

Pharmacokinetics and local responses to submucosal meperidine compared with other routes of administration

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Abstract

The objective of this study was to determine the time course of the plasma levels of meperidine administered by various routes. Ten healthy adults received 0.8 mg/kg of meperidine given intravenous, submucosal, intramuscular, and 1.4 mg/kg orally in a randomized sequence at a minimum of one-week intervals. Blood samples were collected at 0, 10, 20, 30, 45, 60, 90, 120, 180, 240, 360, and 720 min. The plasma was separated by centrifugation at room temperature. Plasma samples were analyzed for unchanged meperidine by a high-pressure liquid chromatographic assay. Pharmacokinetic parameters were calculated according to standard techniques. Data analysis was accomplished using a 4x11 analysis of variance and the Scheffe test for multiple comparisons. Pain response and tissue changes also were assessed using 4-point scales. Significant interaction effects ($P < 0.00001$) were found between the administration route and the time intervals. The maximum observed concentration of meperidine for the IV and SM routes occurred at the first sample point at 10 min, for the IM route at 20 min, and for the PO route at 45 min. There were no significant differences between the IV and the SM routes at any time interval measured. Post hoc comparisons of the peak values demonstrated significant differences between the IM and PO values (1.4 mg/kg) when compared with the IV and SM routes ($P < 0.01$). SM route caused greater tissue response and pain reaction, however, the differences were not statistically significant. (Pediatr Dent 16:190-92, 1994)

Introduction

Meperidine (ethyl, 1-methyl-4 phenyl-4 piperidine-carboxylate hydrochloride) is a synthetic opioid which was first synthesized in 1939. Since its introduction, there has been a gradual yet steady increase in its popularity. In a 1982 survey of the members of the American Society of Dentistry for Children, Aubuchon found that this drug continued to be popular for pediatric dental sedation.¹

Despite the popularity of meperidine, kinetic studies comparing various routes of administration have been limited. Suitability of meperidine for submucosal (SM) injection has never been tested, and information regarding plasma levels following intravenous (IV), intramuscular (IM), and oral (PO) administration of the drug has never been compared with plasma levels reached following SM administration of this drug. The SM route was extremely popular in pediatric dentistry until the drug alphaprodine hydrochloride was withdrawn from the US market in 1986. Caudill, et al.² and Gross, et al.³ showed the rapid and efficient absorption rates achieved with SM administration in both humans and monkeys utilizing the short-acting narcotic alphaprodine. No other studies of this administration route were attempted with other narcotics.

The objective of this study was to measure the plasma levels of meperidine following SM, IM, IV, and PO administration of the drug and to assess the suitability of meperidine for submucosal administration.

Methods and materials

Ten healthy adult volunteers — five males and five females — ranging in age from 21 to 51 years old, were included in this study. None of the subjects had a history of allergic reaction to narcotic analgesics, a history of hepatic or renal disease, or were taking any medications. All volunteers were instructed to fast for a minimum of 6 hr prior to receiving the drug. A minimum of 1 week was planned between appointments. The order of drug administration was randomized so that no specific order of administration would be favored. The volunteers were monitored for changes in blood pressure and respiration rate every 5 min and for heart rate and hemoglobin oxygen saturation rates continuously.

For each administration, a Teflon catheter was inserted into a vein on the dorsum of a hand. A baseline blood sample of 8 ml then was collected. Blood samples were also collected at 10, 20, 30, 45, 60, 90, 120, 180, 240, 360, and 720 min following the drug administration. All blood samples were collected in heparinized test tubes and stored in ice for liquid chromatographic analysis through methods previously described by Fung and coworkers.⁴

Pain response and tissue changes were assessed at the site of injection on 4-point scales following drug administration (Table 1).

Each subject received 0.8 mg/kg of meperidine via IM, IV, and SM routes. SM injection was administered into the mucobuccal fold in the area between the first

Table 1. Percentage of subjects with pain or tissue response following administration of meperidine

Scale	Pain Response				Tissue Changes			
	PO	IM	IV	SM	PO	IM	IV	SM
None	100	0	0	0	100	70	30	0
Mild	0	20	40	0	0	30	60	40
Moderate	0	40	60	60	0	0	10	60
Severe	0	40	0	40	0	0	0	0

and second premolars following application of topical anesthetic. IM injection was administered into the vastus lateralis muscle. Negative aspiration was achieved for both the IM and SM routes of administration. IV infusion was given through a vein on the dorsum of the hand opposite the hand previously accessed for blood samples. All drug administrations were performed by the principal author (MS).

Plasma was collected and frozen at -20°C until analysis. To extract the drug, the plasma was alkalinized with pH 10.4 carbonate buffer, 100 ng of diphenhydramine was added as the internal standard, and the sample was extracted with 7.0 ml hexane. The residue obtained by evaporation of the hexane layer was reconstituted with 200 µl of mobile phase, and 100 µl was injected onto the high performance liquid chromatograph column. The mobile phase consisted of: 55% acetonitrile; 20% methanol; and 25% pH 7.0, 15 mM phosphate buffer. We used a 250x4.6-mm 5-micron CN (cyano) column. Detection was performed by UV detector set to 205-nm wavelength. Standard curves were linear from 15 to 1000 ng/ml, and the CV for the assay was less than 15% at 50 ng/ml.

