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Pharmacokinetics, Bioequivalence, and Spray Weight Reproducibility of Intranasal Butorphanol After Administration With 2 Different Nasal Spray Pumps

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Systemic nasal delivery is dependent on many factors. Lipophilicity, concentration, and molecular weight of the drug and formulation characteristics such as pH, osmolality, and viscosity have an impact on nasal absorption.^{1,2} The delivery device also plays a critical role in absorption by determining nasal deposition patterns and systemic exposure.³⁻⁷ However, there is a paucity of in vitro/in vivo data correlating nasal delivery characteristics and systemic exposure.

Butorphanol tartrate (BT) NS is a multidose (MD), intranasal (IN) spray pump product delivering a potent synthetic analgesic agent that exhibits both agonist and mixed agonist-antagonist activity at the κ -opioid and μ -opioid receptors. This product delivers approximately 14 to 15 (1 mg/spray) doses following the initial priming procedure.⁸

An MD pump may not be the most suitable spray pump for administration in some situations. Pump priming may affect proper patient use and self-administration,

results in wasted drug, and adds another step to the dosing procedures. Microbial contamination of liquid contents can occur with multiple uses. Providing multiple doses of BT in a single unit may encourage inappropriate use by the patient, health care personnel, or others who have access to the unused portion.

A unit dose (UD) nasal delivery device for IN BT would alleviate the concerns listed above while offering other potential advantages such as (1) a sterile product, (2) removal of potentially irritating antimicrobial preservatives,⁹⁻¹¹ (3) eliminating product contamination after single use, and (4) prescribing and dispensing based on individual patient requirements.

This study was designed to compare the influence of the accuracy and precision of spray weight delivery of UD and MD pumps on the single-dose pharmacokinetics of butorphanol. The UD and MD pumps were used to administer the identical BT nasal formulation and compared standard bioequivalence (BE) parameters, inter- and intrasubject variability of the pharmacokinetic parameters, and reproducibility and precision of the spray weight delivery of the 2 pumps.

METHODS

Subjects

Healthy volunteers participated in this randomized, incomplete block study. All subjects were nonsmoking,

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between 20 and 40 years of age, and within 20% of ideal body weight. Subjects were excluded based on clinically significant laboratory values, including a drug abuse screen. Female subjects ($n = 7$ out of 16) were excluded for positive urine pregnancy test results. Volunteers were determined to be in good health following a physical examination, nasal examination, and medical history review. Written informed consent was obtained from all subjects. This study was conducted in compliance with the tenets of the Declaration of Helsinki and was approved by the University of Kentucky Institutional Review Board.

Drug and Spray Pump Systems

Two intranasal spray pump systems, 1 UD and 1 MD, containing an identical BT 10-mg/mL solution (Stadol NS, lot 9H09013, Apoteco) were compared. Both pumps are intended to deliver 100 μ L, providing 1 mg of BT per spray. The MD pump (model VP3, Valois S.A., Le Neubourg, France) was used as the commercially available reference spray. Each MD pump was primed according to the manufacturer's guidelines on the morning of dosing. The UD test spray pump (UD, Pfeiffer unit dose system, Pfeiffer of America, Princeton, NJ) was filled with BT using a pipettor and assembled by hand. The filling volume of the UD was 125 μ L for a nominal delivery of 100 μ L. No priming was required for the UD pump.

The UD and MD spray pumps were weighed using a Mettler (Mettler Toledo, Columbus, Ohio) balance (model AG204) prior to and after patient doses were administered. Target delivery weight of 2 sprays was 0.2 g.

A separate in vitro spray weight evaluation was performed for UD and MD pumps. The UD spray pumps ($n = 30$) were filled using pipettors with 125 μ L of deionized water and assembled by hand. The MD spray pumps ($n = 30$) were hand-filled with 2.5 mL deionized water. Each MD spray pump was actuated 10 times for priming before obtaining spray weight data. After priming, net spray weight measurements were taken for 10 consecutive actuations. Target delivery weight for each single spray was 0.1 g.

