The Iontophoresis of Fentanyl Citrate in Humans


Background: Iontophoresis is a method of transdermal administration of ionizable drugs in which the electrically charged components are propelled through the skin by an external electric field. This study was designed to determine whether iontophoresis could be used to deliver clinically significant doses of fentanyl in humans and whether there is a charge-dose relation in the delivery of fentanyl by iontophoresis.

Methods: Five adult volunteers were tested three times on separate days, once receiving passive treatment of 0.0 mA for 2 h (0 mA·min), iontophoresis 1.0 mA for 2 h (120 mA·min), and iontophoresis 2.0 mA for 2 h (240 mA·min) in an open, randomized, crossover design. Respiratory rate, heart rate, blood pressure, and hemoglobin oxygen saturation were monitored throughout the study. Plasma fentanyl concentrations were measured several times before, during, and after iontophoresis. Plasma fentanyl concentrations were measured by radioimmunoassay.

Results: No fentanyl was detected after passive (0.0-mA) fentanyl delivery. The following results were obtained for the 1.0- and 2.0-mA deliveries, respectively. Mean times to detectable concentrations of plasma fentanyl were 33 and 19 min; mean times to maximum concentration were 122 and 119 min; maximum concentrations were 0.76 and 1.59 ng/ml (P = 0.010); mean areas under the curve of the plasma fentanyl concentration versus time relation were 233 and 474 ng·ml⁻¹·min (P = 0.003); and mean elimination half-lives were 354 and 413 min (P = 0.326). Only minor adverse side effects related to iontophoresis occurred. However, typical opioid-related effects occurred frequently in the 1.0- and 2.0-mA administration groups.

Conclusions: Clinically significant doses of fentanyl can be administered by iontophoresis for delivery periods of 2 h. A charge-dose relation exists after administration with currents of 1.0 and 2.0 mA. Future research into the iontophoresis of fentanyl as a method of potent opioid administration is indicated. (Key words: Analgesics, opioid; fentanyl. Anesthetic techniques: iontophoresis.)

THERE is increasing interest in noninvasive drug delivery systems.1-3 Reports have documented the use of oral transmucosal fentanyl citrate for sedation and analgesia,4-6 EMLA7,8 and iontophoresis of lidocaine9-15 for skin anesthesia, and transdermal fentanyl for long-term analgesia.16,17

Passive transdermal fentanyl is an effective method of providing long-term opioid analgesia.17,18 However, slow onset time, the inability to change quickly the amount of delivered drug, and prolonged drug elimination make this delivery system unsatisfactory for some patients.

Iontophoresis is a method of transdermal administration of ionizable drugs in which the electrically charged components are propelled through the skin by an external electric field. Iontophoresis of lidocaine for analgesia before superficial surgical procedures has been reported.9,14 In addition, iontophoresis has been used to deliver corticosteroids for the treatment of pain in the joints.19,20 It has been documented that iontophoresis can be used as a method of delivering clinically significant doses of morphine.21

This study was designed to determine whether iontophoresis could be used for noninvasive delivery of clinically important doses of fentanyl in humans4 and whether there is a charge-dose relation in the delivery of fentanyl by iontophoresis.
Materials and Methods

Approval was obtained from the Human Institutional Review Board of the University of Utah Health Sciences Center, and informed written consent was obtained from five healthy adult male volunteers. Subjects were nonsmokers whose body weight deviated no more than 15% from ideal; they had no history of drug or ethanol abuse and were not taking any medications.

Subjects fasted overnight before each study session. At the start of each study session, a peripheral 18-G intravenous catheter was inserted for maintenance fluid administration (lactated Ringer’s solution 1.5 ml · kg⁻¹ · h⁻¹). In addition, an 18-G intravenous catheter was inserted into a large antecubital vein and attached to a saline pressure system (prepared with heparin 10 U/ml saline) to maintain patency. This system was used to obtain venous blood samples for fentanyl analysis.

In an open, randomized, crossover fashion, each subject was tested three times, once receiving passive treatment 0.0 of mA for approximately 2 h (0 mA · min), iontophoresis of 1.0 mA for approximately 2 h (120 mA · min), and iontophoresis of 2.0 mA for approximately 2 h (240 mA · min). Each study session was separated by at least 2 weeks.

The fentanyl solution was prepared with powdered fentanyl citrate, 4% lidocaine hydrochloride, and sterile water, yielding a solution containing lidocaine hydrochloride 2% with 3 mg/ml fentanyl citrate at a pH of 4.5.

