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Ototoxicity of Povidone-Iodine applied to the middle ear cavity of guinea pigs

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ABSTRACT

Objective: Povidone-Iodine preparation is used as a disinfectant in otological surgeries. The ototoxicity of Povidone-Iodine preparation was evaluated using infant, young and adult guinea pigs. The effects of different concentrations and of different exposure durations on compound action potentials were also studied.

Materials & methods: Povidone-Iodine was used to fill one middle ear cavity of the guinea pig, and the compound action potential (CAP) was measured from the round window membrane at 24 h, 7 days, and 28 days. The contralateral side was filled with saline as control. Test sounds used were clicks and tone bursts of 2, 4, and 8 kHz.

Results: At 24 h, Povidone-Iodine solution showed a significant toxic effect in the infant group. In the young animal group, no toxic effect was seen. In the adult group, a mild degree of deafness for 2 kHz was found.

At 7 days, the young group showed significant hearing loss for all frequencies, but the adult group did not show any hearing loss. With a half strength solution, both young and adult group did not show hearing loss.

At 28 days, with a full strength solution, hearing loss became prominent for all sound stimulation. With 1/8th dilution, the young group showed a moderate hearing loss, but the adult group did not.

Conclusion: The thicker round window membrane in human is expected to provide more protection to the human cochlea than in the guinea pig model that we have studied. Mild hearing loss at 24 h and 7 days using 10% solution, but no hearing loss with 5% solution at 7 days may indicate that rinsing of the middle ear cavity with saline during surgery should minimize the ototoxic effect of this product.

The age of the animals does influence the outcome of the ototoxicity experiment.

From this experiment, Povidone-Iodine preparations in the infant should be used with caution. Povidone scrub should not be used for otologic surgery.

1. Introduction

The purpose of this study is to evaluate the cochleo-toxicity of Povidone-Iodine solution, which is widely used as pre-operative disinfectant in ear surgery. Povidone-Iodine solution has been marketed in the USA by the name of Betadine® and in Japan by the name of Isodine®. Povidone-Iodine is effective at killing bacteria as well as fungus, therefore, it has been used not only for the middle ear surgery to disinfect surgical fields but also to irrigate the middle ear cavity to treat intractable middle ear discharge. The worldwide use of this product has prompted us to re-evaluate the possible ototoxicity of this product.

2. Materials and methods

To evaluate the ototoxicity of Povidone-Iodine preparation (ISODINE ® solution 10% Meiji Seika, Japan), albino Hartley guinea pigs were used.

To study the effect of animal maturity on ototoxicity, animals were divided into 3 age groups.

The infant group were between 5 and 7 days of age and had body weights of 100 ± 10 grams.

The young group were between 12 and 16 days of age with body weights of 200 ± 20 grams.

The adult groups were over 6 weeks with body weights of 400 ± 30 grams.

One middle ear cavity was filled with Isodine ® 10% solution, while the contralateral side was filled with isotonic saline solution. We evaluated the following: (1) the effect on the action potential threshold of Isodine ® 10% solution at 24 h, at 7 days, and at 28 days after topical application, (2) the effect of 2 and 8 fold diluted Isodine ® solution on the CAP at 24 h, at 7 days, and at 28 days.

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Repeated measurements from the same animal were not done due to the possibility of introducing infection.

In a separate animal group, the effect of Isodine® Scrub was also studied.

This protocol was approved by Fukuoka University Animal Ethics Committee.

2.1. Anesthetics

The animals were anesthetized with sodium pentobarbital (30 mg/kg) and were secured in a custom-made head holder. Xylocaine 0.5% was infiltrated into the surgical area before making the skin incision for access to the middle ear cavity.

2.2. Surgery

The bulla was exposed using a retro-auricular incision. A small hole, about 2 mm in diameter, was made using a dental drill, and the round window membrane was visualized with a 40× operating microscope.

2.3. Drug application

One side of the middle ear cavity was filled with Isodine ®, and the contra-lateral ear was filled with saline as a control. The amount of fluid necessary to fill the middle ear cavity was about 0.2 ml.

2.4. Sound system

Asynchronous tone bursts of 2 kHz, 4 kHz, 8 kHz (1-ms rise and fall time, 10-ms plateau time), and click sounds were given as stimuli at a pulse rate of 20 per second, from 80 dB (re 20 μPa) to thresholds with 10 dB increments. The speaker used was a Telephonics TDH-39P, and the sound source was placed 15 cm away from the auricle. The free field sound pressure was monitored and calibrated with a Brüel & Kjær half-inch condenser microphone.

