

## 이명에 대한 Glutamate 길항제의 치료효과

아주대학교 의과대학 이비인후과학교실

정연훈 · 박홍준 · 송정환 · 유상준 · 문성균 · 박기현

### Treatment Effects of Glutamate Antagonist for Tinnitus

Yun-Hoon Choung, DDS, MD, Hong-Joon Park, MD, Jung-Whan Song, MD,  
Sang Jun Ryu, MD, Sung-Kyun Moon, MD and Keehyun Park, MD

Department of Otolaryngology, Ajou University School of Medicine, Suwon, Korea

#### ABSTRACT

**Background and Objectives** : Tinnitus is one of the most widespread disorders of the auditory system, affecting approximately 17% of the general population, with the frequency increasing to about 33% in the elderly. However, little is known about the underlying physiological mechanism that causes tinnitus and there is no definite treatment. Recently, several studies have showed that subjective tinnitus is mostly generated at the synapse between inner hair cells and their afferent nerves and in addition, some have showed that glutamate is likely to act as the neurotransmitter. The aim of this study has been to evaluate the effective use of caroverine hydrochloride and memantine hydrochloride for tinnitus treatment and to determine their appropriate indication of glutamate antagonist therapy. **Materials and Method** : From May 1998 through June 2000, 188 patients with subjective tinnitus were treated with caroverine hydrochloride (Spamon<sup>®</sup>). Of the patients, 153 were followed, and 20 of these patients who did not respond to caroverine hydrochloride were treated additionally with memantine hydrochloride (Akatinol<sup>®</sup>). Audiological evaluations were performed in all of the patients. Pre and post-treatment status was analyzed by handicap inventories. **Results** : Subjective tinnitus was improved in 55 (35.9%) of 153 patients who were treated with caroverine hydrochloride and 11 (55.0%) of 20 patients with memantine hydrochloride. The response group had tendency of shorter duration history of tinnitus than the non-response group. There was no difference between the response group and the non-response group in age, sex, site, and tinnitus characteristics. **Conclusion** : We suggest that glutamate antagonists such as caroverine hydrochloride and memantine hydrochloride can be used as an alternative modality for treatment of subjective tinnitus. (Korean J Otolaryngol 2003;46:935-9)

**KEY WORDS** : Tinnitus · Glutamate antagonists · Therapeutics.

17%, 1/3, 8)9) glutamate가  
20% , 10) glutamate NMDA(N - methyl -  
d - aspartate) AMPA( - amino - 3 - hydroxy - 5 - me-  
thyl - 4 - isoxazone - propionic acid)가 11)  
glutamate  
glutamate  
가 Oestreicher  
glutamate  
가 12)  
가  
glutamate caroverine hydrochloride

5) , 6) , 7) , 1)2) , 3)4)

: 2003 3 25 / : 2003 9 19  
: , 442 - 749 5 가

: (031) 219 - 5263 · : (031) 219 - 5264  
E - mail : yhc@ajou.ac.kr



**Table 2.** Factor analysis according to the effect of caroverine hydrochloride

|                                | Effect (+)        | Effect (-)        | p-value |
|--------------------------------|-------------------|-------------------|---------|
| Sex (male/female)              | 28/27             | 61/37             | .173    |
| Age (years)                    | 46.5<br>(18 - 68) | 45.3<br>(20 - 76) | .675    |
| Site (right/left/both)         | 19/24/12          | 37/34/27          | .523    |
| Durations (months)             | 22.5              | 30.3              | .370    |
| Bone conduction threshold (dB) | 34.6              | 32.7              | .570    |