Clinical Procedure

This was a consecutive, 3-period, partial replicate inpatient study with a 1-week washout between treatments. Subjects fasted for 8 hours prior to and 4 hours after drug administration. Water was allowed ad lib except within 1 hour of dosing. Caffeine and alcohol were not permitted within 48 hours prior to the start or throughout each treatment phase.

Subjects were administered BT in a semirecumbent position for 3 consecutive periods according to a pregenerated randomization schedule (UD:MD:UD, MD:UD:UD, UD:MD:MD, or MD:UD:MD). Subjects gently blew their nose before administration and were not allowed to blow their noses again for 60 minutes. A standard BT 2-mg dose was given by the same physician during each period. Subjects received either 2 sprays, one per naris, from a single MD pump or 2 UD pumps.

Blood samples were collected from an indwelling intravenous catheter, and blood pressure and pulse rate were obtained at 0, 5, 10, 15, 20, 30, and 45 minutes and 1, 2, 3, 4, 6, 8, 12, and 16 hours after dosing. Nasal examinations were performed at predose and 2 to 4 hours after drug administration. Subjects were continuously monitored for adverse events.

Analytical Methods

Plasma samples were stored at or below -70°C prior to analysis. Butorphanol and added internal standard, levallorphan, were extracted from plasma samples using solid-phase extraction, separated by reverse-phase high-performance liquid chromatography (HPLC) and detected by a PE/Sciex API III + liquid chromatography/mass spectrometry/mass spectrometry (LC/MS/MS) system in MS/MS mode. Quantitation is achieved by monitoring the product ions (m/z 310 for butorphanol and m/z 199 for levallorphan) of precursor ions m/z 328 and m/z 284 for butorphanol and levallorphan, respectively. The lower limit of quantitation was 20 pg/mL of plasma. Coefficients of variation for within- and between-batch analyses ranged from 2.0% to 13.3% and 7.4% to 10.9%, respectively.

Pharmacokinetic Evaluation

Values for the maximum concentration (C_{max}) and time to C_{max} (t_{max}) were determined by inspection of the concentration versus time data. Standard noncompartmental methods were used to calculate pharmacokinetic parameters using WinNonlin (Pharsight Corp, Palo Alto, Calif). The area under the concentration versus time curve from time 0 to infinity ($\text{AUC}_{0-\infty}$) was calculated by a combination of the linear and logarithmic trapezoidal rules, with extrapolation to infinity by dividing the last measurable serum concentration by the elimination rate constant (λ_z). Clearance/bioavailability (CL/F) was determined by dividing the dose of butorphanol base by $\text{AUC}_{0-\infty}$. Volume of distribution for elimination/bioavailability (V_z/F) was determined by moment curves.¹²

Statistical Analyses

Bioequivalence statistical criteria from the Food and Drug Administration (FDA) guidance were used to analyze both average and individual bioequivalence.¹³ WinNonlin was used for analysis with fixed effects for sequence, treatment, and period for replicated cross-over designs. For average BE, ratios and 90% confidence intervals (CI) of the geometric means for C_{\max} and AUC values were calculated. The CI within the 80% to 125% range was considered BE. Within-subject variances for each spray pump were determined by WinNonlin. Subject-by-treatment interaction variances are from analysis of variance (ANOVA) with factors subject, treatment, subject-by-treatment interaction, and period. Individual BE was assumed for any individual difference ratios (IDR) <1.25 . Using the first 2 treatment periods, the Pitman-Morgan F test¹⁴ was used to compare variances of t_{\max} and log-transformed C_{\max} , AUC_{0-t} , and $AUC_{0-\infty}$ parameters at a significance level of 0.05. Note that we use the variance term *subject-by-treatment*, whereas the references refer to this as the *subject-by-formulation*, because in this study, the same formulation was used in 2 different spray pumps.

Mean weights of the actual spray delivered from the 2 pumps were compared with a 2-sample t test. The t tests were also used to evaluate differences between individual spray weights from the UD pump (ie, spray 1 vs spray 2 for each dose) and for comparison of each mean weight to the target delivery weight. Coefficients of variation and 95% confidence intervals were calculated with respect to a target delivery weight of 0.2 g. A Pitman-Morgan F test was used to compare variances. For the separate in vitro spray weight comparisons, a t test was used to compare mean values for each pump to the target delivery weight (0.1 g). Variances were compared using an F test. A $P < .05$ was considered significant for all comparisons. McNemar's test was used to consider differences in adverse event frequency for each pump for the first 2 periods. The linear correlation between total spray weight and $AUC_{0-\infty}$ was calculated.

