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Evaluation of the Efficacy of a Onetime Injectable Dexamethasone Administered Orally in the Pediatric Emergency Department for Asthma Exacerbation

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OBJECTIVE This study assessed the efficacy of injectable dexamethasone administered orally in pediatric patients who presented to the emergency department with asthma exacerbation.

METHODS This was a retrospective study of patients 0 to 18 years of age who presented to and who were directly discharged from the emergency department at Moses H. Cone Memorial Hospital between September 1, 2012, and September 30, 2015, for the diagnosis of asthma or asthma exacerbation. Patients had to receive a onetime dose of injectable dexamethasone orally prior to discharge. Patients were followed for a 30-day period to identify the number of asthma relapses.

RESULTS Ninety-nine patients were included in this study. The average weight-based dose ± SD of dexamethasone was 0.35 ± 0.18 mg/kg (range, 0.08–0.62 mg/kg) and the actual dose ± SD was 10.58 ± 1.92 mg (range, 5–16 mg). Over a 30-day period, 6 patients (6%) had one repeated emergency department visit, 6 patients (6%) were admitted to the hospital, and 3 patients (3%) presented to an outpatient clinic for asthma-related symptoms.

CONCLUSIONS Injectable dexamethasone administered orally may be an efficacious treatment for asthma exacerbation in pediatric patients. A randomized control trial comparing injectable dexamethasone administered orally to other dexamethasone formulations/routes of administration should be performed to adequately assess the bioequivalence and effectiveness of the former formulation.

ABBREVIATIONS cm, centimeter; ED, emergency department; mg, milligram; mL, milliliter

KEYWORDS asthma; dexamethasone; injection; oral; pediatrics; pharmacokinetics; therapeutic equivalency

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Introduction

Asthma is an inflammatory airway disease that is one of the most common chronic diseases in childhood. Asthma exacerbation accounts for 2.3% of all pediatric emergency department (ED) visits in the United States annually.[1] In 2011, there were 611,000 ED visits by children younger than 15 years that were classified as asthma related.[2] Owing to their anti-inflammatory properties, systemic corticosteroids have long been a mainstay of treatment for asthma exacerbation. The Expert Panel of the National Asthma Education and Prevention Program's 2007 guidelines recommend using oral corticosteroids, as they have similar efficacy to the injectable formulations and require less invasive administration.[3,4] Prednisone and prednisolone are the most frequently used oral corticosteroids for treating asthma exacerbation, owing to their accessibility, low cost, and practitioners' experience with their use, but the short pharmacodynamic effect of these agents necessitates a 3- to 5-day course of therapy.[5] Dexamethasone has become a promising alternative, as its longer pharmacodynamic effect allows for onetime to two-time dosing to treat childhood asthma exacerbation in the ED with similar efficacy to a 3- to 5-day regimen of prednisone/prednisolone.[6,7]

Many institutions elect to administer injectable dexamethasone solution orally instead of using the commercially available oral dexamethasone solutions. Reasons for this practice may include patients' taste preference, smaller dose volume requirements for patients, and cost savings.[7] Recently, Toledo et al[8] performed a pharmacokinetic analysis of injectable dexamethasone given orally compared to dexamethasone oral concentrate in healthy adults. In this study, the mean ± SD $AUC_{0-\infty}$ of an 8-mg dose of injectable dexamethasone given orally and dexamethasone oral concentrate were 5591 ± 3075 and 6136 ± 2577 ng/dL/hr, respectively, with a 90% confidence interval of 79.0% to 105.2%. Mean C_{max} ± SD for injectable dexamethasone given orally and oral dexamethasone concentrate were 790 ± 229 and 942 ± 151 ng/dL, respectively, with a 90% confidence interval of 76.8% to 91.7%.[8] Both of these ranges fell outside of the accepted US Food and

Drug Administration range for bioequivalence of 80% to 125%.[9] The authors concluded that these 2 formulations of dexamethasone given orally are not bioequivalent.[8]

Despite the potential pharmacokinetic differences between these formulations, the overall absorption and systemic exposure of injectable dexamethasone given orally is believed to be clinically efficacious, and many health systems and practitioners have experience using it in this way.[8] Data are available demonstrating the efficacy of injectable dexamethasone given orally for pediatric patients with bronchiolitis,[10,11] but such data do not currently exist for asthma exacerbation in pediatric patients presenting to the ED. We therefore performed this study to evaluate the efficacy of this dexamethasone formulation in this latter population.

