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For the Pentoxifylline Study Group

A Randomized, Placebo-Controlled Double-Blind Trial

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The efficacy and safety of pentoxifylline were assessed in 297 adult patients with ischemic stroke in a multicenter, double-blind, randomized and placebo-controlled trial. Treatment was started within 12 hours after the stroke onset. Study medication was administered intravenously continuously (16 mg/kg/day, maximum 1,200 mg/day) for 3 days and per os (400 mg t.i.d.) for the remainder of 28 days. Demographic data were comparable, and functional impairment and mortality (pentoxifylline 12%, placebo 10%) were not different between the two groups. Neurologic deficit scores improved from baseline admission scores during the 4-week study in both groups but did not differ between groups at admission or throughout the study except during the first few days when the consciousness level (Days 1 and 2), motor function (Days 1 and 2), cranial nerve function (Days 1-4), and total neurologic deficit scores (Days 1 and 2) were better in the pentoxifylline group than in the placebo group, especially in a subset of patients with severe deficits at admission. Laboratory values and side effects were also comparable between groups. Our study indicates that pentoxifylline can be given safely in patients with acute ischemic stroke. Although pharmacologic effects were present during the first few days, the clinical benefits were small and not sustained. (Stroke 1988;19:716-722)

Advances in hemorheology have raised the possibility that modification of intrinsic flow properties of blood may be useful in the treatment of occlusive vascular disorders. In ischemic cerebrovascular disease, the therapeutic potential of hemorheologic agents is suggested by several clinical observations. Elevated hematocrit, decreased erythrocyte deformability, platelet activation, increased fibrinogen levels, and abnormal erythrocyte aggregation, all of which may unfavorably affect blood flow, have been observed in patients with ischemic strokes. The therapeutic modification of blood viscosity through hemodilution has been proposed as an alternative therapy for acute ischemic stroke. Pentoxifylline (PTX) is a hemorheologic agent that has been recently introduced for the treatment of intermittent claudication in patients with occlusive peripheral vascular disease in the United States. The exact mechanisms of action of PTX in improving microcirculatory flow and tissue oxygenation remain to be determined but may be 1) increase of erythrocyte deformability by raising ATP content, 2) inhibition of platelet aggregation, and 3) reduction of plasma fibrinogen concentrations. These effects of PTX may contribute to the reduction of whole blood viscosity. In animal studies, PTX prevents ischemic deterioration of cerebral metabolism and death in gerbils and vasogenic cerebral edema in cats. Several clinical studies have suggested a potential therapeutic or prophylactic efficacy of PTX in ischemic cerebrovascular disorders. Our study was designed to assess the efficacy and safety of PTX on the survival, neurologic deficits, and extent of recovery after acute nonhemorrhagic stroke using a randomized, placebo-controlled, double-blind protocol.

Subjects and Methods

A total of 297 patients from 13 medical centers were enrolled into the protocol (Appendix 1). The enrollment of approximately 300 patients to obtain at least 250 analyzable subjects was based on the potential efficacy of PTX to reduce mortality by half (from an estimated 20% to 10%) and to improve neurologic deficit scores by 25% with a power of 0.8 (1 - P) and at a significance level of 0.05 (a). The study protocol was approved by the institutional review board for human research at each center. An independent review panel (Appendix 1) periodically reviewed the safety of the ongoing trial in an unblinded manner. Adult patients at least 35 years of age with the onset of symptoms within 12 hours were enrolled into the
protocol after appropriate screening. All patients gave informed consent. Patients who had any of the following conditions were excluded: 1) pregnancy, 2) previous stroke, 3) transient ischemic attack (TIA), 4) coma, 5) cerebral hemorrhage, 6) significant systemic diseases, 7) intracranial lesion other than stroke, or 8) indication for anticoagulant therapy at entry.

The patients were stratified into carotid (anterior circulation) and vertebrobasilar artery (posterior circulation) groups. Patients in either group at each center were then randomized into PTX or placebo groups in a double-blind fashion. The following methods were applied:

**Screening.** A complete history and physical examination were conducted. Electrocardiogram, chest x-ray, cranial computed tomogram (CT), and admission (baseline) laboratory tests including complete blood count and serum chemistries were obtained before the initiation of therapy. The same laboratory tests were also obtained 3 days after the initiation of treatment, at hospital discharge (usually on Day 7), and at the end of treatment (Day 28).

**Treatment.** Patients in the PTX group received an intravenous loading dose of 50 mg PTX over 1 minute followed by a continuous intravenous infusion (16 mg/kg/day up to 1,200 mg/day) for 72 hours. At the end of the infusion, patients were started with 400 mg PTX p.o. three times a day for 25 days. Patients in the placebo group received vehicle (isotonic saline) and matching placebo tablets in an identical fashion.