Before iontophoresis, the skin was prepared by gentle cleaning with 70% isopropyl alcohol at the intended sites of the drug and dispersive electrodes. The skin temperature of the arm was not held constant.

On the upper arm opposite the arm through which venous blood samples were obtained, the patient received iontophoresis of fentanyl citrate from the Phoresor II PM-700 Drug Delivery System and the TransQ 1 electrode (Iomed, Salt Lake City, UT) (fig. 1). The rate at which the current was increased depended on patient comfort.

Respiratory rate, heart rate, blood pressure, and hemoglobin oxygen saturation (SpO₂) were monitored throughout the study with a noninvasive automatic blood pressure cuff, a single-lead electrocardiogram, and a pulse oximeter, respectively.

Venous blood samples (4 ml) for fentanyl analysis were obtained immediately before the beginning of iontophoresis (baseline); 5, 10, 15, 20, 25, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 165, 180, 195, and 210 min after the beginning of iontophoresis; and then hourly until 10 h after administration.

If SpO₂ decreased to less than 90%, subjects were encouraged to take a deep breath. If SpO₂ did not increase to more than 90% after three prompts, supplemental oxygen was administered by nasal cannula at the rate of 3 l/min. Transient hemoglobin oxygen desaturation was defined as an SpO₂ of less than 90% for less than 30 s, hypoxemia as an SpO₂ of less than 90% for more than 30 s, hypoventilation as a respiratory rate of less than 8 breaths/min for 1 min, and apnea as a respiratory rate of 0 breaths/min for more than 30 s. All adverse reactions were recorded.

All blood samples were injected into glass tubes that had been prepared with heparin and were placed immediately on ice. Plasma was separated from red cells with a refrigerated centrifuge, placed in polypropylene tubes, and frozen at −20 °C until analysis of fentanyl.

Plasma fentanyl concentrations were measured by radioimmunoassay using the technique described by Schütter and White. The assay was sensitive to 0.2 ng/ml with a coefficient of variation of 3.8% at 0.23 ng/ml, 2.3% at 2.31 ng/ml, and 3.8% at 4.93 ng/ml.

The area under the curve (AUC) of the plasma fentanyl concentration versus time relation after passive application at 0.0 mA, iontophoresis at 1.0 mA, and iontophoresis at 2.0 mA was calculated from the time of administration of fentanyl to the last measurable plasma concentration (or the last sample available) by the linear trapezoid method. Extrapolation of the AUC

Fig. 1. Iontophoretic delivery device: Phoresor II PM-700 Drug Delivery System and TransQ 1 electrode (Iomed).
from the time of the last measurable fentanyl concentration (or last sample taken) to infinity was calculated by dividing the last plasma concentration by the first-order rate constant of the terminal phase of the profile. This first-order rate constant was determined by linear regression on the log-transformed plasma fentanyl concentration data from the terminal log-linear phase of the plasma concentration profile. The sum of these two components was the estimate of the total AUC. The terminal elimination half-life of fentanyl was calculated from the first-order rate constant of the terminal phase of the profile of plasma concentration versus time.

Paired t tests were used to compare AUCs, maximum fentanyl concentrations, and elimination half-life calculations between groups when indicated. Regression analysis was completed for the AUC versus charge. The model used was AUC = constant \times \text{charge}. Times to maximum concentrations were compared by using Wilcoxon’s signed-rank test. Most analyses were performed with the SYSTAT statistical package (SPSS, Inc., Chicago, IL) for International Business Machines-compatible microcomputers. A P value \leq 0.05 was considered significant.

Results

All five subjects completed the study, and all were of American Society of Anesthesiologists physical status 1. Their mean age was 25.8 (range 19–41) yr, mean height 177.8 (range 175.3–182.9) cm, and mean weight 66.1 (range 58.7–73.9) kg.

The mean delivery charge was 0.0 mA \cdot \text{min} for the 0.0-mA administration, 120.1 (SD 0.2) mA \cdot \text{min} for the 1.0-mA administration, and 239.4 (SD 0.9) mA \cdot \text{min} for the 2.0-mA administration. Median administration time was 120 min for all deliveries.

Plasma fentanyl concentrations for each study group are shown in figures 2–7. No fentanyl was detected after passive (0.0-mA) fentanyl delivery, indicating that...
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Fig. 5. Plasma fentanyl concentration versus time (0–120 min) for each subject after 120-min iontophoretic delivery at a current of 2.0 mA·min.

Fig. 6. Plasma fentanyl concentration versus time (0–660 min) for each subject after 120-min iontophoretic delivery at a current of 1.0 mA·min.

