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Etizolam, an Anti-anxiety Agent, Attenuates Recurrence of Chronic Subdural Hematoma

—Evaluation by Computed Tomography—

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Abstract

Etizolam, an anti-anxiety agent which is an antagonist of platelet-activating factor receptors, was administered to patients with chronic subdural hematoma (CSH) after hematoma removal to assess the effectiveness for preventing recurrence compared with control patients not given the drug after surgery. The remaining volumes of subdural hematomas on brain computed tomography were measured approximately 1 month after removal. Volume in the etizolam group (15 patients) was significantly smaller than in the control group (24 patients). Hematoma recurrence was not detected in the etizolam group 3 months after surgery, but occurred in the control group. The difference was significant. Etizolam administration may be useful for the prevention of recurrence of CSH.

Key words: chronic subdural hematoma, etizolam, platelet-activating factor receptor antagonist

Introduction

The origin and enlargement of chronic subdural hematomas (CSHs) cannot be fully explained by any current hypothesis. Inflammation may be an important element in the pathogenesis of CSH,[4] and eosinophils infiltrating the membrane of the hematoma may contribute to bleeding into the cavity.[3,9] Increased plasma levels of the inflammatory mediator platelet-activating factor (PAF) and anti-PAF immunoglobulin G levels are observed after head injury in patients with CSH but not in patients with other types of head injury or in normal subjects,[1] which suggests the involvement of PAF in the formation of CSH. Further, PAF concentrations are higher in acute than in chronic CSH, whereas PAF acetylhydrolase activity is lower in acute than in chronic CSH.[2] In addition, PAF has been localized to the perisinusoidal vessels in the outer membrane.[2] These biochemical and histochemical observations indicate that PAF contributes to the development of CSH.

Etizolam (6-(*o*-chlorophenyl)-8-ethyl-1-methyl-4*H*-s-triazolo[3,4-c]thieno[2,3-e][1,4]diazepine) has anti-PAF activity in vivo and in vitro.[5,7] Etizolam is widely used for the medical treatment of anxiety due to depression, neurosis, tension headache, and others. We assessed the effect of etizolam against recurrence of CSH after hematoma removal using computed tomography (CT).

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Methods and Materials

This study included 48 consecutive patients undergoing the first surgical procedure for unilateral CSH at the Toyama Medical and Pharmaceutical University Hospital from March 1996 to November 1998. Informed consent was obtained from all patients. Burrhole irrigation was performed in all patients. Alternate patients were assigned to the group treated with etizolam after hematoma removal or to the control group treated only surgically. No concomitant therapy such as corticosteroid or mannitol was given. Twelve of 24 patients (50%) showed somnolence as a side effect of etizolam. Nine patients were dropped from the study because the duration of drug administration was less than 3 days. The etizolam group consisted of 10 men and five women aged 50 to 79 years (mean 65.7 years), and the control group included 18 men and six women aged 47 to 77 years (mean 66.7 years). Patients in the etizolam group were intended to receive 3.0 mg etizolam orally per day for 30 days after surgery. However,

