Amitriptyline in the Prophylaxis of Central Poststroke Pain
Preliminary Results of 39 Patients in a Placebo-Controlled, Long-Term Study

Christian Lampl, MD; Kambiz Yazdi, MD; Christoph Röper, MD

Background and Purpose—We performed a double-blind, placebo-controlled study to investigate the effectiveness of amitriptyline for the prophylactic treatment of patients with acute thalamic stroke in preventing central poststroke pain.

Methods—Subject received, in a randomized sequence, either amitriptyline titrated from 10 to 75 mg in extended-release form or placebo over a therapy period of 365 days. We documented the time when pain developed; the intensity, type, site, and distribution of pain; and the presence/absence and type of allodynia.

Results—Thirty-nine patients (23 women and 16 men; age range, 36 to 68 years) with central poststroke pain participated. The placebo group showed a pain rate of 21% within 1 year after the diagnosis of thalamic stroke compared with 17% in the group under prophylactic treatment with amitriptyline. Average (SE) time to pain was 318 (23) days for patients in the placebo group and 324 (24) days for patients in the amitriptyline group.

Conclusions—With the achieved sample sizes of this study and a pain rate of approximately 21% in the placebo group, any near-perfect pain protection would have been detected. Near-perfect pain protection, in this context, refers to pain in <2.4% of the recruited patients treated with amitriptyline or in approximately 89% of placebo-treated patients. Larger studies are recommended to test the hypothesis that prophylactic amitriptyline reduces but does not completely prevent central poststroke pain. (Stroke. 2002;33:3030-3032.)

Key Words: amitriptyline ■ antidepressive agents ■ cerebrovascular accident ■ pain ■ thalamic diseases

Central poststroke pain (CPSP) was first described by Dejerine and Roussy1 in 1906 as a spontaneous pain after a thalamic stroke. It has been known as “thalamic pain syndrome” for decades, and its management is still a challenge for treating physicians today. Since the discovery of the effects of carbamazepine and tricyclics, these substances have been used in the treatment of CPSP. In a carefully controlled trial performed in 15 patients with CPSP, the authors were unable to demonstrate a statistically significant effect of carbamazepine, whereas amitriptyline produced a statistically significant reduction of pain compared with placebo.2

Thus far, no studies on CPSP have been published to answer the question of whether treatment at the beginning of stroke demonstrates a prophylactic effect in preventing central pain mechanism. The primary objective of this study was to evaluate, under controlled conditions, the efficacy of amitriptyline for preventing CPSP. We performed a placebo-controlled, double-blind study to determine whether amitriptyline at an increasing dose could significantly reduce CPSP in patients with thalamic stroke.

Subjects and Methods
The study was performed as a randomized, double-blind, placebo-controlled trial. Patients were randomized after they had provided informed consent to administration of amitriptyline or placebo within the first day after the onset of stroke was diagnosed. The study medication was slowly titrated from 10 to 75 mg in extended-release form within 3 weeks, and all placebo medication used throughout this study matched the study medication in smell and optical appearance. This dosage was then kept constant for the subsequent 365-day therapy period.

During 1995–1999, 39 patients (23 women and 16 men) who had suffered a thalamic stroke were included in this pilot study, which was submitted to the relevant ethical review board and started after approval. The following inclusion criteria were applied: (1) unequivocal thalamic stroke verified by MRI; (2) no symptoms of constant or intermittent pain in the face, arm, or leg; and (3) physical and mental ability to give informed consent to participate in the study. Exclusion criteria were known contraindications to amitriptyline.

Possible adverse reactions were recorded throughout the entire treatment period. The adverse reactions were classified as follows: (1) no adverse reactions; (2) mild adverse reactions with no change in treatment; (3) moderate adverse reactions requiring a dose reduction; and (4) severe adverse reactions requiring withdrawal of the study medication.

The primary end point of the study was to evaluate whether poststroke pain occurred within 1 year in subjects under prophylactic treatment with the study medication and, if so, the frequency of the poststroke pain. Patients were instructed to record the exact day when the possible symptoms of thalamic pain occurred for the first time, in which case they were advised to visit the pain clinic as soon as possible. In patients who experienced pain, the intensity, type,
site, and distribution of pain as well as the presence/absence and type of allodynia were documented.

The statistical analysis software used for analysis of the study data was SPSS Version 10 for Windows. The power calculations were performed with the use of MATHCAD 8.0 professional software designed for the same operating system on IBM-compatible PCs.

After a first blinded statistical evaluation in which all major results were documented in writing, unblinding of the random assignment was performed; group A patients had received placebo, and group B patients were treated with amitriptyline.

Results

Thirty-nine patients were included in the study. Twenty patients (mean age, 64 years) were randomly assigned to treatment group A, and 19 patients (mean age, 57 years) were assigned to group B. One patient in each group was excluded because of a protocol violation. All patients had lesions in the ventroposterior thalamic region.

The results of the statistical evaluation of age and sex are given in Table 1; these data did not achieve any acknowledged level of statistical significance ($P>0.10$).

In group A ($n=19$), 4 subjects (patients 12, 20, 21, and 23) suffered poststroke pain within 1 year, whereas in group B ($n=18$), 3 patients (patients 3, 6, and 18) developed thalamic pain during the study period (for details, see Table 2). The placebo group showed a pain rate of 21% within 1 year after the diagnosis of thalamic stroke compared with 17% in those under prophylactic treatment with amitriptyline. With the use of the standard 5% level of 2-sided significance and a power of 80%, a critical difference of approximately 19% could be detected by the sample size of this study.

