Methadone

Lorna Frame1
BMSc (Hons), MBChB (Hons), Core Medical Trainee

Gerry McKay1
BSc (Hons), FRCP, Consultant Physician

Miles Fisher1
MD, FRCP, Consultant Physician

1Glasgow Royal Infirmary, Glasgow, UK

Correspondence to:
Dr Lorna Frame, Department of Diabetes, Endocrinology and Clinical Pharmacology, Glasgow Royal Infirmary, 84 Castle Street, Glasgow G4 0SF, UK; email: l.frame@nhs.net

Introduction
Methadone is a schedule 2 synthetic strong opioid which was developed in Germany in 1938 as an antispasmodic agent. Nowadays, it is primarily used as a substitute drug for patients with heroin addiction, although it also has a potential role in the management of chronic pain states, including neuropathic pain.

Pharmacology
Methadone has a number of unique characteristics when compared to other opioids. It has agonist affinity for both the mu and delta opioid receptors, it acts as an inhibitor at the presynaptic N-methyl-D-aspartate (NMDA) receptors, and it blocks the reuptake of serotonin and noradrenaline. This reduces the incidence of side effects such as confusion, sedation and myoclonus. Elimination is predominantly biliary, and dosing does not therefore have to be adjusted in the context of renal impairment. Some methadone formulations have a high sugar content, although sugar-free preparations are available.

Trials of safety and efficacy
While there is evidence that methadone reduces withdrawal symptoms and drug use in patients with opioid addiction, study numbers are generally small. In one double-blind trial eight patients received a tapering
dose of methadone over a 12-day period while eight received placebo. Withdrawal symptoms were assessed using the Subjective Opiate Withdrawal Scale (SOWS) and Objective Opiate Withdrawal Scale (OOWS). Both the SOWS and OOWS scores were significantly lower in the methadone group, and there was a significant improvement in six of 16 individual SOWS symptoms compared to placebo. In a retrospective chart review of 91 patients enrolled in a methadone maintenance programme, patients who continued with treatment (44 patients) showed a statistically significant reduction in opiate (p<0.0001), cocaine (p<0.0001) and benzodiazepine (p=0.02) use, as assessed by urine screening; no such reductions were observed in those who withdrew from treatment. Two small studies have demonstrated the analgesic value of methadone in the management of neuropathic pain. One study measured pain intensity in 18 patients using the Visual Analogue Scale (VAS), and mechanical allodynia and paroxysmal (shooting) pain were assessed clinically. The mean pre-treatment VAS ± SD was 7.7±1.5cm, and this dropped significantly to 1.4±1.7cm on a stable dose of methadone (p<0.0001). Nine of 13 patients (70%) experienced full resolution of mechanical allodynia, and all eight patients with shooting pain described complete control of this symptom. The median stable dose of methadone was 15mg per day. Side effects were in general very mild, and no patients stopped taking methadone as a result of side effects.

A double-blind randomised controlled crossover trial evaluated the benefits and potential adverse effects of a daily dose of methadone in 18 patients with a diverse range of chronic neuropathic pain syndromes, all of whom had responded poorly to traditional analgesic regimens. Compared to placebo, a 20mg daily dose resulted in statistically significant improvements in patient VAS ratings of maximum pain intensity, average pain intensity and pain relief recorded at the same time every day. Additionally, the analgesic effects extended over 48 hours, as shown by statistically significant improvements in all three outcomes on rest days instituted between each daily dose. With regard to adverse effects, nausea, vomiting, dizziness and headache were most commonly reported. Patient compliance was high throughout the trial.

**Specific evidence for use in diabetes**

There appears to be scant literature regarding the use of methadone in diabetes, both in the context of harm reduction and pain management. In two small studies already described there is some evidence that methadone is effective in diabetic peripheral neuropathy. In the first of these a patient suffering from diabetic polyneuropathy reported a pre-treatment VAS of 9, and this fell to 3 on a stable dose of 9mg of methadone per day. Additionally, complete resolution of mechanical allodynia was achieved; shooting pain was not a feature in this particular case. In the second study, four of the 18 patients had a diagnosis of diabetic polyneuropathy, and inter-patient analysis revealed that the analgesic effects of methadone were not restricted to any specific type of neuropathic pain.

Interestingly, there is evidence that chronic administration of mu opioid agonists is associated with a disease state similar to type 2 diabetes. In a preclinical study, rats given daily methadone over a 35-day period demonstrated increased resting serum glucose and impaired oral glucose tolerance compared to unexposed controls. They also demonstrated impairment in key enzymes related to glucose metabolism: the glycolytic activity of hexokinase and phosphofructokinase-1 activity was diminished, leading to less breakdown of plasma glucose, and the gluconeogenic activity of glucose-6-phosphatase and fructose-1,6-biphosphatase was increased, leading to augmented production of plasma glucose. Furthermore, a series of neuroendocrine challenge tests, performed both in men participating in a methadone maintenance programme and in normal controls, showed a clinically evident delayed and inhibited insulin response to food ingestion with resulting mild hyperglycaemia in the methadone group, and increased fasting insulin levels have been noted in methadone-maintained patients. Finally, the authors of the previously mentioned retrospective chart review noted that while 9.6% of the general population suffer from diabetes mellitus, 18% of their methadone maintenance population had this diagnosis.

**Discussion**

Methadone is used for harm reduction in patients with opioid addiction, and has been proven to reduce withdrawal symptoms and drug use effectively in this population. However, chronic administration may be associated with an increased risk of diabetes mellitus. While this risk appears to be independent of the preparation used, sugar-free forms should be prescribed where possible, and certainly in all patients with diabetes in order to avoid unnecessary fluctuations in blood glucose levels. Regarding its alternative uses, methadone has unique pharmacological properties that give it a distinct advantage over other opioids in the treatment of neuropathic pain. Studies suggest that it is valuable in reducing patient VAS ratings with minimal side effects, and the optimal dose appears to be around 15–20mg per day. Additionally, there is anecdotal evidence of its use in painful diabetic peripheral neuropathy, but further research is needed to confirm its efficacy and safety in this context.

**Declaration of interests**

There are no conflicts of interest declared.

**References**

References are available online at www.practicaldiabetes.com.
Drug notes

Methadone

References