2.5. Recording system

An 0.08-mm-diameter Teflon-insulated silver wire with an exposed ball tip was carefully placed with a micromanipulator on the peripheral round window membrane. An Ag–AgCl reference electrode was placed in the neck muscles. The obtained CAP responses were averaged 200 times with a Traveler Express ER-22 (Biologic Systems Corp., USA).

2.6. Analysis of the data

A threshold response was defined as an N1–P1 signal with amplitude of 10 μV. Saline-treated ears and Isodine® treated ears were compared. An unpaired *t*-test was used to define statistical significance.

3. Results

In total, 70 animals were studied successfully.

Table 1 shows the results of CAP at 24 h. The figure in the tables indicates the sound pressure (in dB) necessary to elicit a 10 μV threshold of CAP.

At 24 h, Povidone-Iodine showed a significant toxic effect in the infant group. In the young animal group, no toxic effect was seen. In the adult group however, a mild degree of deafness for 2 kHz was found (Table 1).

Table 1
Maturity of the animals divided into three groups (infant, young, and adult group) and changes in CAP with Isodine® full strength (10% solution) at 24 h. The figures indicate the sound pressure level in dB to elicit 10 micro volts threshold.

	Full strength after 24 h		
	Infant group ($N=6$)	Young group ($N=7$)	Adult group ($N=6$)
Click			
Povidone iodine	61.8 ± 11.7	48.2 ± 6.8	49.7 ± 9.2
Saline	39.2 ± 14.0*	43.5 ± 10.8	40.8 ± 5.2
TB 8 kHz			
Povidone iodine	83.6 ± 7.8	52.0 ± 9.3	57.0 ± 9.5
Saline	45.9 ± 12.8*	53.4 ± 16.4	49.5 ± 3.5
TB 4 kHz			
Povidone iodine	79.4 ± 11.8	61.2 ± 10.1	70.0 ± 14.3
Saline	54.3 ± 24.2*	55.2 ± 14.3	69.1 ± 4.6
TB 2 kHz			
Povidone iodine	77.4 ± 10.1	67.6 ± 5.4	72.8 ± 9.9
Saline	55.7 ± 11.0*	67.0 ± 10.3	63.1 ± 5.9*

(dB re SPL).
* $p < 0.05$. Mean ± S.D.

Using Povidone Iodine Scrub, CAP was completely abolished for all age groups, hence these data was not included in this table.

At 7 days, the young group showed significant hearing loss for all frequencies except for tone bursts at 4 kHz. At 7 days, only 2 animals out of 7 survived in this young group, thus the small number of the animals and large variation of the data resulted in a seemingly insignificant result for this sound (Table 2, left column).

The adult group did not show significant hearing loss at 7 days (Table 2, middle column).

After 28 days, however, in the adult group, only 2 out of 7 survived; these showed extensive hearing loss at all frequencies (Table 2, right column).

The original 10% Isodine solution was diluted with saline to 5% and applied into the middle ear cavity.

With this half strength solution, after 7 days, both the young and adult group did not show significant hearing loss (Table 3).

At 28 days, with a full strength solution, hearing loss became prominent for all sound stimulation, as shown in Table 2, right column. With an 8 fold dilution, it was interesting to find that the young group showed a moderate hearing loss, but the adult group did not (Table 4).

Tone burst at 8 kHz did not show significant difference in the young group because of the large standard deviation. However, a difference in susceptibility is consistent with the observed results (Table 4).

Table 2
Changes in CAP at 7 days for young and adult group, and at 28 days for adult group.

	Full strength after 7 days and 28 days		
	Young group	Adult group	
	After 7 days ($N=2$)	After 7 days ($N=6$)	After 28 days ($N=2$)
Click			
Povidone iodine	68.8 ± 5.4	42.4 ± 4.4	67.3 ± 1.8
Saline	35.4 ± 2.7*	37.5 ± 4.1	30.9 ± 1.6*
TB 8 kHz			
Povidone iodine	113.0 ± 0.0	44.8 ± 6.5	77.7 ± 1.6
Saline	36.9 ± 8.7*	39.2 ± 8.2	38.0 ± 14.1*
TB 4 kHz			
Povidone iodine	91.0 ± 21.2	49.5 ± 7.9	77.6 ± 0.5
Saline	46.0 ± 7.1	46.3 ± 4.7	37.4 ± 1.9*
TB 2 kHz			
Povidone iodine	67.1 ± 0.9	57.8 ± 6.5	84.3 ± 4.3
Saline	57.4 ± 2.1*	58.0 ± 3.2	53.9 ± 1.6*

(dB re SPL).
* $p < 0.05$. Mean ± S.D.