

Systemic Absorption of Topical Gentamicin Sinus Irrigation

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ABSTRACT

Objective: Evidence surrounding systemic absorption of gentamicin during intraoperative irrigation of the paranasal sinuses is lacking. The objectives of this study were to determine (1) if topical gentamicin is absorbed from the paranasal sinuses, (2) if hearing loss occurs following topical administration of gentamicin, and (3) if gentamicin placed within the sinuses travels retrograde (against mucociliary clearance) up the auditory tube to the middle ear.

Design: Consecutive, prospective case series.

Setting: Tertiary centre.

Methods: A series of patients undergoing sinus surgery were identified. Fluorescein-stained gentamicin was used to irrigate the sinus cavities intraoperatively. Otoscopy using a filtered light source was performed 30 minutes postoperatively.

Main Outcome Measures: (1) Serum gentamicin levels preirrigation and at 30 minutes postirrigation and (2) change in pure-tone average and threshold at 8 kHz pre- and postoperative audiograms.

Results: Twenty patients were enrolled. Serum gentamicin levels were detectable in three patients. Fluorescein irrigation solution was not visualized in the middle ear space. No significant hearing loss was observed in any of the patients.

Conclusions: Gentamicin may be absorbed from the nasal mucosa during intraoperative irrigation of the sinuses. However, detectable serum levels were well below therapeutic levels. The clinical significance of this finding requires further study to determine if topical sinus irrigation with gentamicin is a safe procedure.

SOMMAIRE

Objectif: Nous manquons d'informations autour de l'absorption systémique de la gentamicine au cours de l'irrigation intraopératoire des sinus paranasaux. L'objectif de cette étude était de déterminer (1) si la gentamicine topique est absorbée dans les sinus paranasaux, (2) s'il y a une perte d'audition après l'administration de la gentamicine, et (3) si la gentamicine placée dans les sinus peut suivre un trajet rétrograde (contre la clairance mucociliaire) via la trompe d'Eustache jusqu'à l'oreille moyenne.

Devis: Série de cas prospective.

Localisation: Centre tertiaire.

Méthodes: Une série de patient subissant une chirurgie des sinus ont été identifiés. Nous avons irrigué les sinus avec de la gentamicine marquée à la fluorescéine lors d'une opération. Une otoscopie utilisant une lumière filtrée a été faite 30 minutes après l'intervention.

Variables évaluées: (1) Le niveau de la gentamicine sérique préirrigation et 30 minutes postopératoire et (2) le changement dans la moyenne de l'audiométrie tonale et le seuil à 8 kHz entre pré- et postopératoire.

Résultats: Nous avons évalué 20 patients. Des niveaux sériques de gentamicine ont été détectés chez trois patients. La solution marquée avec la fluorescéine n'a pas été vue dans l'oreille moyenne. Aucune perte d'audition significative n'a été observé chez nos patients.

Conclusion: La gentamicine peut être absorbée à partir de la muqueuse nasale durant l'irrigation intraopératoire des sinus. Cependant, des niveaux sériques détectables étaient beaucoup plus bas que le niveau thérapeutique. La signification clinique de ces données exige d'autres études pour déterminer si l'irrigation topique des sinus avec la gentamicine est un procédé sécuritaire.

Key words: gentamicin, hearing loss, paranasal sinuses, postoperative complications, sensorineural, surgery

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Topical irrigation of the maxillary sinuses with gentamicin solution during functional endoscopic sinus surgery (FESS) is a widely accepted practice among rhinologists. The rationale for using topical gentamicin irrigation is to eradicate bacteria that may be present in the maxillary cavity and responsible for the chronic sinusitis. Gentamicin is an aminoglycoside antibiotic that is used primarily to treat infections caused by gram-negative bacteria. It is poorly absorbed from the gastrointestinal tract and therefore must be given intramuscularly, intravenously, or topically to be effective. The primary limiting factor for widespread use is its side-effect profile.