Materials and Methods

Patients and Study Design. Patients were included if they were between the ages of 0 to 18 years and presented to and were directly discharged from the ED at Moses H. Cone Memorial Hospital, which is a part of Cone Health, between September 1, 2012, and September 30, 2015, for the diagnosis of asthma or asthma exacerbation. Patients were excluded if they presented with a codiagnosis of croup, viral respiratory infection, community-acquired pneumonia, migraines, nausea/vomiting, strep pharyngitis, or bronchospasm, as these clinical conditions may confound the results of this study. Patients were also excluded if they received additional steroid therapy (i.e., prednisone or prednisolone) on day of presentation or at discharge. Since this study specifically examined the use of injectable dexamethasone given orally, patients who had received the commercially available oral formulations or the intravenous formulation given parentally or intramuscularly were excluded.

The primary objective of this retrospective study was to assess the efficacy of injectable dexamethasone administered orally in pediatric patients who presented to the ED with asthma exacerbation. Resolution of asthma symptoms was considered successful if a relapse was not documented within 30 days of medication administration. Relapse was defined as patients who presented to either the outpatient clinic or the ED or who were hospitalized for asthma-related symptoms within that 30-day window. This study also evaluated the average dose of dexamethasone to determine if patients received an adequate dose of this medication prior to discharge.

Data Collection. After gaining approval from the Institutional Review Board, a report was generated via the electronic medical record, listing all patients who had received all formulations of dexamethasone in the ED. A retrospective chart review was performed on the patients who had met the inclusion criteria. The baseline demographics, dosage and drug route of dexamethasone, and rate of relapse were documented.

Table. Baseline Characteristics

Characteristic	Result
Age, yr	
Mean ± SD (range)	8.4 ± 3.8 (2–18)
Male sex, No. (%)	54 (54.5)
Weight, kg	
Mean ± SD (range)	40.2 ± 23.7 (11–122.5)
Race, No. (%)	
African American	73 (73.7)
Caucasian	22 (22.2)
Other	4 (4.04)
Total dose, mg	
Mean ± SD (range)	10.6 ± 1.9 (5–16)
<10, No.	10
10, No.	64
>10 and <16, No.	18
16, No.	7
Weight-based dose, mg/kg	
Mean ± SD (range)	0.35 ± 0.18 (0.08–0.62)
<0.3, No.	42
0.3, No.	5
>0.3 and <0.6, No.	32
0.6, No.	14

kg, kilogram; mg, milligram

The site of follow-up for asthma relapses in a 30-day period was also documented (i.e., outpatient clinic, ED, and hospital admission).

Statistical Analysis. STATA Statistics/Data Analysis, Release 12.1 (College Station, TX) was the statistical software used in the data analysis of this study. As there was no comparator group, the mean, median, range, and standard deviation were reported for the baseline characteristics. For the primary outcome, the frequency was calculated and the percentage occurrence was recorded. Unless otherwise noted, data are presented as mean ± SD.

Results

From September 2012 to September 2015, a total of 1754 pediatric patients presented to the ED at our institution and received dexamethasone for asthma exacerbation. Of those patients, 1655 were excluded as they did not meet the inclusion criteria; most of these patients were diagnosed with bronchiolitis or croup. As a result, 99 patients were included in this cohort. The baseline characteristics of the study population are noted in the Table. The mean age was 8.35 ± 3.82 years and the average weight was 40.21 ± 23.66 kg.

