
The Use of Recombinant Tissue-Type Plasminogen Activator for the Treatment of Sudden and Chronic Hearing Loss

Renzo Mora, Massimo Dellepiane, Francesco Mora, and Barbara Jankowska
Ear, Nose, and Throat Department, University of Genoa, Genoa, Italy

Abstract: We treated 80 patients with sudden hearing loss and 70 patients with chronic decreasing cochlear function to date with intravenous infusion of a glycoprotein analogous to recombinant tissue-type plasminogen activator (rt-PA): 3 mg dissolved in 250 mg of physiological saline given every 12 hours intravenously. Specifically excluded were patients with known abnormal coagulation. We treated no patient for longer than 20 days. Before therapy, 6 months therapy began, and at the end of treatment, all patients underwent the following instrumental examinations: prothrombin and fibrinogen level measurements, liminal tonal audiometry, tympanometry, and assessment of otoacoustic emissions and otoacoustic products of distortion. Daily during the treatment, we monitored the patients by liminal tonal audiometry and assessment of otoacoustic emissions with linear click emission and otoacoustic products of distortion. We discharged patients when their audibility threshold stabilized. No patient experienced side effects due to the treatment, and functional results were excellent in all (even more so if compared with the protocols of therapy previously used for these kinds of diseases). The tissue plasminogen activator was used with remarkable success for the treatment of sudden hearing loss; this study shows remarkable success with a very low dose of rt-PA as compared to the standard dosage used for treatment of myocardial infarction.

Key Words: chronic decreasing cochlear function; sudden hearing loss; tissue-type plasminogen activator

Sudden hearing loss and chronic decreasing cochlear function are two of the most common health problems that can affect people at any age [1,2]. Hearing impairment is associated with important adverse effects on the quality of life, and these effects are perceived as severe handicaps even by individuals with only mild to moderate degrees of hearing loss [3]. The causes of the aforementioned diseases are varied and often unidentified; they may involve vascular, viral, autoimmune, and traumatic episodes or may occur as a result of pressure changes but, in the end, the result of most of them is a microthrombotic vascular lesion [4-6].

Therapeutic approaches normally used for these patho-

logical conditions include the systemic and local administration of cortisone, vasoactive substances, anticoagulants, and even vitamin B complexes [4,5]. However, until now, no standard therapeutic protocol was available for the management of these conditions. Nearly 10 years ago, Hagen [7] reported on the use of 100 mg of a recombinant tissue-type plasminogen activator (rt-PA [Actilyse]) for its fibrinolytic effect in the treatment of sudden hearing loss. Hagen observed in affected patients an average decreased plasma viscosity and a marked improvement in hearing.

Because bleeding complications are a problem during any high-dose fibrinolytic regimen, whether a lower dose of the fibrinolytic agent might show promise in treating acute hearing loss is worth exploring [8,9]. The aim of our study was to determine the efficacy and feasibility of the administration of a low dose of rt-PA for sudden hearing loss and chronic decreasing cochlear function.

Reprint requests: Renzo Mora, MD, Via dei Mille 11/9, 16147 Genoa, Italy. Phone: +39-010-3537631; Fax: +39-010-3537684; E-mail: renzomora@libero.it

SUBJECTS AND METHODS

We selected 80 patients who were between the ages of 16 and 85 years, were affected by a mild to severe sudden hearing loss (average loss, 55 dB of audibility threshold demonstrable by hearing test), and provided informed consent. We divided them randomly into two groups, A and B. We also included 70 patients with a "chronic" history of sudden hearing loss and divided them into two groups, C and D. The characteristics of patients in groups A and C are itemized in Table 1.

We have not treated patients with known abnormal coagulation; bleeding diathesis; suspected aortic dissection; recent serious bleeding episode (including a history of brain hemorrhage); active internal bleeding; hemorrhagic retinopathy; current gestation or nursing; history of damage to central nervous or urinary tract systems within the previous 3 months; cirrhosis; hepatic insufficiency; neoplasia; or recent surgical operations or trauma other than the incident leading to the acute loss of hearing.

