



# Safety of ofloxacin (OFLX) and fosfomycin sodium (FOM) ear drops

T. Yamano<sup>\*</sup>, T. Morizono, K. Shiraishi, M. Miyagi, A. Imamura, T. Kato

Department of Otolaryngology, Fukuoka University Nanakuma, Jonan-ku, Fukuoka City, Japan

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## KEYWORDS

Ear drops;  
Ototoxicity;  
Ofloxacin;  
Fosfomycin sodium;  
Guinea pig

## Summary

**Objective:** The objective of this study is to evaluate the safety of two ear drops, Ofloxacin (OFLX: Tarivid Otic Solution<sup>®</sup>, Daiichi Seiyaku) and Fosfomycin sodium (FOM: Fosmicin S<sup>®</sup>, Meiji Seiyaku).

**Methods:** Albino guinea pigs were used as experimental animals, and the ototoxicity was evaluated by means of threshold changes in the compound action potentials (CAP), when topically applied to the middle ear cavity of the guinea pig. The sound stimuli applied were; click sound, with tone bursts of 8 kHz, 4 kHz, and 2 kHz. In one group of animals, after one application of the ear drops in the right middle ear cavity, the change in CAP was compared with a contralateral saline control at 24 h, one week, and four weeks. In other group of animals, the ear drops were applied into the middle ear cavity for seven consecutive days and the CAP was measured at 24 h.

**Results:** At 24 h the CAP threshold for click, 8 and 4 kHz elevated significantly for both the saline and ear drop treatment, but the threshold returned to normal when measured at 7 days and 28 days. Seven consecutive days of ear drops administration resulted in no reduction in the CAP for either ear drops.

**Conclusions:** Based on the lack of changes in the CAP, these two ear drops studied did not show any significant ototoxicities.

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## 1. Introduction

Otic drops have been used worldwide for the treatment of acute or chronic otitis media. In the past, many workers reported an undesirable ototoxicity of otic preparations. It is important to be aware of

the potential ototoxicity of any drugs, vehicle, or antiseptics that are used in the middle ear. This is not the first investigation of ototoxicity of ofloxacin or fosfomycin [1,2]. Nevertheless, it is important to confirm or refute the results of previous investigations. Previous work mentioned in the discussion utilized analysis of electrocochleogram or brainstem evoked responses [1,2], and both of the methods are less sensitive than our method which utilized the whole nerve action potentials [3–5].

<sup>\*</sup> Corresponding author. Tel.: +81 92 801 1011.  
E-mail address: yamano@minf.med.fukuoka-u.ac.jp  
(T. Yamano).

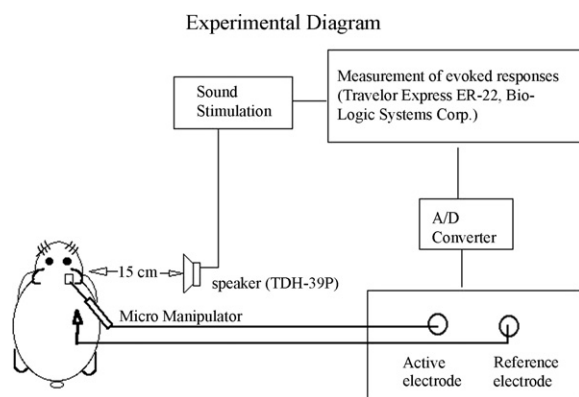


Fig. 1 Block diagram outlining the experiment.

The purpose of this study is to evaluate the safety of recently marketed ear drops available in Japan.

## 2. Materials and methods

To evaluate the ototoxicity of two otic preparations, ofloxacin (OFLX) and fosfomycin sodium (FOM), albino Hartley guinea pigs were used. They were 4–5 weeks old, and the body weight ranged from 250 to 350 g. In one group of animals, the middle ear cavity of one ear was filled with the ear drops, while the contralateral middle ear cavity was filled with saline as a control, then the compound action potentials (CAP) by the round window recordings were measured at 24 h, 1 week and 4 weeks after treatment. In the second group of animals, ear drops were instilled daily for seven consecutive days from a small plastic tube securely cemented to the bulla. The untreated contralateral ear served as a control.

