JPPT | Randomized Crossover Bioavailability Trial

The Bioavailability of CHF6563, an Ethanol-Free, Sublingual Neonatal Buprenorphine Formulation: A Bridging Study Conducted in Adults

Walter K. Kraft, MD; Irene Barneschi, MSc; Maria Bocchi; Debora Santoro, MSc; and Massimo Cella, PhD

OBJECTIVE Sublingual buprenorphine has demonstrated efficacy for treatment of the neonatal opioid withdrawal syndrome (NOWS), but the current formulation used in clinical practice contains 30% ethanol. Ethanol as a pharmacologically active excipient ideally should be removed from neonatal formulations. The objective of this study was to determine the relative bioavailability of a novel ethanol-free formulation (CHF6563) compared with the commonly used ethanolic solution in a phase I, open-label, 2-period, single-dose, crossover study in healthy adults.

METHODS Eighteen adult opioid-naïve volunteers were administered one of the formulations in a randomized crossover treatment. After a 10-day washout period, subjects received the other formulation. Serial blood samples were drawn for pharmacokinetic analysis over 48 hours.

RESULTS The geometric mean ratio (90% CIs) of the ethanol-free buprenorphine solution AUC_{0-last} was 0.80 (0.65–0.99) and C_{max} was 0.81 (0.66–0.99) compared with reference ethanolic formulation. The ethanol-free formulation had a greater degree of intersubject variability than the ethanol-containing reference formulation (coefficient of variation of 59% vs 31.5%, respectively, for AUC_{0-last}).

CONCLUSIONS In an adult population, a novel ethanol-free formulation of buprenorphine containing widely used excipients demonstrated a slight decrease in bioavailability when compared with an ethanolic solution. These results will inform those seeking to develop ethanol-free pediatric drug formulations.

ABBREVIATIONS AUC_{0-last}, area under the curve from time zero to last concentration; C_{max}, maximum concentration; CV, coefficient of variation; NOWS, neonatal opioid withdrawal syndrome

KEYWORDS buprenorphine; ethanol; formulation; neonatal opioid withdrawal; neonate

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Introduction

Buprenorphine is efficacious for the pharmacologic treatment of the neonatal opioid withdrawal syndrome (NOWS) in randomized controlled trials,[1] retrospective reviews,[2] and in the context of quality improvement projects.[3] All published data using sublingual buprenorphine in neonates have been using a 30% ethanol–containing formulation. Ethanol has the advantages of increasing solubility and antimicrobial stability. Both contribute to longer shelf life of locally compounded formulations. However, the use of ethanol and other pharmacologically active excipients in pediatric formulations is discouraged owing to potential safety concerns.[4] CHF6563 is an ethanol-free formulation of sublingual buprenorphine developed for treatment of NOWS. Optimized use of a new formulation should be informed by differences in anticipated bioavailability in patient populations. Because it is not ethical or feasible to conduct a formal bioavailability study in neonates, the US Food and Drug Administration has endorsed the use of studies done in adults to bridge use to pediatric populations.[5] This study examined the relative bioavailability of an ethanol-containing buprenorphine solution (reference formulation) and an ethanol-free formulation (CHF6563). The goal of this investigation was to define the relative bioavailability of an ethanol-free buprenorphine solution in adults. This information could inform use in the neonatal population requiring pharmacotherapy for NOWS.

Methods

This was a 2-period, crossover study in 18 adult opioid-naïve volunteers between 18 and 55 years of age, performed at the Thomas Jefferson University Clinical Research Unit. There was a washout of 2 weeks between study drug administration. Subjects were in good health as based on medical history, physical examination, electrocardiogram, and clinical laboratory

Table 1. Formulations

	Buprenorphine Concentration	Buprenorphine Source	Ethanol Concentration	Other Excipients	Dose Administered
CHF6563	0.075 mg/mL	Buprenorphine HCL	0%	Citric buffer pH 6, Natrosol 250 HX (hydroxyethylcellulose)	0.675 mg
Reference ethanolic formulation	0.075 mg/mL	Buprenorphine for injection (0.3 mg/mL)	30%	Simple syrup USP	0.675 mg

