Ofloxacin Otic Solution in Patients With Otitis Media

An Analysis of Drug Concentrations

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Objective: To measure the concentration of ofloxacin in otorrhea, serum, and middle ear mucosa after topical administration of 0.3% ofloxacin otic solution.

Design: Study of 0.3% ofloxacin otic solution administered in a single dose of 0.5 mL in adults or 0.25 mL in children with chronic suppurative otitis media and perforated tympanic membrane, with serial sampling of otorrhea and serum up to 8 hours after dosing and middle ear mucosa up to 2 hours after dosing.

Setting: Three hospitals in Kagoshima, Japan.

Patients: Thirty-eight patients (age range, 3-81 years) with chronic suppurative otitis media and perforated tympanic membrane; 20 patients had sampling of otorrhea and serum and 18 patients (who required middle ear surgery) had middle ear mucosa and serum sampling.

Results: High concentrations of ofloxacin were measured in otorrhea samples taken immediately after dosing, followed by a rapid, nonlogarithmic decline. Elimination of the drug through otorrhea was believed to be related to loss from the application site with ear drainage, rather than to biologic mechanisms. Maximum concentration of ofloxacin in otorrhea was seen at the initial sampling time, 30 minutes after dosing, with concentrations measured up to the last sampling at 8 hours. Very low concentrations of ofloxacin were found in serum after topical administration of the drug. Concentrations were not detected in serum samples of most of the patients. The highest concentration measured was 10 ng/mL. Drug concentrations were detected primarily in samples obtained up to 1 hour after the dose was administered. Mucosal drug concentrations were highly variable, ranging from nondetectable to 602 µg/g. For the 6 bacterial strains isolated from the middle ear, the highest minimum inhibitory concentration of ofloxacin was covered by otorrhea drug concentrations measured at up to 8 hours after dosing in some patients. No adverse events were observed. No clinically significant adverse changes in laboratory test results or audiometric results were observed.

Conclusions: Drug concentrations were high in otorrhea, very low or not detected in serum, and highly variable in middle ear mucosa. Nonbiologic loss of the drug with the ear drainage through the external auditory canal and eustachian tube was probably related to the high concentration in otorrhea samples. Drug concentrations in middle ear mucosa suggest that the drug reaches the infection site.


OFLOXACIN IS a synthetic, broad spectrum antimicrobial quinolone. This fluorinated carboxyquinolone exerts antibacterial activity via antagonism of the interaction between DNA gyrase (a topoisomerase II peculiar to bacteria) and DNA.

Administered systemically, ofloxacin has demonstrated its efficacy in the treatment of chronic middle ear infections in Japan and Europe.1,2 The efficacy of ofloxacin is attributed to its penetration into the tissues of the ear, nose, and throat, and the sensitivity of the pathogens usually encountered in these infections (eg, Pseudomonas aeruginosa, Staphylococcus aureus, and Proteus species).12 In addition to efficacy against pathogens causing acute upper respiratory tract infections such as Streptococcus pneumoniae, Haemophilus influenzae, and Moraxella catarrhalis.3

Topical antimicrobial treatment of patients with infections of the external and middle ear has been used with caution in patients with questionable integrity of the tympanic membrane because of the ototoxic effects of many of these agents. However, 0.3% ofloxacin otic solution was demonstrated to be efficacious without ototoxic effects in preclinical and clinical investigations4-7 and, in 1992, was approved in Japan for the treatment of otitis externa and otitis media.
PATIENTS, MATERIALS, AND METHODS

