Clinical Investigation

Injectable Dexamethasone Sodium Phosphate Administered Orally? A Pharmacokinetic Analysis of a Common Emergency Department Practice

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BACKGROUND: The injectable formulation of dexamethasone has been administered orally, for the treatment of pediatric asthma and croup. The practice is followed in emergency departments around the country, but pharmacokinetic data supporting this practice are lacking.

OBJECTIVES: This study evaluated the relative bioavailability and pharmacokinetics of dexamethasone sodium phosphate for injection (DSPI) administered orally compared to dexamethasone oral concentrate (DOC) in healthy adults.

M**ETHODS:** This was an open label, crossover study of 11 healthy adults 18 to 45 years of age. All subjects received 8 mg of dexamethasone oral concentrate initially. After a 1-week wash-out period, subjects received 8 mg of DSPI administered orally. Dexamethasone levels were measured by liquid chromatography in tandem mass spectrometry. C_{max} and area under the curve ($AUC_{(0\text{-}t)}$ and $AUC_{(0\text{-}\infty)}$) were calculated and compared between groups using the paired *t* test.

RESULTS: The mean ± SD $AUC_{(0\text{-}t)}$ for dexamethasone oral concentrate and DSPI were 5497.23 ± 1649 and 4807.82 ± 1971) ng/dL/hr, respectively; 90% confidence interval (CI) was 78.8%-96.9%. The mean ± SD $AUC_{(0\text{-}\infty)}$ for dexamethasone oral concentrate and DSPI were 6136.43 ± 2577 and 5591.48 ± 3075 ng/dL/hr, respectively; 90% CI was 79.0% -105.2%. Mean C_{max} ± SD for DOC and DSPI were 942.94 ± 151 and 790.92 ± 229 ng/dL, respectively; 90% CI 76.8%-91.7%. The relative bioavailability of DSPI administered orally was 87.4% when using $AUC_{(0\text{-}t)}$ and 91.1% when using $AUC_{(0\text{-}\infty)}$. The calculated absolute bioavailability was 75.9%.

CONCLUSIONS: DSPI is not bioequivalent to dexamethasone oral concentrate when administered orally. The existing literature supports the efficacy of DSPI despite this. Dosing adjustments may be considered.

INDEX TERMS: asthma, bioequivalence, bronchiolitis, croup, dexamethasone, dexamethasone sodium phosphate, oral concentrate

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INTRODUCTION

Dexamethasone is a fluorinated derivative of prednisolone with very high systemic anti-inflammatory potency and minimal mineralocorticoid effects.[1] The efficacy of oral dexamethasone in children with croup has been well established and has been shown to be comparable to the intramuscular route.[2–4] Studies that have used the intravenous formulation, dexamethasone sodium phosphate for injection (DSPI), to prepare an oral suspension have also been published.[5,6] Some hospitals have made it their practice to administer the intravenous formulation orally with either a commercially available sweetened suspension[7] or only a small amount of juice to enhance palatability. This method of administration has become popular as higher concentration intravenous formulations (10 mg/mL, Baxter, Deerfield, IL; or 4 mg/mL, American Regent, Shirley, NY) require smaller volumes to administer compared to commercially available oral elixirs (0.5 mg/5 mL; Morton Grove, Morton Grove, IL) or concentrates such as dexamethasone intensol (1 mg/mL; Roxane, Columbus, OH)]. In addition, the oral concentrate is formulated with 30% alcohol, which may cause the mixture to be unpalatable or cause vomiting. The immediate availability of this method of delivery is thought to save resources by negating the time spent crushing pills, compounding, or storing suspensions.

Because DSPI is a water-soluble solution with a pH between 7.0 and 8.5, we reasoned that differences in solubility, pH, and salt may affect the rate and extent of absorption of this formulation when given orally. Although studies comparing the pharmacokinetics of intramuscular and oral dexamethasone exist, we could find no pharmacokinetic data for DSPI given orally.[8–9] Given that some institutions may be hesitant to adopt this off-label practice, we concluded that pharmacokinetic data would also be useful in justifying the use of DSPI orally in an emergency department (ED) setting. We therefore compared the pharmacokinetics of DSPI to those of a commercially available formulation in healthy adult volunteers.