testing. The 2 treatment arms are listed in Table 1. After an overnight fast, subjects were randomly assigned to receive either CHF6563 in period 1 and reference formulation in period 2, or reference formulation in period 1 and CHF6563 in period 2. The reference ethanol-containing solution is the standard-of-care formulation used at Thomas Jefferson University Hospital and is compounded locally by the pediatric pharmacy service (Supplemental Table S1). Because the concentration of the solutions used in this study was chosen to facilitate dosing in neonates, the rationale for dose selection was that a high enough dose was required to capture sufficient pharmacokinetic data points, but with a volume that could be properly administered under the tongue. Therefore, subjects received 0.675 mg of study drug administered as 3 consecutive aliquots every 2 minutes with a syringe (doses were split to avoid excess volume at any 1 dose). This dose is below that used in prior studies in opioid-naïve volunteers.[6] Subjects were instructed to maintain the solution under their tongue without swallowing. Blood for pharmacokinetic analysis was collected pre dose, at 15, 30, 45, 60, 75, 90 minutes, and at 2, 3, 4, 6, 8, 12, 16, 24, 36, and 48 hours following study drug dosing. The study was approved by the Thomas Jefferson University Institutional Review Board and written informed consent was obtained by all research participants.

Buprenorphine and norbuprenorphine (its major active metabolite) were assayed by using a validated ultraperformance liquid chromatography and tandem mass spectrometry detection using positive ion electrospray method developed and conducted by PPD Laboratories (Middleton, WI). The standard curve concentrations were 20.0 to 10,000 pg/mL. Pharmacokinetic analysis was conducted with WiNonLin version 6.4. AUC_{0-last} (the area under the plasma concentration–time curve from 0 to the last quantifiable concentration) was computed by using the linear trapezoidal rule. The relative bioavailability of the test formulation was calculated as $F = AUC_{0-last(CHF6563)}/AUC_{0-last(reference)} \times 100\%$. AUC_{0-last} and C_{max} were log-transformed and analyzed by using a linear model including treatment, sequence, period, and subject within sequence as fixed effects. The ratios of adjusted geometric means between CHF6563 and reference formulation were calculated with 90% 2-sided CIs.

Results

Eighteen subjects were randomly assigned to 1 of 2 treatment sequences (Table 2). One subject was lost to follow-up after period 1 and was excluded from the pharmacokinetic analysis population but remained in the safety population. The geometric mean buprenorphine AUC_{last} (hr·pg/mL) of CHF6563 was 1507.3 compared with 1885.5 for reference formulation (Table 3). The geometric mean ratio of CHF6563 and reference formulation for AUC_{last} was 0.80 (90% CI, 0.65–0.99)

Table 2. Subject Characteristics

	Total (N = 18)
Age, mean ± SD, y	39 ± 11
Sex, n (%)	
Male	17 (94)
Female	1 (6)
Race, n (%)	
Black	14 (78)
White	4 (22)
Weight, mean ± SD, kg	83.7 ± 14.5
Body mass index, kg/m^2	27.7 (3.7)

Table 3. Geometric Mean (CV%) Pharmacokinetic Parameters of Buprenorphine by Treatment

Parameter	CHF6563 (N = 17)	Reference (N = 17)
AUC_{0-last}, hr·pg/mL	1507.3 (59.0)	1885.5 (31.5)
C_{max}, pg/mL	287.0 (54.6)	352.1 (21.3)
T_{max}, hr*	1 (0.5, 2.0)	1 (0.5, 2.0)

AUC_{0-last}, area under the curve from time zero to last concentration; C_{max}, maximum concentration; CV, coefficient of variation; T_{max}, time of maximum concentration

* Median (minimum, maximum).

and for C_{max}, 0.81 (90% CI, 0.66–0.99) (Table 4). Compared with the relative bioavailability of CHF6563 at 80% for AUC_{0-last} and 81% for C_{max}, norbuprenorphine demonstrated a similar decrease in C_{max} (83%) and lower AUC_{0-last} (62%) for CHF6563 than the reference formulation (Supplemental Table S2; Supplemental Figure). The coefficient of variation (CV%) was higher for CHF6563 AUC_{0-last} (59.0%) and C_{max} (54.6%) than for the reference formulation (31.5% and 21.3%, respectively). There were no serious adverse events. Adverse events were noted in 83% of subjects receiving CHF6563 and 88% of those receiving the reference formulation. All were mild in severity. The most common events were dizziness (78%), nausea (56%), somnolence (33%), and fatigue (28%), which occurred at similar rates between formulations.