Three study sites, all hospitals in Kagoshima, Japan, enrolled patients. Ethical committee approval of the protocol and the informed consent document was granted at each institution. Eligible were patients of either sex and any age, who were hospitalized or ambulatory, had a diagnosis of chronic suppurative otitis media and a perforation or patent ventilation tube in the tympanic membrane, and had provided written informed consent (or parental consent for children). Group A eligibility additionally required a persistent purulent discharge (sufficient for sampling). Group B patients were eligible if they required middle ear surgery (but a discharge was not required). Excluded from eligibility for either group were patients who had chronic petrositis or cholesteatomatous otitis, had a concurrent systemic infection requiring any antibiotic, had been treated with any local or systemic antibiotic within 3 days prior to study entry or with a fluoroquinolone within 7 days, had a known allergy to quinolones, had participated in another clinical trial within 30 days prior to study entry, were receiving cancer chemotherapy, or were pregnant or nursing. Prior to enrollment, patients were screened by X-P (Law projection and Stenvers projection) and by examination of otorrhea for cholesterol crystals to exclude those with cholesteatomatous otitis. Thirty-eight patients were enrolled consecutively in this study from June 23, 1994, to November 24, 1994. All enrolled patients completed the study, although deviations from the pharmacokinetic sampling schedule occurred.

Of the 38 patients, 20 had sampling of otorrhea and serum (group A) and 18 had sampling of middle ear mucosa and serum and were patients who required middle ear surgery (group B); 19 were male and 19 were female. Patients ranged in age from 3 to 81 years. Four were children younger than 12 years (3, 5, 8, and 9 years). All 38 patients had otorrhea media. Persistent purulent discharge was documented only in group A. In group B, the surgical interventions (during which middle ear mucosa samples were collected) were tympanoplasty in 17 patients and myringoplasty in 1. Granulation tissue was observed in the middle ear cavity of patients undergoing tympanoplasty, but not in the one undergoing myringoplasty. Mastoids were opacified only in patients undergoing tympanoplasty.

Ofloxacin, 0.3%, otic solution was administered in a single dose (10 drops [0.5 mL] in patients aged ≥12 years or 5 drops [0.25 mL] in patients <12 years) into the affected study ear to the 2 groups of patients, all with chronic suppurative otitis media and perforated tympanic membrane. The 20 patients in group A did not require middle ear surgery, whereas the 18 patients in group B did. In group A, concentrations of ofloxacin in otorrhea and serum were evaluated. In group B, concentrations of ofloxacin in middle ear mucosa and serum were evaluated.

In group A, otorrhea samples were to be taken from the affected study ear just prior to dosing, at 30 minutes after dosing, and at 2 or more additional time points (2, 4, 6, and 8 hours) after dosing. Serum samples were to be drawn just prior to dosing, 30 minutes after dosing (adults only), and at the time of the last otorrhea sample. Safety parameters were to be assessed by means of a physical examination and clinical laboratory tests before and after treatment, and by reports of adverse events. In addition, audiological examinations were to be performed before and after treatment.

In group B, middle ear mucosa samples were to be taken at 1 and 2 hours after dosing. Serum samples were to be drawn just prior to dosing and at 1 and 2 hours after dosing. Safety assessments consisted of a physical examination and clinical laboratory tests before and after treatment and reports of adverse events.

Drug administration took place with the patient recumbent or lying with the head on the side, affected ear up. Instillation took place by letting the drops fall into the entrance of the external ear canal while pulling the auricle up and back to facilitate penetration into the tympanic cavity through the tympanic membrane. The patient remained in position for about 10 minutes. If the infection was bilateral, only 1 ear was treated with ofloxacin and assessed. In group A, otorrhea samples were collected by absorption onto paper disks, placed in microtubes, and venous blood samples were collected. In group B, intratympanic mucous membrane or granulation samples were collected during a surgical intervention and placed in microtubes; venous blood samples were collected at the same time points. Samples were stored and shipped at −20°C. Microtubes (containing a paper disk for otorrhea samples) had been preweighed and were weighed again after sampling, together with the otorrhea (with paper disk) or mucous membrane sample, thawed at room temperature, within 4 days after retrieval of the sample. An electronic balance was used and the weight, in grams, was measured to the fourth decimal place.

Measurement of drug concentrations in the samples was conducted by high performance liquid chromatography. The detectable ranges were 1 to 100 ng/mL in serum, 0.5 to 300 µg/g in middle ear mucosa, and 1 to 3500 µg/g in otorrhea.