METHODS AND MATERIALS

This study took place at the ED of Morristown Memorial Medical Center (MMMC) of Atlantic Health Systems (AHS) in Morristown, NJ, a community hospital with approximately 85,000 ED visits per year. The study was approved by the institutional review board at MMMC, and all subjects provided informed consented. Sera were analyzed by Quest Diagnostics Nichols Institute (San Juan Capistrano, CA). An open-label, single-dose, crossover study was carried out in 11 healthy volunteers between March and April 2009. The volunteer pool included staff from the ED, including emergency medicine attending physicians, residents, nursing personnel, and ancillary staff. A general announcement was made to all groups through email describing the study and provided phone numbers and emails for contact if interested. Recruitment occurred in a group setting to reduce possibility of coercion. Inclusion criteria required that subjects be healthy males or females 18 to 45 years of age and, if male, >50 kg or >45 kg if female. Exclusion criteria included pregnancy, allergy to study medication, any prescription medication taken 2 weeks prior to study enrollment, use of corticosteroids 30 days prior to study, and hypertension or diabetes. All participants had a complete blood count test, basic chemistry profile, liver function testing, morning cortisol levels, and, if female, a serum pregnancy test. Only those with clinically normal levels were allowed to participate.

Once subjects volunteered, their schedules were arranged so that sleep cycles were the same for each collection date, including the rule that each volunteer would not have worked clinically the night prior to study medication or baseline sample collection. Participants were asked not to take any prescription medications for 2 weeks prior to the study and to fast 4 hours before study medication administration and 4 hours post medication.

Participants were asked to present to a designated area at 6:30 AM on all 3 study days. On day 1, baseline plasma cortisol levels were obtained at 8 AM, 10 AM, 3 PM, and 5 PM.

For study drug collection day, on week 1, subjects received 8 mL of dexamethasone oral concentrate (1 mg/mL; Roxane) orally, followed by a 1-week wash-out period, with administration of 2 mL (4 mg/mL) of DSPI (American Regent) orally at week 2. On each study day, blood samples were obtained at 0 (predose), 1, 2, 4, 6, 8, and 11 hours post drug administration to test for plasma dexamethasone and serum cortisol levels. Blood samples were collected in 10-mL tubes with 10 mL of blood drawn at each epoch for a total of 70 mL per day. All specimens were labeled at each blood draw with unique patient identifiers and time of sample.

After being collected, blood was allowed to clot for 20 minutes and then centrifuged for 15 minutes at 3000 rpm. Plasma was then removed using disposable pipettes and transferred to polypropylene tubes with screw tops. Plasma samples were frozen at −20°C and stored in the MMMC laboratory until shipment in dry ice to the Nichols Institute by overnight express, where it was also stored at −20°C until specimens for all time periods were received, at which time analysis was performed. Plasma dexamethasone levels and cortisol suppression in plasma were measured using high-turbulence liquid chromatography tandem mass spectrometry (HTLC-MSMS) using validated assays.

HTLC-MSMS sample preparation methods for plasma samples were identical for detection of cortisol and dexamethasone and were carried out as follows. The sample was prepared by acidifying 150 µL of plasma or saliva with 10% formic acid to release the analyte from any binding proteins. The internal standard (prepared in deuterated methanol) was added, and the sample was vigorously mixed prior to incubation at room temperature for 30 min, prior to being placed in a refrigerated auto-sampler. The Aria TX-4 HTLC unit (Cohesive Technologies Inc., Franklin, MA) injected the prepared sample onto an extraction column at high flow rate. The analytes were eluted and transferred to a reverse-phase C_{12} analytical column (Synergi-Max RP; Phenomenex, Torrance, CA). They were then quantitated using a TSQ Quantum Ultra (ThermoFisher Scientific; San Jose, CA) tandem mass spectrometer. The tandem mass spectrometer permits the isolation of the parent compound to within ± 0.5 m/z within the first quadrupole (Q1). In Q2, the parent ion collides with an inert gas (argon) to generate daughter ions, and the appropriate daughter ion(s) is selected in Q3. Inclusion of deuterated internal standards enabled more precise quantitation of the analytes by correcting for procedural losses or ion suppression caused by matrix effects in the atmospheric pressure chemical ionization process. Detection of 2 daughter ions for both the analytes and the internal standards increases the specificity by permitting use of ion ratios, thereby reducing the risk of quantitating isobaric interfering substances. The analytes were quantitated against a standard curve in which the standards were processed in the same manner as the samples. Peak area ratios between the analytes and the internal standard were used for quantitation. The whole process of extraction, separation, and detection was automated through the use of the Aria TX-4 system.

