Effects of Hemodialysis on Methadone Pharmacokinetics and QTc

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ABSTRACT

Purpose: Effects of hemodialysis on pharmacokinetic properties and QTc were studied in 4 patients taking daily methadone dose of 100 mg (range, 60–120 mg).

Methods: Methadone in serum, dialysate, and urine were measured by LC-MS/MS. QTc was calculated with Bazett's formula.

Findings: The serum C_{min} methadone level was 1124 nmol/L (range, 547–1581 nmol/L). Methadone dialysate clearance was 17.1 mL/min (range, 13.7–20.6 mL/min). Total loss in dialysate was 2.30% (range, 1,25–3,70%) of daily methadone intake. QTc increased from 391 msec (range, 369–406 msec) to 445 msec (range, 407–479 msec), independently of serum methadone level, which may be explained by normalization of serum electrolytes.

Implications: Methadone dose adjustment is not needed because of hemodialysis. (*Clin Ther*. 2015;▮:▮▮▮–▮▮▮)

Key words: hemodialysis, methadone, methadone maintenance treatment, pharmacokinetics, QTc, renal failure.

INTRODUCTION

Some patients undergoing methadone maintenance treatment (MMT) develop hemodialysis-dependent renal failure because of serious recurrent infections with renal AA amyloidosis.[1] Methadone is metabolized to 2-ethylidene-1, 5-dimethyl-3, 3-diphenylpyrrolidine (EDDP) and 2-ethyl-5-methyl-3, 3-diphenylpyrroline (EMDP) in the liver by CYP3A4/CYP3A5 and CYP2B6 and to a much lesser degree by CYP1A2, CYP2C9, CYP2C19 and CYP2D6. A small amount of all 3 compounds are hydroxylated followed by glucuronidation. The excretion of methadone and its metabolites is mainly renal, and approximately 30% is excreted into the intestine. Approximately 90% of serum methadone is bound to lipoproteins, α_1-acid glycoprotein, and albumin.[2–4]

Previous studies limited to only 2 patients taking low-dose methadone (40–50 mg) have found poor removal by hemodialysis.[5,6] The daily methadone dose in patients undergoing MMT in Norway is usually much higher, averaging 100 mg. We wanted to examine the degree of methadone loss during hemodialysis in patients taking high-dose methadone.

Methadone[7,8] and possibly reduction in serum potassium and magnesium[9] during hemodialysis might prolong QTc, an ECG change associated with fatal arrhythmias. Furthermore, we investigated the associations among serum methadone, electrolytes, and QTc during 4 hours hemodialysis.

MATERIALS AND METHODS

Materials

The study includes 4 hemodialysis-dependent patients with end-stage renal disease due to secondary renal AA

Preliminary abstract of this work was presented as poster at European Association of Clinical Pharmacology and Therapeutics Annual Meeting, 28-31 August, 2013, Geneva, Switzerland

Accepted for publication April 15, 2015.
http://dx.doi.org/10.1016/j.clinthera.2015.04.009
0149-2918/$ - see front matter

amyloidosis undergoing MMT at the Department of Nephrology at Oslo University Hospital during 2011–2012. One female and 3 males were taking stable methadone doses (median, 100 mg; range, 60–120 mg) at least 2 weeks before inclusion. The study was approved by The Norwegian Regional Ethic Committee. The patients signed written consent forms to participate.

Methods

Hemodialysis was performed using the Artis hemodialysis system (Gambro, Lakewood, Colorado) and a high-flux 170 filter with a pore size of 40 000 Da in patients 1, 2, and 3 and a Fresenius 4008H with Gambro polyflux with the same pore size in patient 4. Total hemodialysis time was 4 hours. The flow rate was 500 mL/min for dialysate solution, A-concentrate 892 (patients 1–3) from ScanMed (Omaha, Nebraska), and 873 (patient 4) from Fresenius Medical Care (Arkwright, Georgia).

