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CLINICAL INVESTIGATION

Formulation of Buprenorphine for Sublingual Use in Neonates

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OBJECTIVES The only medication used sublingually in the neonate is buprenorphine for the treatment of neonatal abstinence syndrome (NAS). Compared with morphine, buprenorphine reduces the length of treatment and length of hospitalization in neonates treated for NAS. The objective of this study was to characterize the stability of ethanolic buprenorphine for sublingual administration.

METHODS Buprenorphine solution was prepared and stored in amber glass source bottles at either 68°F to 77°F (20°C–25°C) or 36°F to 46°F (2.2°C–7.8°C). Samples were collected from each of these batches on days 0, 3, 7, 14, and 30. Additional samples were withdrawn at baseline from each batch and placed in oral dispensing syringes for 3 and 7 days. Buprenorphine concentration was assessed by liquid chromatography–electrospray ionization–tandem mass spectrometry.

RESULTS Neither storage temperature ($p=0.65$) nor storage time ($p=0.24$) significantly affected buprenorphine concentrations. All of the mean concentrations, regardless of storage temperature, were above 95% of the labeled concentration, and the potency was maintained for samples stored either in the original amber glass source bottles or in oral syringes.

CONCLUSIONS An ethanolic buprenorphine solution is stable at room temperature for 30 days.

INDEX TERMS buprenorphine, drug stability, newborn infant, pharmaceutical chemistry, sublingual administration

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INTRODUCTION

The cessation of placental transfer of maternally ingested opioids is associated with signs of withdrawal in the newborn. This condition, called neonatal abstinence syndrome (NAS), is associated with irritability, poor feeding, autonomic dysfunction, and occasionally seizure. Significant heterogeneity continues to exist in the diagnosis and treatment of neonates at risk for opiate withdrawal.^{1,2} Cochrane Reviews,^{3,4} the American Academy of Pediatrics,⁵ and expert review⁶ identify opioid replacement as the ideal treatment for the withdrawal symptoms associated with *in utero* exposure to opiates.

The standard of care at Thomas Jefferson University Hospital is an oral morphine solution administered every 4 hours. This therapy is associated with a 4 to 6-week length of hospital-

ization.⁷ Compared to morphine, investigations with sublingual buprenorphine as a treatment for NAS show about a 30% decrease in both the length of treatment and length of hospitalization.^{8,9} The formulation used in these preliminary studies was buprenorphine 0.3 mg/mL (Buprenex, Reckitt Benckiser, Richmond, VA) and simple syrup in a 30% ethanolic solution. The use of 30% ethanol was mandated by the Food and Drug Administration during initial investigational new drug discussions. After an initial cohort employed a solution of buprenorphine of 0.06 mg/mL, the concentration was increased to 0.075 mg/mL. The stock bottle and individual doses were stored at room temperature with a 72-hour expiration date. A pharmacokinetic/pharmacodynamic model-generated bioavailability estimate of buprenorphine on an individual infant basis is 12% to 56%,¹⁰ a range within the 95% confidence interval of the 33% value seen in adults