Ototoxicity is the most significant adverse outcome of gentamicin use from an otolaryngologic point of view. Literature examining intraoperative absorption of topical gentamicin from the paranasal sinus mucosa is lacking. Anecdotal reports of individuals demonstrating hearing loss following sinus surgery with topical gentamicin irrigation exist. Studies have confirmed systemic absorption of gentamicin with subconjunctival administration, otic preparations, and surgical implants irrigated with gentamicin.¹⁻³ Hearing loss has been documented in patients using topical gentamicin solution with a tympanic membrane perforation and in patients undergoing trans-tympanic administration.^{4,5} This poses the question of whether topical gentamicin instilled into the sinuses can be absorbed into the systemic circulation and if the absorption is significant enough to cause hearing loss.

This study was designed to determine if patients undergoing sinus surgery for chronic sinusitis and receiving intraoperative irrigation of the paranasal sinuses with topical gentamicin would have (1) gentamicin absorption from the paranasal sinuses, (2) any hearing loss following topical administration of gentamicin, and (3) retrograde flow of the gentamicin up the auditory tube and into the middle ear.

Methods

A prospective study was conducted of consecutive patients undergoing FESS for chronic sinusitis at the St. Paul's Sinus Centre in Vancouver, British Columbia. The study protocol was approved by the institutional Clinical Ethics Review Board. Written informed consent was obtained from all patients.

Exclusion criteria included pregnancy, children under 18 years of age, hepatic or renal disorders, and any patient who had been treated with gentamicin within the past 12 months. All eligible patients underwent preoperative testing that included the following: baseline

gentamicin blood levels, creatinine, glomerular filtration rate (GFR), complete blood count, and a preoperative audiogram.

A single surgeon (A.R.J.) operated on all patients. At the completion of surgery, irrigation of both maxillary and frontal sinuses was performed. Irrigation solution consisted of 1.5 mL of gentamicin (60 mg), 1.5 mL of Triamcinolone Acetonide, and 0.1 mL of 1:1000 fluorescein. Fluorescein is a dye that fluoresces when excited by a light source between 494 and 525 nm, allowing the observer to visualize the path of the solution. Thirty minutes following sinus irrigation, serum gentamicin levels were obtained.

Using a standard 0° scope with the appropriate light source and filters, otoscopy was performed 30 minutes postirrigation (while the patient was in the recovery room). Any fluorescence observed from the fluorescein solution during otoscopy was documented.

All patients were followed up in clinic 2 weeks postoperatively. During this time, an audiogram was performed. Comparison of the pre- and postoperative audiograms was performed to determine if there was any change in hearing thresholds and speech discrimination. Pure-tone averages (PTAs) were compared at 0.5, 1, 2, 4, and 8 kHz pre- and postoperatively.

Results

Twenty patients were enrolled (18 males and 2 females), ranging from 21 to 81 years of age.

Preoperative Testing

All patients had undetectable levels of gentamicin in their blood preoperatively. No abnormalities were detected on preoperative blood work. All patients had normal creatinine values and GFR.

Gentamicin Serum Levels

Serum gentamicin levels were taken 30 minutes postirrigation for all patients. Serum gentamicin levels were detected in 3 of the 20 patients postirrigation, at levels of 0.3, 0.3, and 0.4 mg/L.

Postirrigation Otoscopy

No fluorescein was visualized behind the tympanic membrane in any of the 20 patients.

Audiogram Analysis

Audiograms were performed on all patients preoperatively as well as during the 2-week postoperative visit. PTAs ranged from 2.5 to 50 dB (preoperatively) and 5 to 47.5 dB (postoperatively). All 20 patients' postoperative PTA was within 10 dB compared with the preoperative PTA.

Hearing thresholds at 8 kHz ranged from 10 to 90 dB (preoperatively) and 10 to 100 dB (postoperatively). All 20 patients' postoperative threshold at 8 kHz was within 10 dB compared with preoperative values.