Fig. 7. Plasma fentanyl concentration versus time (0–660 min) for each subject after 120-min iontophoretic delivery at a current of 2.0 mA·min.

Fig. 8. The area under the curve (AUC) of the plasma fentanyl concentration versus time relation (nanograms·milliliter⁻¹·minute) after 120-min iontophoretic delivery of fentanyl in delivery currents of 0.0, 1.0, and 2.0 mA.

there was no passive drug delivery with the delivery time used in this study. The maximum fentanyl concentration for the 1.0-mA administration group, 0.762 (SD 0.227) ng/ml, was approximately half that for the 2.0-mA administration group, 1.586 (SD 0.229) ng/ml ($P < 0.010$).

The AUC and elimination half-life are reported in Figure 8 and Table 1. The mean elimination half-life for the 1.0-mA administration, 354 (SD 100) min, was not different than the mean elimination half-life for the 2.0-mA administration, 412.8 (SD 106.1) min ($P = 0.326$).

For the 1.0- and 2.0-mA administrations, respectively, the mean times to the initial detection of fentanyl were

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Table 1. Pharmacokinetic Parameters Following Iontophoretic Delivery of Fentanyl

<table>
<thead>
<tr>
<th>Current (mA)</th>
<th>t_{max} (min)</th>
<th>C_{max} (ng/ml)</th>
<th>Elimination Half-life (min)</th>
<th>AUC (ng·min^{-1}·min^{-1})</th>
<th>Time to 0.5 ng/ml (min)</th>
</tr>
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<tbody>
<tr>
<td>0.0 mA</td>
<td>NA</td>
<td>0.0</td>
<td>NA</td>
<td>0.0</td>
<td>NA</td>
</tr>
<tr>
<td>1.0 mA</td>
<td>122.0</td>
<td>0.76</td>
<td>354.0</td>
<td>232.6</td>
<td>92.0</td>
</tr>
<tr>
<td>SD</td>
<td>14.4</td>
<td>0.227</td>
<td>100.0</td>
<td>474.2*</td>
<td>36.0*</td>
</tr>
<tr>
<td>2.0 mA</td>
<td>119.0</td>
<td>1.59*</td>
<td>412.8</td>
<td>474.2*</td>
<td>36.0*</td>
</tr>
<tr>
<td>SD</td>
<td>7.4</td>
<td>0.229</td>
<td>106.1</td>
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</tr>
</tbody>
</table>

AUC = area under the curve; NA = not applicable; SD = standard deviation.

\* P < 0.05 for 1 mA versus 2 mA delivery sessions.

33 (range 10–50) and 19 (range 15–20) min; the mean times to 0.5 μg/ml were 92 (SEM 12) and 36 (SEM 4) min (P < 0.01); and the mean times to the maximum concentration were 122 (SD 14.4) and 119 (SD 7.4) min.

Mean AUCs were 233 and 474 ng·ml^{-1}·min for the 1.0- and 2.0-mA deliveries, respectively (P = 0.003). The regression analysis of AUC versus total charge is shown in figure 9. The analysis revealed a highly statistically significant relation (P < 0.001), confirming a charge-dose relation.

Adverse effects are listed in table 2. Pruritus occurred once during the 1.0-mA administration and five times during the 2.0-mA administration. Erythema, described as mild redness under the location of the dispersive electrode, was reported for one subject after a 1.0-mA administration and for two subjects after the 2.0-mA administration. The erythema resolved within 24 h in all subjects.

Transient hemoglobin oxygen desaturation occurred frequently during iontophoresis in both groups receiving active administration (table 2). Transient hemoglobin oxygen desaturation occurred 17 times in four of five subjects receiving 1.0-mA administration and 16 times in four of five subjects receiving 2.0-mA administration. Hypoxemia (SpO₂ < 90% for >30 s) occurred

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>0 mA</th>
<th>1 mA</th>
<th>2 mA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pruritus</td>
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<td>2</td>
</tr>
<tr>
<td>No. of subjects</td>
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<td>1</td>
<td>5</td>
</tr>
<tr>
<td>No. of events</td>
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<td>1</td>
<td>3</td>
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<tr>
<td>Erythema</td>
<td>0</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>No. of subjects</td>
<td>0</td>
<td>1</td>
<td>3</td>
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<tr>
<td>No. of events</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Numbness</td>
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<td>0</td>
<td>2</td>
</tr>
<tr>
<td>No. of subjects</td>
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<td>1</td>
<td>4</td>
</tr>
<tr>
<td>No. of events</td>
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<td>17</td>
<td>16</td>
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<tr>
<td>Transient hemoglobin oxygen desaturation</td>
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<td>4</td>
<td>4</td>
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<td>No. of events</td>
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<tr>
<td>No. of events</td>
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<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Fig. 9. The area under the curve (AUC) of the plasma fentanyl concentration versus time relation by total charge.
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four times in three of five subjects in both active-administration groups. Hypoventilation occurred twice in one subject during the 1.0-mA administration. Apnea occurred once in one subject during the 1.0-mA administration. No episodes of transient hemoglobin oxygen desaturation, hypoventilation, apnea, or hypoxemia occurred during the 0.0-mA administration.

