International Journal of Pediatric Otorhinolaryngology 75 (2011) 915–918

Contents lists available at ScienceDirect

International Journal of Pediatric Otorhinolaryngology

journal homepage: www.elsevier.com/locate/ijporl

Ototoxicity caused by topical administration of gentamicin versus tobramycin in rabbits

Fatih Oghan [a,*], Tayfun Apuhan [b], Fahrettin Yılmaz [c]

[a] Department of Otorhinolaryngology, Faculty of Medicine, Dumlupinar University, Kutahya, Turkey
[b] Department of Otorhinolaryngology, Faculty of Medicine, Abant Izzet Baysal University, Bolu, Turkey
[c] Department of Otorhinolaryngology, Faculty of Medicine, Bezmi-Alem Vakif University, Istanbul, Turkey

ARTICLE INFO

Article history:
Received 1 February 2011
Received in revised form 3 April 2011
Accepted 6 April 2011
Available online 17 May 2011

Keywords:
Aminoglycosides
Cochlear toxicity
Otoacoustic emission

ABSTRACT

Aim: To investigate the possible differences in cochleotoxic effects in rabbits between twice-daily administration of topical gentamicin and tobramycin throughout the perforated tympanic membrane with the use of distortion-product otoacoustic emissions (DPOAEs).
Materials and methods: Twenty female rabbits were studied prospectively daily for 21 days. The rabbits' ears were divided into two groups: right and left ear groups. Twice-daily for 21 days after paracentesis, 0.3% gentamicin was administered topically in the left ears, and 0.3% tobramycin was administered topically in the right ears. For 21 days, the cochlear activity of the right and left ears of all rabbits was examined every 7 days using DPOAEs. The numerical values of the distortion product (DP) intensity recorded on days 7, 14 and 21 of drug administration were compared between the two groups.
Results: Cochlear activity was reduced earlier in the gentamicin group in the 2–4 kHz frequencies compared to the tobramycin group in the second DPOAE measurement (day 7 of the experiment). In two rabbits in the gentamicin group, the third DPOAE measurement showed that cochlear activity was reduced in all frequencies. In six rabbits in the tobramycin group, the third DPOAE measurement showed that cochlear activity was reduced in all frequencies. There was no statistical significance between the two groups except day 7 in the 2 and 3 kHz frequencies ($p < 0.05$).
Conclusion: We concluded that low frequencies (2 and 3 kHz) are more sensitive to the administration of topical gentamicin than to topical tobramycin. Early cessation of tobramycin drops may be minimally cochlear toxic compared to gentamicin within the first 7 days when these drugs are misused in treating chronic otitis media.

1. Introduction

Aminoglycosides are bactericidal aminoglycosidic aminocyclitols. Drug-induced loss of hearing or vestibular function captured the awareness of the medical community upon the addition of aminoglycosides to the list of "ototoxic" drugs in the mid-1940s. They were the first class of drugs to call attention to the problem of ototoxicity when streptomycin and dihydrostreptomycin were used to treat tuberculosis [1].

The development of successors to the initially discovered streptomycin such as neomycin, kanamycin, tobramycin, gentamicin, and amikacin widened the application of this class of drugs but did not eliminate the problem of ototoxicity. Today, aminoglycoside-induced hearing loss is most prevalent in developing countries where these drugs frequently are the only economically affordable antibiotics. However, ototoxicity is also a factor of concern in industrialized countries where topical aminoglycosides are misused as an antibacterial agent for treating chronic otitis media, as in some clinics in Turkey.

No therapy currently exists to attenuate the potential ototoxicity of parenterally aminoglycoside antibiotics, although improved therapeutic regimens have lowered the risk. The incidence of cochlear toxicity has been reported to range from a few percent to up to 33% of patients while balance may be affected in about 15% [2]. In some studies of tobramycin, patients with cystic fibrosis have shown no apparent side effects [3], but other studies observed an incidence of hearing impairment of 16–20% [4].

In the last two decades, animal experiments have supported the efficacy of high doses of aminoglycosides for severe Gram-negative infections [5]. The aim of the present study was to investigate in rabbits the possible differences in cochlear toxic effects between twice-daily administration of topical gentamicin and tobramycin

* Corresponding author at: DPU Merkez Kampus, Tavsanli Yolu 10. km, Tip Fakultesi, KBB AD, 43270 Kutahya, Turkey. Tel.: +90 505 7267375.
E-mail addresses: fatihoghan@hotmail.com, foghan74@hotmail.com (F. Oghan).

