Failure of Fluorescence to Reveal Middle Ear Penetration of Quinolone Drops

Graham T. Whitaker, MD; William O. Collins, MD; Patrick J. Antonelli, MD

Objective: To evaluate the utility of fluorescence to assess penetration of quinolone ear drops (EDs) through tympanostomy tubes (TTs), the middle ear, eustachian tube, and into the oropharynx.

Design: Before-and-after trial.

Setting: Academic, tertiary care hospital.

Patients: Young children undergoing TT placement for otitis media and adolescents or adults undergoing repair of tympanic membrane (TM) perforations were included.

Interventions: Fluorescence of ofloxacin otic solution and serial dilutions was assessed with a Wood's lamp in vitro. Passage of ototopically administered ofloxacin into the pharynx was assessed in patients at the time of TT placement or TM repair. The oropharynx was visualized for fluorescence with a UV light for up to 2 hours after otic instillation.

Main Outcome Measure: Oropharyngeal fluorescence.

Results: Ofloxacin otic fluorescence was visible at up to a 1:4 dilution. Fluorescence was confirmed in vivo by placing 1 drop of ofloxacin into the posterior pharynx and visualizing it transorally. Fluorescence was not identified in any of 20 patients after TT placement and in any of 6 patients prior to tympanoplasty. Two patients undergoing tympanoplasty reported tasting the EDs.

Conclusion: Fluorescence is not a satisfactory method of assessing quinolone ED penetration through TTs and TM perforations, the middle ear, and into the nasopharynx.


Fluoroquinolone ear drops (EDs) have been proven efficacious in the treatment of post-tympanostomy tube (TT) otorrhea.1 This has led to the presumption that EDs enter the middle ear space, but not all EDs penetrate TTs equally.2 Ohyama et al3 found high concentrations of ofloxacin in otorrhea samples after instillation of a single dose. However, samples were taken through the same tympanic membrane (TM) defect (ie, a perforation or a TT) as administration, not at a more removed site (eg, mastoid or eustachian tube) that might truly reflect penetration of the ED. Their analysis of middle ear mucosa samples taken 1 to 2 hours after instillation into ears with or without active otorrhea revealed highly variable concentrations. Mills et al4 reported that the presence of middle ear effusion can impact middle ear penetration of EDs through TTs.

A number of observations suggest that deep penetration of EDs throughout the tubotympanum may not be necessary to yield clinical efficacy. It has long been known that instillation of a single dose of ED5 and TT coatings6 can significantly reduce the rate of post-TT otorrhea. A single exposure of a TT to an ED can significantly reduce bacterial growth on and around the TT.7 If improved clinical outcomes can be achieved with modifications in and around the TT, novel therapeutic strategies might be possible. Elucidation of the extent of ED penetration in the presence of otitis media may help to direct therapeutic investigation.

Fluoroquinolones are the only agents currently approved by the US Food and Drug Administration for instillation into the middle ear. Fluoroquinolones fluoresce, or emit light in the visible range, on exposure to UV light. Ciprofloxacin and ofloxacin possess fluorescent excitation peaks at 330 nm and 380 nm, respectively,8,9 which is within the spectrum of Wood's lamps and most commercially available UV lights. Fluorescence of otic drops in the pharynx with UV light has been described.10 To our knowledge, quinolone fluorescence has not been formally investigated as a means of assessing the penetration of quinolone EDs through TTs, the tubotympanum, and into the pharynx. The purpose of this study was to assess the use of utility of fluorescence to demonstrate the penetration of quinolone EDs through a TT or perforation, middle ear, eustachian tube, and into the pharynx.
METHODS

HUMAN PARTICIPANTS

This study was approved by the institutional review board, and informed consent was obtained from all participants or their legal guardians prior to partaking in the study. All children (<12 years old) undergoing TT placement and adolescents or adults (≥12 years old) undergoing repair of TM perforations were eligible for participation. Patients were enrolled based on availability of the lead investigator (G.T.W.). Children receiving TTs were included without regard to middle ear status or indication for the TTs. This group represented cases typical for ED administration. Adolescents and adults undergoing tympanoplasty were selected for inclusion in the study only if their preoperative evaluation suggested a TM perforation without evidence of otorrhea, granulation tissue, or cholesteatoma. This group was biased toward patients who were more likely to have unimpeded penetration of the ED through the TM, thereby serving as the best possible positive control. This older group could also relate other changes that might suggest penetration of the ED, such as a change in taste.