Discussion

Iontophoresis is a method of transdermal administration of ionizable drugs in which the electrically charged components are propelled through the skin by an external electric field (Fig. 10). The technique of iontophoresis of lidocaine for analgesia for superficial surgical procedures has been described. In addition, iontophoresis has been used to deliver corticosteroids for the treatment of pain in the joints.

Since this technique was conceived in 1740, drug delivery from the positive electrode has been limited by the generation of hydrogen ions. The hydrogen ions compete for charge transport and thus decrease the amount of drug that can be delivered. In addition, the generation of hydrogen ions leads to a decrease in pH within the electrode, which can lead to significant skin burns. Finally, the current passing from a metal electrode frequently causes its dissolution, resulting in additional competing ions within the drug delivery compartment and reducing efficiency. Because of these problems, drug delivery times have been limited.

Recent research has led to the development of a silver electrode. With the use of chloride solutions of positively charged drugs, the use of the silver electrode allows iontophoresis of positively charged molecules while generating insoluble silver chloride at lower voltages than those required for electrolysis of water. As a result, ionic competition is minimized and iontophoresis treatment times can be increased.

This study demonstrated that analgesic doses of fentanyl can be administered by iontophoresis for delivery periods of 2 h. Fentanyl concentrations continued to increase during the entire 2-h delivery time, indicating that iontophoresis of fentanyl approximates a zero-order infusion.

Because the sample was small, this study should be considered a preliminary study on the use of this technique in humans; studies in larger numbers of subjects are indicated to confirm the results. Fentanyl delivery by iontophoresis appears to be related to the delivery current. This charge-dose relation could allow the development of noninvasive patient-controlled analgesia using fentanyl. The elimination half-life of both active groups approximated that seen with intravenous administration of fentanyl.

Gourlay et al. estimated the blood concentrations of fentanyl needed for analgesia after upper and lower abdominal surgery. The minimum concentration found to relieve pain was 0.23–1.18 (mean 0.63) ng/ml, concentrations that were obtained after iontophoresis of fentanyl citrate.

Although this study demonstrates that iontophoresis can be used to deliver clinically significant doses of fentanyl in humans, the pharmacokinetics of this system should be defined more clearly. The goal of future research should include the determination of the rate of fentanyl’s appearance in the systemic circulation as a function of iontophoresis current.

The adverse side effects reported associated with iontophoresis rather than with intravenous delivery of fentanyl appear to be minimal. Erythema, usually at the location of the dispersive pad, was seen but resolved without treatment within 24 h. All other adverse side effects were related to the delivered drug and not the delivery mode.

Passive transdermal fentanyl delivery has been proven to be effective in the management of pain requiring the administration of an opioid in selected popula-
However, because of its long onset time, inability to rapidly adjust drug delivery, and long elimination half-life, it is not recommended for the treatment of acute pain and may be associated with unacceptable adverse side effects when used in this and other settings. Patients who have pain requiring the long-term administration of opioids, such as cancer pain, benefit from constant, time-contingent opioid administration. In addition to time-contingent opioid administration, these patients frequently benefit from rapid administration of potent opioids for the management of breakthrough and incident pain. Iontophoresis may allow long-term steady-state opioid administration plus rapid administration of additional amounts of fentanyl for the management of incident and breakthrough pain. Currently, there are several options for time-contingent opioid administration plus as-needed opioid administration for breakthrough pain. These options include the oral route, which is excellent for time-contingent dosing, but the delayed onset decreases this route’s effectiveness for the delivery of as-needed oral opioids. In addition, many patients with cancer have difficulties tolerating oral medications at some time before their death. Intravenous drug administration is an excellent method but requires the placement and maintenance of intravenous access, which is associated with significant risks. Others are evaluating the use of transmucosal drug delivery for the management of breakthrough pain. In conclusion, iontophoresis can be used to deliver clinically significant doses of fentanyl, and the amount of fentanyl administered is related to the delivery current used. Adverse side effects related to the drug delivery mode are minimal. Further research on the iontophoresis of fentanyl is warranted.

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