Blood samples were drawn from the arterial line of the extracorporeal system into empty Vacutainers before morning intake of methadone and repeated every 30 minutes during hemodialysis. An evening blood sample was taken directly from the central venous catheter. The blood tubes were centrifuged for 10 minutes at 3655 rpm. Dialysate samples were collected into sterile containers (Sarstedt, Nümbrecht, Germany) every 30 minutes during hemodialysis.

Each patient emptied the bladder before hemodialysis. After completing hemodialysis, urine was collected, except from patient 4 due to anuria. All samples were stored in a refrigerator (4–8°C) until analyzed for methadone. Leftover material was stored in a biobank at –20°C, and samples were thawed for EDDP analysis.

Methadone Analysis

Serum or dialysate, 100 μL, was mixed with 50 μL of 3000 nmol/L internal standard of methadone-D_3 dissolved in methanol and 150 μL of acetonitrile. The solution was centrifuged at 3500 rpm for 15 minutes.

Urine, 100 μL, was mixed with 100 μL of methadone-D3, 50 μL of ammonium acetate 0.5 M (pH 5), and 50 μL of β-glucuronidase 10 000 units enzyme activity/mL. The samples were hydrolyzed (heating block, 3 hours, 60°C) before dilution with ultrapure water and centrifugation (10 minutes at 3500 rpm).

Methadone in serum, dialysate, and urine was measured by ultraperformance LC (UPLC)–MS/MS (Quattro Premier XE Acquity; Waters Corp, Milford, Massachusetts) using an Acquity UPLC BEH C18 (2.1 × 100 mm, 1.7 μm) column. A gradient elution with solvent A (0.1% acetic acid in hypergrade water) and solvent B (0.1% acetic acid in methanol) were used. The total run time for the sample was 9 minutes.

Dialysate was read off the calibration curve for serum. The standard range was 100 to 3000 nmol/L for serum and 100 to 10 000 nmol/L for urine. The standard curves were linear with an R^2 of 0.98. Limit of quantification in serum was validated down to 20 nmol/L. The variation coefficient of imprecision and day-to-day variation was $<10\%$ at control levels of 20, 150, 700, and 1500 nmol/L in serum and 120, 3000, and 9500 nmol/L in urine. The accuracy at all control levels in serum or urine compared with spiked levels was $<115\%$.

Unconjugated EDDP Analysis

The following were added to a 1-mL sample: 1 mL of water, internal standard (bupranol), and 0.5 mL of 2 M ammonium acetate buffer (pH 5). The material was applied to Varian Nexus LRC 60-mg SPE columns. The columns were washed with water before elution by methanol.

Calibration curves (18–1800 nmol/L) were prepared in autonorm, negative dialysate, and negative urine. Analysis of EDDP was performed with a 1290 Infinity HPLC coupled to a 6490 Triple Quadrupole (electrospray ion source in positive mode) (Agilent Technologies, Santa Clara, California). Separation of the compounds was obtained by gradient elution using a Zorbax Eclipse XBD-C8, Narrow Bore RR 100 × 2.1 mm, 3.5 μm particle size (Agilent Technology) coupled to a Zorbax Eclipse XBD-C8, Narrow Bore RR 12.5 × 2.1 mm, 5 μm particle size guard column (Agilent Technology). The mobile phase consisted of 0.1% acetic acid in 1 mM ammonium acetate and acetonitrile (3–97%) at a flow rate of 400 μL/min. The total run time was 8 minutes.

The limit of detection was 5 nmol/L, and the %CV at 360 nmol/L was 12.6%. The calibration curves were linear and had an R^2 of 0.99.

Pharmacogenetic Analysis

Routine pharmacogenetic analysis of cytochrome CYP3A5, CYP1A2, CYP2B6, CYP2D6, CYP2C9, and CYP2C19 were performed.

Biochemistry Tests

Routine biochemistry analyses in accredited laboratories included tests of kidney function (serum