Case report

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Transdermal buprenorphine ameliorated pruritus complicating advanced hepatocellular cancer

Abstract

Itch is a difficult to treat symptom that may accompany neoplastic disease. At least some of the itch symptoms are due to abnormal endogenous opioid synthesis in the liver. In the past opioid receptor antagonists were found useful to treat itch in such patients. However, their use is limited by the abstinence symptoms experienced by the patient. Another approach would be to use an opioid with high affinity and slow dissociation from the receptor not to allow endogenous opioids to interact with the opioid receptors. In this paper we describe a patient with severe itch due to hepatocellular cancer who responded to the treatment with buprenorphine.

Key words: buprenorphine, pruritus, hepatogenic itch

Introduction

Pruritus is a rare but difficult symptom to treat in the course of neoplastic disease. This symptom does not usually respond adequately to antihistamines [1]. Antihistamines may provide some benefit by virtue of their sedative properties; an effect similar to sedation by benzodiazepines [2]. Recently, new ideas have been launched suggesting that pruritus in liver diseases may be due to the abnormal production of opioids by the sick liver [3]. Opioid receptor antagonists naloxone and naltrexone have both been tried with success. However, these drugs may cause a very unpleasant opioid withdrawal-like reaction [4] and may with time become hepatotoxic. In order to treat pruritus, opioids with different profiles were tried. It was suggested that mu-agonistic opioids are pro-pruritic, while kappa-agonistic opioids are anti-pruritic [5]. Nalmefene, another opioid antagonist with a slightly different pharmacological profile, showed promising results in the treatment of this type of itch [6]. Buprenorphine is a partial opioid agonist of mu opioids receptors. It has an extremely high affinity to mu opioid receptors, whilst stimulating them only weakly. Hypothetically, buprenorphine, with its high affinity and slow dissociation from opioid receptors, may successfully compete with the binding sites, protecting them from interaction with endogenous opioids. A controlled trial with sublingual buprenorphine on 5 patients with pruritis of cholestasis [7] indicated that some patients may respond well to this treatment. However, the trial was prematurely discontinued because of the high toxicity of buprenorphine. Two authors of this article (Zbigniew Zylicz and Małgorzata Krajnik) had previously tried buprenorphine sublingual tablets in one patient and found the therapy to be effective and worthy of reconsideration [8]. When buprenorphine patches (Transtec®) were licensed for use as analgesics in Poland, we decided to try them in a patient with severe intractable itch due to hepatocellular carcinoma. A similar approach was suc-

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cessful in at least one other patient with itch due to primary biliary cirrhosis [9].

Case description

The patient was a 61-year-old man diagnosed eight weeks earlier with advanced hepatocellular cancer. For several years previously he had been treated for heart failure, diabetes mellitus and gout. Initially, he was admitted to the Cardiology Department because of his unexplained deterioration and exacerbation of breathlessness. During his assessment he was diagnosed with liver metastases and transferred to the Oncology Centre. The diagnosis of advanced hepatocellular cancer was confirmed by a biopsy but due to his poor general condition no oncological treatment was offered. At the time of his referral for home palliative care he was suffering from severe generalized itch of 9/10 intensity (according to the Numerical Rating Scale (NRS), where 0 means "no itch at all" and 10 is the "worst imaginable itch"), which left him unable to sleep and exhausted. He complained of occasional breathlessness, a painful oedematous left leg, abdominal pain, constipation, fatigue and low mood. The alkaline phosphatase was 724.03 U/l (normal values: 35–129 U/l) while bilirubin was normal (15.43 umol/l). Two weeks earlier, 5 mg of morphine every 4 hours had apparently been introduced for the treatment of pain and dyspnoea, together with fractionated heparine for suspected but not confirmed thrombotic complications. There was also an extensive list of medications which he had been taking for many years (insulin, glimepiride and metformin, allopurinol, amlodipine, thiazide, irbesartan and pantoprazole). All of these medications were continued at the time of his referral.

During the first home palliative care visit, the patient presented with considerable hepatomegaly, an extended abdomen and dry skin. Despite an apparent lack of jaundice, we hypothesized that cholestasis might be the most probable cause of pruritus. Regular morphine was changed to transdermal buprenorphine (Transtec 35 ug/h) with 5 mg oral morphine offered as a rescue dose in case of pain or dyspnoea. Apart from docusate sodium, a short trial of dexamethasone was prescribed. A regime for skin treatment was implemented, based on tea tree preparations. The intensity of the itch decreased after 2 days to 0–1/10. The patient occasionally complained of a localized itch on the upper and lower extremities, which could be effectively relieved by local measures. The patient deteriorated further and jaundice became clinically apparent. The main problem was back pain, which was satisfactorily controlled by the increase of the buprenorphine dose to 52.5 ug/h and the addition of paracetamol 1 g as needed (up to 3 times a day). The patient only used the breakthrough medication occasionally. Apart from the small dose of insulin, the other previously prescribed drugs were gradually discontinued. The dose of buprenorphine continued for 3 weeks until the patient's death. However, in the 3 days prior to death, morphine (20 mg/24 h), hyoscine butylbromide (40 mg/24 h) and haloperidol (up to 10 mg/24 h) were administered by SC syringe driver and provided satisfactory control of dyspnoea exacerbation, death rattle and restlessness. The patient remained free of itch and died peacefully at home.

Discussion

Buprenorphine, when appropriately titrated, may be helpful in the treatment of the itch accompanying primary biliary cirrhosis [9] and hepatocellular cancer (as in this case). The drug is highly lipophylic and shows a high degree of protein binding (96%), mainly to alpha and beta globulins, and its metabolism is dependent on the activity of liver enzymes [10]. The plasma half-life of buprenorphine may be very long (20–30 hours) and one should expect to achieve a steady state in 7–9 days. Buprenorphine may induce drowsiness and other opioids-related adverse effects. The dose should be carefully titrated and the time of titrations should not be too short. Exogenous morphine administered 2 weeks before referral to palliative care for "pain and dyspnoea" could be, at least potentially, the trigger for the onset of itch. However, later in the treatment of this patient, morphine was successfully used together with buprenorphine and helped to control symptoms. We did not have the impression that it counteracted the effects of buprenorphine. In a patient with rapidly developing hepatic insufficiency, it is important to discontinue all other drugs that may overload the hepatic oxygenase systems. This too may contribute to a better control of itch.

We conclude that carefully titrated transdermal buprenorphine should be further investigated as a potential antipruritic agent.

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