Discussion

Topical gentamicin irrigation of the maxillary sinuses has become common practice during endoscopic sinus surgery. It remains unknown whether side effects seen with other routes of gentamicin administration also apply to the topical route. Fifteen percent of patients (3 of 20) undergoing sinus surgery and intraoperative irrigation of the sinuses with gentamicin demonstrated detectable serum gentamicin levels (0.3 mg/L, 0.3 mg/L, and 0.4 mg/L). These levels were not associated with a change in their hearing. Patients who demonstrate hearing loss from gentamicin administration usually present between 1 and 3 weeks after the first dose.⁶ Our results show that topical gentamicin can be absorbed when used during sinus surgery. The clinical importance of this finding is yet to be determined. Since no solution was seen in the middle ear and gentamicin is poorly or not absorbed from the gastrointestinal tract, it is likely that systemic absorption of gentamicin occurred through the nasal mucosa.

Fluorescein otoscopy performed after application confirmed that no irrigation solution was observed in the middle ear. We chose to perform otoscopy 30 minutes postirrigation because we felt that this allowed for an adequate amount of time for the irrigation solution to retrogradely reflux, if possible, into the middle ear. As well, patients would still be lying supine during this time, allowing for the solution to reflux (passively) into the middle ear against mucociliary flow. Once the patient was sitting up, the irrigation solution would be expected to migrate back into the oropharynx as a result of gravity and natural mucociliary flow.

Risk factors for gentamicin ototoxicity include dose, duration of treatment, age of the patient, and genetic susceptibility. Ototoxicity can develop even when blood levels remain within generally accepted limits, and exceptional cases have been reported with toxicity after a single ordinary dose.⁷ A mutation of mitochondrial

ribonucleic acid, called A1555G, has recently been found to increase susceptibility to gentamicin ototoxicity in certain individuals⁸ and probably explains this idiosyncratic reaction. This susceptibility is passed on genetically through the mother and occurs in as many as 17% of individuals with hearing loss after aminoglycoside exposure.

The side-effect profile of gentamicin may be enhanced with concurrent use of other ototoxic medications, including chemotherapy agents (cisplatin), loop diuretics (furosemide), and other aminoglycoside antibiotics (tobramycin, streptomycin).

The age of the patient appears to be a risk factor for gentamicin toxicity. In general, older patients are at increased risk. This is thought to be secondary to concurrent age-related damage to inner ear neurons and hair cells.⁹ As well, older individuals are more likely to experience decreased renal function, preventing proper excretion of the drug.

All patients in this study were healthy individuals demonstrating normal renal function. With the exception of age (one patient older than 60 years), no other identifiable or obvious risk factors for increased gentamicin susceptibility were found in any of our patients.

There is no literature examining gentamicin absorption through the nasal mucosa in humans. Animal studies involving topical gentamicin application in the nasal mucosa of dogs demonstrate peak serum levels within 30 minutes. The bioavailability of topical nasal gentamicin in dogs was found to be 80% of intravenous administration in one study.¹⁰

The fact that systemic levels of gentamicin were detected in two of our patients is a significant observation. In a patient with an inherent susceptibility to gentamicin ototoxicity, such as mitochondrial mutation, topical gentamicin could have the potential for serious side effects. Even though this risk appears minimal, patients with increased susceptibility (older age, family history) in particular should be informed of the theoretical risks of topical gentamicin.

Conclusion

Gentamicin irrigation is commonly used to irrigate the sinuses during endoscopic sinus surgery. Detectable systemic gentamicin levels were observed in 15% of patients irrigated with topical gentamicin solution. These levels were well below the toxic or therapeutic levels of gentamicin. Gentamicin was probably absorbed systemically through the nasal mucosa since the irrigation solution

was not visualized in the middle ear. The potential for systemic absorption via the nasal mucosa makes it important to monitor for and discuss the risks of ototoxicity when doing FESS. Patients should be informed that there is the potential for hearing loss as systemic absorption does occasionally occur. The clinical risk of hearing loss needs to be further evaluated.

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