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Possible role of plasminogen activator in the occurrence of profuse watery rhinorrhea after topical application of epinephrine to the nasal mucosa*

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SUMMARY

Epinephrine and lidocaine have been used for the diagnosis and treatment of nasal diseases. However, watery rhinorrhea and frequent sneezing occur in many patients after topical application of these drugs to the nasal mucosa. This study was aimed at characterizing these side effects, and developing a means to prevent such side effects. A questionnaire was given to each patient who complained of side effects after treatment with epinephrine and lidocaine, and the answers were analyzed with respect to the occurrence and features of the symptoms after the treatment. Eosinophil and mast cell numbers were determined in nasal smears from the patients with side effects. These side effects were different from rhinitis medicamentosa and allergic rhinitis, and were due to epinephrine, not to lidocaine or to the preservatives in the epinephrine. Tranexamic acd, an inhibitor of plasmin, was effective in blocking the side effects.

Key words: epinephrine, watery rhinorrhea, plasminogen activator, tranexamic acid, sympathetic nerve.

INTRODUCTION

Epinephrine by local nasal application has been used to cause vasoconstriction and to reduce the congestion due to nasal mucosal swelling. Profuse watery rhinorrhea and sneezing, however, result in many patients after topical application by spraying or painting of epinephrine solution, and this is a troublesome problem to both patient and doctor. These side effects of epinephrine have been considered to be due to hypersensitivity to the drug or to vasomotoric rhinitis (Lake, 1946). The details and real cause of these side effects remain unsolved.

Rhinitis medicamentosa is known to be produced after frequent topical application and overuse of imidazoline derivatives of decongestive drugs to the nasal mucosa (Lake, 1946; Graf and Hallen, 1997; Graf, 1997). Epinephrine is another kind of decongestive drug and is a sympathomimetic amine (Stride, 1967; Bende and Loth, 1986). The side effects caused by epinephrine result from only one application in most cases and occur at least a few hours after the topical application. Some patients consider the side effects even as a necessary function for the treatment of the nasal mucosa, and do not complain about the uncomfortable side effects, which may go unnoticed after long usage. In the present study a questionnaire was given to patients with side effects due to epinephrine, and their answers were analyzed with respect to the occurrence of symptoms and distinction from the characteristic of rhinitis medicamentosa and other nasal disorders.

Lidocaine and preservatives contained in the epinephrine solution, which were topically applied to the nasal mucosa along with epinephrine, were studied to determine whether these individual components also could induce the side effects.

When normal persons were stressed by the subcutaneous injection of epinephrine, evidence for activation of the fibrinolytic process was found in the blood (Biggs et al., 1946, Sherry et al., 1955). The inactive plasma protein, plasminogen, is converted to plasmin by an activator which comes directly from the tissues when they are damaged by trauma or anoxia. Plasmin, a proteolytic enzyme, induces lysis of fibrin and other plasma proteins. When fibrin or fibrinogen are decomposed by plasmin, breakdown products are released. There is an increased vascular permeability as one of the actions of the degradation product. The profuse watery rhinorrhea seen after local application of epinephrine onto the nasal mucosa is thought to be related to the increase in the vascular permeability caused by the breakdown products of fibrin or fibrinogen digested by plasmin activated in the nasal mucosa. Thus, the

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influence of tranexamic acid, a plasmin inhibitor, was studied by topical application of it to the nasal mucosa immediately following the application of epinephrine.

MATERIALS AND METHODS

Patients

Forty-two out patients, seen from August 1998 to May 1999, were eligible for the study when they complained of side effects such as profuse watery rhinorrhea and sneezing after topical application of epinephrine and lidocaine by spraying onto the nasal mucosa.

Questionnaire

The questionnaire was composed of the following items:
time interval until occurrence of symptoms of watery rhinorrhea and sneezing after spraying of epinephrine and lidocaine onto the nasal mucosa,
duration time of symptoms,
type of symptoms,
part of nasal cavity in which symptoms occurred, and
frequency of nose blowing.