PROOF OF CONCEPT

A hollow cylinder (10 cm deep and 2 cm in diameter) was constructed of heavy stock nonreflective paper to approximate the oropharyngeal dimensions. A flat backdrop representing the posterior oropharyngeal wall was made using pink paper covered with common plastic wrap. This background was chosen to simulate color and typical reflection due to oropharyngeal secretions. A series of 1:2 dilutions up to 1:16 of 0.3% ofloxacin (Bausch & Lomb, Tampa, Florida) was tested by placing 1 drop of the solution on the prepared background, placing the cylinder over the drop, checking for light leaks around the base of the cylinder using a penlight, and attempting to visually detect fluorescence using the handheld UV light. Each solution was examined 3 separate times against a fresh background in total darkness and with typical operating room ambient lighting before advancing to a more dilute concentration. Plain tap water was used as the control solution. Both a 365-nm long-wave UV Wood’s lamp (model EA-140; Spectroline, Westbury, New York) and a compact UV light (Blacklight 360, Can You Imagine, Chatsworth, California) were used to confirm fluorescence. A second compact UV light (Blacklight 360, Can You Imagine) was modified to reduce the light source’s intraoral profile and thereby improve transoral visualization of the oropharynx. The commercial product was modified by extending the UV bulb from the device through a rigid, opaque polyvinylchloride tube 1 cm in diameter. The end of the tube was capped with a clear plastic covering, and the tube was secured to the device base.

In addition to the in vitro dilutional tests, 1 drop of ofloxacin ED was placed in the oropharynx of a participant to simulate maximal potential in vivo fluorescence (Figure).

PATIENT TESTING

Patients receiving tympanostomy tubes underwent surgery according to the attending surgeon’s standard technique. Middle ear aspiration was typically performed until the myringotomy yielded no additional effusion. Ototopical administration consisted of 10 drops of ofloxacin otic, 0.3% solution (Bausch & Lomb), applied to each external auditory canal followed by 5 tragal pumps, which has been shown to significantly increase penetration of ototopical preparations through tympanostomy tubes. Patients were examined for oropharyngeal fluorescence before the ED was administered, immediately after administration, and every 15 minutes, for up to 2 hours, until discharge from the surgical facility or until fluorescence was seen. Fluorescence examinations of the oropharynx were performed in ambient light, using a UV light and tongue depressor.

Patients undergoing tympanoplasty were tested on arrival in the presurgical holding area. Testing was the same as in the TT group. Patients were also asked to comment if they noted a change in taste at each oropharyngeal examination.

RESULTS

PROOF OF CONCEPT

Ofloxacin was reliably visualized up to a dilution of 1:4 (750 µg/mL) with both the Wood’s lamp and the compact UV light. Questionable fluorescence was seen at a dilution of 1:8. No discernable difference was seen in brightness or color of the solutions between the 2 light sources. Ofloxacin appeared pale green and was readily distinguishable against a pink background. Instillation
of 1 drop into a patient’s oropharynx was readily visualized (Figure).

STUDY POPULATION

The age of the patients receiving TTs ranged from 1 to 6 years old with a mean age of 2.4 years (Table). No patients had craniofacial abnormalities (eg, cleft palate). All pediatric patients underwent unilateral or bilateral TT placement. Two patients received silicone “T” tubes (inner diameter, 1.32 mm; shaft length, 4.8 mm [Gyrus ACMI, Bartlett, Tennessee]), and all others received beveled Armstrong fluoroplastic TTs (inner diameter, 1.14 mm; shaft length, 3.5 mm [Gyrus ACMI]). Three patients underwent concomitant adenoidectomy.

Patients undergoing tympanoplasty had an average age of 55 years (range, 15-83 years). Perforation size ranged from 10% to 80% of the pars tensa surface area. Indications for surgery were notable for traumatic TM perforations in 3 patients.