(Or if saline was used, then “Saline was instilled in the same manner in the contralateral ear as a control”). In both experiments, CAP was measured in all animals before saline or drug instillation. Changes in CAP in response to click sounds, for tone bursts of 8, 4, and 2 kHz, were studied with a maximum sound intensity of 90 dB SPL and successively reduced in 10 dB increments in order to obtain a 10  $\mu$ V threshold of CAP. The repetition rate of the sound was 20 times per second, and the responses were averaged 200 times with a Biologic Systems Traveler Express ER-22. The sound was given in the free field, the sound pressure was monitored adjacent to the orifice of the external canal, using a B & K 1/2 in. condenser microphone. A threshold response was defined as an NI-PI signal with amplitude of 10  $\mu$ V. Non-treated ears and saline-treated ears served as controls. A diagram outlining the experiment is shown in Fig. 1. An unpaired *t*-test was used to define statistical significance.

## 3. Results

At first contralateral saline treated ears were used as a control of drug treated ears, but no difference was found.

Then, the CAP threshold in the untreated ear without saline application ( $n = 31$ ) was used as the control.

Table 1 shows the results from ofloxacin and fosfomycin ear drop at 24 h, at 7 days and at 28 days. Control here denotes the CAP thresholds without any treatment. At 24 h, the CAP threshold for click, 8 and 4 kHz elevated significantly for both the

Table 1 Ten microvolts CAP threshold (in dB SPL) for control and at 24 h, 7 days and 28 days, after drug application into the middle ear cavity

Stimulus sound	Control	Test drugs	Duration after drug application		
			24 h	7 days	28 days
Click	37.8 $\pm$ 4.1 ( $n = 31$ )	OFLX	42.6 $\pm$ 4.3 ( $n = 8$ )	35.2 $\pm$ 5.2 ( $n = 8$ )	41.1 $\pm$ 5.3 ( $n = 8$ )
		FOM	43.1 $\pm$ 4.8 ( $n = 8$ ) <sup>*</sup>	43.1 $\pm$ 6.7 ( $n = 7$ )	41.7 $\pm$ 0.5 ( $n = 2$ )
		Saline	44.9 $\pm$ 8.6 ( $n = 16$ ) <sup>*</sup>	38.3 $\pm$ 7.7 ( $n = 15$ )	36.4 $\pm$ 6.5 ( $n = 10$ )
Tone burst, 8 kHz	43.2 $\pm$ 8.4 ( $n = 31$ )	OFLX	60.0 $\pm$ 8.7 ( $n = 8$ ) <sup>*</sup>	43.2 $\pm$ 15.8 ( $n = 8$ )	49.6 $\pm$ 7.2 ( $n = 8$ )
		FOM	51.3 $\pm$ 12.8 ( $n = 8$ ) <sup>*</sup>	47.3 $\pm$ 10.1 ( $n = 7$ )	44.7 $\pm$ 1.9 ( $n = 2$ )
		Saline	59.4 $\pm$ 12.3 ( $n = 16$ ) <sup>*</sup>	39.3 $\pm$ 10.4 ( $n = 15$ )	47.2 $\pm$ 8.0 ( $n = 10$ )
Tone burst, 4 kHz	48.8 $\pm$ 8.2 ( $n = 31$ )	OFLX	59.1 $\pm$ 13.4 ( $n = 8$ ) <sup>*</sup>	43.1 $\pm$ 8.6 ( $n = 8$ )	51.3 $\pm$ 8.2 ( $n = 8$ )
		FOM	60.6 $\pm$ 15.5 ( $n = 8$ ) <sup>*</sup>	52.6 $\pm$ 15.0 ( $n = 7$ )	51.8 $\pm$ 0.8 ( $n = 2$ )
		Saline	61.4 $\pm$ 14.9 ( $n = 16$ ) <sup>*</sup>	46.9 $\pm$ 8.4 ( $n = 15$ )	53.1 $\pm$ 9.1 ( $n = 10$ )
Tone burst, 2 kHz	62.1 $\pm$ 6.7 ( $n = 31$ )	OFLX	64.0 $\pm$ 7.6 ( $n = 8$ )	54.4 $\pm$ 11.1 ( $n = 8$ )	59.8 $\pm$ 8.2 ( $n = 8$ )
		FOM	64.6 $\pm$ 10.0 ( $n = 8$ )	63.8 $\pm$ 6.0 ( $n = 7$ )	63.0 $\pm$ 0.7 ( $n = 2$ )
		Saline	65.1 $\pm$ 9.4 ( $n = 16$ )	58.4 $\pm$ 10.3 ( $n = 15$ )	64.1 $\pm$ 8.0 ( $n = 10$ )

Unit is dB SPL.

<sup>\*</sup>  $p < 0.01$ .

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