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# Pharmacokinetic evaluation of transdermal buprenorphine in man

I.R. Wilding[a,*], S.S. Davis[a], G.H. Rimoy[b], P. Rubin[b], T. Kurihara-Bergstrom[c], V. Tipnis[c], B. Berner[c], J. Nightingale[1c]

[a]*Pharmaceutical Profiles Limited, 2 Faraday Building, Highfields Science Park, University Boulevard, Nottingham NG7 2QP, UK*
[b]*Department of Therapeutics, Queens Medical Centre, Clifton Boulevard, Nottingham NG7 2UH, UK*
[c]*Ciba Geigy Corporation, 444 Saw Mill River Road, Ardsley, NY 10502, USA*

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**Abstract**

Transdermal delivery of the synthetic opiate analgesic, buprenorphine, was studied in healthy volunteers. Pharmacokinetic, safety and tolerability data were obtained in a group of 12 healthy subjects following administration of a short intravenous infusion and the application of both aqueous- and ethanol-based fillable transdermal therapeutic systems (FTTS), containing 8 and 37.5 mg of drug, respectively. The total amount delivered by the 10 $cm^2$ aqueous reservoir system ranged from 0.11 to 0.67 mg over the 24 h application period and the steady state in vivo flux rates were 0.56–1.91 $\mu g/cm^2/h$. The total amount delivered by the 5 $cm^2$ ethanol-based FTTS ranged from 0.33 to 0.96 mg and the steady state in vivo flux values were 2.14–5.62 $\mu g/cm^2/h$. The results of the feasibility investigation demonstrated that transdermal delivery of buprenorphine produced sustained plasma levels of drug within the range observed after intravenous dosing and that an ethanolic formulation produced approximately a four-fold increase in transdermal flux. The in vivo investigation suggests that transdermal delivery could provide appropriate plasma levels of buprenorphine for sustained analgesic effect.

*Keywords:* Buprenorphine; Transdermal; Pharmacokinetic evaluation; Man

## 1. Introduction

Buprenorphine hydrochloride is a synthetic opiate analgesic with mixed agonist and antagonist properties (Jasinski et al., 1978; Lewis, 1985). It is derived from thebaine and exerts analgesic effects by high affinity binding to $\mu$-sub-class opiod receptors in the central nervous system (Hambrook and Rance, 1976). The drug is used clinically for the relief of both acute and chronic pain (Adrianensen et al., 1985) and experimentally for the treatment of opiod dependence (Amass et al., 1994; Strain et al., 1994). The duration of action is only twice that of morphine but the analgesic potency is some 50 times greater (Downing et al., 1977). After parenteral administration, the

* Corresponding author. Tel. +44 115 9436565; Fax +44 115 9225321.

[1] Present address: Bend Research Inc., Bend, OR 99701-8599, USA.


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terminal phase half-life is estimated to be 3 to 5 h and the recommended frequency of dosing every 6 to 8 h (Bullingham et al., 1980). Following oral dosing, buprenorphine bioavailability has been demonstrated to be as low as 10–15%, principally due to extensive first pass metabolism in the gastrointestinal mucosa and liver (Walsh et al., 1994). Sublingual buprenorphine has been shown to be an alternative route for drug delivery (Adrianensen et al., 1985). All the currently available delivery approaches for buprenorphine rely on repeated administration to maintain the desired clinical effect over a prolonged period of time. Several groups have examined the potential of transdermal delivery of buprenorphine to reduce the first pass effects observed following oral administration and thereby avoid frequent dosing (Szuktak et al., 1990; Hidaka and Murakami, 1991; Hille et al., 1991; Granger, 1991; Roy et al., 1994) but no clinical studies have been published on the pharmacokinetic properties of transdermal buprenorphine in man.

The transition from in vitro studies to man during feasibility assessment for transdermal products can be unnecessarily delayed by waiting for complete production model transdermal therapeutic systems to be available. A fillable transdermal therapeutic system (FTTS) has been developed consisting of a polyester EVA laminate sealed to a microporous polyethylene membrane (Nightingale et al., 1992a,b). A filling port allows the injection of a donor solution into a reservoir and after filling the port is heat sealed to avoid leakage. The FTTS can then be affixed to the skin using a peripheral adhesive. The research described in this paper highlights the value of the FTTS as an expeditious bridge between the in vitro and clinical settings.