When we compared the 2 Kaplan-Meier graphs (Figure) using the log-rank test, a probability value of 0.74 was calculated, which does not achieve any acknowledged level of statistical significance. Of similar importance are the descriptive results of the average time to CPSP (in days) and their associated standard errors: the average time to pain was 318 days ($SE=23$ days) for patients in the placebo group and 324 days ($SE=24$ days; documented in those patients who recorded pain) for patients in the amitriptyline group. These results suggest that a very large difference between the 2 groups is quite unlikely.

Clinical examinations of somatic sensibility showed that hypoesthesia to heat stimulus (40°C) was present in all 7 patients, whereas hypoesthesia to cold (20°C) was found in patients 3, 18, and 20. Hypoesthesia to touch could be detected in patient 20. Allodynia occurred in 5 patients (patients 3, 6, 20, 21, and 23). Three of these patients (patients 3, 21, and 23) had allodynia only to mechanical (pin-prick) stimulus, 1 patient (patient 6) only to heat stimulus, and 1 patient (patient 20) to mixed mechanical and heat stimuli.

Pain rating on the visual analog scale ranged from 3 to 7 (median, 4.7); the median visual analog scale rating was 5.2 in the placebo group and 5.0 in the amitriptyline group, which was not statistically significant. In a total of 5 patients (patients 3, 6, 12, 18, and 23), the maximum pain was in the

![Survival Functions]

Results of Kaplan-Meier survival curves (ie, likelihood of time until first pain in our study) for both study groups. Survival in this context refers to time (in days) until the first documented CPSP pain. These results demonstrate the descriptive (very slight) superiority of the amitriptyline group (group B) compared with the placebo group (group A), which showed a slightly lower level of absence of pain after 1 year. GRPID indicates group identification; Cum, cumulative.

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Group A (Placebo) ($n=19$)</th>
<th>Group B (Amitriptyline) ($n=18$)</th>
<th>Day CPSP Occurred</th>
<th>Burning</th>
<th>Shooting</th>
<th>Aching</th>
<th>Stinging</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>...</td>
<td>+</td>
<td>12</td>
<td>...</td>
<td>+</td>
<td>+</td>
<td>...</td>
</tr>
<tr>
<td>6</td>
<td>...</td>
<td>+</td>
<td>70</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>+</td>
<td>...</td>
<td>36</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>...</td>
</tr>
<tr>
<td>18</td>
<td>+</td>
<td>...</td>
<td>267</td>
<td>...</td>
<td>...</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>+</td>
<td>...</td>
<td>67</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>+</td>
<td>...</td>
<td>209</td>
<td>+</td>
<td>...</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>+</td>
<td>...</td>
<td>246</td>
<td>+</td>
<td>...</td>
<td>+</td>
<td></td>
</tr>
</tbody>
</table>
lower part of the arm. Patient 20 experienced the worst pain in the proximal area of the limb, and patient 21 complained about pain in 1 side of the face. No correlation was found between sensibility changes and pain localization.

The study medication was very well tolerated by almost all patients. Common adverse reactions such as dry mouth and fatigue were reported at the beginning of the therapy. Of 37 patients, 21 reported mild adverse reactions not requiring a change in treatment, and only 2 patients showed moderate adverse reactions, followed by a dose reduction from 75 to 50 mg.

**Discussion**

Thalamic pain is of an intractable nature, and the available treatment options are very limited. The efficacy of antidepressants in the treatment of CPSP, especially of the adrenergic active type, is well documented,

although the mechanisms behind the effect of antidepressants are still not completely understood. A leading hypothesis is that mechanisms involving serotonin and noradrenaline mediate clinical analgesia via descending systems originating in the brain stem and influencing the dorsal horn of the spinal cord.

A drug like amitriptyline acts to elevate levels of serotonin and noradrenaline in the nervous system by blocking the synaptic reuptake of both catecholamines.

This presumed mechanism may not be the only one, however. Furthermore, new observations in a rat study show that amitriptyline acts via the sodium channel to achieve both peripheral and central analgesic components. These drugs may also act as N-methyl-D-aspartate receptor blockers, and some have significant sympatholytic effects.

The present pilot trial was designed as a prophylactic study and is the first of this type. The outcome of this study was that no statistically significant beneficial effects were seen when patients received prophylactic treatment with amitriptyline to prevent the development of CPSP after a thalamic stroke.

The limitation of the study is that with an expected 8% incidence of pain, the small sample size seems to be too small to detect a moderate but clinically useful effect. With standard α and β risks (α=5% 2-sided and 80% power), a future study would require approximately 190 patients per treatment arm in a randomized comparison with an assumed placebo pain rate of 21% versus a treatment regimen that achieves a 50% reduction in pain rate to 10.5%.

However, this pilot study had enough statistical power to detect pain reduction =90% for amitriptyline versus placebo treatment and can now be used as a planning database for additional studies. The reasons why amitriptyline is effective in the treatment of existing CPSP and not as a prophylactic agent should be clarified by additional research. Although amitriptyline was very well tolerated in our patients, it has the potential for important side effects, particularly in the elderly population, and the benefit in terms of reduced pain must outweigh the risks of treating those patients who would not have developed pain were they left untreated.

**Acknowledgments**

The authors are grateful to Professor Troels S. Jensen for reviewing the manuscript and for his important suggestions during preparation of this report. The authors appreciate the useful comments provided by Kurt Neumann, MS, expert witness for statistics certified by the court, Vienna, Austria.

**References**

Amitriptyline in the Prophylaxis of Central Poststroke Pain: Preliminary Results of 39 Patients in a Placebo-Controlled, Long-Term Study
Christian Lampl, Kambiz Yazdi and Christoph Röper

Stroke. 2002;33:3030-3032; originally published online October 10, 2002;
doi: 10.1161/01.STR.0000037674.95228.86
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2002 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/33/12/3030

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org/subscriptions/