Most patients were African American. The average weight-based dose of dexamethasone in 93 patients was 0.35 ± 0.18 mg/kg. Five patients were dosed at 0.3 mg/kg, while 14 patients were dosed at 0.6 mg/kg. The actual dose was 10.58 ± 1.92 mg. Seven patients received the maximum recommended dose of 16 mg, while 64 patients received 10 mg. The dose in mg/kg was not calculated in 6 patients because their weight was not documented at the time of administration. The outcomes for these 6 patients were included in the analysis of the primary outcome.

Over a 30-day follow-up period, 6 patients (6%) had 1 repeated ED visit (none of whom were hospitalized), 6 patients (6%) were admitted to the hospital, and 3 patients (3%) presented to an outpatient clinic for asthma-related symptoms. Of the patients with repeated ED visits, none received the maximum dose of 0.6 mg/kg but one of them received a 16-mg dose (range, 0.12–0.53 mg/kg and 6–16 mg). Only 1 patient who was admitted to the hospital and 1 patient who presented to the outpatient clinic received the recommended 0.6-mg/kg dose (range, 0.17–0.6 mg/kg and 7–16 mg; 0.11–0.6 mg/kg and 9–12 mg, respectively). In general, patients received a maximum dose of 10 mg rather than the recommended 16 mg. The time of relapse ranged from 3 to 30 days for repeated ED visits, 1 to 20 days for hospital admission, and 2 to 10 days for outpatient clinic visits. Of those patients who had a visit due to relapse, it did not appear that the rate of relapse was related to the weight-based dose that was administered at the initial ED encounter; however, this cannot be concluded as this study was not powered to identify the optimal drug dose.

Discussion

To our knowledge, this is the first study looking at the efficacy of using injectable dexamethasone given orally in the ED for the treatment of pediatric asthma exacerbation. Our results indicated that the failure rates from this formulation of dexamethasone were low, as there were a limited number of ED revisits, clinic visits, and hospitalizations within 30 days of medication administration. Although the pharmacokinetic data for injectable dexamethasone given orally showed that it may not be bioequivalent to the commercially available oral concentrate at similar doses in adult patients,[8] it appears to be clinically efficacious when given as a single dose to pediatric patients who presented to the ED with asthma exacerbation in our cohort. Since this aforementioned pharmacokinetic study was only in adults, it will be interesting to see if the same outcomes can be observed in the pediatric population.

While prednisone and prednisolone have been used historically as the oral steroids of choice for treating pediatric asthma exacerbation, previous studies have shown that dexamethasone offers comparable efficacy. Altamimi et al[12] performed a prospective, double-blind study of 110 pediatric patients who presented to the ED with asthma exacerbation. This study showed that a single dose of oral dexamethasone (0.6 mg/kg) was non-inferior to a twice-daily, 5-day course of oral prednisone (2 mg/kg/day) in the amount of time for patient-assessed breathing to return to baseline and improvement in their peak expiratory flow score. Cronin et al[6] followed 245 pediatric patients who presented to the ED for an asthma exacerbation. This study found that the outcomes associated with physician-scored asthma symptoms 4 days after ED presentation were not any worse when comparing a single dose of oral dexamethasone (0.3 mg/kg) to a 3-day course of oral prednisolone (1 mg/kg/day).[6] In 2001, Qureshi et al[7] compared a 2-day course of dexamethasone (0.6 mg/kg/day) to a 5-day course of prednisone (1 mg/kg/day) for treating acute asthma exacerbation in 533 children. No significant difference was observed between the 2 groups in regard to relapse rate, hospitalization rate, and symptom persistence past 10 days of initial presentation. Also, the dexamethasone group had significantly less vomiting and non-compliance and had a lower rate of children missing >2 days of school owing to disease exacerbation.[7] Rehrer et al[13] recently compared a single dose of dexamethasone 12 mg plus placebo to 5 days of prednisone 60 mg in adults with mild to moderate asthma exacerbation. Non-inferiority was unable to be proven among single-dose dexamethasone and 5-day prednisone for relapse rates; however, when compared to national rates of historical relapses, dexamethasone performed substantially better than prednisone and was found to be superior to prednisone.[13] Similarly, Meyer et al[14] performed a meta-analysis of 6 studies and found that a 5-day course of prednisone was not superior to a 1- to 2-day course of dexamethasone in treating children with mild to moderate asthma exacerbations.