**Table 3.** Difference of tinnitus characteristics according to the effect of caroverine hydrochloride N (%)

|           | Effect (+) | Effect (-) |
|-----------|------------|------------|
| Machinery | 32 (58.2)  | 33 (33.7)  |
| Insect    | 17 (30.9)  | 33 (33.7)  |
| Rain      | 4 ( 7.2)   | 6 ( 6.1)   |
| Wind      | 2 ( 3.6)   | 11 (11.2)  |
| Sea       | 0          | 3 ( 3.1)   |
| Others    | 0          | 12 (12.2)  |
| Total     | 55 (100)   | 98 (100)   |

p=.095

**Table 4.** Difference of type of hearing loss according to the effect of caroverine hydrochloride N (%)

|                 | Effect (+) | Effect (-) |
|-----------------|------------|------------|
| Descending      | 26 (47.3)  | 57 (58.2)  |
| High tone only  | 6 (10.9)   | 17 (17.3)  |
| Ascending       | 5 ( 9.1)   | 2 ( 2.0)   |
| Mid-tone        | 3 ( 5.4)   | 2 ( 2.0)   |
| Spared mid tone | 0 ( 0 )    | 4 ( 4.1)   |
| Normal          | 6 (10.9)   | 6 ( 6.1)   |
| Sudden H/L      | 9 (16.4)   | 10 (10.2)  |
| Total           | 55 (100)   | 98 (100)   |

\*H/L : hearing loss

p=.232

(Table 2).

가

(Table 3).

가 가

(Table 4).

4 KHz 8 KHz  
(Table 5),  
10 dBSL

(loudness)

가 가

**Table 5.** Difference of pitch of tinnitus according to the effect of caroverine hydrochloride N (%)

| Frequency (KHz) | Effect (+) | Effect (-) |
|-----------------|------------|------------|
| 0.25            | 10 (18.2)  | 15 (15.3)  |
| 0.5             | 0 ( 0 )    | 6 ( 6.1)   |
| 1               | 0 ( 0 )    | 2 ( 2.0)   |
| 2               | 3 ( 5.5)   | 3 ( 3.0)   |
| 4               | 13 (23.6)  | 13 (13.3)  |
| 8               | 29 (52.7)  | 59 (60.2)  |
| Total           | 55 (100)   | 98 (100)   |

p=.216

**Table 6.** Difference of loudness of tinnitus according to the effect of caroverine hydrochloride N (%)

| Loudness (dBSL) | Effect (+) | Effect (-) |
|-----------------|------------|------------|
| 0 - 10          | 40 (72.7)  | 73 (74.5)  |
| 11 - 20         | 13 (23.6)  | 14 (14.3)  |
| 21 - 30         | 0 ( 0 )    | 6 ( 6.1)   |
| 31 - 40         | 2 ( 3.6)   | 2 ( 2.0)   |
| 41 - 50         | 0 ( 0 )    | 3 ( 3.1)   |
| Total           | 55 (100)   | 98 (100)   |

p=.204

(Table 6).

20%

tocainide가

1)2)

,

가

1-8)

1980 Tonndorf  
reocilia)

(ste-

14)

Lieberman King  
(single fiber)  
taneous activity)가

, aminoglycoside  
(spon-  
가

가  
15) Eggermont  
tympani)

(Scala

16)  
 . 1983 Ehrenberger Brix 가 가  
 caroverine hydrochloride  
 9) mont 가 , 24  
 ,<sup>8)</sup> 1990 Egger- 35.9% Denk<sup>18)</sup>  
 glutamate가  
 (subsynaptic afferent 가  
 dendritic membrane) glutamate ionotropic caroverine hydrochloride  
 NMDA AMPA가 glutamate  
<sup>10)</sup> NMDA AMPA  
 (dual receptor system) , Oestreicher memantine  
 (sound induced depolariza- hydrochloride  
 tion) ,<sup>12)</sup> 가  
 , glutatmate 30%  
<sup>11)</sup> 1990 Felix Ehrenberger<sup>17)</sup>  
 glutamate  
 가  
 1997 Denk<sup>18)</sup> - (Cochlear syna-  
 ptic tinnitus, CST) caroverine hydro-  
 chloride 63.3% infusion  
 ionotropic glutamate ,  
<sup>11)</sup>  
 tropic 가 iono- caroverine  
 metabotropic 가 memantine , caroverine  
 memantine  
 Caroverine hydrochloride quinoxaline caroverine 35.9%, mementine 55.0%  
 가  
 glutamate  
 AMPA , NMDA  
 가  
 . Memantine hydrochloride  
 glutamate . NMDA Glutamate caroverine hydrochloride(Spa-  
 mon<sup>®</sup>) memantine hydrochloride(Akatinol<sup>®</sup>)  
 가  
 가