RESULTS

Fifteen of the 16 subjects enrolled completed all treatment periods. One subject was withdrawn from participation in the third phase due to nausea and vomiting. The mean (range) age and weight of all subjects was 26.3 (20-40) years and 68.5 (50.5-86.3) kg, respectively. Of the 16 subjects, 14 were Caucasian, 1 was African American, and 1 was Asian.

No serious adverse events occurred throughout the study. Frequently reported side effects are reported in

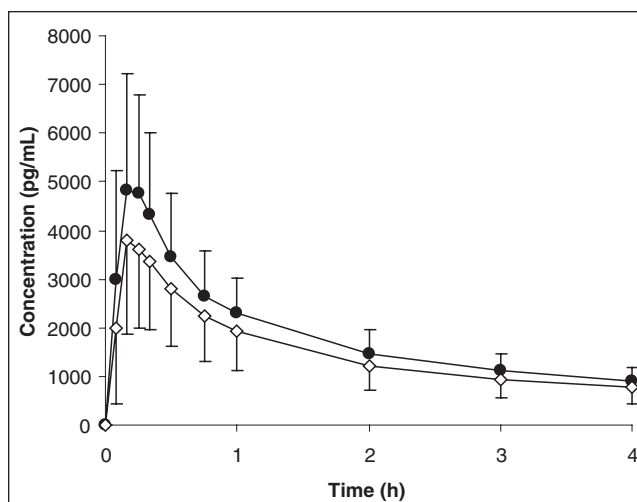


Figure 1. Mean plasma butorphanol concentrations (0-4 hours) following 2 mg butorphanol tartrate intranasal administration using a unit dose (filled circles) or multidose (open diamonds) spray pump. Error bars represent standard deviation.

Table I (online-only version). Statistical tests of the adverse events indicated no significant differences in adverse event frequency. Nasal exams revealed no clinically significant changes.

Mean plasma concentration-time plots for butorphanol for MD and UD pumps are shown in Figure 1. The mean profiles are parallel, but higher concentrations were observed after UD BT delivery. Pharmacokinetic parameters are listed in Table II.

Average BE methods did not support bioequivalence for C_{\max} or AUC values (Table III, online-only version). The upper BE limit of 1.25 was exceeded by the 90% CI in all cases, suggesting that greater exposure occurs after administration with the UD spray pump. Individual BE methods did show equivalence for the 2 pumps based on IDR <1.25 for $AUC_{0-\infty}$ and AUC_{0-t} . However, C_{\max} was not found bioequivalent using this technique. The UD within-subject variation was much smaller than the within-subject variation observed following MD administration. The C_{\max} parameter was the most variable, as evidenced by the largest subject-by-treatment interaction in comparison to AUC interaction values. The F tests for equality of variances were significant for log-transformed C_{\max} ($P = .005$), AUC_{0-t} ($P < .0001$), and $AUC_{0-\infty}$ ($P = .002$), with lower variance favoring the UD pump. t_{\max} variances from the 2 spray pumps were found to be equal. Carryover effects for the pharmacokinetic parameters were not significant ($P > .1$).

Spray weights taken during the clinical trial demonstrated statistically significant differences in both the mean weight delivered ($P < .001$) and the variance ($P <$

Table II Pharmacokinetic Parameters After Intranasal Administration of 2 mg Butorphanol Tartrate

Parameter	Unit Dose (n = 23)		Multidose (n = 24)	
t _{max} , h ^a	0.167	(0.083-0.5)	0.167	(0.167-0.5)
C _{max} , pg/mL	5562	(37)	4216	(42)
AUC _{0-t} , pg•h/mL	11 281	(29)	9298	(38)
AUC _{0-∞} , pg•h/mL	12 111	(31)	10 009	(38)
t _{1/2} , h	5.1	(22)	5.4	(47)
CL/F, L/h	122	(30)	177	(84)
V _z /F, L	789	(37)	1715	(214)

Values are presented as arithmetic mean (% coefficient of variation).
a. Median (range).

