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Pharmacokinetics of meperidine (pethidine) in rabbit oral fluid: correlation with plasma concentrations after controlled administration

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Received January 19, 2018, accepted March 14, 2018

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Pharmazie 73: 324–328 (2018) *doi: 10.1691/ph.2018.8014*

Oral fluid assays for quantifying drugs are useful in forensic toxicology and drug monitoring. Compared with blood and urine specimens, oral fluid collection is simple, non-invasive, and more difficult to adulterate. Therefore, we investigated whether meperidine and its metabolites could be detected in oral fluid and whether there was a predictable relationship between oral fluid and plasma concentrations. Male New Zealand white rabbits (n = 10) were administered meperidine hydrochloride (20 mg/kg, intravenous). Then, plasma and oral fluid were collected at various time points up to 10 h after administration. We developed a simple and sensitive gas chromatography–mass spectrometry method for the determination of meperidine and normeperidine in oral fluid and plasma. We estimated the apparent pharmacokinetic parameters for meperidine in oral fluid and plasma and determined the ratio and correlation between oral fluid and plasma concentrations. The results demonstrate that this method has excellent specificity, linearity, precision, and recovery. Meperidine and normeperidine were detected in both body fluids; meperidine was the most abundant analyte in oral fluid. The oral fluid-to-plasma drug concentration ratios did not differ significantly over time ($p > 0.05$). In addition, oral fluid and plasma levels of meperidine and normeperidine were significantly correlated over time (r = 0.713 and 0.725, respectively; $p < 0.05$). These results provide context for interpreting meperidine and metabolite concentrations in oral fluid and support the utility of oral fluid as an alternative matrix in clinical and forensic testing.

1. Introduction

Oral fluid tests are being used increasingly as an analytical tool in pharmacokinetic studies, therapeutic drug monitoring, and detection of illicit drugs (Kintz and Samyn 2002). Oral fluid has several advantages over blood and urine, as its collection is non-invasive, convenient, and does not cause discomfort compared with blood sampling (Choo and Huestis 2004). In addition, an adequate sample volume is easy to obtain (Parzynski et al. 2008), and oral fluid is more difficult to adulterate than urine (Kintz et al. 1998). However, oral fluid has several disadvantages, since some routes of administration (e.g., smoking, nasal inhalation, and oral ingestion) may affect drug concentration, and oral sample drug quantification may be affected by pH and saliva flow rate (Cone 2001).

Several studies have indicated that therapeutic drug monitoring (Cone 2001) and recent drug-of-abuse use can be confirmed with oral fluids (Drummer 2006; Bosker and Huestis 2009) and most alkaline drugs correlate well with plasma and oral fluid levels. Oral fluid drug quantification reflects its free or unbound plasma concentration, and drug detection times (5–48 h) are similar to those of blood (1–2 d), whereas detection in urine can be much longer. Due to such short detection times, oral fluid can indicate recent drug use or current drug use status.

Meperidine, or pethidine, is a synthetic narcotic analgesic that predominately acts on μ-opioid receptors. It is widely prescribed to treat moderate to severe pain, but has a high potential for abuse. Normeperidine is the main active metabolite, but it contributes little to analgesic activity and mostly causes central nervous system stimulation and neurotoxicity, especially after accumulation due to chronic dosing (Clark et al. 1995; Latta et al. 2002). In oral fluid tests, meperidine is presumably the primary target; however, there is a lack of data on the disposition of metabolites in oral fluid (Depriest et al. 2015). Two studies suggested a good correlation between meperidine concentrations in oral fluid and plasma. In both studies, oral fluid meperidine concentrations were higher than that in plasma, with average oral fluid-to-plasma ratios of 1.37–2.60 (Samyn et al. 1999) and 5.5 (Freeborn et al. 1980). There is little data in the literature regarding the systematic study of meperidine and normeperidine clearance from oral fluid after controlled administration.

In this study, we developed and validated a sensitive gas chromatography–mass spectrometry (GC–MS) method to determine meperidine and normeperidine concentrations in rabbit plasma and oral fluid. This method was successfully applied to study the pharmacokinetics of meperidine and determine the correlation between plasma and oral fluid levels following a single intravenous (i.v.) dose of meperidine. The aim of this experiment was to determine whether oral fluid testing for meperidine can be used as a proxy for plasma assays.