The lower limits of quantitation and detection of dexamethasone assay were 20 ng/dL and 10 ng/dL, respectively. Intra-assay variability and accuracy were 13.3% and 93.3%, respectively, at 30 ng/dL and 9.9% and 95.5%, respectively, at 300 ng/dL. Interassay variability and accuracy were 12.1% and 94.2%, respectively, at 30 ng/dL and 13.7% and 94.4%, respectively, at 300 ng/dL. The analytical measurable range was 20 to 1000 ng/dL. The assay used has no cross-reactivity with 45 endogenous and exogenous steroidal compounds. Recovery ranged from 98.2% to 103.2% across 9 different patient discard samples spiked with dexamethasone at known concentrations. These analytes are stable for 24 hours at room temperature, 7 days at 4 to 8°C, and 2 years at to 20°C.

Pharmacokinetic variables were determined using standard non-compartmental methods with log linear least square regression analysis to determine the elimination rate constants, using PK Solutions version 2.0 software (Summit Research Services, Montrose, CO). Area under the curve $(AUC)_{(0\text{-}t)}$, $AUC_{(0\text{-}\infty)}$, half-life (t1/2), and maximum concentration (Cmax) were also calculated using the same software. The relative bioavailability (*F*) was determined by the formula [$F = AUC_A \times Dose_B / AUC_B \times Dose_A$]. Data were analyzed comparing all parameters between dexamethasone formulations.

Bioequivalence was assessed by estimating the 90% confidence interval (CI) for the means of the test-to-reference products ratio, using log normal transformed data. Statistical analysis was performed using Minitab 16 statistical software (Minitab, Inc., State College, PA). The 2-tailed paired *t* test was used to compare pharmacokinetic variables between the study medications. Bioequivalence was defined as a 90% confidence interval of the ratio of the means (CI) between 80% and 125% for AUC, Cmax, and t1/2. Unless otherwise noted, data are means ± standard deviations.

RESULTS

All 11 subjects completed the study through all time points without adverse events. Subjects mean age was 34.9 ± 5.9 years old, and mean body mass index was 26.8 ± 5. Seven subjects were male. Figure 1 shows the concentrations plotted against time for dexamethasone oral concentrate and DSPI. The Table summarizes the key pharmacokinetic parameters. The $AUC_{(0\text{-}t)}$ for dexamethasone oral concentrate and DSPI were 5497.23 ± 1649 and 4807.82 ± 1971 ng/dL/hr, respectively (90% CI: 78.8%-96.9%). The $AUC_{(0\text{-}\infty)}$ for dexamethasone oral concentrate and DSPI were 6136.43 ± 2577 and 5591.48 ± 3075 ng/dL/hr, respectively (90% CI: 79.0-105.2%). Cmax for dexamethasone oral concentrate and DSPI were 942.94 ± 151 and 790.92 ± 229 ng/dL, respectively (90% CI: 76.8-91.7%). Dexamethasone half-lives for the oral concentrate and DSPI were 2.57 ± 1.03 and 2.85 ± 1.02 hours, respectively (90% CI: 96.2-127.0%).

The relative bioavailability of DSPI adminis-

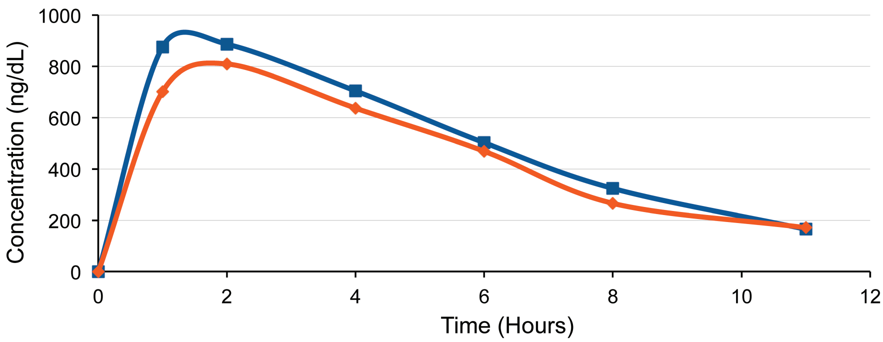

Figure 1. Mean plasma concentration profiles after a single 8-mg dose of 2 formulations of dexamethasone in 11 healthy adult volunteers.
■ DOC; ◆ DSPI
DOC, dexamethasone oral concentrate; DSPI, dexamethasone Sodium Phosphate.

