Anesthesiology
82:1146–1153, 1995


# The Iontophoresis of Fentanyl Citrate in Humans

*M. A. Ashburn, M.D.,* J. Streisand, M.D.,* J. Zhang, Ph.D.,† G. Love, M.S.N., R.N.,‡ M. Rowin, M.D.,§ S. Niu, M.D.,‖ J. K. Kievit, drs.,# J. R. Kroep,# M. J. Mertens, drs.#*

***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 $ng \cdot ml^{-1} \cdot min$ ($P = 0.003$); 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.)**

* Associate Professor, Department of Anesthesiology, University of Utah Health Sciences Center.

† Research Assistant Professor, Department of Anesthesiology, University of Utah Health Sciences Center.

‡ Clinical Nurse Coordinator, Acute Pain Service, Department of Anesthesiology, University of Utah Health Sciences Center.

§ Pediatric Intensive Care Fellow, Department of Pediatrics, Primary Children's Medical Center, Salt Lake City, Utah.

‖ Postdoctoral Research Associate, Department of Anesthesiology, University of Utah Health Sciences Center.

# Research Assistant, Department of Anesthesiology, University of Utah Health Sciences Center.

Received from the Department of Anesthesiology, University of Utah Health Sciences Center, Salt Lake City, Utah. Submitted for publication July 28, 1994. Accepted for publication January 25, 1995. Supported in part by a grant from the Utah Pain Research Foundation, Salt Lake City, Utah. Presented at the annual meeting of the International Anesthesia Research Society, Orlando, Florida, March 1994.

Address reprint requests to Dr. Ashburn: Department of Anesthesiology, University of Utah Health Sciences Center, 5 North Medical Drive, Salt Lake City, Utah 84132.

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] EMLA[7,8] and iontophoresis of lidocaine[9–15] 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 humans[4] 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 $ml \cdot kg^{-1} \cdot h^{-1}$). 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 *p*H 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 ($Sp_{O_2}$) 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.

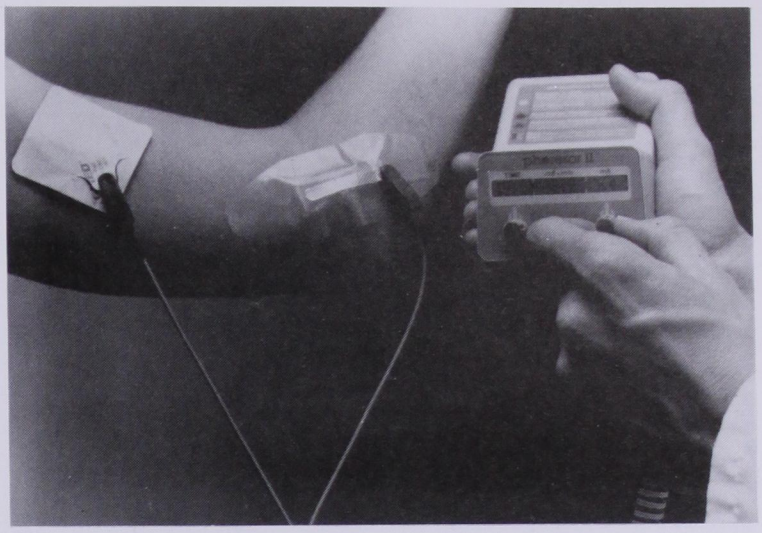

**Fig. 1. Iontophoretic delivery device: Phoresor II PM-700 Drug Delivery System and TransQ 1 electrode (Iomed).**

If $Sp_{O_2}$ decreased to less than 90%, subjects were encouraged to take a deep breath. If $Sp_{O_2}$ 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 $Sp_{O_2}$ of less than 90% for less than 30 s, hypoxemia as an $Sp_{O_2}$ 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 Schüttler and White.[22] 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.[23] Extrapolation of the AUC