Drug

The commercial epinephrine solution (Daiichi Co. Ltd.) contained epinephrine (1 mg/ml) and chlorobutanol (3 mg/ml) and sodium bisulfite (0.5 mg/ml) as preservatives. In the out-patient clinic, the epinephrine was diluted 5-fold with physiological saline to 0.2 mg/ml, and 0.3 ml was sprayed into each nostril. To test the effect of the preservatives used alone, we prepared a mixed solution of chlorobutanol (Daiici Co. Ltd.) and sodium bisulfite (Daiici Co. Ltd.) at concentrations of 0.6 mg/ml and 0.1 mg/ml, respectively, in physiological saline. Next, 0.3 ml of the mixed solution was applied to the nasal mucosa of each nostril. An epinephrine solution without chlorobutanol and sodium bisulfite was not made. Lidocaine hydrochloride (Fujisawa Co. Ltd.) at a concentration of 5 mg/ml in physiological solution (0.3 ml) was sprayed into each nostril. When used, tranexamic acd solution (0.3 ml, 1.0g/10 ml, Daiici Co. Ltd.) was also sprayed into each nostril.

Study design

The questionnaire was given to the patients who came to see the doctor in the out-patient clinic again after the previous treatment and who had complained of profuse watery rhinorrhea and sneezing after topical spraying of epinephrine (0.2 mg/ml) and lidocaine (5 mg/ml).
The content and character of the complaints were studied by analyzing the answers to the questionnaire. Forty-two patients responded to the questionnaire from October 1998 to May 1999, 10 males and 32 females with an age of 35-81 years.
Then, only lidocaine (5 mg/ml) or epinephrine (0.2 mg/ml) or a solution containing only the preservatives of chlorobutanol (0.6 mg/ml) and sodium bisulfite (0.1 mg/ml) or epinephrine (0.2 mg/ml) and 10% tranexamic acid was sprayed topically onto the nasal mucosa of the patients reporting the side effects. A drug was first tested on the nasal mucosa of each of the 42 patients. The reaction and the side effect of the drug on the nasal mucosa were evaluated when the patient returned to the clinic several days later. Several days after checking the reaction or the side effect, another drug was applied onto the nasal mucosa. The selection of the patient and the practice of the application of the drug to the nasal mucosa were done for every patient who was confirmed to have the reaction or the side effect to the drug. The order of application of these drugs to the nasal mucosa was as follows: lidocaine, epinephrine, epinephrine and tranexamic acid (a solution of 10 % tranexamic acid sprayed onto the nasal mucosa immediately following topical application of epinephrine to the nasal mucosa), chlorobutanol and sodium bisulfite. The number of patients whose reaction to or side effect of each drug on the nasal mucosa was examined was 42 cases for lidocaine, 25 cases for epinephrine, 24 cases for epinephrine and tranexamic acid, and 20 cases for chlorobutanol and sodium bisulfite. The final number of patients who were observed to have the reaction or the side effect to all test drugs was 20. The cytology of eosinophils and mast cells was studied by microscopic examination of Hansel's-stained smears of the nasal secretion from 10 patients who complained of side effects after spraying of epinephrine and lidocaine onto the nasal mucosa (Sasaki et al., 1977).
Grade of red or pale colour and grade of swelling of the nasal mucosa were observed by rhinoscopy.

RESULTS

1) The time interval between the topical nasal application of drug and the onset of symptoms such as watery rhinorrhea and sneezing was about 30 to 60 minutes in most cases (Table 1). The symptoms usually lasted for about 2 days, though in a few cases the duration was 2-3 hours or as long as 3 days (Table 2). After the spontaneous disappearance of the symptoms, no other trouble remained. At first, most patients with the side effects suffered from profuse watery nasal discharge (n=42) and sneezing (n=28). There was a number of patients who complained of watery rhinorrhea without sneezing. Some patients had a tingling pain (n=9) in the nose especially during respiration through the nose. There were itches (n=4) in the nose, headache (n=1) and dysphoria (n=1) as other symptoms reported.
   There were no patients who complained of nasal obstruction as a remarkable feature.
   The character of rhinorhrea was like water without viscidity and was not stagnant. It did not stay in the nasal cavity and continuously flowed out of the nostrils. Rhinorrhea was discharged as drops, and the patients had to keep holding a handkerchief or tissue paper to their nostrils to remove the running watery rhinorrhea. Most patients blowed their nose an unmeasured number of times, though some reported 5 or 10 times an hour due to the profuse rhinorrhea. However, most of the time, they wiped

Table 1. Time interval until occurrence of symptoms of watery rhinorrhea and sneezing after spraying of epinephrine to the nasal mucosa.