Patients were monitored closely for adverse reactions. Patients who did not tolerate the study medication were given a smaller dosage (8 mg/kg/day i.v., 400 mg p.o. twice a day). The study medication was discontinued in patients who could not tolerate even the low dose. These patients, however, were followed according to the protocol despite early termination of medication.

All adverse signs and symptoms were recorded, and their relevance to the study medication was assessed. When, in the opinion of the investigator, the potential risk from adverse reactions outweighed the potential therapeutic benefit, the study medication was reduced and, if necessary, discontinued. At regular intervals during the study, all adverse reaction data were submitted to an independent review panel (Appendix 1) for unblinded review. The study was then continued only with the positive recommendation of the panel.

The effects of treatment were assessed by mortality, neurologic deficits, and functional impairment. Neurologic deficits were scored using a weighted scale that ranged from a normal total score of 100 (level of consciousness, 30; motor function, 30; cranial nerve function, 17; higher cortical function, 20; and sensory function, 3), with lower scores for neurologic dysfunction. Neurologic deficits were scored by the same physician investigator at entry (baseline), daily throughout the 72-hour infusion (Days 1–4), on Days 7, 14, and 21, and at the end of the study (Day 28). Functional impairment (Barthel Index) was assessed on Days 7, 14, 21, and 28.

The statistical analyses were as follows:

**Demographic factors.** Demographic characteristics of the PTX and placebo groups were analyzed using Fisher's exact test, except for age, which was analyzed using the two-sample t test with equal variance.

**Efficacy variables.** Differences in time-specific mortality and neurologic deficit (individual category and total) scores between groups were analyzed using an extended Mantel-Haenszel test. Difference in overall mortality was analyzed using Fisher's exact test. Within groups, differences from baseline for neurologic deficit (individual category and total) scores was assessed using the Wilcoxon signed rank test. Difference in functional impairment between groups was determined by multivariate repeated measures. Logistic and linear regression models were applied, which demonstrated adequate investigator homogeneity regarding mortality and neurologic assessment, respectively.

**Safety variables.** Differences in laboratory values and vital signs categorized as low, normal, or high were analyzed using Fisher's exact test. Within groups, differences from admission (baseline) for laboratory and vital signs categorized as low, normal, or high were analyzed using McNemar's or the Stuart-Maxwell test. Numerical variables were analyzed using the two-sample t test.

**Statistical significance.** In the analyses of efficacy variables, one-tailed tests were used for comparisons with placebo. Two-tailed tests were used for other analyses including baseline comparisons, comparisons within groups, and assessments of side effects. Test results were considered significant if p < 0.05.

**Results**

Among the 297 patients enrolled, 270 were considered "protocol-analyzable." Analyses were made for all 297 patients enrolled (intention-to-treat method of analysis) and for the 270 protocol-analyzable patients. Some patients were considered not protocol-analyzable because of violations of inclusion and exclusion criteria or the study protocol. Since similar conclusions were reached by both methods of analysis, only the results of protocol-analyzable patients are described and discussed here. Demographic characteristics and risk factors were examined thoroughly and were found to be not different between groups.

There were 33 deaths, 18 in the PTX group (12% of 151) and 15 in the placebo group (10% of 146), with an overall mortality rate of 11% (33 of 297). Three deaths in the PTX group actually occurred within 1 week after completion of the study (between Days 29 and 35); nevertheless, they were included in the PTX mortality. Among the 270 protocol-analyzable patients, there were 15 deaths in the PTX group (11% of 139) and 14 deaths in the placebo group (11% of 131). Four patients in the PTX group and five in the placebo group died within 1 week, while 11 in the PTX group and nine in the placebo group died between 8 and 35 days after the stroke. Death was considered to be neurologic in eight patients in the PTX group and in 10 patients in
the placebo group. Two patients in the PTX group and three patients in the placebo group died of infection. The remaining patients (five in the PTX group, one in the placebo group) died of miscellaneous causes (cardiac death, pulmonary aspiration, ischemic enteritis, respiratory failure). Mortality categorized by timing (early, death within 7 days or late, death between 8 and 35 days) or by cause (neurologic, infection, and others) did not differ between the groups.

**Neurologic Deficits**

The effects of the study medication on protocol-analyzable patients were analyzed for differences between groups and for time-dependent changes.

**Level of consciousness.** Mean baseline level of consciousness was not different between groups. Significant differences in favor of the PTX group were noted on Days 1 and 2. The trend in favor of the PTX group persisted from Days 3 through 28, but the difference between groups was not significant (Figure 1).