tered orally was 87.4% when calculated using $AUC_{(0\text{-}t)}$ and 91.1% when using $AUC_{(0\text{-}\infty)}$. Although no specific data for the bioavailability of the intensol preparation could be found, the reported mean bioavailability of the commercially available elixir is 86.9%.[10] Assuming the intensol and elixir are absorbed similarly, the calculated absolute bioavailability would be 75.9%.

Total cortisol levels at baseline and for both preparations for all subjects are shown in Figure. 2. The total cortisol suppression graph suggests that cortisol falls quickly and suppression is sustained in an equal manner between preparations. These findings are consistent with other studies measuring cortisol suppression of dexamethasone by various routes.[11,12]

DISCUSSION

To our knowledge, no other study has evaluated the pharmacokinetics of an intravenous dexamethasone formulation given orally. Some hospital formularies have been hesitant to adopt the use of DSPI orally because of a lack of pharmacokinetic data. We found DSPI is satisfactorily absorbed via the gastrointestinal tract. Significant differences could be found between pharmacokinetic parameters of dexamethasone oral concentrate and those of DSPI in our study. The US Food and Drug Administration considers 2 products bioequivalent if the 90% CI of the relative mean Cmax, $AUC_{(0\text{-}t)}$, and $AUC_{(0\text{-}\infty)}$ of the test to reference agent are within 80.0% to 125.0% in the fasting state.[13] Our data suggest that DSPI does not fall within this range compared to dexamethasone oral concentrate.

The benefit to incorporating DSPI in a pediatric emergency center is the amount of resources and time spent administering the medication that could be saved. The smaller volume may help with drug administration in the uncooperative pediatric patient. Smaller volumes can be administered more quickly, with less chance of being spit up. The time spent crushing pills, compounding, or stocking elixirs would also be saved. There is also a potential for the use of single-dose DSPI given orally in the pediatric asthma population. Recent reports suggest a single dose of oral dexamethasone is no worse than longer courses of twice-daily prednisolone in the management of mild to moderate asthma in children.[15–17] A cost analysis of a 2-day regimen of dexamethasone versus 5 days of prednisolone

Table. Pharmacokinetic Parameters for Dexamethasone Oral concentrate and Dexamethasone Sodium Phosphate

Parameter	DOC Concentration*	DSPI Concentration*	90% CI for Test Means:Test Reference Ratio
$AUC_{0\text{-}t}$ (ng/hr/dL)	5497.23 ± 1649	4807.82 ± 1971	78.8%-96.9%
$AUC_{0\text{-}\infty}$ (ng/hr/dL)	6136.43 ± 2577	5591.48 ± 3075	79.0%-105.2%
t1/2 (hr)	2.57 ± 1.03	2.85 ± 1.02	96.2%-127.0%
C_{max} (ng/dL)	942.94 ± 151	790.92 ± 229	76.8%-91.7%

AUC, area under the concentration time curve; Cmax, maximum concentration; DOC, dexamethasone oral concentrate; DSPI, dexamethasone sodium phosphate; T1/2, half-life
* Means ± standard deviations.