.001) for the UD versus MD pumps (Table IV, online-only version). No statistical difference was detected in delivery weight between the first (n = 23, mean = 0.1038 g) and second (n = 23, mean = 0.1022 g) UD spray pumps that were used in each individual (P = .3). The UD test pump delivered 3% above the target weight (P < .001), whereas the MD reference pump delivered 10% below the target weight (P < .003). The 95% CI for the UD pump is narrower and closer to the 0.2-g weight than the MD pump, suggesting less variability and more precise delivery. Figure 2 (online-only version) contains a graph of the actual spray weights delivered from each pump for each dose. A significant linear correlation (Pearson correlation coefficient = 0.55, P < .0001) exists between spray weight for each dose and AUC_{0-∞} (Figure 3, online-only version).

DISCUSSION

In this BE study, statistical differences were observed in the pharmacokinetics of BT administered by the UD and MD nasal spray pumps. Higher C_{max} and AUC values were observed following BT administration with the UD versus the MD pump. Average and individual BE methods demonstrated that the pumps did not generate equivalent pharmacokinetics.

Data from Table II can be compared to a previous report and the product label for a 2-mg nasal BT employing the same MD pump.^{8,15} Shyu et al¹⁵ reported a C_{max} of 2740 pg/mL, t_{max} of 15 minutes, and an AUC of 10 900 pg•h/mL. This study reported similar mean and standard deviation data for t_{max} and AUC for the MD pump, but not C_{max}, compared to the Shyu et al study.

Clinical spray weight observations suggest that at least 5 of the sprays delivered via the MD pump were considerably less than the target spray weight. The spray weight data indicate that variations in the dose weights delivered from each spray pump appear to be the source of these pharmacokinetic differences. There was a correlation between spray weight and AUC_{0-∞}. The UD pump delivered a spray weight very close to the target weight. The MD pump was much more variable in weight delivery and had an underdosing bias.

The additional in vitro spray weight comparisons support our initial findings of below-target delivery with the MD pump. The variability and the low mean spray weight delivery are most likely related to mechanical performance of the pump. Although the manufacturer’s priming guidelines were followed during this study,⁸ and all spray pumps were used for administration within a 3- to 4-hour window, it is possible that the pumps did not retain their primed state. Independent of priming, other mechanical factors may affect performance. For instance, consistency in piston recharging, volume of solution drawn up into the dip tube, and actuation force are factors influencing spray weight uniformity and variability. The MD pump is operator dependent because it allows variation in actuation force by patients, which contributes to variability in the emitted spray volume. For this reason, the FDA recommends using automated actuation for providing product specifications. This UD pump has a more operator-independent actuation because a certain consistent force is required to initiate actuation. The actual cause of inconsistent and below-target delivery with the MD pump in the present study cannot be determined with the data at hand. Further in vitro testing is needed to explain these differences in spray weight reproducibility.

Due to the design of the UD pump, the primary factor in the amount of spray delivered is the filling volume. A residual volume of approximately 22 to 23 μL remains in the UD device after actuation. The filling volume used in the present study was 125 μL. Therefore, the actual expected delivery weight per spray would be 0.102 to 0.103 g. This is consistent with the observed mean delivery weights for the UD pump, suggesting that manipulation of fill volume will allow on-target delivery.

As summarized in the FDA guidance on nasal sprays for local action, “in vitro methods are less variable . . . but the clinical relevance of these tests . . . cannot always be clearly established.”¹⁶ This experiment clearly demonstrated a pharmacokinetic difference for BT when administered via these 2 pumps. The potential clinical relevance regarding the efficacy rate in treating

a migraine headache would be speculative but could favor the UD product, assuming better dosing precision and accuracy. Adverse event rates were similar between the UD and MD pumps.

In conclusion, these findings have demonstrated that administration of BT intranasal via the MD and UD pumps results in delivery weight, pharmacokinetic, and bioequivalence differences. The UD pump demonstrated more accurate spray weight delivery and resulted in less pharmacokinetic variability. Additional research directed at understanding the pharmacodynamic, efficacy, and safety implications of nasal spray pump performance characteristics is warranted.

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