2. Investigations and results

2.1. Method validation

Figure 1A and B shows representative chromatograms for the determination of meperidine and normeperidine in plasma and oral fluid. Meperidine and normeperidine had retention times of about 6.498 and 7.400 min, respectively. The chromatograms indicated that the analytes were well separated, and no interferences were detected from endogenous substances or metabolites.

The calibration curves showed good linearity over the concentration range in plasma and oral fluid, with correlation coefficients (r) of 0.9950 and 0.9921, respectively. The assay had LODs 0.10 and 0.05 mg/L and LOQs of 0.50 and 0.10 mg/L for meperidine and

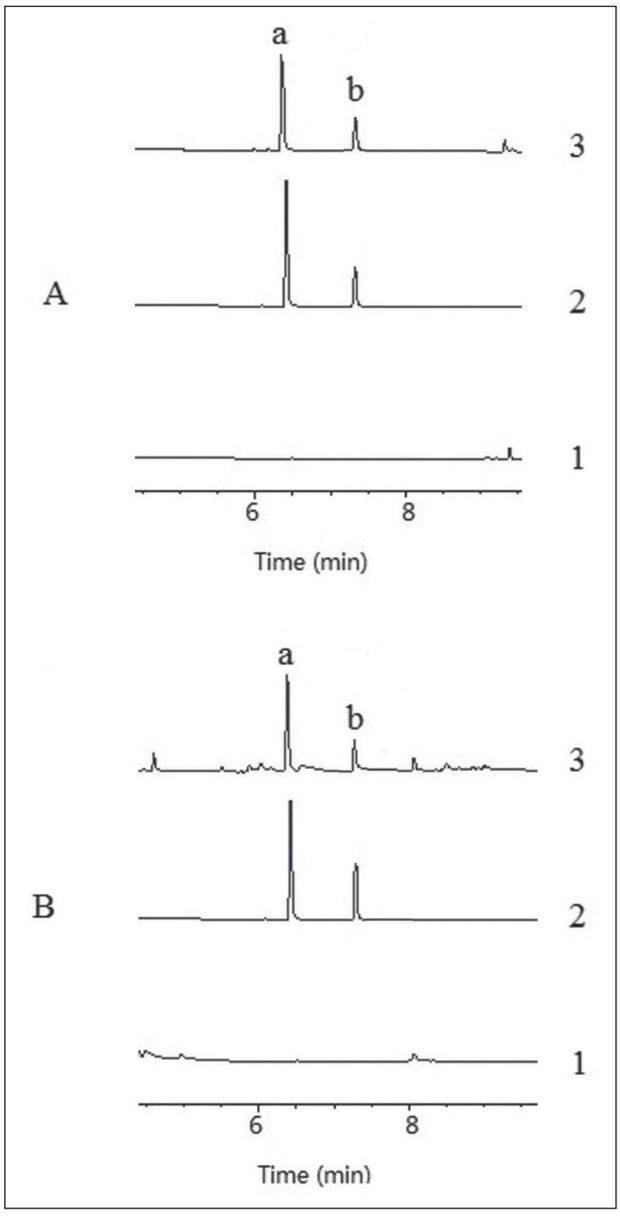

Fig. 1: Representative chromatograms of (A) plasma and (B) oral fluid. Peak (a) represents meperidine and peak (b) represents normeperidine. The number 1 represents the blank plasma or blank oral fluid, 2 represents biological samples spiked with meperidine or normeperidine, and 3 represents the plasma or oral fluid samples following a single intravenous (i.v.) dose of meperidine (20 mg/kg).

normeperidine, respectively, in the plasma and oral fluid samples. These limits were sufficient for studying the pharmacokinetics and determining the correlation between plasma and oral fluid levels following a single i.v. dose of meperidine.

Table 1 summarizes the precision results of the method. For all samples spiked with analytes at both concentration levels, the RSDs of the intraday and interday precisions were below 6.52 and 10.16 %, respectively. The extraction recoveries of meperidine ranged from 81.29 to 85.01 %, while those of normeperidine ranged from 78.47 to 83.93% in rabbit plasma and oral fluid (Table 1).