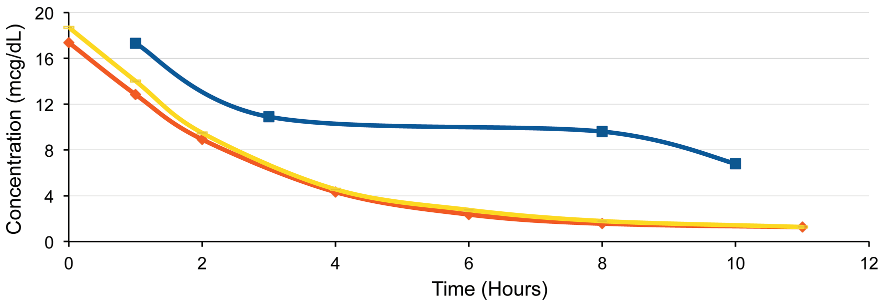

Figure 2. Plasma concentration over time plot of total cortisol at baseline and after administration of two formulations of dexamethasone.
■ Baseline; ◆ DOC; ▬ DSPI

yielded a decreased number of ED visits and hospital admissions within 7 to 10 days of the sentinel ED visit and provided cost savings.[18] Inclusion of DSPI may facilitate outpatient treatment and increase compliance in these cases. Smaller volumes would also be easier to tolerate in the patient in acute respiratory distress, in which intravenous access is not possible or desirable.

Palatability is a concern with any oral agent given to children. We chose to test our subjects without diluting or modifying the taste of the formulations to minimize variations in volume among participants. It is reasonable to dilute the DSPI in juice or other flavoring agent in clinical practice, although this negates the benefit of decreased volumes. Of note, all subjects tested confirmed the unadulterated intravenous preparation was more palatable than the oral concentrate standard.

Limitations

The main limitation of this study was that formulations were tested only in adult volunteers. Although we have shown that oral DSPI is not bioequivalent in the adult population, we cannot with complete certainty extrapolate the data for pediatric use. Of note, the efficacy of DSPI given orally in children is not in question. Existing reports confirm that the dose absorbed via this route, regardless of pharmacokinetics, is effective in children at typical doses.[5,6] The largest variety in pharmacokinetics between adults and children appear to be greatest soon after birth. For example the gastric pH of a newborn infant reaches that of an adult within the first 2 years of life.[19] Serum protein binding for acidic drugs reach adult levels by 1 year of age whereas basic drugs may take until the third or fourth year of life.[19] The volume of distribution also appears to become similar to that in adults at the age of 3 to 5 years.[19] Dexamethasone is metabolized by CYP3A4,[20] and this enzyme gradually increases throughout the developmental period.[19] Dexamethasone is excreted mostly in the urine. Glomerular filtration rate, urine pH, and renal tubular absorption also appear to reach adult levels in the first 8 months post partum.[19] We could find no specific data suggesting the pharmacokinetics of dexamethasone would be vastly different from that of adults in the age range that presents to the pediatric emergency center with croup or asthma. We concede that differences in body fat, water content, and gastrointestinal characteristics in smaller children could affect absorption, distribution, and elimination. However, we believe that, even if a difference exists in the pediatric pharmacokinetics of oral DSPI, it would be small and clinically insignificant. Another limitation is the number of participants. US FDA guidance for industry recommends a minimum of 12 patients for a bioequivalence study when evaluating a drug. Despite our best efforts to recruit volunteers without offering incentives, we could not obtain this number. However, our purpose was to describe the pharmacokinetics of DSPI given orally, and we believe our data had enough statistical power to contribute to the literature.

CONCLUSIONS

We conclude that oral DSPI is not bioequivalent to dexamethasone oral concentrate in a hospital formulary. It is, however, well absorbed. Given that studies to support the efficacy of DSPI in suspension have already been published, it is these authors' opinion that dexamethasone oral concentrate could likely be given at a lower dose with the same effect. Interestingly, the appropriate dose of dexamethasone for croup has been questioned in publications, with some advocating for a much lower dose with the same results.[14]

We believe DSPI given orally is absorbed sufficiently to continue its use in the ED.

This study opens the question whether other intravenous formulations in select circumstances can be administered orally, and the most appropriate methodology for testing this. Clinical studies have the ability to measure direct patient effects and are important when formulations are used off label. However, well-designed studies testing pharmacokinetic parameters appear to have equal potential. We hope this study motivates interest and further research into the use of intravenous formulations via the oral route.

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Abbreviations AHS, Atlantic Health System; AUC, area under the curve; Cmax, maximum concentration; DSPI, dexamethasone sodium phosphate for injection; ED, emergency department, EM, emergency medicine; F, bioavailability; HTLC-MSMS, high-turbulence liquid chromatography tandem mass spectrometry; MMMC, Morristown Memorial Medical Center; t1/2, half-life

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