

*Clinical Note*

# Clearance of Meperidine and Its Metabolite Normeperidine in Hemodialysis Patients With Chronic Noncancer Pain

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**Abstract**

**Context.** Normeperidine accumulates in patients with impaired renal function and may cause central neurotoxicity. However, some uremic patients still undergo meperidine treatment for chronic pain.

**Objectives.** To prevent normeperidine side effects and complications, we investigated the clearance rate and extraction ratio of meperidine and normeperidine in hemodialysis patients with chronic pain.

**Methods.** Three hemodialysis patients, with diagnoses of chronic pancreatitis, chronic back pain, and intractable intra-abdominal pain, received long-term (more than six months) administration of meperidine for chronic noncancer pain. During regular hemodialysis, 72 blood samples in total were collected from the afferent port, efferent port, and ultrafiltrate port at eight time points. The plasma concentrations of meperidine and normeperidine were determined by high-performance liquid chromatography.

**Results.** The prehemodialysis plasma concentrations of meperidine and normeperidine were  $2963 \pm 315$  and  $2369 \pm 1974$  ng/mL, which declined to  $591 \pm 109$  and  $853 \pm 765$  ng/mL, with 80% and 65% reduction, respectively. The plasma clearance and extraction ratios of meperidine were  $22.7 \pm 9.8$  mL/minute and  $10.1 \pm 5.6\%$  and for normeperidine  $26.0 \pm 11.4$  mL/minute and  $10.8 \pm 2.5\%$ , respectively.

**Conclusion.** Hemodialysis can efficiently remove meperidine and its active metabolite, normeperidine, in uremic patients receiving long-term meperidine therapy for chronic noncancer pain. *J Pain Symptom Manage* 2014;47:801–805.  
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**Key Words**

*Hemodialysis, meperidine, normeperidine, chronic noncancer pain*

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## Introduction

Meperidine, a synthetic opioid agonist, is usually prescribed as a second-line agent for the treatment of moderate-to-severe acute pain. In the treatment of chronic pain, meperidine is not recommended in Taiwan<sup>1</sup> because of its short duration of action and a risk of neurotoxicity associated with its metabolite normeperidine. However, in patients who cannot tolerate side effects of other opioid agonists, meperidine is briefly used for acute pain management in operative or medical procedures.

Normeperidine, the active metabolite of meperidine, has been known to cause central nervous system (CNS) toxicity.<sup>2</sup> It accumulates in uremic patients<sup>3–5</sup> and prevents common use of meperidine in them. Nevertheless, long-term meperidine therapy has clinically been an alternative for uremic patients who experience intolerable side effects with morphine or fentanyl because there are only three potent opioids (morphine, fentanyl, and meperidine) available in Taiwan. The toxic dose has not been determined in uremic patients on regular hemodialysis, and the efficacy of hemodialysis in reducing the blood concentrations of meperidine and normeperidine has not been well studied.<sup>6</sup> In this study, we aimed to determine the clearance rate and extraction ratio of meperidine and normeperidine during hemodialysis in three uremic patients on long-term administration of meperidine (from six to 48 months).

## Methods

After obtaining institutional review board approval from Tri-Service General Hospital (TSGHIRB-097-05-098) and written informed consent, three uremic patients on chronic meperidine administration in our outpatient department were recruited for this study from January 2009 to December 2009. The diagnosis of chronic noncancer pain and combined prescriptions were recorded. Meperidine was the only analgesic. Meperidine was prescribed on an as-needed basis, with 50 mg administered intramuscularly. The duration of hemodialysis was four hours three times per week, with average weight loss of  $3 \pm 0.5$  kg for one to three years. Vascular access for hemodialysis was obtained by insertion of a catheter into an

arteriovenous shunt in the arm. The dialyzer F7HPS (Fresenius, Bad Homburg, Germany; polysulfone; effective surface area:  $1.6 \text{ m}^2$ ; ultrafiltration coefficient: 16; urea mass transfer area coefficient: 789) was connected to patients, with a blood flow rate of 200 to 300 mL/minute and a dialysate flow rate of 500 mL/minute.

Each 3 mL blood sample was collected from the arterial and venous sampling ports and from dialysate solution at eight different time points (0, 5, 10, 20, 30, 60, 120, and 240 minutes) from the start of hemodialysis and stored in a heparin-rinsed tube. The baseline blood sample was set as time zero, when the patient was put on the dialyzer. Meperidine and normeperidine concentrations in plasma and dialysate fluid were measured by high-performance liquid chromatography (HPLC).

The HPLC system consisted of a pump (LC-10AD; Shimadzu Corp., Kyoto, Japan), an automatic sampler (Model 542; ESA Inc., Sunnyvale, CA), a UV detector (SPD-10 A; Shimadzu Corp.), and a Silica column ( $150 \times 4.6$  mm, 3  $\mu\text{m}$  particle size; Keystone Scientific, State College, PA). For the column system, a precolumn ( $10 \times 4$  mm inner diameter, 5  $\mu\text{m}$  particle size; Keystone Scientific) also was used. The assay for meperidine was performed using a mobile phase of 5 mM sodium acetate buffer (pH 5.45):acetonitrile (40:60 v/v) and a UV detector (200 nm). A flow rate of 1.0 mL/minute at 30°C was used and yielded a back pressure of about  $108 \text{ kg/cm}^2$ . The limits of detection for meperidine and the metabolite normeperidine were 10 and 5 ng/mL, respectively, extracted from a 1 mL sample. The coefficient of variation of meperidine by extraction was determined at these concentrations to be between 1.7% and 6.5% as well as for the metabolite normeperidine to be between 1.9% and 5.9%.

The equations<sup>6</sup> for the plasma reduction and extraction ratios as well as the clearance rates of meperidine and normeperidine by four-hour hemodialysis are illustrated in Fig. 1. The estimated clearance rates of meperidine and normeperidine by hemodialysis are calculated from the relationship with urea.<sup>7</sup> The urea clearance for most standard dialyzers varies between 150 and 200 mL/minute.

All statistical calculations were performed using SPSS Statistics, version 19 (SPSS Benelux

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