patient showed no ill effects and was fully conscious on methadone doses >200 mg daily, in contrast to the marked sedation recorded in six individuals receiving 100 mg of methadone per day (12). There was nothing unusual about our patient, whose use of illicit opioids was similar to that of many other addicts attending the Addiction Unit; however, he did develop signs of drowsiness at plasma concentrations of 2.8 mg/L when receiving 360 mg of methadone per day.

Our patient complained of inadequate pain relief while taking normal postoperative quantities of both morphine and diamorphine, suggesting that he might also have been tolerant to the analgesic effect of narcotic opioids. We consider this probable because, after repeated administration of narcotic drugs, the narcotic receptors on cells in the nervous system that modulate pain undergo a change (down regulation) and become less responsive, which greatly reduces the effectiveness
of narcotics as analgesics (13, 14).

When our patient was given greater-than-normal doses of morphine and diamorphine to alleviate pain, relief was only short-lived. A similar change in the receptors was probably taking place in our patient, whereby the receptors became less responsive to, and more dependent on, narcotics. The prescription of very high doses of methadone, however, was initially successful in relieving pain—probably because of the prolonged clearance of methadone in relation to the other narcotic analgesics (15). As a long-acting narcotic, methadone may have been able to maintain a sufficient degree of receptor binding to avert withdrawal symptoms and any pain associated with withdrawal.

For adequate pain relief, it is important to maintain sufficient drug at the receptor binding sites that modulate pain. Possibly our patient complained of pain and withdrawal discomfort (at 140 mg/day, a higher dose of methadone than normally prescribed for addiction) because, as a consequence of the rapidity of the dosage reduction, concentrations of methadone at the receptor binding sites decreased to less than that required for analgesia. Other postoperative patients who can tolerate very high doses of methadone may have similar problems if reduced to a lower dose too quickly. It is also possible that, in these patients, prescription of a short-acting narcotic will not provide pain relief. Decreasing the dose over a longer period may be a more stable way of providing relief (15).

Clinicians who both treat opioid addiction and prescribe for the control of pain have to rely on self-reported assessment to optimize treatment. Therapeutic management of an opioid addict during and after surgery is complicated by the likelihood that normal pain control may not be adequate. However, in our experience, some patients prescribed methadone often give unreliable information for their self-assessment report. Some patients were found to be consuming twice what they had been prescribed. We assessed compliance in these individuals by prescribing a non-enzyme-inducing dose of phenobarbital (methadone:phenobarbital, 8:1) and monitoring both drugs in plasma (16). By measuring both drugs, we were able to establish that measurements of methadone alone would give a reliable indication of compliance.

In our case study, only methadone was prescribed during the dosage reduction from 360 to 80 mg of methadone per day. However, during maintenance dosing on 80 mg of methadone per day, our patient was also prescribed 10 mg of phenobarbital per day. Only the results for methadone are shown in Figure 1, but they demonstrate that our patient could tolerate very high concentrations of methadone circulating in his body. The week-to-week variation in the plasma concentration was small, indicating good compliance as well as the stability of this drug during fixed dosing regimes.

Sjoquist and Koike (17) suggested that plasma measurements are better indicators than dose for assessing the efficacy of drug therapy. Dose is a poor predictor of the efficacy of methadone treatment in this case study. Given that our patient was receiving such a high dose of methadone, we decided retrospectively to record the drug concentration in his plasma. Although we might have anticipated that withdrawal discomfort would occur on a reduction regime of 30–90 mg of methadone per day, the plasma measurements help to illustrate how rapidly the drug concentration decreases.

Laboratory measurements might be useful for certain subjects who require more careful monitoring, e.g., methadone maintenance patients infected with the HIV virus. These patients may need doses of methadone greater than normal to treat or provide pain relief from the opportunistic infections associated with the progression of this disease. HIV-infected patients may also need high doses of methadone if prescribed zidovudine (azidothymidine; AZT) because this drug may increase methadone metabolism (18). In these cases, plasma measurements should provide a far better aid to patient management than reliance on drug dosage.

Our case study suggests that plasma measurements may be of value to the clinician in certain situations. There being no therapeutic range for methadone, in contrast to, e.g., anticonvulsants or bronchodilators, methadone concentrations in plasma may be determined by the degree of opioid dependence and hence the methadone dose. We have recently shown a good linear correlation between plasma concentration and methadone dose in patients under steady-state conditions (7). We conclude that measurements of methadone in plasma may be valuable in instances where high doses of the drug are required, where it is necessary to monitor treatment closely, and where there is uncertainty about an individual's compliance.

References