Minutes	30	60	120	180	240	360
No. of patients	19	16	2	1	1	3

Table 2. Duration of symptoms.

Duration (days)	one-half	one	two	three
No. of patients	9	10	20	3

off the rhinorrhea rather than blew their nose.

Symptoms usually manifested in both side of the nasal cavity (n=29), but in some patients they appeared in only one side of the nasal cavity (n=9 in the left one, n=4 in the right one).

Most patients experienced their nasal symptoms of profuse watery rhinorrhea after the first application of epinephrine to the nose, but in a few patients the symptoms appeared only after several applications.

2) A few patients had nasal allergy to house dust or pollen in their history. But just before and after these side effects, they did not show any allergic symptoms. Neither eosinophils nor mast cells appeared in the nasal secretion.

3) The local findings for their nasal mucosa revealed congestion and redness, but there was no paleness or hypertrophy to cause nasal obstruction or stuffiness.

4) For the patients who had complained of profuse watery rhinorrhea after the local application of epinephrine and lidocaine, abnormal symptoms appeared again only when epinephrine was sprayed onto the nasal mucosa (in all 25 patients), but not when lidocaine only was used (in all 42 patients).

5) The solution of chlorobutanol and sodium bisulfite caused no side effects after the topical application to the nasal mucosa of 20 patients who had complained of profuse watery rhinorrhea and sneezing after the topical use of epinephrine and lidocaine. Accordingly, the influence of only epinephrine without the preservatives was not studied.

6) When a 10 % solution of tranexamic acid was sprayed onto the nasal mucosa immediately after the topical use of epinephrine in 24 patients with side effects to epinephrine, 22 patients out of the 24 did not show any side effects of abnormal rhinorrhea and sneezing.

7) A 10 % solution of tranexamic acid was locally applied onto the nasal mucosa of 23 patients without any side effects of epinephrine and lidocaine on their nasal mucosa previously before this study started, and they did not show any particular findings or any side effects.

DISCUSSION

There are two main groups of decongestant and vasoconstrictor agents i.e., imidazoline derivatives and sympathomimetic amines. Prolonged overuse of local decongestant of imidazoline derivatives such as oxymetazoline in the nose results in stuffiness and rebound swelling of the nasal mucosa after the disappearance of the decongestive effect. The patient becomes increasingly dependent on the drug, which results in drug habituation. The symptoms are dissimilar to those found in allergic rhinitis. Profuse mucoid nasal discharge, narrowed nasal airway, and edematous or congestive swollen mucosa are characteristic. This phenomenon is called rhinitis medicamentosa (Lake, 1946; Hallen and Graf, 1995; Graf, 1997).

Epinephrine is one of the sympathomimetic amines and is weaker in decongestive and vasoconstrictor function than imidazolines such as oxymetazoline (Stride, 1967; Empey and Medder, 1981). Epinephrine, however, has been used with topical application for the purpose of diagnosis and treatment of nasal diseases. Lidocaine is a local narcotic, and reinforces the action of epinephrine. The successive topical use of epinephrine and lidocaine has been applied to increase the decongestive and vasoconstrictor action on the nasal mucosa in nasal diseases. In the present study, profuse watery nasal discharge and sneezing occurred after the successive use of lidocaine and epinephrine in many patients. However, topical nasal application of only lidocaine did not produce any watery rhinorrhea and other symptoms.

Epinephrine contains chlorobutanol and sodium bisulfite as preservatives. The topical nasal application of chlorobutanol and sodium bisulfite did not induce any side effect such as watery rhinorrhea, sneezing or others. Only epinephrine induced these side effects, and epinephrine remarkably did not cause any obstruction, thus showing a feature different from the obstruction found in rhinitis medicamentosa due to oxymetazoline and other imidazolines.