Discussion

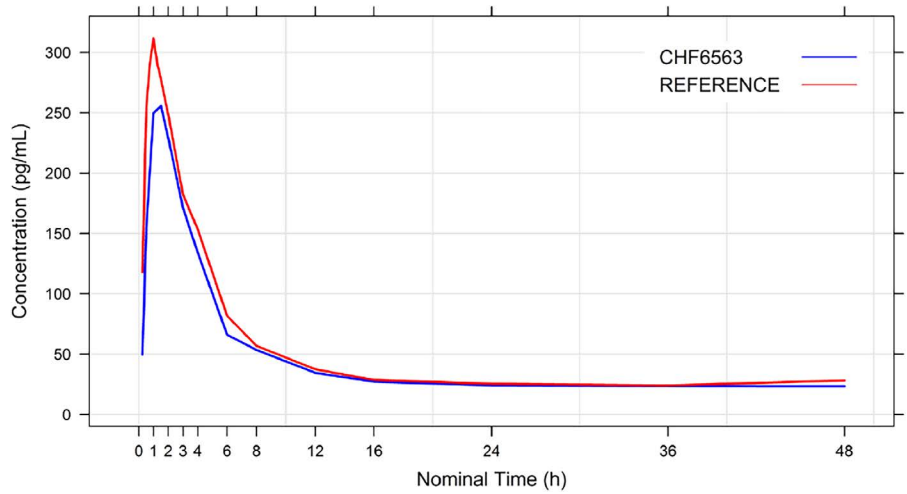
Buprenorphine has been identified as a promising agent for the treatment of NOWS,[7] and for which there would be utility in an extemporaneously compounded non-sterile preparation.[8] Investigations in the 1990s demonstrated an absolute bioavailability of a 30% ethanolic solution of 28% to 51% in adults.[9,10] All published pharmacokinetic investigations of sublingual buprenorphine in neonates have used an ethanol-containing formulation. In adults buprenorphine in ethanolic solution is absorbed in 2 to 4 minutes, and longer retention is not associated with increased systemic drug exposure.[10,11] This is consistent with a large number of sublingually administered drugs, in which bioavailability is time dependent only at higher doses.[12] In infants, buprenorphine is placed under the tongue and followed by a pacifier. The pharmacokinetic profile of ethanol-containing buprenorphine in neonates with NOWS has been described.[13–15] These studies have been largely limited to examinations of drug exposure and elimination kinetics. A full characterization of absorption kinetics requires multiple blood samples soon after a dose is administered. The density of such blood draws is not feasible in neonates. As such the absorption kinetics have not been established in this patient population, but quick absorption in adults suggests the holding pattern of drug in the sublingual fossa between infants and adults would not represent significant differences in absorption time. Buprenorphine dose is titrated to

Table 4. Geometric Mean Ratio of Buprenorphine AUC and C_{max}

Parameter	CHF6563 (90% CI) (N = 17)	Reference (90% CI) (N = 17)	GMR (90% CI)	Intrasubject CV
AUC_{0-last}, hr·pg/mL	1493.4 (1283.7, 1737.3)	1865.0 (1603.1, 2169.6)	0.80 (0.65–0.99)	36.7
C_{max}, pg/mL	284.5 (246.5, 328.5)	351.8 (304.6, 406.2)	0.81 (0.66–0.99)	34.8

AUC_{0-last}, area under the curve from time zero to last concentration; C_{max}, maximum concentration; CV, coefficient of variation; GMR, geometric mean ratio

Figure. Geometric mean plasma concentration vs time profile of buprenorphine by treatment (pharmacokinetic population).



control of withdrawal symptoms, and as such not affected to any degree by modest differences in bioavailability. An ethanol-free formulation would not change buprenorphine distribution, metabolism, or excretion. This report adds to the literature for those seeking to develop an alcohol-free formulation of buprenorphine. More broadly, this report may inform those seeking to understand the effect of ethanol on the sublingual absorption of a lipophilic, biopharmaceutics classification system class II drug such as buprenorphine. In conclusion this report details the relative bioavailability of an alcohol-free formulation and provides guidance for the use of alcohol-free sublingual formulations of buprenorphine in the treatment of NOWS.

Article Information

Affiliations. Department of Pharmacology, Physiology and Cancer Biology (WKK), Thomas Jefferson University, Philadelphia, PA; Global Clinical Development (IB, MB, DS) and at the time of submission MC, Chiesi Farmaceutici, Parma, Italy. MC is currently with NMS, Global Clinical Development, Nerviano Medical Sciences S.r.L., Nerviano, Italy.

Correspondence. Walter K. Kraft, MD; Walter.Kraft@jefferson.edu

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