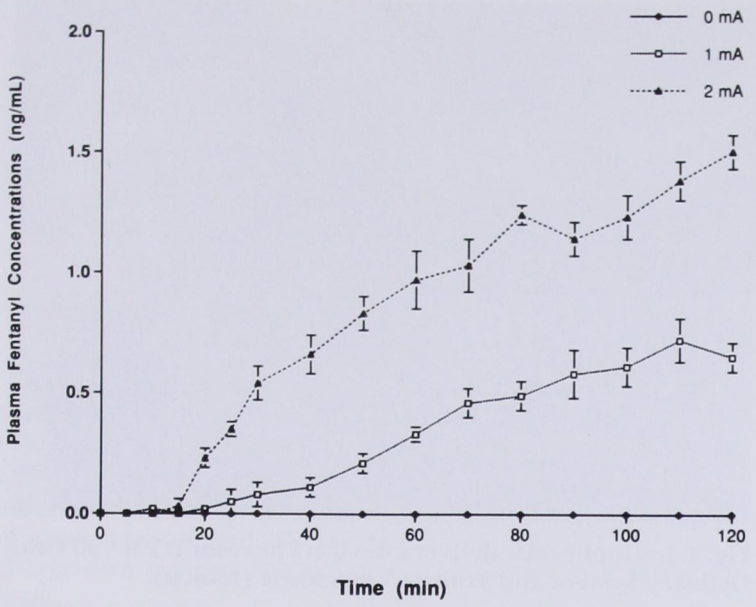


**Fig. 2. Mean ± SEM plasma fentanyl concentration *versus* time (0–120 min) after 120-min iontophoretic delivery.**

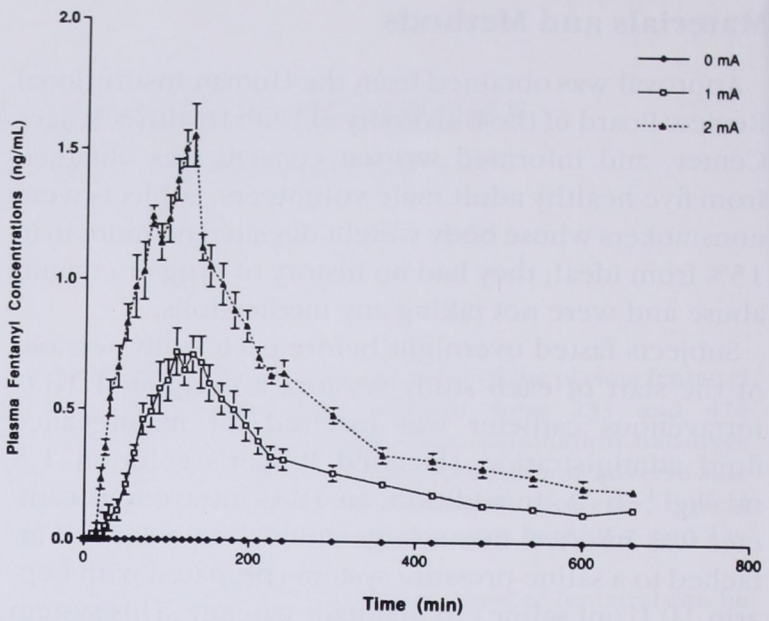


**Fig. 3. Mean ± SEM plasma fentanyl concentration *versus* time (0–660 min) after 120-min iontophoretic delivery.**

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 × 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 · min for the 0.0-mA administration, 120.1 (SD 0.2) mA · min for the 1.0-mA administration, and 239.4 (SD 0.9) mA · 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

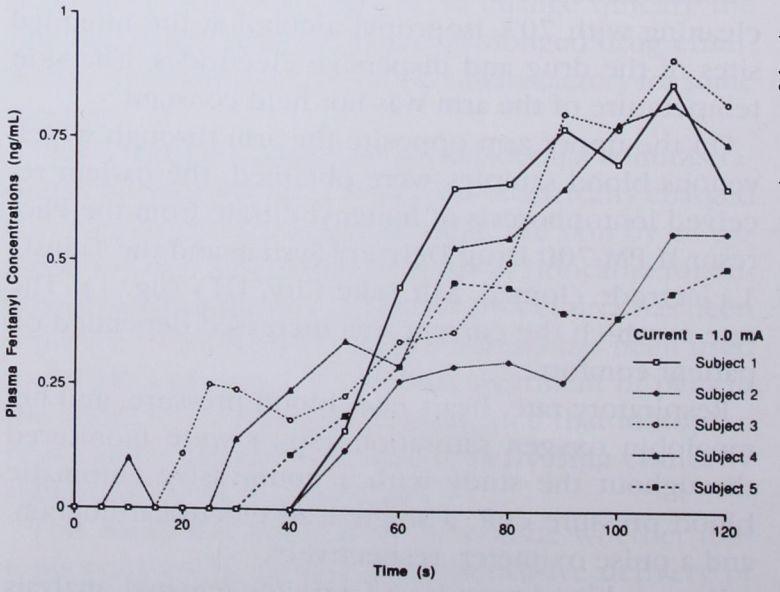


**Fig. 4. Plasma fentanyl concentration *versus* time (0–120 min) for each subject after 120-min iontophoretic delivery at a current of 1.0 mA · min.**