2.2. Meperidine and normeperidine in oral fluid and plasma

Meperidine and normeperidine were detected in rabbit oral fluid and plasma after a single i.v. administration (n = 10) (Fig. 2). Trace normeperidine was measured in both oral fluid and plasma,

Table 1: Precision and recovery of the method used for the determination of meperidine and normeperidine in rabbit plasma and oral fluid (n = 6)

Biological sample	Drug	Concentration (mg/L)	Precision (RSD)		Recovery
			Intraday	Interday	Mean ± SD (%)
Plasma	Meperidine	1	5.25	10.16	85.01 ± 8.35
		5	4.82	7.83	83.17 ± 6.84
	Normeperidine	1	4.51	5.47	80.02 ± 3.61
		5	2.80	9.39	82.13 ± 5.92
Oral fluid	Meperidine	1	4.47	6.76	81.29 ± 4.13
		5	6.52	3.91	83.33 ± 7.15
	Normeperidine	1	3.80	4.88	78.47 ± 2.21
		5	5.32	7.61	83.92 ± 6.68

Abbreviations: RSD, relative standard deviation; SD, standard deviation.

accounting for 4.1~12.3 % and 6.2~10.7 % of the parent drug, respectively. Oral fluid meperidine concentrations were much higher than those in simultaneously collected plasma ($p < 0.05$). However, the oral fluid and plasma concentration profiles were similar, and the oral fluid-to-plasma ratios at 0.25–1 h did not differ significantly ($p > 0.05$) for meperidine (mean, 1.183) and normeperidine (mean, 1.132) (Fig. 3). Meperidine and normeperidine had oral fluid-to-plasma ratios of 1.860~2.831 and 1.635~2.030, respectively, between 2–10 h. The oral fluid and plasma concentrations of meperidine and normeperidine correlated well over time (r = 0.713 and 0.725, respectively; $p < 0.05$). These results indicate that oral fluid concentrations can be used to evaluate plasma meperidine and normeperidine concentrations.

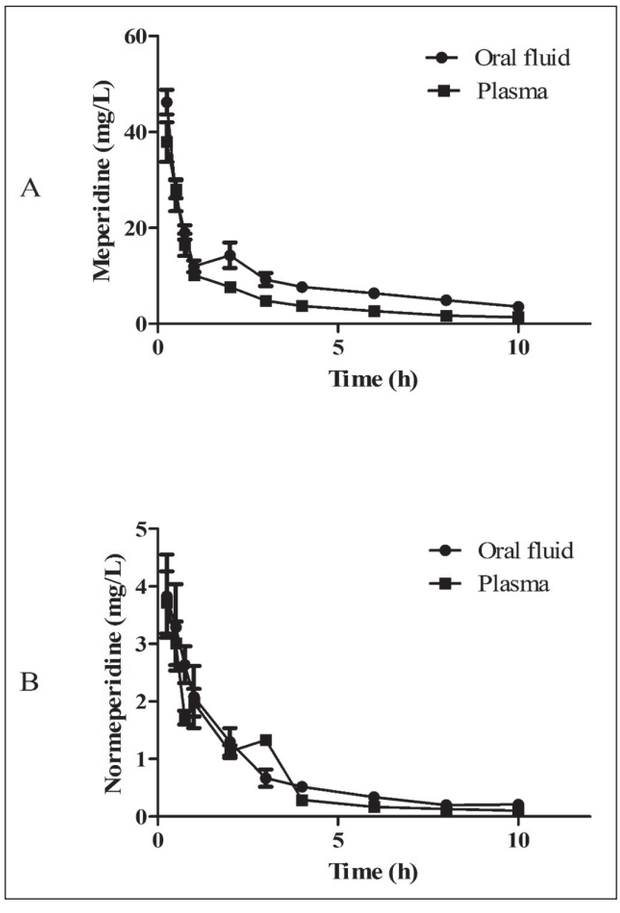

Fig. 2: Mean (A) meperidine and (B) normeperidine concentrations over 10 h in rabbit oral fluid and plasma (n = 10) after a single i.v. dose of meperidine (20 mg/kg). Note: y-scales vary by magnitude.