The main objective of the research programme was to investigate the feasibility of transdermal buprenorphine delivery from ethanol and aqueous FTTS.

## 2. Methods

The objectives of the study were to obtain pharmacokinetic, safety and tolerability data on buprenorphine in healthy subjects following the application of both aqueous- and ethanol-based FTTS and administration of a short intravenous infusion of buprenorphine hydrochloride. This was a randomised three-way crossover study in which 12 healthy male subjects received 0.3 mg of buprenorphine by a 20-min intravenous infusion and single 24-h applications of 5 $cm^2$ ethanol- and 10 $cm^2$ aqueous-based FTTS to the lower back, with a 7–15-day washout period between treatments.

### 2.1. Transdermal systems

The FTTS consisted of a pouch formed from a microporous membrane heat-sealed to an impermeable backing of larger circumference than the membrane. An outer ring of adhesive on the peripheral portion of the impermeable backing, where the membrane was not present, was used to affix the system onto the skin. The FTTS devices were filled with either an ethanol- or aqueous-based reservoir ointment by means of a syringe through the gap, after which it was sealed with a heat-sealing tool. The ointment for the ethanol-FTTS consisted of 75 mg buprenorphine HCl/ml solution 50:50 (v/v%) ethanol/water with 0.5% hydroxypropylcellulose at pH 4. The 5 $cm^2$ FTTS was filled with 0.5 ml of ointment corresponding to 37.5 mg of drug. For the aqueous FTTS, ointment was manufactured containing 16 mg buprenorphine HCl/ml solution in 100% deionised water with 0.5% hydroxypropylcellulose, again at pH 4. The 10 $cm^2$ FTTS was filled with 0.5 ml of ointment corresponding to 8 mg of drug. In vitro experiments using human cadaver skin in flow-through diffusion cells showed that the median flux rate of buprenorphine was 0.78 and 3.63 $\mu g/cm^2/h$ for the aqueous and the ethanol-based FTTS, respectively.

### 2.2. Intravenous administration

After priming a Braun Infusomat with the 0.6 $\mu g/ml$ buprenorphine HCl infusion solution, 13 ml of infusion set effluent was flushed and collected from the system. An additional 2-min (5

ml) sample was collected in a small glass vial. The subject was then infused intravenously with the 0.6 mg/ml buprenorphine solution for 20 min at 2.5 ml/min (50 ml), resulting in a 0.3 mg dose. Immediately following the 20-min infusion, a 2-min (5 ml) sample was collected. Overall, absorption onto the infusion tubing was not high with < 3% of the drug being lost.

### 2.3. Study procedures

The protocol was approved by the Ethics Committee at the University of Nottingham Medical School. The study was explained to each subject by the investigator and written informed consent was obtained. The subjects were screened within 3 weeks prior to the first study day. Screening included obtaining a medical history, physical examination, ECG, routine laboratory testing (blood chemistry, haematology) and urinalysis. Formulations were administered at approximately 08.00 h on all study days. Baseline blood pressure and heart rate measurements were obtained just before dosing and were also measured throughout the evaluation period, up to 24 h during the intravenous phase and 48 h during the transdermal investigations. Subjects were monitored for signs of drug activity during study days. The application site and the transdermal systems were examined upon removal at 24 h after application.

Venous blood samples (7 ml) were collected for plasma buprenorphine measurements via an indwelling cannula, irrigated with heparin. For the i.v. infusion study days, blood samples were taken from the opposite arm to that used for drug administration. Blood was removed from the cannula using a plastic syringe, collected in heparinized glass tubes and gently mixed. The blood was centrifuged and the plasma transferred to labelled glass tubes, prior to freezing at −20°C. Samples were stored frozen until analysis.