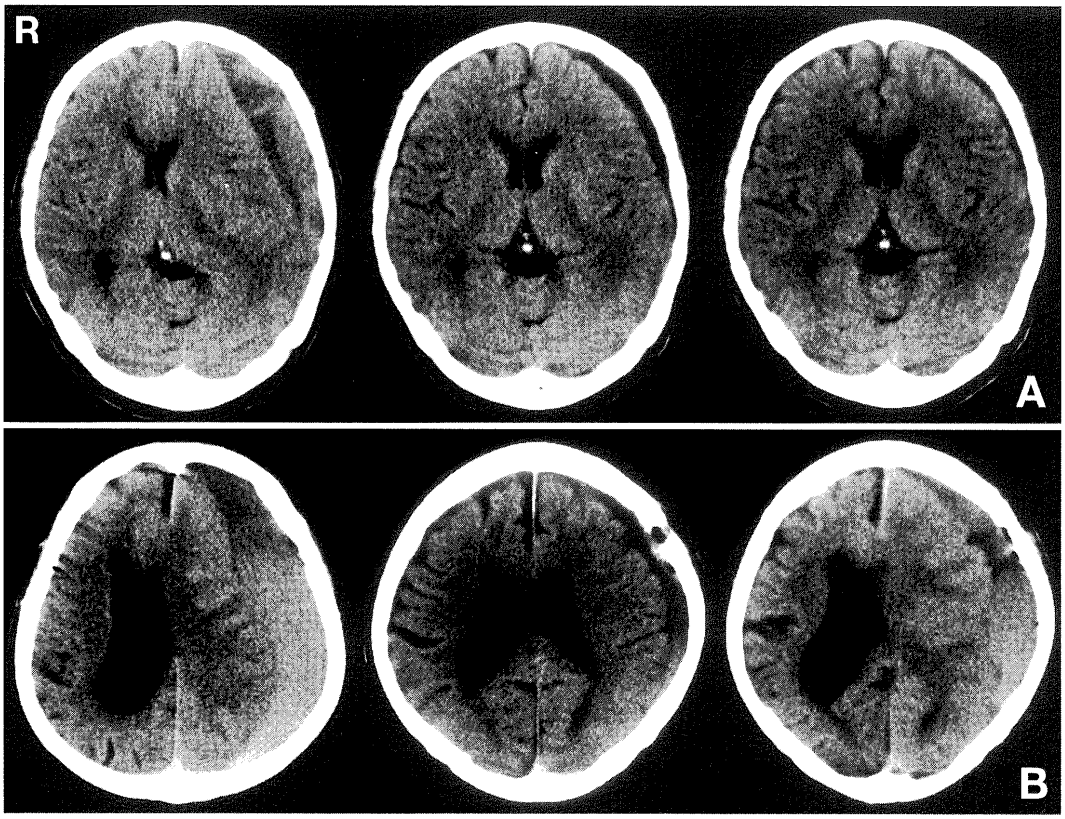

Fig. 1 Serial computed tomography scans of patients with chronic subdural hematoma. A: Chronic subdural hematoma disappeared after surgery in a patient treated with etizolam (*left to right*: preoperative, 1 month postoperative, and 2 months postoperative). B: Chronic subdural hematoma recurred 3 weeks after surgery in a control patient (*left to right*: preoperative, 2 weeks postoperative, and 3 weeks postoperative).

1.5 to 3.0 mg etizolam per day was given for 11 to 42 days (mean ± SD 30.2 ± 8.20 days).

CT was performed before surgery and repeated two times in the first month and then monthly until 3 months after surgery. Recurrence of hematoma was defined as changes in density from low to high or increased hematoma volume (Fig. 1). The volumes of hematoma before surgery and the volumes of residual hematoma or dilated subdural space after surgery were measured from brain CT slices 5 mm thick. The hematoma or dilated subdural space was outlined with the cursor on serial slices in one direction, and the volume was calculated by integration of the cross-sectional surfaces of the outlined area.

Data are expressed as mean ± SD. Student's *t*-test was used for the comparison of hematoma volume before and after surgery between the etizolam and control groups. The chi-square test was used to compare the incidence of recurrence between groups. A p value less than 0.05 was accepted as statistically significant.

Results

The volume of CSH prior to surgery was 91.8 ± 49.8 ml in the etizolam group (n = 15) and 87.2 ± 43.2 ml in the control group (n = 24) with no significant difference. However, at approximate 1 month after surgery (30.8 ± 10.2 days in the etizolam group and 32.1 ± 8.41 days in the control group), the volume of residual hematoma or dilated subdural space was 21.3 ± 9.91 ml in the etizolam group and significantly smaller than 37.6 ± 8.32 ml in the control group ($p < 0.05$, Student's *t*-test).

