Clinical Note

Changing M3G/M6G Ratios and Pharmacodynamics in a Cancer Patient During Long-Term Morphine Treatment

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Abstract

A cancer patient receiving long-term oral sustained-release morphine treatment and periodically presenting with unusually high plasma M3G/M6G ratios is described. We found the patient’s formation of M6G more unstable and perhaps delayed compared to the formation of M3G. There is no apparent explanation for this phenomenon and the high M3G/M6G ratios had no implications for the patient’s pain experience or side effects from the morphine treatment.

Key Words

Morphine metabolism, morphine-6-glucuronide, morphine-3-glucuronide, pain, side effects

Introduction

Morphine is one of the most widely used opioids in the world. The major pathway for morphine metabolism is conjugation with the co-substrate uridine diphosphate (UDP)-glucuronic acid, a process that is catalyzed by a UDP glucuronyltransferase (UDPGT). Metabolism takes predominantly place in the liver. Only 10% of a morphine dose is excreted unconjugated through the kidneys. The two qualitatively and quantitatively most important morphine metabolites are morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G). M6G binds to opioid receptors and may even be more potent than morphine itself. In contrast, M3G does not bind to opioid receptors, but may be able to elicit neurotoxic side effects such as hyperalgesia, allodynia and myoclonus. Furthermore, results from some animal studies have demonstrated that M3G may antagonize the analgesic effect of morphine and M6G. It has been suggested that patients’ analgesic response to morphine depends on the M3G/M6G ratio.

Studies in patients receiving long-term oral morphine treatment have found M3G/M6G ratios within stable limits. The mean or median plasma values have been 5.0–8.5, and the upper range has never exceeded 15.

We describe a patient receiving long-term oral sustained release (SR) morphine treatment who exhibited very varying M3G/M6G ratios throughout the period of treatment. This had no observable effect on his analgesic response or side effects.
Case Report

A 64-year-old man diagnosed with a prostate cancer was referred to the Multidiciplinary Pain Clinic at Herlev Hospital for treatment of pain due to bone metastases localized in the hips and shoulders. At the time of referral, his daily medication was SR morphine, immediate release ketobemidone on demand, a nonsteroidal anti-inflammatory drug (NSAID), an anti-androgen, and laxatives. After referral, the patient’s pain was treated with palliative radiation, and titration of SR morphine dose was done according to his needs.

During the following 55 weeks of pain treatment at the Multidiciplinary Pain Clinic, pharmacokinetic and pharmacodynamic assessments were obtained in association with 10 of 17 SR morphine dose changes. Blood samples for evaluation of plasma morphine, M3G, and M6G were obtained from an antecubital vein and analyzed by high-performance liquid chromatography. To evaluate steady-state conditions, the daily dose of SR morphine was kept stable for at least 3 days before assessments and blood sampling took place. A minimum of 180 minutes passed between the last ingestion of an opioid and an assessment.

Pharmacodynamic assessments consisting of evaluation of pain intensity by a visual analogue scale (VAS; 0 mm representing “no pain” and 100 mm representing “worst possible pain”) were obtained immediately before blood sampling. Side effects potentially due to morphine treatment (pruritus, nausea/vomiting, dryness of the mouth, hallucinations, nightmares, dizziness, myoclonus, allodynia/hyperalgesia) were registered as present or not present. The patient’s renal and hepatic function, as evaluated by serum creatinine, aspartate aminotransferase, lactate dehydrogenase, and PP (% of normal prothrombin complex activity), was within normal limits throughout the observation period, after which the assessments stopped for logistic reasons.

Periods between each assessment varied between 4 and 9 weeks. Because of failures in the analytical procedures, plasma morphine was not obtained at the second assessment. Values for morphine metabolite ratios are presented in Table 1. There were strong correlations between daily dose of SR morphine and plasma morphine ($r = 0.84$), plasma M3G ($r = 0.91$), and plasma M6G ($r = 0.80$).

Except for complaints of nausea and dizziness at the ninth assessment, the patient had no side effects potentially due to the morphine treatment at any of the assessments. Pain VAS (PVAS) and M3G/M6G ratios are presented in Figure 1.