Intravenous infusion plasma samples were obtained at 0, 0.17, 0.33 (end of infusion), 0.42, 0.58, 1.08, 1.33, 1.83, 2.33, 3.33, 4.33, 5.33, 6.33, 8.33, 10.33, 14.33 and 24.33 h and 0, 1, 2, 3, 4, 6, 8, 12, 16, 20, 24, 24.5, 25, 26, 28, 34, 38 and 48 h after application of the aqueous- and ethanol-based transdermal systems.

### 2.4. Analytical procedures

Plasma concentrations of buprenorphine HCl were determined using an established and validated radioimmunoassay. The method involves the separation of buprenorphine from its glucuronide metabolite by selective extraction from plasma. The dried extract was reconstructed in an assay buffer and subjected to a sensitive double-antibody disequilibrium radioimmunoassay procedure. The limit of quantification (sensitivity) was 50 pg/ml and the assay was linear ($r = 0.999$) over the concentration range of 50–1000 pg/ml. During the course of sample analyses, calibration curves were constructed on each day the assay was run. Buprenorphine HCl concentrations in the samples were calculated by interpolation from the linear regression line of the calibration curve. Quality control samples consisting of human control plasma spiked with known amounts of buprenorphine HCl (80, 400 and 800 pg/ml) were prepared on each day the assay was run, and analysed with the study samples.

Plasma concentration–time profiles for buprenorphine HCl after each of the three treatments were characterised in terms of their peak concentrations ($C_{max}$), times to peak ($T_{max}$), lag times and area under the curve (AUC) from 0 h to the last collection timepoint. From the individual pharmacokinetic profiles, the total amount of drug delivered over 24 h and the steady state in vivo flux rate over 24 h were calculated.

## 3. Results

### 3.1. Clinical observations

Significant adverse experiences were limited to nausea and vomiting. This occurred in 6 of the 12 subjects during the course of the study. The highest incidence occurred during the day that buprenorphine was administered intravenously (4 out of 12), while 3 of the 12 subjects experienced this effect on the same day that the ethanol-based system was applied and 2 of the 12 on the day following application of the aqueous-based system.

Table 1
Peak buprenorphine concentrations (pg/ml) after administration of a 0.3 mg intravenous infusion and after application of the aqueous- and ethanol-based FTTS to healthy male volunteers

| Subject No. | Intravenous infusion (0.3 mg) | Ethanol-based FTTS | Aqueous-based FTTS |
|---|---|---|---|
| 01 | 3514 | 356 | 191 |
| 02 | 6947 | 261 | 176 |
| 03 | 2261 | 164 | 261 |
| 04 | 1077 | 489 | 199 |
| 05 | 5787 | 649 | 541 |
| 06 | 5995 | 471 | 281 |
| 07 | 4382 | 498 | 163 |
| 08 | 4094 | 547 | 160 |
| 09 | 2388 | 698 | 294 |
| 10 | 5192 | 607 | 393 |
| 11 | 4036 | 208 | 251 |
| 12 | 4687 | 790 | 420 |
| Mean | 4197 | 478 | 278 |
| SD | 1701 | 198 | 119 |

### 3.2. System adhesion and skin irritation

Drug crystals were observed on the application site following removal of the ethanol-based systems of some subjects. This is due to the rapid permeation of ethanol into the skin, causing excess drug to crystallize. No cases of drug crystals on the application site were observed after removal of the aqueous-based transdermal systems. Underlying skin appeared wrinkled and was moulded to the shape of the aqueous FTTS; these are typical signs of occlusion. No signs of skin irritation were recorded with either transdermal system. System adhesion was noted as being good in most cases for both the aqueous- and ethanol-based systems.

### 3.3. Pharmacokinetic data

The pharmacokinetic parameters resulting from application of both ethanol- and aqueous-based transdermal systems and a 20-min intravenous infusion of 0.3 mg buprenorphine are listed in Tables 1 to 3. Mean plasma concentration–time profiles for the transdermal study days are provided in Fig. 1.