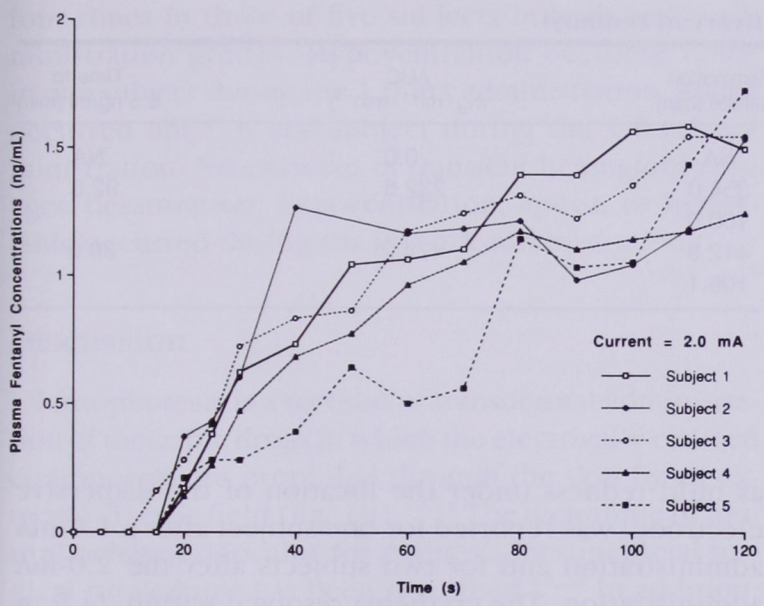


**Fig. 5. Plasma fentanyl concentration *versus* time (0–120 min) for each subject after 120-min iontophoretic delivery at a current of 2.0 mA · min.**

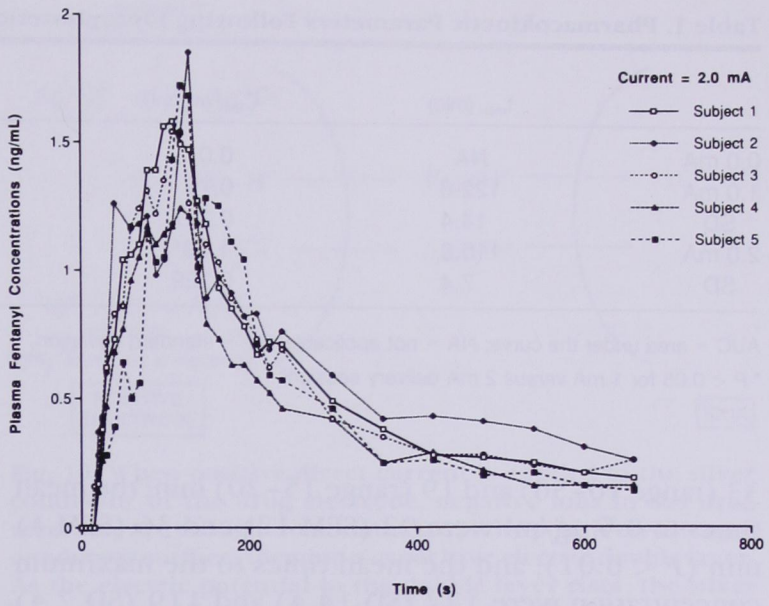


**Fig. 7. Plasma fentanyl concentration *versus* time (0–660 min) for each subject after 120-min iontophoretic delivery at a current of 2.0 mA · min.**