Microbiological testing was performed by streaking otorrhea specimens on culture medium for isolation and identification of organisms. The minimum inhibitory concentration of ofloxacin has been determined by the standard agar dilution method.9

Pure tone audiometry of air and bone conduction was to be performed before and after dosing in group A and the results compared. Frequencies of the tone were 125, 250, 500, 1000, 2000, 4000, and 8000 Hz. Averages of 4 and 6 frequencies were calculated for comparisons.

RESULTS

No adverse events were reported by the patients or observed by the investigators during or after dosing. The results of clinical laboratory tests indicated that, although specimens were not available for all planned data points, there were no clinically significant adverse changes associated with treatment with ofloxacin otic solution.

Of the 38 patients, 4 were nonevaluable (2 in group A and 2 in group B). Five other patients had minimal ofloxacin concentrations in their predose otorrhea samples. This might be attributed to probable, but undocumented, prior treatment with the drug.
Table 1 shows ofloxacin concentrations in otorrhea and serum in group A (18 patients) measured at the time points indicated. Table 2 shows ofloxacin concentrations in middle ear mucosa and serum in group B (16 patients) measured at the time points indicated. The required number of samples were not obtained from all patients, and there were deviations from the specified sampling times. It was not always feasible for the investigators to obtain samples at time points stated in the protocol. (Predose samples were not taken for patient K-07 in group A and patient I-02 in group B.)

**GROUP A**

The maximum otorrhea drug concentrations were seen at 15 to 30 minutes after administration of the dose (the initial sampling time), and ranged from 388.8 to 2849.8 µg/g at 30 minutes. The upper end of the range was close to the concentration of the drug solution itself, which was 3000 µg/mL. A rapid, nonlogarithmic decline in drug concentration was seen, although for the 2 patients with otorrhea samples at 8 hours, the concentrations were 404.6 and 653.0 µg/g. Nonbiologic loss of the drug with the ear drainage through the external auditory canal is believed to be related to the high concentration in otorrhea samples.

Serum sampling was inconsistent and not done in several patients. Drug concentrations were below the limit of detection in most of the serum samples. At 30 minutes after the dose administration, 4 of the 7 patients sampled had concentrations ranging from 1.4 to 10.0 ng/mL. Drug concentrations were also detected at 1, 4, and 6 hours, in 1 case each, at lower levels.

Pretreatment and posttreatment audiometric data were available for 3 patients. None of these patients showed hearing loss after treatment with ofloxacin otic solution.

In microbiological testing, 7 organisms were isolated from the middle ear of 6 patients: *S aureus*, *Alcaligenes* species (2 isolates), *Corynebacterium* species, *Alcaligenes xylosoxydans*, *Staphylococcus epidermidis*, and fungi. The minimum inhibitory concentrations of these organisms ranged from 0.39 µg/mL (*S aureus*) to 100 µg/mL (*A xylosoxydans*). The 2 patients who had 8-hour otorrhea samples had ofloxacin concentrations that covered this range of minimum inhibitory concentrations.
Middle ear mucosa concentrations had a high patient-to-patient variability among the 16 patients evaluated. Concentrations were not detected in any samples from 5 patients, but ranged from 253 to 602 µg/g in 3 patients.

Serum drug concentrations were measured with more consistency in group B than in group A. Concentrations were very low (up to 4.1 ng/mL at 1 hour) or not detected.

We present the findings of a study of 0.3% ofloxacin otic solution administered in a single dose of 0.25 mL in children or 0.5 mL in adults with chronic suppurative otitis media and perforated tympanic membrane. Drug concentrations were high in otorrhea, very low or not detected in serum, and highly variable in middle ear mucosa. The variability of findings of middle ear mucosal sampling might be attributed to factors such as the function of the eustachian tube and the site of the mucosal biopsy. The elimination of the drug in otorrhea was probably not due to biologic mechanisms. Because the ear canal was not completely evacuated and dried between sampling points, the reported concentrations may represent admixtures of concentrations representing middle ear and auditory canal concentrations from previous time points. Although this study was not designed to assess efficacy, middle ear mucosa sampling suggested that ofloxacin was present at the site of infection at therapeutic concentrations in at least a few patients. Variability may be due to the site of the mucosal biopsy relative to the pooling of drug and secretions in the middle ear. The dose was well tolerated, with no reports of adverse events.

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