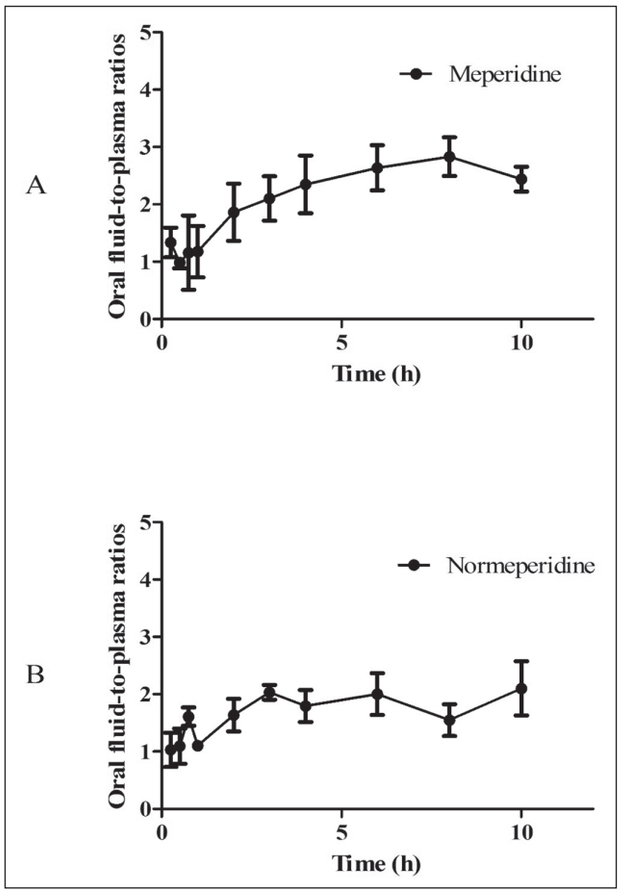

Fig. 3: Mean oral fluid-to-plasma ratios over 10 h for (A) meperidine and (B) normeperidine ($n = 10$) after a single i.v. dose of meperidine (20 mg/kg).

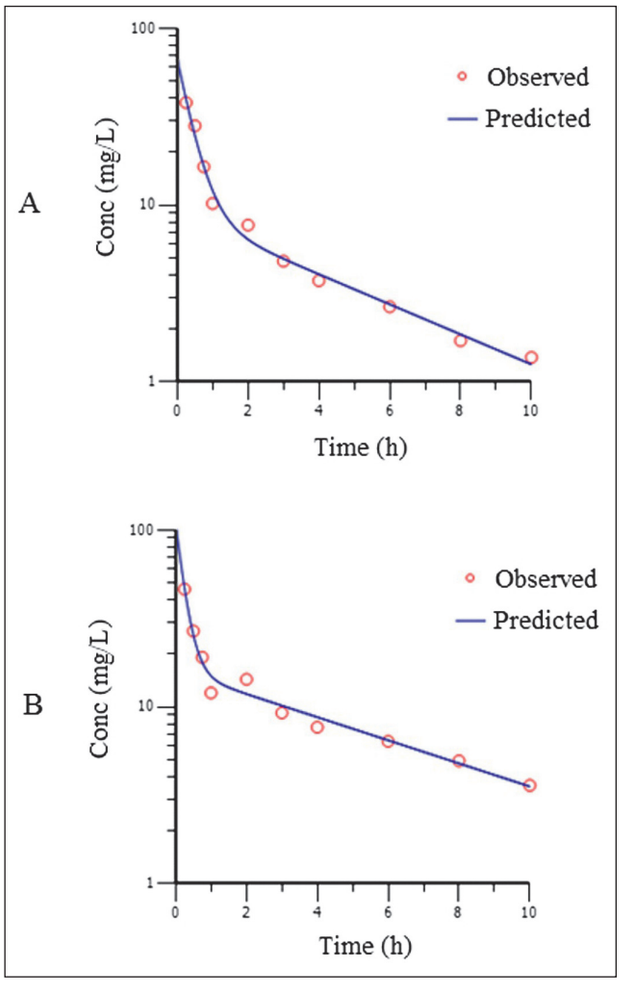

Fig. 4: The predicted concentration curve over time in (A) plasma and (B) oral fluid fitted with WinNonlin.