The efficacy of dexamethasone for asthma exacerbation may translate to cost savings as well. A 2012 cost-effectiveness study[15] showed that using a 2-day course of dexamethasone could save money over using the standard 5-day course of prednisone or prednisolone by reducing medication non-compliance and therefore ED relapse and hospitalization. When both relapse and rates of hospitalization were accounted for, an estimated $7000 could be saved per 100 patients by administering 2 days of dexamethasone compared to 5 days of prednisone or prednisolone.[15]

Although dexamethasone provides similar efficacy, benefits may exist with its use when compared to prednisone and prednisolone. The onetime or two-time dosing of dexamethasone can potentially prevent non-compliance and reduce readmission rates, as parents will not have to obtain an additional prescription after discharge. The shorter duration of therapy is due to dexamethasone's pharmacodynamic/metabolic effect of 36 to 72 hours and an approximate 6-fold higher potency than that of prednisone.[14] Also, the oral sus-

pension formulations of prednisone and prednisolone lack palatability, which may deter compliance in pediatric patients. A single-blind taste test by 39 children (mean age 7.1 years) showed that children preferred dexamethasone concentrate over prednisolone liquid overall by rating them visually on a 10-cm scale. The mean score for dexamethasone was 8 cm, while that for prednisolone was 5 cm.[16]

Dexamethasone can be an efficacious alternative to prednisone or prednisolone for pediatric asthma exacerbation, but potential barriers exist in regard to administering the currently available dexamethasone oral formulations to pediatric patients. The compounded injectable solution for oral use may help overcome these barriers. The commercially available 1-mg/mL Intensol concentrate contains 30% w/w alcohol, which may affect taste and tolerability in infants and children and make it difficult to administer despite diluting it with semisolid foods or drinks as the manufacturer recommends.[17] Conversely, the solution for injection has been successfully compounded into a 1-mg/mL suspension by using an appropriate commercially available sweetened suspending vehicle,[18] and institutions such as ours have experience in mixing injectable dexamethasone solution with a small amount of juice to deliver the required dose. These methods may help mask the medicinal taste and improve tolerability. Dose volume is another concern when administering liquid medications to children. To deliver a 10-mg dexamethasone dose of the commercially available 0.5 mg/5 mL oral elixir, a volume of 100 mL is required. An extemporaneously compounded formulation using the 10-mg/mL injectable solution would require only 1 mL, a 100-fold reduction in the dosing volume. As children are usually difficult to administer oral medications to, this smaller volume could provide a huge benefit by ensuring that they receive the entire dose.

Another benefit of using the injectable dexamethasone solution in lieu of the commercially available elixirs or Intensol concentrate is cost. Oral dexamethasone is commercially available as an elixir (0.5 mg/5 mL, Morton Grove Pharmaceuticals, Morton Grove, IL) and an Intensol concentrate (1 mg/mL, Roxane Laboratories, Columbus, OH). These formulations cost $63.69 per 240 mL and $28.98 per 30 mL, respectively,[19] an average cost of $0.53/mg and $1.04/mg, respectively. Dexamethasone sodium phosphate solution for injection is commercially available in 2 concentrations: 4 mg/mL (American Reagent Inc, Shirley, NY) and 10 mg/mL (West-Ward Pharmaceutical Corp, Eatontown, New Jersey), the latter being the concentration that is more often administered orally. The 10-mg/mL vials can be purchased for approximately $4.99 each,[19] an average price of approximately $0.05/mg. This is 10- to 20-fold cheaper than either of the commercially available oral formulations and could potentially provide significant cost savings that would benefit many institutions, although it should be noted that the average cost for different formulations may vary by acquisition contracts.