Discussion

The M3G/M6G ratios in this patient varied considerably, ranging between 7.5 and 36.3 (mean 17.8). According to the literature, these values would be very rare.9–13 Other studies in patients receiving long-term oral morphine treatment have found mean or median M3G/M6G ratios between 5.0 and 8.5.9–13

The patient’s M3G/M and M6G/M ratios also varied considerably between assessments. This is not divergent from other studies of patients receiving long-term oral morphine treatment, which have found that M3G/M and M6G/M ratios also vary a great deal. Mean or median M3G/M ratios have been demonstrated

<table>
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<th>Assessment</th>
<th>Dose (nmol/l)</th>
<th>M</th>
<th>M3G</th>
<th>M6G</th>
<th>M3G/M</th>
<th>M6G/M</th>
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in the range of 22 to 109 and M6G/M ratios in the range of 3.79 to 17.9–13

As seen in Table 1, measurements showing high M3G/M6G ratios are characterized by a low production of M6G compared to the M3G production. The correlation between the daily SR morphine dose and plasma M3G is stronger than the correlation between the daily dose of SR morphine and plasma M6G, indicating that the formation of M6G is more unstable and may be delayed compared to the formation of M3G.

It is unclear whether one or two UDPGTs are responsible for the glucuronidation of morphine.14,15 One UDPGT would be capable of catalyzing the glucuronidation process in the 3-OH as well as the 6-OH position, but at different rates or with different affinity to each of the sites. In case of two different UDPGTs, varying amounts of the enzymes present could explain the fluctuating amounts of metabolites formed. The varying formation of M3G and M6G in our patient could be explained by both hypotheses. Age, disease status, genetic background, and exposure to certain drugs have been suggested to account for the often large interindividual variations in UDPGT activity.16 In vitro and human studies have shown that oxazepam,17 tricyclic antidepressants,18 and ranitidine19 may influence the metabolism of morphine and the ratio between M3G and M6G, but our patient received none of these drugs. Thus, there is no apparent explanation why UDPGT activity concerning the formation of M6G periodically was affected in our patient.

Several animal studies have demonstrated that M3G may antagonize the analgesic effect of morphine7 and M6G.6 There are no reports of M3G having been administered to humans. Assuming that M6G has potent analgesic properties2,3 and M3G anti-analgesic properties,5,7 it might be expected that patients with very high M3G/M6G ratios had poorer pain relief than patients with low M3G/M6G ratios. Nevertheless, the clinical evidence for this hypothesis is lacking. A case of a patient with intolerable pain and very high cerebrospinal levels of M3G in the presence of immeasurable levels of M6G has been reported,4 but in 11 cancer patients with very poor pain relief despite oral or subcutaneous morphine administration, the M3G/M6G ratios in plasma as well as cerebrospinal fluid were found similar to patients with well-controlled pain.13 As Figure 1 shows, we found no relationship between the very varying plasma M3G/M6G ratios and PVAS, and in our patient, the abnormal M3G/M6G ratios thus did not seem to influence pain experience.

Studies in rodents have found that M3G and high-dose morphine administered by the intracerebroventricular20,21 or intrathecal22,23 routes produced symptoms of altered pain behavior such as hyperalgesia, allodynia, and myoclonus. Clinically the symptoms of hyperalgesia, allodynia, and myoclonus have primarily been observed in cancer patients receiving high doses of morphine. In some of the reports describing these symptoms, very high plasma levels of morphine and M3G have been observed, as well as accumulation of M3G relative to morphine24 and M6G.1,5 Two patients with plasma M3G/M6G ratios as high as 85 and 101 accompanied by myoclonic spasms have been reported.5 However, the neurotoxic effects related to M3G may also occur in the presence of normal M3G/M6G ratios.5 On the other hand, a plasma M3G/M6G ratio as high as 940 has been described in a cancer patient receiving continuous subcutaneous morphine without any report of untoward side effects.25 Despite elevated M3G/M6G ratios our patient had no signs of hyperalgesia, allodynia, and myoclonus at any time, indicating that an increase of this size does not lead to neurotoxic side effects. Other factors such as very high plasma and cerebrospinal fluid concentrations of morphine or M3G probably also play a significant role.5

In conclusion, we describe a patient receiving long-term oral SR morphine treatment who peri-

Fig. 1. Relationship between pain score (PVAS) and plasma M3G/M6G ratios during the period of assessments.
odically presented with unusually high plasma M3G/M6G ratios without any implications for the pain experience or side effects.

References


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