The arteries, arterioles, and venae of the nasal mucosa are surrounded by a rich adrenergic plexus (Dahlstrom and Fuxe, 1965; Nomura and Matsuura, 1972). These adrenergic nerves controll both the capacitance vessels regulating mucosal blood content and the resistance vessels regulating mucosal blood flow. Epinephrine is an alpha 1 and alpha 2 adrenoceptor ago-

nist. Both alpha 1- and alpha 2- adrenoceptors exist on the resistance vessels, i.e., those vessels that determine the blood flow, and on the capacitance vessels, i.e., those vessels that contain most of the blood volume in the nasal mucosa. On the other hand, imidazoline derivatives such as oxymetazoline and xylometazoline have an alpha-adrenoceptor-stimulating effect (Andersson and Bende, 1984; Bende and Loth, 1986; Malm, 1994). Whether the distinction of the adrenoceptor agonist of epinephrine and imidazoline derivatives might be related to the occurrence of the different side effects caused by these two kinds of decongestants applied topically onto the nasal mucosa is unknown. The profuse watery rhinorrhea after topical application of epinephrine onto the nasal mucosa appeared to look like water, was discharged as drops, and was not viscid. Nasal secretions may contain mucous glycoproteins, secreted protein such as albumin, IgA, secretory IgA (sIgA), IgG, transferrin, lactoferrin, and lysozyme, as well as inorganic ions, plasma cells, mast cells, basophils, eosinophils, epithelial cells, etc. Secretions may originate from the vascular system, and glands such as goblet cells, seromucous glands, and cells within the nasal mucosa. The character and contents of nasal secretions change according to nasal provocation by histamine, methacholine, allergen, or viral or bacterial infection. Methacholine provocation does not induce itch, sneezing or stuffiness, but elicits exclusively nasal glandular products and parasympathetically mediated mucosal output. Histamine challenge produces both clinical symptoms such as sneezing, itch, profuse watery rhinorrhea and nasal protein secretion through stimulation of H-1 receptors and through increased permeability (Brofeldt et al., 1986). The nasal secretory response induced by stimulation of histamine or methacholine was abrogated by each pretreatment with the antagonistic drug corresponding to each stimulant, i.e., antihistamine or atropine, respectively. After histamine challenge in the face of atropine pretreatment, all subjects developed the usual histamine associated symptoms, but these symptoms and signs could be significantly inhibited by the pretreatment of an H-1 antihistamine (Raphael et al., 1988; Raphael et al., 1989).

In the present study, the successive topical application of tranexamic acid, an inhibitor of plasmin, after the use of epinephrine, prevented the watery nasal rhinorrhea and sneezing. This finding suggested that plasmin probably would be related to the occurrence of profuse watery rhinorrhea after topical application of epinephrine onto the nasal mucosa. Whether antihistamine or anticholinergic agents are effective to prevent the side effects of watery rhinorrhea after topical application of epinephrine onto the nasal mucosa remains to be determined. Also the properties and contents of rhinorrhea after the application of epinephrine should be analyzed and compared with those after nasal provocation by histamine or methacholine or capsaicin.

Plasminogen activator has been found in the veins and venules in the nasal mucosa, especially in the plexus cavernous concharum of the nose (Sasaki et al., 1957). The localization of plasminogen activator in the nasal mucosa was recognized by fibrinolysis caused by nasal mucosa tissue on a fibrin plate or in fibrin clots treated with an extract of nasal mucosa (Sasaki et al., 1957). It was suggested that substances concerned with fibrinolysis were released from endothelial cells of the vessel wall into the circulation in certain condition such as ischemia (Kwaan et al., 1956). Plasminogen activator was recently detected in the adventitia, smooth muscle layer, and endothelium of the arterial vessel wall (Peng et al., 1999). The fibrinolysis resulted from plasmin formed from plasminogen existing in the fibrin by plasminogen-activator in the nasal mucosa. Plasminogen activator in the nasal blood vessels contributes to the maintenance of the fluidity of the blood in the nasal mucosa and is associated with the regulation of temperature and humidity of the air during respiration. Sympathetic and sensory neurons have been investigated for their relationship with plasminogen activator, which is involved in neurite outgrowth, cell migration, and other functions (Pittman, 1985; Seed et al., 1997; Peng et al., 1999). Tissue-plasminogen activator in axon terminals responded to alpha-1 adrenergic receptor stimulation by phenylephrine and was released from blood vessel walls into the blood in an animal experiment (Peng et al., 1999). Human plasminogen contains lysine binding sites that interact with tranexamic acid and with fibrin. The lysine binding sites of plasminogen and plasmin have high affinity for tranexamic acid. The interaction of plasmin and fibrin is virtually completely blocked by tranexamic acid, which makes plasmin or plasminogen unable to bind to fibrin (Hoylaerts, 1981; Verstraete, 1985).

