International Journal of Pediatric Otorhinolaryngology (2008) 72, 97–102

ELSEVIER

International Journal of Pediatric Otorhinolaryngology

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Pharmacokinetics of CIPRODEX® otic in pediatric and adolescent patients☆

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Received 10 May 2007; received in revised form 24 September 2007; accepted 28 September 2007
Available online 26 November 2007

KEYWORDS
Ciprofloxacin;
Dexamethasone;
Pharmacokinetics;
Tympanostomy tubes;
Acute otitis externa;
Acute otitis media

Summary

Objective: Describe the pharmacokinetics of ciprofloxacin and dexamethasone after administration of CIPRODEX® Otic Suspension (CIP/DEX) into the middle ears of children.
Design: Open-label, single-dose, pharmacokinetic studies, administering four drops of CIP/DEX instilled into each middle ear through the tympanostomy tubes immediately following tube placement. Blood was collected for 6 h and analyzed for ciprofloxacin and dexamethasone concentrations using a validated liquid chromatography and tandem mass spectrometry (LC/MS/MS) method.
Setting: The study was conducted through a referral pediatric otolaryngology practice with actual surgical procedures performed in an ambulatory care center.
Patients: Twenty-five randomly selected patients, 1–14 years of age (mean age, 5 years), receiving tympanostomy tubes.
Results: Peak ciprofloxacin plasma levels were observed at about 1 h, with a mean C_{max} of 1.33 ± 0.96 ng/mL (range <0.5–3.45 ng/mL) and an estimated half-life of 3.0 ± 1.2 h. Peak dexamethasone plasma levels were observed within 2 h with a mean C_{max} of 0.90 ± 1.04 ng/mL (range <0.05–5.10 ng/mL) and an estimated half-life of 3.9 ± 2.9 h.
Conclusion: These results demonstrated low systemic exposure of ciprofloxacin and dexamethasone following topical otic administration in pediatric patients.

☆ Presented in part at the American Society for Pediatric Otolaryngology Annual Meeting, Phoenix, AZ, May 2004.
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0165-5876/$ – see front matter
doi:10.1016/j.ijporl.2007.09.017

1. Introduction

CIPRODEX® Otic Suspension (Alcon Laboratories Inc., Fort Worth, TX) (CIPRODEX® is a registered trademark, of Bayer AG, licensed to Alcon Inc.) (CIP/DEX) is a combination of ciprofloxacin (0.3%, w:v) and dexamethasone (0.1%, w:v) approved in the United States for the topical treatment of acute otitis externa and acute otitis media in pediatric patients with tympanostomy tubes [1].

The pharmacokinetics and disposition of ciprofloxacin and dexamethasone after systemic administration have been well studied in adults. However, data on ciprofloxacin and dexamethasone in children are limited specifically to topical dermatological or ocular administration. One previous study has evaluated the pharmacokinetics of ototopically administered ciprofloxacin 0.3% solution alone in children [2]. After three times daily dosing for 7 days to children with tympanostomy tubes and otorrhea, ciprofloxacin plasma concentrations, both pre-dose and 1 h after the morning dose on Day 7, were below the assay quantitation limit (<5 ng/mL). No previous ototopical pharmacokinetic data on dexamethasone was found in the literature.

We examined the pharmacokinetics of ototopically administered CIP/DEX in children at the time of tympanostomy tube insertion in an open-label clinical trial. This study was conducted as a regulatory requirement for the approval of CIP/DEX. This is the first report in the literature of levels of ciprofloxacin and dexamethasone obtained following topical administration of CIP/DEX to the middle ears of children.

2. Methods

Two pharmacokinetic studies (Alcon studies C-00-68 and C-02-58) were conducted according to good clinical practices and were approved by institutional review boards. The studies were of identical clinical design and combined in order to accumulate the total number of patients required for regulatory approval. All patients or caregivers signed informed consent prior to study participation.

An outline of the study is provided in Table 1. To be eligible for study entry, patients had to be candidates for tympanostomy tube placement based on the criteria outlined in the clinical practice guideline for otitis media of the American Academy of Pediatrics [3]. These children experienced either multiple episodes of recurrent acute otitis media, or middle ear effusion of prolonged duration. All patients underwent myringotomy in the operating room under general anesthesia. An Armstrong grommet tympanostomy tube was placed in the myringotomy incision, and four drops of CIP/DEX were instilled through the tube. The identical procedure was then performed on the opposite ear. Blood samples were drawn from the patients' dedicated intravenous line prior to the myringotomy and after the induction of anesthesia, then immediately after the drops in the second ear were instilled, and then again at 15 min, 30 min, 1 h, 2 h, 4 h, and 6 h post-operatively.

Table 1 Summary of the pharmacokinetic study design for CIP/DEX

Design	Phase I, open-label, randomized, single-dose study
Duration	1 day duration with a follow-up visit
Treatment	Topical otic CIP/DEX
Regimen/dose	A single-dose of four drops per ear instilled through the tympanostomy tubes after insertion. The total dose was equal to 280 μg dexamethasone and 840 μg ciprofloxacin
Sampling times	0 h, 0.25 h, 0.5 h, 1 h, 2, h 4 h and 6 h post-dose

Plasma concentrations of ciprofloxacin and dexamethasone were determined using validated high-performance liquid chromatography/tandem mass spectrometry (HPLC/MS/MS) method. The working range of quantification for ciprofloxacin was from 0.50 ng/mL to 100 ng/mL, and that for dexamethasone was from 0.050 ng/mL to 50.0 ng/mL.

The pharmacokinetic assessments in each study included plasma drug concentrations at each sampling time and the model-independent derived

Table 2 Demographics

	N	%
Age (years)		
Infants and toddlers (0–1 year)	4	16.0
Children (2–11 years)	18	72.0
Adolescent (12–17 years)	3	12.0
Sex		
Male	21	84.0
Female	4	16.0
Race		
Caucasian	17	68.0
Black	4	16.0
Hispanic	3	12.0
Other	1	4.0
Ears dosed		
Both ears	25	100.0