가 , glutamate  
가  
: Glutamate

#### REFERENCES

- 1) Jung YG, Yoo HK. *Clinical studies of the mangement of tinnitus with intravenous lidocaine and oral dilantin. Korean J Otolaryngol* 1987; 30:677-84.
- 2) Hulshof JH, Vermeij P. *The value of tocinide in the treatment of tinnitus: A double-blind controlled study. Arch Otorhinolaryngol* 1985; 241:279-83.
- 3) Donaldson I. *Tegretol: A double blind trial in tinnitus. J Laryngol Otol* 1981;95:947-51.
- 4) Guth PS, Risey J, Briner W, Blair P, Reed HT, Bryant G. *Evaluation of amino-oxyacetic acid as a palliative in tinnitus. Ann Otol Rhinol Laryngol* 1990;99:74-9.
- 5) Johnson RM, Brummentt R, Schleuning A. *Use of alprazolam for relief of tinnitus: A double-blind study. Arch Otlaryngol Head and Neck Surg* 1993;119:842-5.
- 6) Dobie RA, Sakai CS, Sullivan MD, Katon WJ, Russo J. *Antidepressant treatment of tinnitus patients: Report of a randomized clinical trial and clinical prediction of benefit. Am J Otol* 1993;14:18-23.
- 7) Holgers KM, Axelsson A, Pringle I. *Gingko biloba extract for the treatment of tinnitus. Audiology* 1994;33:85-92.
- 8) Ehrenberger K, Brix R. *Glutamic acid and glutamic acid diethyl ester in tinnitus treatment. Acta Otolaryngol (Stockh)* 1983;95:599-605.
- 9) Eggermont JJ. *On the pathophysiology of tinnitus: A review and peripheral model. Hear Res* 1990;48:111-24.
- 10) Pujol R, Puel JL, Gervais d'Aldin C, Eybalin M. *Pathophysiology of the glutamatergic synapse in the cochlea. Acta Otolaryngol (Stockh)* 1993;113:330-4.
- 11) Ehrenberger K, Felix D. *Receptor pharmacological models for inner ear therapies with emphasis on glutamate receptor: A survey. Acta Otolaryngol (Stockh)* 1995;115:236-40.
- 12) Oestreicher E, Arnold W, Ehrenberger K, Felix D. *New approaches for inner ear therapy with glutamate antagonists. Acta Otolaryngol (Stockh)* 1999;119:174-8.
- 13) Newman CW, Jacobson GP, Spitzer JB. *Development of the tinnitus handicap inventory. Arch Otolaryngol Head Neck Surg* 1996;122:143-8.
- 14) Tonndorf J. *Stereociliary dysfunction, a cause of sensory hearing loss, recruitment, poor speech discrimination and tinnitus. Acta Otolaryngol* 1991;91:469-71.
- 15) Liberman MC, Kiang NYS. *Acoustic trauma in cats. Acta Otolaryngol Suppl (Stockh)* 1978;358:1-69.
- 16) Eggermont JJ. *Tinnitus: Some thought about its origin. J Laryngol Otol Suppl* 1984;9:31-5.
- 17) Felix D, Ehrenberger K. *A microiontophoretic study of the role of excitatory aminoacids at the afferent synapse of mammalian inner hair cells. Eur Arch Otorhinolaryngol* 1990;248:1-3.
- 18) Denk DM, Heinzl H, Franz P, Ehrenberger K. *Caroverine in tinnitus treatment. Acta Otolaryngol (Stockh)* 1997;117:825-30.
- 19) Newman CW, Sandridge SA, Jacobson GP. *Psychometric adequacy of the tinnitus handicap inventory (THI) for evaluating treatment outcome. J Am Acad Audiol* 1998;9:153-60.