During the intravenous phase, plasma levels of buprenorphine increased rapidly and achieved peak levels of 1077–6947 pg/ml (mean 4197 pg/ml) at 0.17–0.33 h after the start of the infusion. The levels then declined in a tri-exponential manner, and by 24 h were below the quantification limit of the assay in the majority of the subjects. The half-life values for the three phases of elimination following the intravenous infusion, estimated from the mean plasma level data, were 1.72 min, 1.54 h and 15.4 h, respectively. Individual areas under the curve (0–24.33 h) for the intravenous dose ranged from 4044 to 9646 pg h/ml (mean 5925 pg h/ml).

There was a lag time of 1 to 20 h after application of the FTTS with the aqueous-based reservoir before measurable levels of the drug were detected. Thereafter, the levels increased to achieve essentially constant levels over the remainder of the system application time. The maximum levels attained ranged from 160 to 541 pg/ml with a mean of 278 pg/ml; the times at which these maxima occurred ranged from 12 to 28 h after system application. Removal of the system was associated with relatively small changes in levels over several hours. Plasma levels were detectable in 8 out of the 12 subjects at 48 h after system application. The areas under the curve (0–48 h) for the aqueous reservoir system varied from 2052 to 17426 pg h/ml with a mean of 6662 pg h/ml. Based on a comparison with the

Table 2
Time to peak buprenorphine concentrations (h) after administration of a 0.3 mg intravenous infusion and after application of the aqueous- and ethanol-based FTTS to healthy male volunteers

| Subject No. | Intravenous infusion (0.3 mg) | Ethanol-based FTTS | Aqueous-based FTTS |
|---|---|---|---|
| 01 | 0.33 | 12 | 24 |
| 02 | 0.33 | 25 | 24.5 |
| 03 | 0.17 | 25 | 26 |
| 04 | 0.33 | 6 | 24.5 |
| 05 | 0.33 | 16 | 12 |
| 06 | 0.33 | 8 | 24.5 |
| 07 | 0.33 | 6 | 16 |
| 08 | 0.33 | 24.5 | 25 |
| 09 | 0.33 | 24.5 | 24.5 |
| 10 | 0.33 | 8 | 28 |
| 11 | 0.33 | 24.5 | 24.5 |
| 12 | 0.17 | 4 | 20 |
| Mean | 0.30 | 15.3 | 22.8 |
| SD | 0.06 | 8.8 | 4.6 |

intravenous data the total amount delivered by the 10 $cm^2$ aqueous reservoir system ranged from 0.11 to 0.67 mg (mean 0.34 mg) over the 24 h application period. The steady state in vivo flux rates were calculated to be 0.56–1.91 $\mu g/cm^2/h$ (mean 1.09 $\mu g/cm^2/h$).

Individual lag times to detectable drug levels from the ethanol-based system ranged from 1 to 6 h. Thereafter, the levels increased and achieved peak concentrations of 164–698 pg/ml at 4–25 h after system application. Plasma levels did not fall significantly for 1 to 2 h after removal of the FTTS system. Measurable plasma levels were detected in 9 of the 12 subjects at 48 h after system application or 24 h after system removal; the mean concentration at this time point was 94.3 pg/ml with a range of $< 50$ to 223 pg/ml. The areas under the curve for the FTTS with the ethanol-based reservoir ranged from 4593 to 19 656 pg h/ml (mean 12 090 pg h/ml). Therefore, the total amounts delivered by the ethanol-based system ranged from 0.33 to 0.96 mg (mean 0.60 mg) and the steady state in vivo flux values over 24 h were 2.14–5.62 $\mu g/cm^2/h$ (mean 3.75 $\mu g/cm^2/h$).

## 4. Discussion

The plasma concentration–time profiles for buprenorphine were consistent with an extended duration of drug absorption after application of the FTTS to the lower back. However, the delay in appearance of measurable drug levels was shorter for the FTTS with the ethanol-based reservoir as compared to the FTTS with the aqueous reservoir; the respective median lag times were 2 and 6 h. Plasma levels achieved with the former were higher than those with the latter system, the mean (SD) peak concentrations being 478 (198) and 278 (119) pg/ml, respectively. Removal of either system did not produce the expected fall in plasma levels, suggesting continued delivery of the drug into the circulation from a skin depot at the application site.