Before therapy, 6 months therapy began, and at the end of therapy, all patients underwent the following instrumental examinations: routine blood examination, blood-clotting factor analysis (assessment of prothrombin and fibrinogen levels), liminal tonal audiometry, tympanometry, and assessment of otoacoustic emissions and otoacoustic products of distortion. Daily during the treatment, we performed liminal tonal audiometry and assessment of otoacoustic emissions with linear click emission and otoacoustic products of distortion.

To patients in groups A and C, we administered rt-PA intravenously at a dose of 3 mg dissolved in 250 mg of physiological solution twice daily. Group B and D (control) patients received steroids, vasoactive substances, and multivitamins administered in the same way. We discharged patients when their audibility

Table 1. Characteristics of Patients with Sudden Hearing Loss

Characteristics	Group A (n = 40) (mean ± SEM)	Group C (n = 35) (mean ± SEM)
Age	52.3 ± 4.23	58.9 ± 5.31
Tinnitus	12	9
Vertigo	2	2
Diabetes mellitus	8	4
Smoking	14	11
Treatment days with rt-PA	13.2 ± 1.29	15.7 ± 1.44
Pretreatment prothrombin (%)	95.4 ± 0.78	98.1 ± 0.85
Posttreatment prothrombin (%)	95.2 ± 0.52	98.3 ± 0.47
Pretreatment fibrinogen (mg/dl)	303.9 ± 13.83	311.9 ± 12.83
Posttreatment fibrinogen (mg/dl)	340.7 ± 13.73	311.4 ± 12.47

SEM = standard error of the mean.

Table 2. Hearing Improvement in Group A and Group C

Frequency (Hz)	Group A (n = 37) (mean ± SEM)	Group C (n = 20) (mean ± SEM)
125	17.1 ± 2.29	—
250	16.2 ± 1.97	—
500	29.2 ± 1.75	19.8 ± 2.57
1,000	18.8 ± 2.22	21.2 ± 2.23
2,000	22.9 ± 3.30	24.3 ± 3.23
4,000	23.7 ± 3.88	22.5 ± 2.44
8,000	16.1 ± 3.19	—

SEM = standard error of the mean.

threshold stabilized. We treated no patient for longer than 20 days.

Comparison of groups was made by the unpaired *t*-test, and correlations were analyzed by regression analysis; probability values at less than .05 were regarded as significant. Comparisons of groups also were made for repeated measures by analysis of variance. No patient experienced side effects from this treatment.

RESULTS

Of the patients in group A, 37 showed improvement of hearing after receiving rt-PA. Mean hearing improvement for these patients ranged from 16.1 to 29.2 dB across the 125- to 8,000-Hz range examined (Table 2). Hearing improved in 20 patients (57%) in group C and was unchanged in 15 patients (43%); mean hearing improvement for these patients ranged from 19.8 to 24.3 dB across the 500- to 4,000-Hz range examined. The characteristics of the hearing test are summarized in Table 2. In no patient of the two groups (A and C) have we noticed significant modifications of the prothrombin and fibrinogen levels after treatment.

In all the patients who showed an improvement in auditory function, the evoked otoacoustic emissions revealed an improvement from "fail" to "pass." Otoacoustic distortion products, which were previously absent, were evoked at frequencies of the tonal field normally examined.

DISCUSSION

Sudden sensorineural hearing loss is one of the most controversial issues in otology. General agreement surrounds the definition of the clinical entity: unilateral sensorineural hearing loss of at least 30 dB for three consecutive frequencies on the tonal audiogram with onset within the last 3 days. However, pathogenesis and appropriate treatment remain open questions [10]. Sev-

eral experimental studies have attempted to reproduce the mechanisms of infection, ischemic trauma, or autoimmunity leading to sudden-onset cochlear dysfunction, but extrapolation to the clinical situation is hazardous [11,12].