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

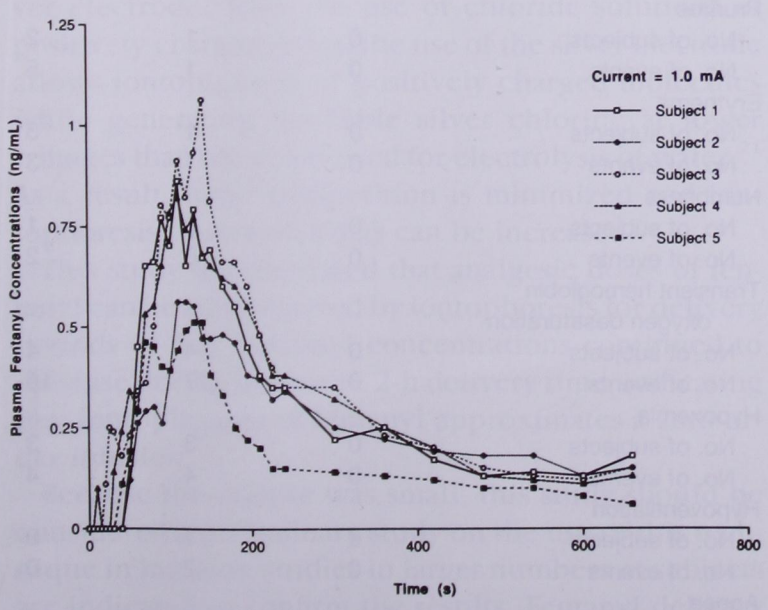


**Fig. 6. Plasma fentanyl concentration *versus* time (0–660 min) for each subject after 120-min iontophoretic delivery at a current of 1.0 mA · min.**

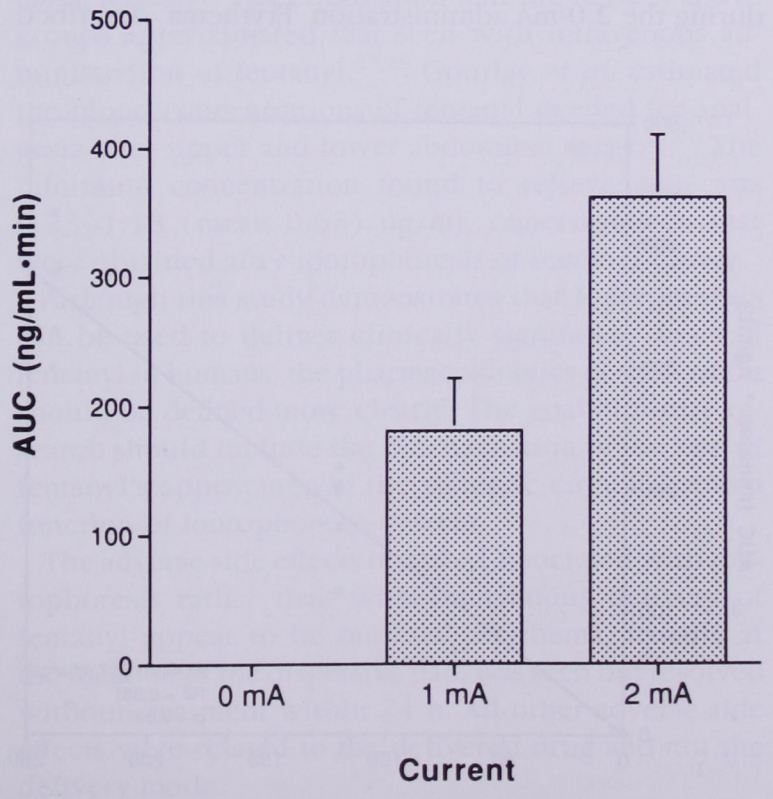


**Fig. 8. The area under the curve (AUC) of the plasma fentanyl concentration *versus* time relation (nanograms · milliliter$^{-1}$ · minute) after 120-min iontophoretic delivery of fentanyl in delivery currents of 0.0, 1.0, and 2.0 mA.**

**Table 1. Pharmacokinetic Parameters Following Iontophoretic Delivery of Fentanyl**

| | $t_{max}$ (min) | $C_{max}$ (ng/ml) | Elimination Half-life (min) | AUC ($ng \cdot ml^{-1} \cdot min^{-1}$) | Time to 0.5 ng/ml (min) |
|---|---|---|---|---|---|
| 0.0 mA | NA | 0.0 | NA | 0.0 | NA |
| 1.0 mA | 122.0 | 0.76 | 354.0 | 232.6 | 92.0 |
| SD | 14.4 | 0.227 | 100.0 | | |
| 2.0 mA | 119.0 | 1.59* | 412.8 | 474.2* | 36.0* |
| SD | 7.4 | 0.229 | 106.1 | | |

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 $ng \cdot ml^{-1} \cdot min$ 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 ($Sp_{O_2} < 90\%$ for >30 s) occurred