This study has several limitations. Of the 6 patients who had repeated ED visits within 30 days of their initial visit, 5 received a dose of dexamethasone that was under the usual recommended dosing of 0.6 mg/kg for asthma exacerbation. Only 14 patients overall received at least the recommended dose of 0.6 mg/kg (maximum: 16 mg/dose), with most patients receiving a onetime 10-mg dose regardless of their weight. The 7 patients who received 16 mg of dexamethasone received the maximum dose based on weight. The significant number of patients who received only 10 mg might have been due to the fact that dexamethasone 10 mg is the recommended maximum dose for other indications such as airway edema in the pediatric population, and it is also the usual single maximum dose for adults. The clinicians might not have known that the single maximum dose can go up to 16 mg/dose for asthma exacerbation. As there is currently no randomized controlled trial that compares the efficacy of 10 mg/dose with 16 mg/dose of dexamethasone for asthma exacerbation, the former may be an adequate dose clinically for this indication. Nonetheless, this discrepancy in dosing may make interpreting our results difficult. Though, it is important to note that since these doses were universally low, our relapse rates might have been artificially higher than if all patients had received the recommended dose of dexamethasone.

As with any retrospective study, our study was unable to control for other interventions that might have occurred between the time the patient left the ED and the time of evaluation of the relapse. This study did not evaluate environmental factors that might have impacted asthma control, such as elimination of smoke or pet dander exposure, nor did it consider the appropriateness of patients' asthma medications; however, previous asthma studies[12–14] also did not take these factors into consideration. At our facility, counseling on avoidance of environmental factors is a major part of our standard asthma education, so it is a possibility that those patients who were included in this study had lifestyle changes that prevented them from having further exacerbations.

Another limitation of this study was the inability to record repeated clinic visits, ED visits, and hospital admissions outside of the Cone Health system. Cone Health comprises a large network of outpatient physicians that also uses EPIC as the electronic medical record and our included patients mostly got their care within this network. In other words, if the included patients had follow-up visits at their primary care physicians' office, most of those cases would have been captured since those physicians use the same medical record system. However, patients who presented elsewhere in the 30-day window after the initial visit would not have been accounted for. This potentially could have falsely

lowered the rate of the primary endpoint in our analysis. The last potential limitation is the small sample size of this study. Although our cohort had only 99 patients, we accounted for potential confounders by excluding patients codiagnosed with croup and respiratory tract infections to ensure that the rate of relapse was not affected by inadequately treated or misdiagnosed infections and other clinical conditions.

While the overall low rates of repeated ED visits, hospital admissions, and clinic visits point toward the efficacy of administering injectable dexamethasone orally for pediatric asthma exacerbation, it is difficult to determine its relative efficacy without a comparator. A head-to-head randomized trial comparing injectable dexamethasone given orally to dexamethasone oral solution, dexamethasone tablet formulation, and intravenous/intramuscular dexamethasone using the same endpoints would be beneficial in further assessing the appropriateness of interchanging these formulations for pediatric patients with asthma exacerbation who are to be discharged from the ED.

Conclusions

Although a previous pharmacokinetic study of injectable dexamethasone given orally in adults questioned the difference in its bioavailability, our retrospective study demonstrated that injectable dexamethasone given orally as a onetime dose for asthma exacerbation in pediatric patients presenting to the ED appears to be efficacious in preventing relapse within 30 days of medication administration. A randomized control trial comparing injectable dexamethasone administered orally to other formulations/routes of administration should be performed to adequately assess the bioequivalence and effectiveness of these treatments for asthma exacerbation in this population.

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