2.3. *Pharmacokinetics of meperidine in oral fluid and plasma*

Meperidine distribution in oral fluid and plasma fit a two-compartment model; Table 2 lists the pharmacokinetic parameters (mean±standard deviation [SD]). A statistical comparison confirmed significant differences between oral fluid and plasma based on the *AUC*, $t_{1/2}\alpha$, $t_{1/2}\beta$, and *CL* of meperidine. A significant difference in the *AUCs* of oral fluid and plasma was observed ($p < 0.05$). Meperidine had a faster distribution phase ($t_{1/2}\alpha$, 0.159) in oral fluid than plasma ($t_{1/2}\alpha$, 0.276) followed by a relatively slower elimination phase ($t_{1/2}\beta$, 4.604) in oral fluid than plasma ($t_{1/2}\beta$, 3.542) ($p < 0.05$). Meperidine clearance was significantly prolonged in oral fluid compared with plasma ($p < 0.05$), allowing for a longer detection window in oral fluid. Figure 4 shows the predicted concentration-time curve in plasma and oral fluid fitted with WinNonlin, which suggested that the observed data were best fitted with a two-compartment model.

Table 2: Mean pharmacokinetic parameters in rabbit oral fluid and plasma after intravenous administration of meperidine (mean ± standard deviation [SD], $n = 10$).

Parameter (unit)	Oral fluid	Plasma
$t_{1/2}\alpha$ (h)	0.159 ± 0.046*	0.276 ± 0.054
$t_{1/2}\beta$ (h)	4.604 ± 0.583*	3.542 ± 0.387
$AUC_{0-\infty}$ (h·mg/L)	127.646 ± 7.934*	68.649 ± 3.475
CL (L/h)	0.470 ± 0.029*	0.874 ± 0.044

The oral fluid and plasma meperidine values represent the mean ± SD of 10 rabbits; significant difference $p < 0.05$: * mean oral fluid concentration versus plasma.
Abbreviations: $AUC_{0-\infty}$, area under the curve from time zero until infinity; $t_{1/2}\alpha$, distribution phase half-life; $t_{1/2}\beta$, elimination phase half-life; *CL*, clearance.

3. Discussion

Meperidine offers little-to-no therapeutic advantage over other opioids, and may be more prone to abuse. The determination of meperidine, tramadol, and oxycodone in human oral fluid collected is possible using the Quantisal® oral fluid collection device with a combination of solid-phase extraction and GC–MS (Freeborn et al. 1980). We developed a liquid–liquid extraction and GC–MS method for the determination of meperidine and its primary metabolite, normeperidine, in rabbit plasma and oral fluid. The method is accurate and reproducible for the determination of meperidine and normeperidine in rabbit plasma and oral fluid. The recovery data indicate that the biological sample preparation procedure is satisfactory and can achieve acceptable extraction recovery (Table 2). Precision and recovery of the method were comparable to those in humans, demonstrating that this analytical method can be applied to human samples.

We measured meperidine and normeperidine in rabbit oral fluid and plasma after a single i.v. administration. Meperidine was the predominant analyte found in oral fluid, and the oral fluid concentration-time profiles were in agreement with those in plasma (Fig. 2). Several studies have indicated that the parent drug is the most commonly detected moiety in blood and oral fluid, whereas metabolites typically predominate in urine. For example, cocaine is the major compound present in oral fluid

after use (Schramm et al. 1993), and heroin and 6-acetylmorphine are the dominant species in oral fluid after heroin abuse (Jenkins et al. 1995), whereas tetrahydrocannabinol is the predominant species found in urine after smoking of cannabis products (Wille et al. 2015).

In this study, oral fluid meperidine and normeperidine concentrations exceeded those in plasma (Fig. 1). This can be explained by their alkalinity and ion trapping in the lower-pH oral fluid compared with blood. Our results were in agreement with those of Samyn and Freeborn (Freeborn et al. 1980; Samyn et al. 1999), who found that meperidine in human oral fluid was significantly higher than that in plasma. These results have been replicated in other basic drug studies. For example, oral fluid concentrations of basic drugs, such as amphetamines, 3,4-methylenedioxy (MDMA), cocaine, and several opioids, exceed those in human blood (Freeborn et al. 1980; Samyn et al. 1999).