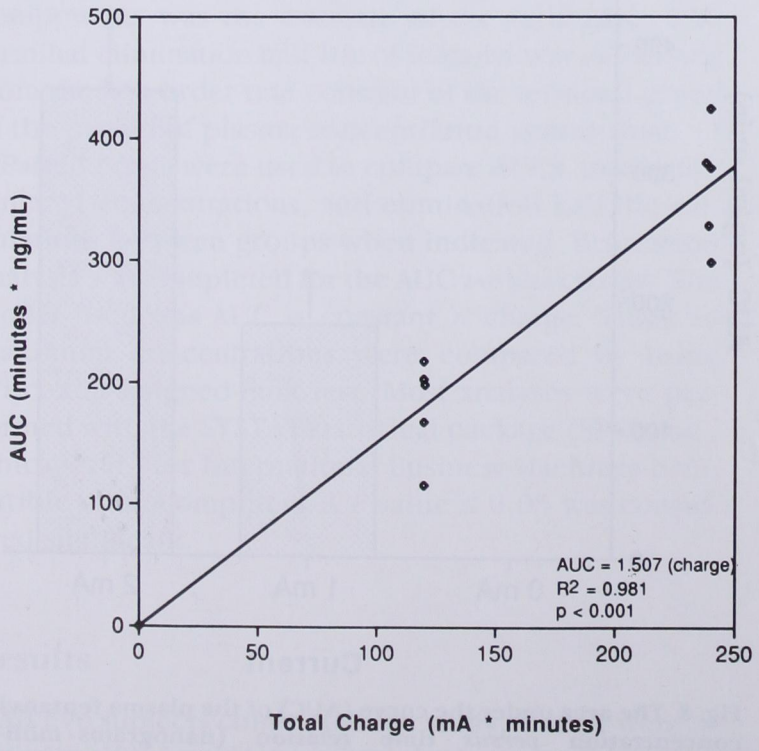


**Fig. 9. The area under the curve (AUC) of the plasma fentanyl concentration *versus* time relation by total charge.**

**Table 2. Adverse Side Effects Following Iontophoresis of Lidocaine**

| Adverse Effect | Treatment Group 0 mA | 1 mA | 2 mA |
|---|---|---|---|
| Pruritus | | | |
| No. of subjects | 0 | 1 | 2 |
| No. of events | 0 | 1 | 5 |
| Erythema | | | |
| No. of subjects | 0 | 1 | 3 |
| No. of events | 0 | 1 | 3 |
| Numbness | | | |
| No. of subjects | 0 | 0 | 1 |
| No. of events | 0 | 0 | 2 |
| Transient hemoglobin oxygen desaturation | | | |
| No. of subjects | 0 | 4 | 4 |
| No. of events | 0 | 17 | 16 |
| Hypoxemia | | | |
| No. of subjects | 0 | 3 | 3 |
| No. of events | 0 | 4 | 4 |
| Hypoventilation | | | |
| No. of subjects | 0 | 1 | 0 |
| No. of events | 0 | 2 | 0 |
| Apnea | | | |
| No. of subjects | 0 | 1 | 0 |
| No. of events | 0 | 1 | 0 |

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).[20,24] The technique of iontophoresis of lidocaine for analgesia for superficial surgical procedures has been described.[25,26] In addition, iontophoresis has been used to deliver corticosteroids for the treatment of pain in the joints.[20]

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 *p*H 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 lead 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.[21] 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.[27,28] Gourlay *et al.* estimated the blood concentrations of fentanyl needed for analgesia after upper and lower abdominal surgery.[29] 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.