Clinical findings were unremarkable for all subjects. Significant adverse experiences were limited to nausea, vomiting and dizziness but the overall incidence was low, which is consistent with the quantity of drug delivered and the resulting plasma levels. A significant difference between baseline and treatment blood pressure was shown for both systolic and diastolic blood pressure for

Table 3
In vivo flux rate and area under the plasma concentration–time curve (pg h/ml) between 0 and 24 h after administration of a 0.3 mg intravenous infusion and between 0 and 48 h after application of the aqueous- and ethanol-based FTTS to healthy male volunteers

| Subject No. | AUC (pg h/ml) | | | Flux rate ($\mu$g/cm$^2$ h) | |
|---|---|---|---|---|---|
| | Intravenous infusion (0.3 mg) | Ethanol-based FTTS | Aqueous-based FTTS | Ethanol-based FTTS | Aqueous-based FTTS |
| 01 | 5164 | 9860 | 2544 | 3.64 | 0.80 |
| 02 | 5243 | 5812 | 4322 | 2.23 | 0.72 |
| 03 | 4044 | 4593 | 6025 | 2.14 | 1.34 |
| 04 | 5225 | 12 407 | 3442 | 4.80 | 0.69 |
| 05 | 9646 | 19 656 | 17 246 | 3.74 | 1.48 |
| 06 | 6742 | 14 328 | 6724 | 3.57 | 1.06 |
| 07 | 6558 | 9154 | 3550 | 2.51 | 0.56 |
| 08 | 5881 | 17 831 | 2052 | 5.15 | 0.64 |
| 09 | 7757 | 14 720 | 7923 | 2.92 | 0.99 |
| 10 | 4496 | 12 329 | 10 339 | 5.62 | 1.91 |
| 11 | 4344 | 5068 | 5554 | 2.82 | 1.31 |
| 12 | 6297 | 19 328 | 10 230 | 5.88 | 1.60 |
| Mean | 5925 | 12 090 | 6662 | 3.75 | 1.09 |
| SD | 1600 | 5336 | 4319 | 1.32 | 0.43 |

both transdermal formulations. Heart rate did not differ significantly from baseline during treatment with buprenorphine, although there were variations through the study period. Conclusions cannot be drawn about these observations in the absence of a placebo treatment.

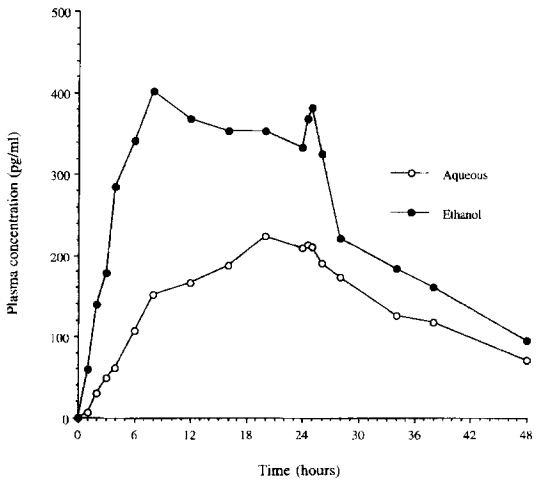


Fig. 1. Mean plasma concentration of buprenorphine following single application of ethanol and aqueous FTTS to a group of 12 healthy male volunteers (coefficient of variation at 24 h post-application was 43 and 48% for the ethanol and aqueous FTTS, respectively).

## 5. Conclusions

The results of these studies demonstrate that transdermal systems with ethanol- or aqueous-based reservoirs produced sustained plasma levels of buprenorphine which are within the range observed after intravenous administration of therapeutic doses. The ethanol-based system had a shorter onset of delivery and produced higher levels over 24 h despite its smaller surface area of delivery. The roughly four-fold difference in flux rates for the ethanol-based, as compared with the aqueous-based reservoir system, is consistent with the in vitro data obtained for the same systems in contact with cadaver skin, though the absolute in vivo values are consistently higher. Both systems were well-tolerated by the subjects. It will be important to tailor carefully the pharmaceutical properties of the transdermal system with the clinically required plasma levels for sustained analgesic therapy.

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