Breakthrough Pain Associated with a Reduction in Serum Buprenorphine Concentration during Dialysis

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ABSTRACT

Purpose: To describe a case of breakthrough pain associated with a reduction in serum buprenorphine concentration during dialysis.

Methods: Pharmacokinetic sampling of total and free buprenorphine and norbuprenorphine in an 80 year old male undergoing haemodialysis three times per week who received 5760 μg oral and transdermal buprenorphine daily was performed. The patient's serum albumin concentration was 23g/l (reference range: 35–52 g/l).

Findings: Pharmacokinetic sampling revealed a free buprenorphine fraction of 32% (consistent with the hypoalbuminaemia), which was markedly reduced at the end of dialysis (free buprenorphine concentration 2.4 μg/l before vs. <0.1 μg/l after dialysis).

Implications: Clinicians should be aware that some patients may require extra buprenorphine doses during dialysis to prevent significant falls in the concentration of active drug. (*Clin Ther.* 2016;38:212–215)

Key words: Breakthrough pain, buprenorphine, haemodialysis, pharmacokinetics.

INTRODUCTION

Buprenorphine is a potent μ-opioid receptor agonist and κ-opioid receptor antagonist. It is licensed for the treatment of moderate to severe chronic pain, particularly in cases in which nonopioid analgesics and weak opioids have proven ineffective.[1] Buprenorphine is preferentially used in patients with impaired renal function because it is mainly nonrenally (70–90%) eliminated.[2–4]

Due to its high lipophilicity (volume of distribution = 430 L) and plasma protein–binding capacity (96% bound to α- and β-globulin), buprenorphine is excreted slowly via feces (68%) and urine (27%).[5] It primarily undergoes N-dealkylation by CYP3A4 to norbuprenorphine and glucuronidation by UGT-isoenzymes (mainly UGT1A1 and 2B7) to buprenorphine 3β-O-glucuronide.[5] Norbuprenorphine is an active metabolite, but its analgesic potency is reduced compared with its parent compound by a factor of 50. Data from in vitro and animal studies have shown buprenorphine glucuronides to be pharmacologically active and possibly contributive to the overall pharmacology of buprenorphine.[6] The elimination of buprenorphine follows a complex bi- or tri-exponentional model, which is probably due to its complex distribution within the body, including the reabsorption from the gastrointestinal tract (enterohepatic circulation) and a slow diffusion from fat tissue. In addition, the mode of administration (transdermal or oral) has an impact on the pharmacokinetic properties of buprenorphine.[7] For these reasons, and also depending on the assay used to quantify buprenorphine in serum, different half-lives for buprenorphine have been determined. This range varies from 3 to 44 hours.[7] Because of the long-lasting and variable binding time to receptors, the duration of action does not correlate directly with serum concentration or half-life of buprenorphine. In a study of the pharmacokinetics of buprenorphine and norbuprenorphine in patients with severely impaired renal function, no differences in pharmacokinetic parameters

Accepted for publication October 7, 2015.
http://dx.doi.org/10.1016/j.clinthera.2015.10.009
0149-2918/$ - see front matter

compared with patients with normal renal function were observed for buprenorphine; however, there was a median 4-fold increase in norbuprenorphine concentrations.[8] In another study, the effect of hemodialysis on the pharmacokinetics of transdermal buprenorphine, up to a dose of 70 μg/h, was investigated.[9] No differences in plasma buprenorphine or norbuprenorphine concentrations were observed after dialysis. Therefore, buprenorphine is considered to be the opiate of choice and is licensed for patients undergoing hemodialysis. The effect of higher buprenorphine doses and of hypoalbuminemia on the pharmacokinetic behavior of buprenorphine is not known.

CASE DESCRIPTION

An 80-year-old patient (108 kg) who received buprenorphine to control bronchial tumor-associated pain complained of increased pain toward the end of his 3-hour hemodialysis sessions, which took place 3 times per week. Clinically, the patient had diabetic nephropathy, and type 2 diabetes mellitus had been diagnosed 13 years previously. He was dialyzed with a high-flux filter (FX-80, Fresenius Medical Care AG & Co, KGaA, Bad Homburg, Germany). His medical history also included chronic obstructive pulmonary disease and diabetic retinopathy. A hypoalbuminemia of 23 g/L (reference range: 35–52 g/L) was measured on routine monitoring. His medication consisted of transdermal buprenorphine (140 μg/h or 3360 μg/day), sublingual buprenorphine (400 μg) every 4 hours as required and paroxetine (20 mg/day).

It was not clear in this case whether the breakthrough pain after dialysis might have been related to a fall in buprenorphine or norbuprenorphine concentrations or related to the psychological stress of dialysis. However, we suspected, that due to hypoalbuminemia, the patient might have a high unbound buprenorphine and norbuprenorphine concentration, and that these unbound fractions might be dialyzable. Rather than empirically increase the buprenorphine dose, we decided to determine total and free buprenorphine and norbuprenorphine plasma concentrations before and after a single dialysis session.

A total of 4 samples were taken: 1 pair of arterial and venous blood samples shortly after the beginning of hemodialysis and another pair towards the end of hemodialysis. Samples were stored frozen at −20°C until analysis in the laboratories of the Institute of Clinical Chemistry, University Hospital Zürich, Switzerland. Total burprenorphine and norbuprenorphine was measured after protein precipitation by a fully validated LC-MS/MS method using deuterated internal standards on a TSQ Quantum Access Max (Thermo Fisher Scientific, Reinach, Switzerland). Chromatography was performed on an Uptisphere (Interchim, Montluçon, France) C18 column (125 × 2 mm, 5-μm particle size). As mobile phases,10-mM ammonium acetate in water + 0.1% formic acid (mobile phase A) and 10-mM ammonium acetate in methanol/acetonitrile 50/50 + 0.1% formic acid (mobile phase B) were used. Within-day imprecision was <5.1% for buprenorphine and <10% for norbuprenorphine. Between-day imprecision was <4.6% for buprenorphine and <7.8% for norbuprenorphine. The lower limit of quantification was 0.05 μg/L for both buprenorphine and norbuprenorphine. Using the postcolumn infusion method, no significant matrix effect could be detected. To assure quality, regular participation at an external quality assurance scheme, provided by Arvecon GmbH (Walldorf, Germany) was mandatory. Free buprenorphine and free norbuprenorphine were measured using the same method after ultrafiltration of 1-mL plasma for 1 hour at 1000*g* with Centricon centrifugal filter units (EMD Millipore, Billerica, Massachusetts) with a mass cutoff of 30,000 Da (Merck Millipore, Schaffhausen, Switzerland). Buprenorphine glucuronide metabolites were not measured. Due to the limited sample volume available for analysis, all measurements were done only once. On the day of sampling, the patient was under continuous treatment with transdermal buprenorphine 140 μg/h without oral administration of sublingual buprenorphine. The day before, the patient had also received 2.4 mg of sublingual buprenorphine.

The arterial total and free buprenorphine concentrations were higher than the venous concentrations at both time points (Figure). The free fraction of buprenorphine was higher than expected in normal subjects (32% instead of 4% as expected with a protein-binding capacity of 96%). This finding was most probably due to the hypoalbuminaemia of 23 g/L. The free buprenorphine concentration (active fraction) decreased rapidly and significantly during dialysis from 2.4 μg/L before dialysis to <0.1 μg/L after dialysis. The half-life of buprenorphine (administered as transdermal buprenorphine) in this patient during dialysis was 11 hours, compared to 30 hours without dialysis.[1]