Normeperidine is a major meperidine metabolite with about half the analgesic activity, and is not usually found in plasma after a single administration. In two previous reports, meperidine was detected, but normeperidine was not (Freeborn et al. 1980; Samyn et al. 1999). Our results confirmed trace levels of unconjugated normeperidine, with higher concentrations in oral fluid than plasma. The trends of meperidine concentrations in oral fluid and plasma were in agreement with data from humans, indicating that the distribution of normeperidine in human oral fluid and plasma is similar to that in rabbit.

Sample collection can alter drug concentrations. Moreover, rabbit oral fluid secretion is inconsistent and difficult to obtain, and stimulation of oral fluid secretion can increase oral fluid pH to the degree that it approaches plasma pH (Desrosiers et al. 2013). For alkaline drugs, this can increase drug concentrations in the oral fluid to plasma concentrations. In our study, we collected oral fluid by stimulation with pilocarpine nitrate administration, which increases fluid secretion, but can reduce the overall concentration of meperidine. Regardless, meperidine in oral fluid still exceeded that of the plasma, so any effect of pilocarpine nitrate was likely minimal or non-significant.

Meperidine was readily detectable in oral fluid and had similar pharmacokinetic features to those in plasma (see Table 2). Meperidine had a rapid distribution phase followed by a relatively slow elimination phase in oral fluid compared with plasma, while meperidine clearance in oral fluid was significantly slower than that in plasma. Therefore, we conclude that, although the drug in oral fluid reflects its free or unbound form in plasma, the detection window of meperidine in oral fluid is longer than that in plasma. Based on Pearson's correlation coefficients, the oral fluid and plasma concentrations were statistically significant, which was in agreement with previous studies on meperidine (Freeborn et al. 1980; Samyn et al. 1999) and other opioids, including codeine, diamorphine (Pourzitaki et al. 2006), methadone (Shiran et al. 2005), morphine (Kopecky et al. 1997), oxycodone (Hardy et al. 2012), and dihydrocodeine (Skopp et al. 2001), which have been studied in similar fashions.

Previous studies suggest that the oral fluid-to-plasma ratios of most opioids exceed 1, indicating that oral fluid is suitable for testing this drug class (Kunkel et al. 2005). We observed a relatively consistent oral fluid-to-plasma ratio, and the meperidine and normeperidine ratios were typically >1 from 0.25 to 10 h. Therefore, oral fluid testing for meperidine and normeperidine may be a suitable proxy for testing plasma levels in both rabbits and humans. At 0.25–1 h after a single i.v. dose of meperidine, the oral fluid concentrations were similar to those of plasma, suggesting that oral fluid meperidine and normeperidine concentrations can reflect those of plasma in the initial 0.25–1 h after administration. The ratios of meperidine and normeperidine from 2 to 10 h were much higher than those 0.25–1 h after administration. Although there was a good correlation between plasma and oral fluid concentrations over time, care should be taken when predicting plasma concentrations from oral fluid concentrations more than 2 h after administration.

4. Experimental

4.1. Chemicals

All reagents and solvents were analytical grade. Meperidine and normeperidine standards were purchased from Sigma Aldrich (St. Louis, MO, USA). Meperidine hydrochloride was purchased from Qinghai Pharmaceutical Factory Co., Ltd (Xining, China). Pilocarpine nitrate was supplied by Tianjin Jinyao Amino Acid Co. (Tianjin, China). Sterile oral fluid collection tubes were purchased from Changchun Boyan Technology Instrument Co. Ltd (Changchun, China).

4.2. Sample collection

Male New Zealand white rabbits (3.0±0.2 kg) were provided by Shanxi Medical University Experimental Animal Center (Taiyuan, China). All rabbits were given meperidine hydrochloride (20 mg/kg) via the left auricular vein within 5 min. Oral fluid and blood specimens were collected from rabbits before dosing and 0.25, 0.5, 0.75, 1, 2, 3, 4, 6, 8, and 10 h after administration. All experiments were approved by the Animal Ethics Committee of Shanxi Medical University.

Oral fluid excretion was stimulated by pilocarpine nitrate administration (subcutaneous injection) 15 min before each collection time point, and oral fluid was collected in sterile oral fluid collection tubes. Peripheral blood was drawn from the right common carotid artery and stored in 5-mL ethylenediaminetetraacetic acid (EDTA) anticoagulation tubes. Specimens were centrifuged at 3,000 rpm for 15 min within 1 h of collection, and the supernatant was stored at 4 °C until analysis.