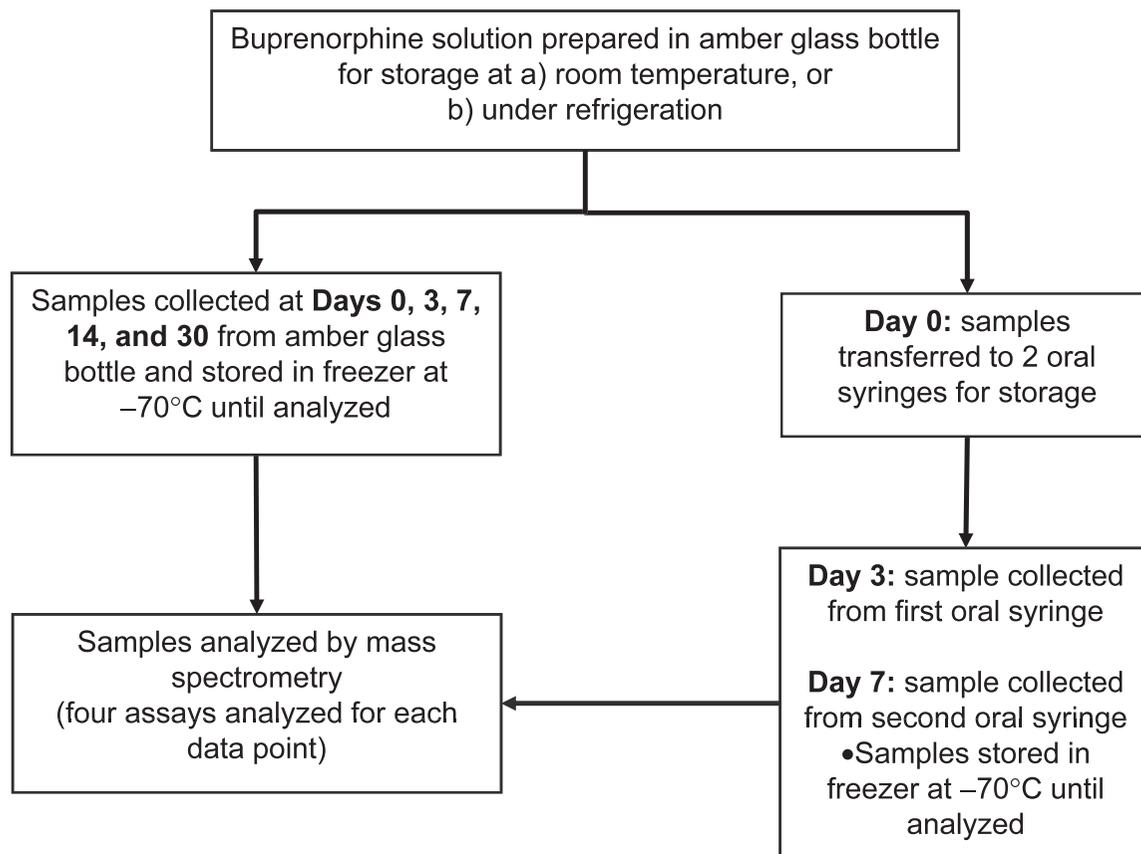


Figure 1. Study procedure

All samples were transferred to 1-mL polypropylene tubes either directly from the amber glass source bottle or from an oral syringe. The tubes were stored at -70°C until sent for stability analysis.

for an ethanol-based solution.¹¹ The current investigation was undertaken with a goal of characterizing the stability of ethanolic buprenorphine for sublingual administration.

MATERIALS AND METHODS

Two batches of buprenorphine solution were prepared. One batch was stored at room temperature, 68°F to 77°F (20°C - 25°C), while the other was refrigerated at 36°F to 46°F (2.2°C - 7.8°C). The pH of the formulation is 5.4. From each of these batches, samples were withdrawn from the amber glass bottle into 1-mL polypropylene tubes on days 0, 3, 7, 14, and 30 and stored at -70°C (Figure 1) until analysis was conducted. Two additional samples were withdrawn at baseline from an amber glass bottle and placed into the oral syringes (1-mL Exacta-Med oral dispensers, item number 172-3733, Baxa, Englewood, CO) used to dispense the solution at Thomas Jefferson University Hospital. On days 3 and 7, the samples from the oral syringes

were transferred to 1-mL polypropylene tubes and stored in the -70°C freezer. Samples were assessed within 6 months of collection.

Buprenorphine was measured by liquid chromatography–electrospray ionization–tandem mass spectrometry essentially as described by Moody et al¹² The assay was designed for biological samples, and the same method of extraction was used in this study. Buprenorphine- d_4 and nobuprenorphine- d_3 were added as the internal standards. The limit of quantification was 0.1 ng/mL. Samples were assayed on 2 days within 6 months of collection. During method validation the intraassay accuracy (% target)/precision (%CV) at 0.1, 0.25, 1, and 5 ng/mL were 109/6.4, 92/2.6, 102/2, and 94.2/1.1, respectively. The respective interassay accuracy and precision were 105/3.8, 92.4/3.5, 103/3.9, and 95.6/3.6. During the 2 analytical runs for study samples the mean accuracy and precision at 0.25, 2, and 7.5 ng/mL were 94/19.5, 102/4.4, and 98/2.2, respectively.