**Motor function.** The grading of motor function in this study consisted of motor strength (total normal score = 24) and motor coordination (ataxia) (normal = 6). They were analyzed separately. Mean baseline motor strength was comparable between groups. Significant differences were noted on Days 1 and 2 in favor of PTX. The differences were associated with worsening from baseline in the placebo group and improvement from baseline in the PTX group (Figure 2). A trend for greater motor strength in the PTX group was noted on Days 3–28, but the differences were no longer significant. For motor coordination (ataxia), Figure 3 shows no significant differences between the two groups.

**Cranial nerves.** A significantly higher mean baseline cranial nerve function score was noted in the placebo group. When the groups were compared using mean change from baseline, with p values adjusted for baseline difference between groups, significant differences were noted on Days 1–4 favoring PTX (Figure 4).

**Higher cortical function.** Mean baseline higher cortical function scores were comparable between groups. Subsequent improvements thereafter were also comparable (Figure 5).

**Sensory function.** Mean baseline sensory function scores were comparable between groups. Improvements were noted in both groups, and a trend in favor of placebo was not significant (Figure 6).

**Total neurologic deficit scores.** Mean baseline total neurologic deficit scores were comparable between groups. Significant differences were noted on Days 1 and 2 in favor of PTX (Figure 7).

**Functional Impairment**

Mean functional impairment scores were comparable between groups on Days 7, 14, 21, and 28. No significant difference was noted during the study period (Figure 8). Since functional impairment was not graded at admission, no change from baseline could be recorded.

**Analysis of Severe Stroke Subset**

Statistical analysis of treatment was also made on a subset of patients with more severe neurologic deficits (total neurologic deficit scores less than median score of 79) at admission. The results were similar to those
for all the protocol-analyzable patients. Between groups, level of consciousness (Days 1 and 4), motor strength (Days 1 and 2), cranial nerve function (all days), and mean total neurologic deficit scores (Days 1 and 2) were significantly better in the PTX group than in the placebo group. No differences between groups were noted for ataxia, higher cortical function, or sensory function. Differences in mean change from baseline for total neurologic deficit scores between groups were significant only on Days 1 and 2 even though the trend in favor of the PTX group was noted throughout the study period (Figure 9).

Safety Concern

Vital signs. No significant differences between PTX and placebo groups were noted. A tendency for both systolic and diastolic blood pressures to decline over the study period were noted in both groups.

Electrocardiogram. The electrocardiograms obtained at admission, during the study period, and at the end of the study showed no increased frequencies of abnormalities in the PTX group compared with the placebo group.

Laboratory variables. Hemoglobin and hematocrit tended to be lower 28 days after admission for both PTX and placebo groups. It is likely that hemoconcentration was present immediately after the stroke at entry into the protocol. Alterations in hemoglobin and hematocrit from admission to the end of the study period were comparable for both groups. No significant differences in other laboratory variables were noted between groups.

Adverse effects. Of the 151 patients who received PTX, 58 reported side effects; in 47 the side effects were considered to be possibly or probably related to the study drug. Of the 146 placebo patients, 53 reported side effects; in 40 the side effects were considered to be possibly or probably related to the study drug. As expected from previous experience with PTX, the most frequently reported side effects that could probably be attributed to drug treatment were nausea (22 PTX patients and 12 placebo patients) and vomiting (8 PTX patients and 13 placebo patients). The differences between groups were not significant. Side effects were also analyzed according to organ systems. No significant differences were noted between groups. Seven PTX patients and five placebo patients permanently discontinued treatment because of side effects.

Discussion

Our study was designed to evaluate the effects of PTX, a hemorheologic agent. One important criterion for patient entry into this trial was completing diagnostic procedures (including CT scan) and obtaining informed consent within 12 hours after the onset of
symptoms. Despite difficulties, a total of 297 patients from 13 centers in three countries were enrolled and study medication was begun early. This blinded, placebo-controlled study, therefore, provided a proper test of PTX under conditions in which early improvement of microcirculatory flow might alter the natural history of the disease. It is interesting to note the deterioration of neurologic deficit scores in the placebo group during the first 2 days, perhaps partially reflecting the very early entry into the protocol.

In our study, the overall mortality of 11% (33 of 297) was lower than the 30-day mortality of ischemic stroke reported in the United States Stroke Survey and in a recent study at the Toronto Stroke Unit. The lower mortality we observed was probably related to the patient population as defined by the inclusion and exclusion criteria, which, for example, excluded patients who rapidly became comatose. A similar low mortality rate was also found in another recent stroke study with a similar patient population. Adding the three deaths occurring in the PTX group after study completion (Days 29–35), the mortality rate for all patients entered was slightly higher with PTX than with placebo (12% vs. 10%). However, the difference was not significant. The all-cause mortality rate was also found in another recent stroke study with a similar patient population. 35 Adding the exclusion criteria, which, for example, excluded patients who rapidly became comatose. A similar low mortality rate was also found in another recent stroke study with a similar patient population. 35 Adding the three deaths occurring in the PTX group after study completion (Days 29–35), the mortality rate for all patients entered was slightly higher with PTX than with placebo (12% vs. 10%). However, the difference was not significant. The all-cause mortality rate was also found in another recent stroke study with a similar patient population. 35