4.3. Sample preparation

Aliquots (1 mL) of calibrators, controls, and samples were transferred to labeled and silanized glass tubes. Meperidine and normeperidine were extracted from the samples via liquid–liquid extraction using dichloromethane. Briefly, 1 mL of sample was diluted with 1 mL of phosphate buffer (pH 12.0) to concentrate the meperidine and normeperidine. The sample was extracted with 2 × 5 mL of dichloromethane. The organic phase was separated and evaporated until dry under a nitrogen stream. Dried extracts were reconstituted in 20 µL of methanol for the GC–MS analysis.

4.4. GC–MS analysis

Dried extracts were analyzed using a TRACE™ gas chromatograph coupled to a DSQ™ mass spectrometer (Finnigan MAT, San Jose, CA, USA). The mass spectrometer was operated in the electron impact ionization and selected ion monitoring acquisition mode. Ion mass-to-charge ratios of 71 and 57 *m/z* were selected for the quantification of meperidine and normeperidine, respectively. First, 1 mL of reconstituted residue was injected into the capillary column (DB-5MS; 30 m × 0.25 mm × 0.25 µm; J W Scientific, Folsom, CA, USA), and the instrument was operated in split mode (20:1 split ratio). Helium was used as the carrier gas at a constant rate of 1.0 mL/min. The initial column temperature of 100 °C was held for 1 min, which was then increased to 270 °C at a rate of 25 °C/min. The final temperature was held for 3 min. The injection port, interface, and ionizer temperatures were 250 °C, 250 °C, and 200 °C, respectively.

4.5. Method validation

Meperidine and normeperidine stock solutions were prepared in methanol at concentrations of 1.0 mg/mL. A series of working solutions was obtained by diluting the stock solutions in methanol. All solutions were stored at 4 °C until further use. Two concentrations (1.0 and 5.0 mg/L) of quality control (QC) samples were prepared by spiking the appropriate amount of working solution into drug-free rabbit plasma and oral fluid.

The linearity of the method for the determination of meperidine and normeperidine was evaluated with a calibration curve. Calibration standard samples were prepared by adding a range of concentrations of the meperidine and normeperidine standards to blank plasma and oral fluid. The calibration curves were constructed by plotting the integrated chromatography peak areas (Y) *versus* the corresponding concentrations of the injected standard solutions (X) using the $1/x^2$ weighted linear least-squares regression model. The limits of detection (LODs) and limits of quantitation (LOQs) of the developed method for each compound were determined at signal-to-noise ratios of 3 and 10, respectively. Any specimens found to be beyond the linear range of the assay were diluted so as to be quantified within the linear portion of the curve.

We used two concentrations (1.0 and 5.0 mg/L) of meperidine and normeperidine QC samples to evaluate the assay precision. The intraday precision was calculated by analyzing the 2 concentrations with 6 determinations per concentration on the same day, while the interday precision was measured over 3 consecutive days. The variability was defined as the relative standard deviation (RSD), which should not exceed 15%, covering the range of actual experimental concentrations.

The extraction recoveries of meperidine and normeperidine were determined at the two QC sample concentrations (1 and 5 mg/L). The recoveries were calculated by comparing the observed peak area ratios in biological samples to those of unprocessed standard solutions at the same concentrations.

4.6. Statistical analysis and pharmacokinetics

Data were analyzed with SPSS ver. 17.0 for Windows (SPSS Inc., Chicago, IL, USA). Pearson correlation coefficients were used to determine the relationship between the oral fluid and plasma drug concentrations, and $p < 0.05$ was considered statistically significant (two-tailed). The oral fluid-to-plasma ratios for meperidine and normeperidine were measured in specimens collected simultaneously. The area under the

curve (*AUC*), distribution phase half-life ($t_{1/2}\alpha$), elimination phase half-life ($t_{1/2}\beta$), and clearance (*CL*) were calculated with a two-compartment model using WinNonlin ver. 6.4 (Pharsight Inc., Mountain View, CA, USA). Comparisons were performed using Student's *t*-tests. Results were considered significant when $p < 0.05$ (two-tailed) for all statistical tests.

Acknowledgments: This work was financially supported by the National Key Technology R & D Program of China (2007BAK26B05).

Conflicts of interest: none declared.

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