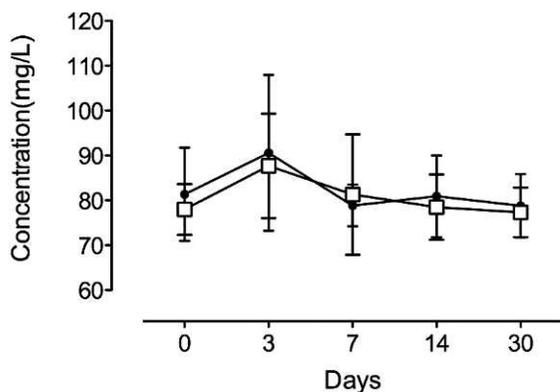


Figure 2. Buprenorphine concentration as a function of time

● = refrigerated samples and □ = samples stored at room temperature.

Each of the 7 samples per batch was assayed 4 times to yield 28 data points for each of the 2 batches of buprenorphine solution. Measured values were compared using 2-way analysis of variance to assess the impact of both storage time and temperature on the buprenorphine concentration. Statistical analysis was performed with JMP version 8.0 (SAS Institute, Cary, NC).

RESULTS

Buprenorphine concentrations throughout the study are shown in Figure 2. No norbuprenorphine was detected. Neither storage temperature ($p=0.65$) nor storage time ($p=0.24$) significantly affected buprenorphine concentration. Of note, all of the mean concentrations, regardless of storage temperature, were above 95% of the labeled concentration of 0.075 mg/mL, the threshold established in the Food and Drug Administration stability testing guidance for the pharmaceutical industry.¹³ This potency was maintained for samples stored either in the original amber glass source bottles or in oral syringes until removed and placed in the polypropylene tubes for analysis.

The correlation coefficients (r) for all storage conditions ranged from 0.032 to 0.23. These results confirmed that there was no statistically significant relationship between the times when samples were collected for analysis and the buprenorphine concentrations ($p>0.1$), indicating minimal drug degradation over the study period.

DISCUSSION

While there is variability in diagnosing and treating neonates at risk for opiate withdrawal,

opiod replacement is considered an ideal treatment for withdrawal symptoms associated with *in utero* exposure to opiates. Sublingual buprenorphine solution is of interest in the treatment of NAS because the lengths of hospitalization for neonates treated with oral morphine solution range from 4 to 6 weeks. An initial comparison of sublingual buprenorphine with oral morphine solution at Thomas Jefferson University Hospital for NAS showed a shorter length of treatment and shorter length of hospitalization with buprenorphine.

The buprenorphine concentrations from samples collected on days 3, 7, 14, and 30 showed no evidence of drug degradation and no apparent relationship to the time from batch preparation. Additionally, little difference was found between concentrations of samples stored at room temperature versus those stored under refrigeration. Samples also maintain their potency when stored in oral syringes for up to 7 days. Based on these results, the expiration dates for buprenorphine solution have been changed in clinical research at Thomas Jefferson University Hospital. The solution stored in glass bottles is given an expiration date of 30 days at room temperature, and the solution stored in syringes is given an expiration date of 7 days at room temperature.

Our study includes certain limitations. The assay used was developed for analysis of biological samples; it was not optimized for evaluation of formulations with single targets of concentrations.¹² While multiple samples were obtained and analyzed for each time point, additional replicate samples would have strengthened the study design. Additionally, the samples were stored at temperatures defined by ranges for room temperature and refrigeration that would reflect practice, rather than a particular actual temperature. While a baseline sample was collected from each of the 2 amber glass source bottles, a separate sample was not obtained from the oral syringes in which the initial samples were placed. Therefore, our reported concentration changes from baseline for the samples stored in oral syringes represent an approximation rather than definitive results.

Based on the results of this study, the 30-day stability of the formulation should allow for convenient storage, less pharmaceutical waste, and decreased cost in future clinical trials of sublingual buprenorphine used for treatment of NAS.

DISCLOSURE Ellena A. Anagnostis, Rania E. Sadaka, Linda A. Sailor, Kevin C. Dysart, and Walter K. Kraft declare no conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria. David E. Moody has received both

consultant and research funding from Reckitt Benckiser, the manufacturer of Buprenex. Walter K. Kraft had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

ABBREVIATION NAS, neonatal abstinence syndrome

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