During the first few days, scores of overall neurologic deficit (Days 1 and 2) and several subscales (level of consciousness, Days 1 and 2; motor function, Days 1 and 2; cranial nerve function, Days 1–4) were significantly better in the PTX group than in the placebo group. The apparent positive effects of PTX during this period were reflected in improvements of neurologic deficit scores in the PTX group in contrast to deterioration in the placebo group. The latter has been frequently noted in clinical practice and could be caused by continuing ischemia and evolving brain edema. Beyond Day 4, the magnitude of the differences in neurologic deficit scores between groups diminished and no longer reached significance. In the analysis of the subset of severely affected patients, a similar conclusion was reached, that there were positive effects of PTX during the first few days, with the differences diminishing thereafter. There were no differences in functional impairment scores between the groups. As functional impairment was not assessed until Day 7, a similar improvement during the first few days could not be excluded.

Since the patients in the PTX group received intravenous PTX infusion during the first 3 days and oral PTX for the remaining 25 days, the possibility exists that the positive effects before Day 4 were related to the route of administration. Studies in young, healthy adults have shown different single-dose pharmacokinetics between the sustained-release tablet used in this study and intravenous PTX. 36 Additional pharmacokinetic studies, preferably using a group of similarly defined acute stroke patients, are needed to further clarify this issue.

With the exception of the expected gastrointestinal symptoms, other side effects or adverse reactions were rare and were not significantly more frequent in the PTX group than in the placebo group. The second most common side effects reported in our study, in the cardiovascular and nervous systems, were anticipated in stroke patients and were found to be equally distributed between the groups. Side effects involving other organs occurred in ≤2% and were not different between groups. No adverse effect of PTX on laboratory variables was noted. These results extend the observations made in other PTX trials and suggest that PTX, at the dosages used in our trial, is a safe drug in patients with acute illness such as stroke.

Several questions remain to be answered after our multicenter trial. The relatively low frequency of side effects and adverse reactions raises the possibility that a higher, possibly more optimal, dose of PTX could be administered by dosage titration in individual patients. Patients with ischemic stroke showing only mild neurologic deficit are more likely to have a good recovery with or without therapeutic intervention. The inclusion in our trial of this type of patient might have diluted the therapeutic efficacy that otherwise would perhaps be more prominent. For instance, in the subset of patients with more severe deficits (below-median
total neurologic deficit scores at admission), differences in the improvement in total neurologic deficit scores after 28 days between the PTX and placebo groups (9.73 ± 2.68, n = 75 vs. 5.29 ± 3.17, n = 70; \( p = 0.118 \)) was more remarkable than the corresponding figures in all the protocol-analyzable patients (6.04 ± 1.68, n = 138 vs. 5.32 ± 1.74, n = 130; \( p = 0.394 \)), even though the sample size was smaller in the subset.

The problems of enrolling patients within hours after stroke onset have been overcome in our study. Nevertheless, therapeutic intervention 10 hours after the ischemic insult (mean delay in our study) may still be too late to limit the ischemic injury and its consequences. PTX is a methylxanthine derivative and, in addition to its hemorheologic effects, has some mild vasodilator, platelet inhibitory, and central nervous system (CNS) stimulant properties. It is not clear whether this mild CNS pharmacologic action of PTX may have contributed to the temporary improvement in patients’ level of consciousness and motivation for better neurologic performance. Finally, the contribution of abnormal hemorheology and the relative importance of different rheologic factors (erythrocyte deformability and aggregation, fibrinogen level, hematocrit, plasma viscosity, leukocyte rheology, etc.) in the pathogenesis of focal cerebral ischemia is unknown. The lack of a beneficial hemodynamic effect of PTX on experimental cerebral ischemia and the recent observation of the lack of efficacy of hemodilution in acute ischemic stroke in community hospitals raise questions about the therapeutic potential of hemorheologic modification in ischemic stroke. Additional experimental and clinical studies are needed to define further the potential efficacy of hemorheologic therapeutics in acute cerebral ischemia.

Appendix 1. Pentoxifylline Study Group


Independent review panel. M.L. Dyken Jr. (University of Indiana), O.M. Reinmuth (University of Pittsburgh), R. Hardy (University of Texas, Houston).

Study monitors. E. Bauer, J. Brobst, G. May, B. Cobert, and J.P. Savitsky (all from the Clinical Research Department, Hoechst-Roussel Pharmaceuticals).

Statisticians. A. Devault, A. Fisher, and W. Stager (all from the Biostatistics Department, Hoechst-Roussel Pharmaceuticals).


References


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