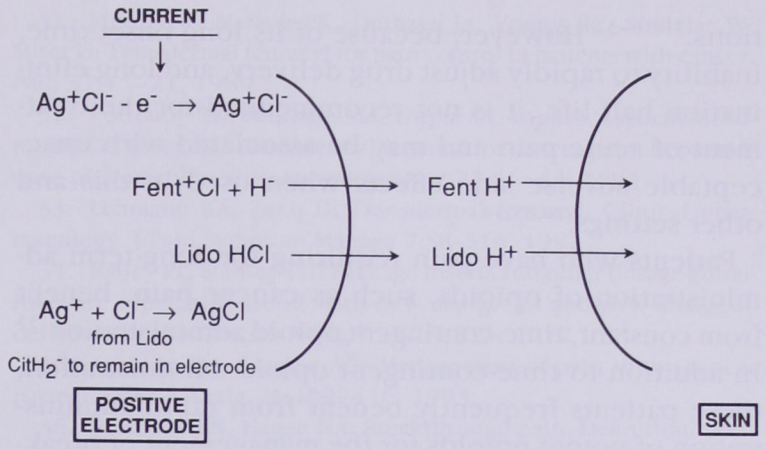


**Fig. 10. When positive direct current is applied to the silver conductor of the drug electrode, negative ions in the drug reservoir are thought to accumulate at the positively charged conductor surface, forming a capacitive electric double layer. As the electric potential in the double layer rises, the silver becomes sacrificial and oxidizes, forming free silver ions in solution. Current then begins to flow across the drug reservoir and into the skin in the form of solvated ions, including fentanyl ($Fent\ H^+$) and lidocaine ($Lido\ H^+$) ions. Silver ions are removed by precipitation of insoluble silver chloride from solution. The chloride ions used to precipitate silver ions are derived from the dissolution of lidocaine hydrochloride (Lido) in the solution. $CitH_2^-$ = citrate ion.**

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-

tions.[16,30–32] 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.[28,33,34]

Patients who have pain requiring the long-term administration of opioids, such as cancer pain, benefit from constant, time-contingent opioid administration.[35] 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.[36] 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.[5,37]

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.

## References

1. Stanley TH, Ashburn MA: Novel delivery systems: Oral transmucosal and intranasal transmucosal. J Pain Symptom Manage 7:163–171, 1992

2. Slattery PJ, Boas RA: Newer methods of delivery of opiates for relief of pain. Drugs 30:539–551, 1985

3. Chandrasekaran SK, Bayne W, Shaw JE: Pharmacokinetics of drug permeation through human skin. J Pharm Sci 67:1370–1374, 1978

4. Streisand JB, Stanley TH, Hague B, van Vreeswijk H, Ho GH, Pace NL: Oral transmucosal fentanyl citrate premedication in children. Anesth Analg 69:28–34, 1989

5. Ashburn MA, Fine PG, Stanley TH: Oral transmucosal fentanyl citrate for the treatment of breakthrough cancer pain: A case report. ANESTHESIOLOGY 71:615–617, 1989

6. Ashburn MA, Streisand JB, Tarver SD, Mears SL, Mulder SM, Floet AW, Luijendijk RW, Elwyn RA, Pace NL, Stanley TH: Oral transmucosal fentanyl citrate for premedication in paediatric outpatients. Can J Anaesth 37:857–866, 1990

7. de Waard-van der Spek FB, van den Berg GM, Oranje AP: EMLA cream: An improved local anesthetic—Review of current literature. Pediatr Dermatol 9:126–131, 1992

8. Maunuksela E-L, Korpela R: Double-blind evaluation of a lignocaine-prilocaine cream (EMLA) in children: Effect on the pain associated with venous cannulation. Br J Anaesth 58:1242–1245, 1986

9. Bezzant JL, Stephen RL, Petelenz TJ, Jacobsen SC: Painless cauterization of spider veins with the use of iontophoretic local anesthesia. J Am Acad Dermatol 19:869–875, 1988

10. Maloney JM: Local anesthesia obtained via iontophoresis as an aid to shave biopsy. Arch Dermatol 128:331–332, 1992

11. Maloney JM, Bezzant JL, Stephen RL, Petelenz TJ: Iontophoretic administration of lidocaine anesthesia in office practice. J Dermatol Surg Oncol 18:937–940, 1992

12. Kennard CD, Whitaker DC: Iontophoresis of lidocaine for anesthesia during pulsed dye laser treatment of port-wine stains. J Dermatol Surg Oncol 18:287–294, 1992

13. Puig CJ, Haenschen RJ, Clark DM, Iwahiro TL, Stephen RL: Iontophoretic anesthesia in hair transplantation. International Journal of Aesthetic and Restorative Surgery 1:9–12, 1993

14. Petelenz T, Axenti I, Petelenz TJ, Iwinski J, Dubel S: Mini set for iontophoresis for topical analgesia before injection. Int J Clin Pharmacol Ther Toxicol 22:152–155, 1984

15. Comeau M, Brummett R, Vernon J: Local anesthesia of the ear by iontophoresis. Arch Otolaryngol 98:114–120, 1973

16. Caplan RA, Ready LB, Oden RV, Matsen FA III, Nessly ML, Olsson GL: Transdermal fentanyl for postoperative pain management. JAMA 261:1036–1039, 1989