0165-5876/$ – see front matter © 2011 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.ijporl.2011.04.005

throughout the experimental perforated tympanic membrane with the use of distortion-product otoacoustic emissions (DPOAEs).

2. Materials and methods

Every effort was made to minimize the animals' pain and discomfort during the study. The experiments were conducted in accordance with the European Communities Council Directive of 1986 and approved by the Ethical Committee of our institution (605-798/2010/9.1). Twenty female, 3-month-old New Zealand rabbits, weighing 1000–1200 g, were studied prospectively daily, for 21 days. All the animals had free access to food and water.

Initially, the cochlear activity of the animals was examined with DPOAEs in a soundproof booth using Otodynamics ILO 288 Echoport equipment (Otodynamics Ltd., Hatfield, UK) for DPOAE recording. The data were processed and evaluated with otoacoustic emission (OAE) software (EZ Screen 2 Otodynamics OAE Screening and Data Management Software, Hatfield, UK). Exclusion criterion from the experiment was abnormal pre-treatment cochlear activity.

The rabbits' ears were divided into two groups (right and left ear groups): 0.3% gentamicin was administered topically twice-daily to the left ears, and 0.3% tobramycin was administered topically twice-daily to the right ears, for 21 days after paracentesis. Before the initial procedure and during the otoacoustic emission measurements, the rabbits were sedated with ketamine (80 mg/kg Ketalar; Pfizer Ltd., Vienna, Austria) and xylazine (5 mg/kg Rompun; Bayer Ltd., Leverkusen, Germany) through intraperitoneal injection. Tympanic membrane perforation was checked during every administration of the drugs. In addition, an experimentally perforated ear model was created. A perforation was made using with the same pick in all ears nearly one-half of the tympanic membrane, and a small piece of gel foam was inserted into the tympanic cavity over the round window. After this initial procedure, DPOAE measurements were made using a human ear speculum on the horizontal plane. After the ear speculum was inserted in the external canal, tympanometry probes were applied in the ear speculum to occlude. Baseline DPOAE measurements were taken from the ears before the solutions were used to compare hearing after the drugs were applied. Three drops of each drug were applied in an ear. Exposition and fullness were obtained for liquid drops in the middle ear. Each intervention was performed under microscopy. Persistence of tympanic membrane perforation was provided with daily control. If required, paracentesis was repeated.

The cochlear activity of the right and left ears of all rabbits was examined every 7 days for 21 days, using DPOAEs in conscious animals. Once the probe was placed with a good seal in the ear canal, the DPOAEs were measured. Equilevel primary tones $f1$ (65 dB) and $f2$ (55 dB) were fixed at $f1/f2 = 1.22$, and DPOAEs were measured at four different frequencies ranging from 2000 to 6000 Hz (2002, 3003, 4004, and 6006 Hz) at first. By calculating the difference between the distortion products and noise ± 2 standard deviations, the signal–noise ratios (SNR) for each frequency were found. Three additional DPOAE measurements were also obtained on days 7, 14, and 21 after the drugs were administered, in order to detect any possible delayed deterioration or improvement in cochlear activity. All measurements were recorded in a quiet room. The numerical values of the intensity of the DP recorded on days 0, 7, 14, and 21 of drug administration were compared for the two groups. To standardize the effects of perforation on the DPOAE values, day 0 values were obtained after paracentesis and the application of gel foam. A Mann–Whitney U-test was used to compare the DPOAE results. The level of statistical significance was set at $p < 0.05$. The Bonferroni correction was used as needed. The results were analyzed with SPSS 15.0 for Windows (SPSS Inc., Chicago, IL).

3. Results

Differences in DPOAE amplitudes, and therefore in cochlear activity, between the two experimental groups were revealed. The decrease in cochlear activity in both groups involved frequencies between 2002 and 6006 Hz on days 7, 14, and 21 of the experiment. Cochlear activity was reduced earlier in the gentamicin group in the 2 and 4 kHz frequencies compared with the tobramycin group in the second DPOAE measurement (day 7 of the experiment). In two rabbits in the gentamicin group (11 and 13), cochlear activity was reduced in all frequencies, according to the third DPOAE measurement. In six rabbits in the tobramycin group (rabbits 6, 8, 10, 12, 14, 19), cochlear activity was reduced in all frequencies, according to the third DPOAE measurement on day 14 (Table 1).

Table 1
DPOAE values of rabbits in 2, 3, 4 and 6 kHz frequencies using gentamicin and tobramycin (R: rabbit, *f*: frequency).