Tranexamic acid has been generally used for the treatment to the pathological bleeding or other diseases in internal medicine or by intravenous injection.

There are some reports about the side effects of tranexamic acid. Antifibrinolytic drugs, tranexamic acid and the related drug epsilon-aminocaproic acid, had been used for about 6 years in the treatment of a woman with hereditary angio-oedema associated with C1-esterase inhibitor deficiency (Quincke' oedema). Her father and four of her siblings also had angio-oedema. Tranexamic acid also was used for her menorrhagia. The patient suffered a stroke and died; and at necropsy, thrombus was found in the left common carotid artery. Two other patients with hereditary angio oedema were also reported, who took tranexamic acid and survived their strokes. There was angiogaphic evidence of occlusion of branches of the cerebral arteries in these patients (Davies, 1977).

Investigations of parenteral administration of tranexamic acid to dogs, 800-1600 mg/kg body weight/day for a year, demonstrated irreversible retinal atrophy located both centrally and quiteperipherally. In the investigations it was not possible to disclose the exact mechanism of the retinotoxic effect. Fourteen patients with hereditary angioneurotic oedema

(Quincke' oedema) were treated for an average period of 6 years with tranexamic acd and they did not show any toxic damage, except a tendency to have loose stools (Theil, 1981). The total dosage of tranexamic acid for the several patients in that investigation was equal to that of the dogs because of the greater weight of the human being and the long duration of the treatment.

The dose of tranexamic acid used for local application onto the nasal mucosa in the present study was extremely less in comparison with that used in internal medicine or by injection for the treatment of other diseases, and no side effect for the local application was found.

Aprotinin is an inhibitor of proteolytic enzymes and is another drug with antifibrinolytic activity besides tranexamic acid. The medical treatment by tranexamic acid and aprotinin has been studied and compared in some diseases (Verstraeta, 1985; Murkin, 1994; Guenther, 1994; O'Brien, 2000), so aprotinin may be useful and effective to prevent the side effects by epinephrine or to understand the mechanisms inducing the side effects.

The study of nasal smears of rhinorrhea from patients complaining of watery nasal discharge after the topical application of epinephrine did not reveal eosinophils or mast cells. These findings mean that these side effects were not due to an allergic reaction.

In this study, profuse watery nasal discharge after topical application of an epinephrine spray was prevented by tranexamic acid, an inhibitor of plasmin. This curative effect would be associated with the biochemical reaction of the plasmin inhibitor with plasminogen activator liberated from vessels and neurons by adrenergic-receptor stimulation by epinephrine.

CONCLUSIONS

The side effects of profuse watery rhinorrhea and sneezing were due to the local application of epinephrine, not to lidocaine, or to chlorobutanol or sodium bisulfite. There was no nasal obstruction. The profuse watery rhinorrhea and sneezing were inhibited by topical application of tranexamic acid immediately after the nasal mucosa had been sprayed with epinephrine.

Symptoms due to epinephrine were different from those of rhinitis medicamentosa or allergic rhinitis. As there is an abundance of plasminogen activator in the blood vessels and of sympathetic and sensory nerves that innervate blood vessels in the nasal mucosa, the effective influence of tranexamic acid may be attributed to the inhibition of plasmin. Plasmin can be generated by the action of plasminogen activator liberated from these tissues by some kind of damage or anoxia due to the local application of epinephrine. As the side effect of profuse watery rhinorrhea naturally disappears in 2 or 3 days without any specific treatment, the cause of that side effect has not been solved, and attempts at countermeasures were given up long ago. However, the results of the present study have indicated the involvement of plasmin activation in these symptoms and suggest a procedure to prevent these side effects. The effect of tranexamic acid provides an important clue to investigate further the pathophysiology of the production of nasal discharge in nasal mucosa and presents an interesting topic of neurophysiology.

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