For at least two reasons, clinicians have had great difficulty in unraveling this clinical entity. First, exploring the inner ear directly is impossible, basically owing to the lack of any usable electrochemical data. Second, therapeutic trials are hampered because of the difficulty of recruiting a sufficiently large population within a reasonable time span [10,13].

Treatment guidelines are controversial and change in accordance with the clinical experience. However, although relative agreement has been reached on the efficacy of corticosteroid therapy, several protocols have been proposed, including vasodilators, anticoagulants, carbogen macromolecules, or antiviral agents [14,15].

The function of the inner ear is to convert mechanical energy into a spatial-temporal pattern of activity within the auditory nerve fibers. The normal function of the cochlea depends on appropriate extra- and intracellular milieus. One component of this, as in any organ, is the efficient delivery of O₂ and nutrients, their metabolism, and the removal of waste products. Cochlear microcirculation is vulnerable, as no possibility exists for shunting from the periphery in case of vascular occlusion. In addition, only a little regulation of blood flow is possible in the cochlea [16]. Therefore, the cochlea likely is susceptible to an impairment of rheological properties of whole blood. Patients with chronic hearing loss display a clear correlation between rheological parameters and the pure-tone threshold. Several studies of patients with acute hearing loss have revealed a significant correlation with increased plasma viscosity and pure-tone threshold between 2 and 4 kHz [17,18]. These findings have led to therapeutic approaches using, for example, batroxobin, a potent enzyme that converts fibrinogen to a soluble fibrin complex.

We found, on those bases, that therapies using rt-PA have a field of action. Actilyse tissue plasminogen activator (rt-PA) is a 68-kD human single-chain fibrin-dependent serine protease; rt-PA forms a complex with fibrin, which converts plasminogen to plasmin. It provides more rapid lysis than that of other serine proteases, produces less systemic fibrinolytic activity, and is not immunogenic; however, it can result in abnormal bleeding as a complication [7,8,19,20]. Under optimal dosage, it induces clot lysis without development of a systemic lytic state. Recanalization is more frequently marked by depletion of fibrinogen, indicating that a systemic lytic state may be present, which may be a marker of pharmacological effects that can lead also to absence of bleeding. The active ingredient in Actilyse,

a recombinant glycoprotein similar to rt-PA, promotes the transformation of plasminogen absorbed by a thrombus of fibrin in plasmin. Plasmin degrades the fibrin into small flakes that are removed by monocytes and macrophages. Although plasmin can also degrade fibrinogen, such action is localized because rt-PA and some forms of urinary plasminogen activator activate the precursor more effectively when absorbed in a thrombus of fibrin [8,9,10,21].

rt-PA was first used with remarkable success for the treatment of sudden hearing loss. Our study also shows remarkable success with a very low dose of rt-PA as compared to the standard dosage used for the treatment of myocardial infarction [7,10,21]. In our protocol, we reduced the full dosage of rt-PA used for a heart attack or a brain stroke (15 mg intravenously, then 50 mg after 30 minutes and 35 mg after 60 minutes, up to a maximum dose of 100 mg) to 3 mg dissolved in 250 mg of physiological saline given every 12 hours intravenously. Through a highly selective process and the much lower dosage we selected, no side effects of our treatment were seen. The recovery of hearing loss was more prominent in cases of sudden hearing loss than in those patients with sudden hearing loss of longer duration.

We believe that older patients can improve better than can younger patients primarily because of the risk of thrombosis in younger patients. It is very interesting that at this lower dosage, the results were as good as they were, even in the chronic patients. Possibly this treatment results in the lysis of microthrombi in the cochlear vasculatures, thereby increasing blood supply to the organ of Corti.

CONCLUSIONS

In previous studies, rheological parameters were regarded as necessary when patients were treated with an intravenous dose of 100 mg of Actilyse. At the strikingly lower dosage we used, measurements of hemorrhagic data were not collected from our patients. Our clinical results, in combination with results of previous reports by others, indicate that rt-PA could be a powerful therapeutic tool even at the lower dose of approximately 6% of cardiac disease dosage per day for a 2-week duration.

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