Upon evaluation of the results obtained from chromatographic analysis of the total sample, it became evident that the 0.8 mg/kg dose for the PO administration was insufficient to be detected consistently by this method. Therefore, an additional series of oral administrations of meperidine was performed at 1.4 mg/kg. This dose then was used for comparative purposes in this study.

Results

Data collected following standardized chromatographic analysis were recorded and tabulated for all routes of administration for each time interval. Data analysis was accomplished using a 4x11 ANOVA and the Scheffe test for multiple comparisons.

Significant interaction effects ($P < 0.00001$) were found between the route of administration and the time intervals. The maximum observed values for the IV and SM routes occurred at 10 min, for the IM at 20 min, and for the PO (1.4 mg/kg) at 45 min (Fig 1).

There were no significant differences between the

IV and SM routes at any time interval measured.

Post hoc comparisons of the peak values demonstrated significant differences between the IM and PO values when compared with the IV and SM routes ($P < 0.01$). There were no significant differences between peak values of the IM and PO (1.4 ml/kg) routes.

Although no statistically significant differences could be demonstrated for pain and tissue response for the parenteral routes of administration, general trends were noted.

While the IM injection caused moderate to severe pain in 80% of the sample, mild pain was reported by all remaining subjects. The IV injection elicited mostly moderate pain response with no pain reported after the initial infusion. The SM injection caused moderate to severe pain in 80% of the subjects, while the remaining subjects exhibited only mild pain (Table 1).

As would be expected, the PO administration did not cause any tissue response, while the IM administration caused mild tissue changes in 30% of the subjects immediately following injection. No detectable tissue changes were observed thereafter. The IV administration caused mild tissue changes in 60% and moderate changes in 10% of the subjects. All these tissue changes returned to normal by the 60th min. The SM route caused the most tissue response with 100% of the subjects exhibiting mild to moderate changes within 10 min, with same responses persisting until the end of experiment (Table 1). No statistical analysis could be performed to assess the significance of pain response and tissue changes due to the small sample size.

No significant changes in blood pressure, heart rate,

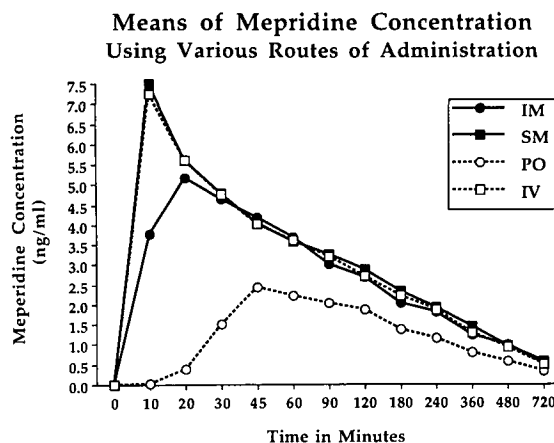


Fig 1. Meperidine levels in ng/ml of plasma using four different routes of administration.

respiratory rate, or hemoglobin oxygen saturation were observed. Nausea and/or vomiting occurred in 70% of the subjects receiving IM meperidine, 60% with IV, 20% with PO, and 60% with SM administration.

Discussion

As indicated by the objectives of this study, the design was never intended to investigate the efficacy of the drug used. Therefore, no implications as to the efficacy of sedation using the various administration routes can be derived from this study. The results of this study suggest that SM administration of meperidine may offer a viable alternative to IV administration of the drug. SM meperidine proved to have a rapid onset and plasma levels comparable to those achieved with the IV route 10 min following administration. This finding is consistent with previous studies showing similar results with the short-acting narcotic, alphaprodine.³ This phenomenon is likely the result of the combined benefits of the rich blood supply of the oral mucosa and bypass of the portal circulation achieved with this technique. Plasma levels of meperidine administered via the IM and PO (1.4 mg/kg) routes were only comparable to IV and SM levels after the 30- and 45-min intervals, respectively, and the peak blood plasma levels for these routes of administration were significantly lower than peak values with IV and SM administration. Due to internal difficulties related to the design of this study, blood samples could not be obtained at the 5-min interval. However, the previous literature shows unequivocally that the peak of IV administered narcotics to be occurring at the 1- or 2-min marker, while the SM administered narcotics occurring at the 10-min marker.²

The poor bioavailability of meperidine administered orally at 1.4 mg/kg and 0.8 mg/kg is not surprising. Meperidine is poorly absorbed through the gastrointestinal tract and is metabolized rapidly during its first pass through the portal circulation. Therefore, sedation of pediatric dental patients utilizing oral meperidine may not be as effective at currently recommended dosages. The use of higher doses of PO meperidine has not yet been assessed and cannot, therefore, be recommended.

One major concern with the SM administration of meperidine is the greater tissue irritation. This poor tissue response might partially be the result of the larger volumes of the drug required with adult volunteers. With lower body weights and smaller drug volume, tissue irritation caused by SM injection in pediatric patients may be minimized.

In spite of the higher occurrence of tissue irritation, SM administration of meperidine may be justified if smaller volumes of the drug can be utilized and IV access is impractical.

Conclusions

1. There were no significant differences between the IV and SM routes at any time interval measured.
2. There were significant differences between the peak values of the IV and SM routes when compared with the peak values of the IM and PO (1.4 mg/kg) routes.
3. Bioavailability of PO meperidine is greatly reduced. Appropriate adjustment in dosage calculations to compensate for such a loss requires further research.
4. SM administration of meperidine is associated with a higher incidence of tissue irritation and discomfort.

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