All patients were observed in the outpatient clinic. No recurrence of hematoma was detected in the etizolam group for approximately 1 month after surgery. In contrast, seven of 24 hematomas recurred in the control group. The rate of recurrence was significantly higher in the control group than in the etizolam group ($p < 0.05$, chi-square test). Furthermore, no recurrence of hematoma was observed in the 12 observed patients in the etizolam group between 2 and 3 months after surgery. Five of the

seven recurrent hematomas in the control group were treated by surgery, and two were treated conservatively. No new recurrence was detected in the control group between 2 and 3 months after surgery.

Discussion

Etizolam, developed as an anti-anxiety agent,[6,8] specifically inhibits PAF-induced platelet aggregation and PAF receptor binding.[5] Etizolam also inhibits PAF-induced bronchoconstriction, PAF-induced hypotension, and lethal PAF-induced shock.[7] We do not know whether the mechanism of CSH recurrence resembles that of the origin or development of CSH. Nonetheless, we attempted to assess the effect of etizolam administration on the postoperative recurrence of CSH. No recurrence of hematoma was detected for 3 months after operation in patients treated with etizolam, and hematoma volumes in the etizolam group were significantly smaller than those in the control group approximately 1 month after surgery.

Our results show that etizolam effectively protects against the recurrence of CSH after surgery. Nine patients withdrew from this study due to sleepiness, a known side effect of etizolam. Administration of 1.5 to 3.0 mg per day may be excessive in some patients, especially the elderly. However, administration of etizolam after removal of CSH appears to be of value for preventing recurrence.

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Commentary on this paper appears on the next page.

Commentary

This paper mentioned the usefulness of etizolam for preventing the recollection of chronic subdural hematoma (CSH) after irrigation of the hematoma cavity. This method is so simple that all patients of CSH can be followed after the initial treatment. But I have some questions which the authors should consider. The authors should comment on the concentration of PAF in the subdural hematoma and the difference in the concentrations of PAF between the PAF and control groups. The tendency of recollection of CSH can be observed in patients with more atrophied brain. In Fig. 1, the grade of atrophic change is larger in the control than in the PAF group. The authors should refer to the grades of atrophy of the brain in both groups. I look forward to seeing further clinical investigations from the authors.

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The authors have reported an interesting pilot study of the use of etizolam, a common anti-anxiety agent, for the prevention of recurrence of chronic subdural hematoma (CSH). Etizolam is an antagonist of platelet-activating factor (PAF) receptors, and PAF may be important in the development of CSH. In this study, there was no recurrence of CSH in the etizolam group (15 patients). However, seven of 24 patients in the control group developed recurrence, which was an unusually high recurrence rate. Although only a small number of patients are reviewed, the observations in this pilot study are of interest. A larger, double-blind, placebo-controlled study is recommended to determine the usefulness of etizolam in the management of CSH.

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The authors present evidence for a reduction of the recurrence of chronic subdural hematoma (SDH) by the platelet-activating factor (PAF) antagonist etizolam. They note that PAF is elevated in acute SDH, and it is localized to outer membrane vessels in chronic SDH, so that a trial of etizolam seems justified in these patients. No recurrence of the chronic SDH was found in either the study (n = 15) or control (n = 24) groups between 2–3 months. But 7 recurrent SDHs were found in the control group (of whom 5 returned to surgery) and none occurred in the etizolam group during the first month after initial surgery. Although the study plan called for 3 mg etizolam daily for a month, the dose was lowered in some patients because of somnolence caused by the drug — and 9/24 study patients were unable to complete the planned course of treatment presumably because of the somnolence. It would be interesting to know if even the shortened course of etizolam had an effect on SDH recurrence in the 9 study patients who were eliminated. Readers also would be interested to know if the authors currently are using etizolam in patients after removal of chronic SDH and, if so, at what dose. The authors are to be congratulated for this interesting work.

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