FLUORESCENCE TESTING AFTER OTIC INSTILLATION

Testing was performed without difficulty in all patients. Testing duration was an average of 19.5 minutes in the 20 patients undergoing TT surgery and 85 minutes in the 6 undergoing tympanoplasty. None of the patients in either group demonstrated fluorescence at any point in the testing. Two of the patients who underwent tympanoplasty confirmed an immediate bitter taste on administration of the EDs.

COMMENT

The primary aim of this study was to determine if quinolone fluorescence could be used to demonstrate ED penetration through TTs and TM perforations, through the tubotympanum, and into the pharynx. Our proof of concept observations confirmed ofloxacin fluorescence both in vitro (to a 1:4 dilution) and in vivo. However, we were unable to identify fluorescence after otic instillation of 10 drops, even in patients with presumably normal eustachian tube function (ie, traumatic TM perforations). This suggests that transoral detection of pharyngeal fluorescence is not a viable means of assessing ED penetration into the middle ear in vivo.

Failure to detect fluorescence does not equate with failure of the EDs to penetrate the TM defect and the eustachian tube. Two of 6 patients undergoing tympanoplasty related an immediate change in taste. Bitter taste has been reported in up to 17% of patients receiving ofloxacin otic with a TM defect.12 Failure to identify
fluorescence in patients who can taste the EDs suggests that either the EDs are passing through the oropharynx in a sequestered fashion (eg, behind the posterior pillars) or diluted below 750 mg/mL. While it is possible that some aspect of the middle ear or pharyngeal secretions could reduce fluorescence,9,13 our observation of fluorescence after instillation directly into the pharynx makes this less likely. The bulk of our study population likely had significant eustachian tube dysfunction.14 which is one of the principle factors in the pathogenesis of otitis media.15 Thus, our negative results could be due to limited penetration of EDs into the eustachian tube and pharynx.

Our failure to identify fluorescence is at odds with findings of studies reported in Daiichi Pharmaceutical’s new drug application (NDA) to the US Food and Drug Administration.10 The NDA cites 2 studies in which fluorescence was assessed in adults with TTs. Fluorescence was found in 7 of 17 patients without active otorrhea and in 3 of 5 adults with otorrhea. The basis for such dramatic differences is unclear. The NDA does not include the full protocol, making it difficult to draw any conclusions. Explanations include worse eustachian tube obstruction in our primarily pediatric population, shorter duration of assessment, differences in the ED vehicles, and less effective method of inducing and detecting fluorescence.

Other techniques may allow better assessment of ED penetration through the tubotympanum. These include using a more fluorescent preparation, a dye visible without UV light, pledget collection of ED or dye at the eustachian tube ostium, and radioisotope-labeled EDs detectable by nuclear medicine techniques, such as single photon emission computed tomography (SPECT). All techniques would require use of a nonapproved preparation in the middle ear, thereby carrying potential added risks to patients. A radio-labeled ED would allow measurement of the ED throughout the tubotympanum by serial SPECT imaging. Thus, we would view this as the gold standard. Unfortunately, conducting such an experiment poses tremendous operational obstacles (eg, the need for an on-site cyclotron, timing of patient identification to drug preparation) that would likely make the study cost-prohibitive.

In conclusion, the excellent clinical outcomes achieved with quinolone EDs suggest that these agents readily penetrate through TTs and TM perforations. We were unable to demonstrate fluorescence in the pharynx after otic instillation, suggesting that the EDs do not penetrate through the eustachian tube in a rapid or a relatively undilated manner. More sensitive techniques are necessary to detect passage of EDs into the tubotympanum and oropharynx in patients with otitis media.

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Author Contributions: Dr Antonelli 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.

Study concept and design: Whitaker, Collins, and Antonelli. Acquisition of data: Whitaker and Collins. Analysis and interpretation of data: Whitaker, Collins, and Antonelli. Drafting of the manuscript: Whitaker and Antonelli. Critical revision of the manuscript for important intellectual content: Whitaker, Collins, and Antonelli. Administrative, technical, and material support: Whitaker, Collins, and Antonelli. Study supervision: Collins and Antonelli.

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REFERENCES