17. Holley FO, van Steennis C: Postoperative analgesia with fentanyl: Pharmacokinetics and pharmacodynamics of constant-rate I.V. and transdermal delivery. Br J Anaesth 60:608–613, 1988

18. Gourlay GK, Kowalski SR, Plummer JL, Cherry DA, Szekely SM, Mather LE, Owen H, Cousins MJ: The efficacy of transdermal fentanyl in the treatment of postoperative pain: A double-blind comparison of fentanyl and placebo systems. Pain 40:21–28, 1990

19. Bertolucci LE: Introduction of antiinflammatory drugs by iontophoresis: Double blind study. J Orthop Sports Phys Ther 4:103–108, 1982

20. Glass JM, Stephen RL, Jacobson SC: The quantity and distribution of radiolabeled dexamethasone delivered to tissue by iontophoresis. Int J Dermatol 19:519–525, 1980

21. Ashburn MA, Stephen RL, Ackerman E, Petelenz TJ, Hare B, Pace NL, Hofman AA: Iontophoretic delivery of morphine for postoperative analgesia. J Pain Symptom Manage 7:27–33, 1992

22. Schüttler J, White PF: Optimization of the radioimmunoassays for measuring fentanyl and alfentanil in human serum. ANESTHESIOLOGY 61:315–320, 1984

23. Gibaldi M, Perrier D: Absorption kinetics and bioavailability, Pharmacokinetics. Edited by Swarbrick J. New York, Marcel Dekker, 1982, pp 145–198

24. Tyle P: Iontophoretic devices for drug delivery. Pharm Res 3:318–325, 1986

25. Banta CA: A prospective, nonrandomized study of iontophoresis, wrist splinting, and antiinflammatory medication in treatment of early-mild carpal tunnel syndrome. J Occup Med 36:166–168, 1994

26. Pellecchia GL, Hamel H, Behnke P: Treatment of infrapatellar tendinitis: A combination of modalities and transverse friction massage *versus* iontophoresis. J Sport Rehabil 3:135–145, 1994

27. Streisand JB, Varvel JR, Stanski DR, LeMaire L, Ashburn MA, Hague BI, Tarver SD, Stanley TH: Absorption and bioavailability of oral transmucosal fentanyl citrate. ANESTHESIOLOGY 75:223–229, 1991

28. Varvel JR, Shafer SL, Hwang SS, Coen PA, Stanski DR: Absorption characteristics of transdermally administered fentanyl. ANESTHESIOLOGY 70:928–934, 1989

29. Gourlay GK, Kowalski SR, Plummer TL, Cousins MJ, Armstrong PJ: Fentanyl blood concentration—analgesic response relationship in the treatment of postoperative pain. Anesth Analg 67:329–337, 1988

30. Gourlay GK, Kowalski SR, Plummer JL, Cherry DA, Gaukroger P, Cousins MJ: The transdermal administration of fentanyl in the treatment of postoperative pain: Pharmacokinetics and pharmacodynamic effects. Pain 37:193–202, 1989

31. Miser AW, Narang PK, Dothage JA, Young RC, Sindelar W, Miser JS: Transdermal fentanyl for pain control in patients with cancer. Pain 37:15–21, 1989

32. Portenoy RK, Southam MA, Gupta SK, Lapin J, Layman M, Inturrisi CE, Foley KM: Transdermal fentanyl for cancer pain: Repeated-dose pharmacokinetics. ANESTHESIOLOGY 78:36–43, 1993

33. Lehmann KA, Zech D: Transdermal fentanyl: Clinical pharmacology. J Pain Symptom Manage 7:S8–S16, 1992

34. Bailey PL, Stanley TH: Package inserts and other dosage guidelines are especially useful with new analgesics and new analgesic delivery systems. Anesth Analg 75:873–875, 1992

35. Ashburn MA, Lipman AG: Management of pain in the cancer patient. Anesth Analg 76:402–416, 1993

36. Portenoy RK, Hagen NA: Breakthrough pain: Definition, prevalence and characteristics. Pain 41:273–281, 1990

37. Fine PG, Marcus M, De Boer AJ, Van der Oord B: An open label study of oral transmucosal fentanyl citrate (OTFC) for the treatment of breakthrough cancer pain. Pain 45:149–153, 1991