R	Aminoglycosides															
	Gentamicin versus tobramycin															
	0 day (*f*)				7 day (*f*)				14 day (*f*)				21 day (*f*)			
	2 kHz	3 kHz	4 kHz	6 kHz	2 kHz	3 kHz	4 kHz	6 kHz	2 kHz	3 kHz	4 kHz	6 kHz	2 kHz	3 kHz	4 kHz	6 kHz
1	15vs20	10vs25	9vs25	0vs18	2vs0	3vs2	0vs0	0vs0	0vs0	0vs2	0vs0	1vs0	0vs0	0vs2	0vs0	0vs0
2	17vs17	22vs25	25vs28	27vs24	3vs0	2vs0	4vs0	7vs0	0vs0	2vs0	0vs0	0vs0	0vs0	2vs0	0vs0	0vs0
3	10vs2	10vs22	16vs23	15vs30	8vs0	3vs0	0vs0	4vs0	0vs0	0vs0	0vs0	0vs0	0vs0	0vs0	0vs0	0vs0
4	0vs0	18vs20	14vs27	23vs28	0vs0	0vs0	0vs2	1vs0	0vs0	0vs0	0vs2	1vs0	0vs0	0vs0	0vs2	1vs0
5	2vs2	10vs25	20vs25	21vs26	2vs2	2vs8	4vs0	2vs0	0vs2	4vs0	0vs0	2vs0	2vs2	0vs0	0vs0	2vs0
6	5vs2	22vs22	17vs11	21vs7	0vs7	3vs12	2vs2	0vs8	0vs0	0vs0	0vs2	0vs2	0vs0	0vs0	0vs5	0vs0
7	2vs7	26vs24	25vs26	24vs28	3vs4	2vs0	4vs6	4vs0	0vs4	0vs0	0vs6	0vs0	0vs0	0vs0	0vs2	0vs0
8	22vs12	23vs28	27vs26	28vs24	0vs3	0vs0	2vs12	0vs14	0vs0	0vs0	2vs0	0vs0	0vs0	0vs0	0vs0	0vs0
9	7vs6	25vs12	32vs18	25vs7	0vs6	0vs9	0vs8	0vs9	0vs0	0vs4	0vs8	0vs0	0vs0	0vs4	0vs4	0vs0
10	0vs7	14vs7	11vs5	18vs9	0vs9	3vs4	3vs2	4vs14	1vs0	0vs0	0vs2	0vs2	0vs0	0vs0	0vs2	0vs2
11	12vs12	13vs10	25vs25	27vs27	0vs0	6vs0	2vs0	22vs0	0vs0	0vs0	2vs0	0vs0	0vs0	0vs0	2vs0	0vs0
12	10vs7	17vs22	22vs15	25vs22	3vs8	0vs20	6vs17	0vs20	0vs0	0vs0	3vs0	0vs2	0vs0	0vs0	0vs0	0vs3
13	0vs0	12vs8	14vs11	18vs12	0vs0	3vs8	6vs11	24vs0	0vs1	0vs0	2vs2	0vs0	0vs1	0vs0	2vs2	0vs0
14	12vs20	20vs18	17vs25	24vs30	0vs4	3vs8	0vs22	2vs11	0vs0	0vs0	0vs0	4vs0	0vs0	0vs0	0vs0	2vs0
15	14vs22	23vs28	18vs29	28vs29	2vs16	2vs4	6vs8	4vs0	0vs0	0vs4	0vs2	0vs0	0vs0	0vs2	0vs0	0vs0
16	10vs12	22vs9	24vs25	22vs24	0vs7	3vs5	2vs0	0vs0	0vs0	0vs0	2vs0	0vs0	0vs0	0vs0	2vs0	0vs0
17	12vs2	10vs17	20vs19	25vs9	2vs12	1vs12	2vs6	4vs0	0vs0	1vs0	2vs3	4vs0	0vs0	1vs0	0vs0	0vs0
18	0vs7	7vs22	10vs27	12vs26	0vs7	0vs13	2vs0	0vs4	0vs2	0vs0	2vs0	0vs0	0vs0	0vs0	2vs0	0vs0
19	22vs10	25vs12	25vs14	20vs22	5vs9	4vs12	6vs8	2vs20	0vs0	2vs4	0vs2	0vs2	0vs0	2vs0	0vs5	0vs2
20	17vs18	25vs23	28vs28	24vs19	0vs5	0vs22	2vs4	6vs0	0vs0	0vs0	0vs0	0vs0	0vs0	0vs0	0vs0	0vs0