Failure of Aspirin Treatment After Stroke

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Background and Purpose Despite its low efficacy, aspirin is the most widely used drug for secondary stroke prevention. The reasons why stroke recurs while patients are on aspirin are unknown. We have analyzed a series of patients who had recurrent strokes while on aspirin.

Methods Out of 2231 consecutive patients who were admitted to the Tel Aviv Medical Center from May 1988 through December 1992 with the diagnosis of ischemic stroke, 129 admissions were due to recurrent ischemic strokes while the patients were already on aspirin, and these were defined as aspirin failures. The clinical characteristics of those patients in whom aspirin treatment failed were compared with three control groups, each comprising 129 patients who had had only a single ischemic stroke and were then taking aspirin. One control group was matched for aspirin dose and date of first stroke; another control group was matched for age, sex, and date of first stroke; and a third control group was matched for age, sex, date of first stroke, and aspirin dose. Statistical analysis was carried out by two-tailed Student's t test and χ² test.

Results The average period until stroke was longer for patients on higher aspirin doses. Patients matched for aspirin dose and date of first stroke did not differ significantly in age (72.4 years in aspirin failures versus 74.2 years in the first control group) and sex (89 versus 94 men, respectively). Matching for age, sex, and date of first stroke but not for aspirin dose demonstrated a trend toward high frequency of aspirin failure in patients taking lower doses of aspirin (χ² test for trend = 3.5; P = .06). Comparison of aspirin-failure patients with a control group matched for age, sex, date of first ischemic stroke, and aspirin dose demonstrated that these patients more commonly had statistically significant hyperlipidemia (odds ratio, 2.6; 95% confidence interval, 1.0 to 6.8; P = .04) and ischemic heart disease (odds ratio, 2.3; 95% confidence interval, 1.3 to 3.9; P = .002).

Conclusions We conclude that age and sex do not influence the efficacy of aspirin. Lower aspirin dose in patients with stroke recurrence suggests that aspirin doses of 500 mg daily or more should be used in secondary stroke prevention. Hyperlipidemia and ischemic heart disease are risk factors for stroke recurrence despite aspirin treatment, which requires further clinical and laboratory evaluation. (Stroke. 1994;25:275–277.)

Key Words • aspirin • cerebral infarction • epidemiology • stroke prevention

Stroke is the most common disabling neurological disease in adults, and it remains an important health care problem. Recurrent stroke is a major cause of morbidity and mortality among stroke survivors. Large series indicate stroke recurrence rates of 16% to 42% over 5 years. Most strokes are thromboembolic, and it is well known that drugs that suppress platelet function might reduce stroke recurrence in such patients.

Aspirin is well established for secondary stroke prevention. However, aspirin fails to prevent most strokes in patients at risk of recurrence. The reasons for aspirin failure (ASAF), defined as recurrence of stroke in patients taking aspirin, are unclear: Factors that are reported to be associated with ASAF include age, hypercholesterolemia, and inadequate aspirin dose. To evaluate this problem, we have analyzed retrospectively some factors associated with stroke recurrence in patients on aspirin.

Subjects and Methods

All stroke patients admitted to the Tel Aviv Medical Center are included in the Tel Aviv Stroke Register. Patients who were hospitalized during the period May 1988 through December 1992 because of recurrent ischemic stroke (IS) while taking aspirin were included in our study as ASAF. The diagnosis of stroke was based on neurological examination and was confirmed by computed tomography in 71% of the patients. ASAF patients included those in whom aspirin treatment, regardless of dose, had been initiated because of previous IS only and was maintained. Analysis included risk factors for stroke: age, sex, hypertension, ischemic heart disease, diabetes mellitus, smoking, atrial fibrillation, peripheral vascular disease, and hyperlipidemia.

The clinical characteristics of ASAF patients were compared with carefully matched control groups with nonrecurrent strokes, whose initial strokes coincided with the first strokes of the index cases (±3 months). One control group was matched for aspirin dose and date of first IS to examine the role of age and sex in ASAF. Another control group was matched for age (±1 year), sex, and date of first IS but not for aspirin dose. The aim of this matching was to evaluate the dependence of ASAF state on aspirin dose. The third control group was matched for age, sex, date of first IS, and aspirin dose to examine a probable role of some risk factors in ASAF patients and the influence of these factors on aspirin efficacy.

Demographic data and distribution of risk factors among the different groups were analyzed using t test (or ANOVA), χ² test, and χ² for trend test, as appropriate.

Results

A total of 2231 consecutive patients were admitted to the Tel Aviv Medical Center with acute IS from May 1988 through December 1992. Recurrent IS during the study period occurred in 467 patients, of whom 129 were on aspirin, given because of a previous IS. These consisted of 89 men and 40 women, aged 72.4 ± 7.6 years (mean ± SD). Average period from the first-ever stroke...
TABLE 1. Average Period Between the First and Recurrent Stroke According to Aspirin Dose

<table>
<thead>
<tr>
<th>Daily Aspirin Dose, mg</th>
<th>No. of Patients</th>
<th>Mean Time±SD, mo*</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>7</td>
<td>10.0±2.9</td>
</tr>
<tr>
<td>250</td>
<td>68</td>
<td>11.1±3.3</td>
</tr>
<tr>
<td>325</td>
<td>21</td>
<td>14.0±2.7</td>
</tr>
<tr>
<td>500</td>
<td>33</td>
<td>24.1±5.3</td>
</tr>
<tr>
<td>Mean</td>
<td>129</td>
<td>14.8±3.7</td>
</tr>
</tbody>
</table>

*The comparison of mean duration between the first and recurrent stroke in patients with different doses of aspirin, ANOVA, F=6.8, P=.002.

Table 2. Differences In Aspirin Dose: Aspirin Failure Group Versus Control Group

<table>
<thead>
<tr>
<th>Daily Aspirin Dose, mg</th>
<th>Aspirin Failure Group (n=129)</th>
<th>Control Group (n=129)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>100</td>
<td>7</td>
<td>5.4</td>
</tr>
<tr>
<td>250</td>
<td>68</td>
<td>52.7</td>
</tr>
<tr>
<td>325</td>
<td>21</td>
<td>16.3</td>
</tr>
<tr>
<td>500</td>
<td>33</td>
<td>25.6</td>
</tr>
</tbody>
</table>

*x^2 for trend, x^2 (1)=3.5, P=.06. The aspirin failure group consisted of patients with recurrent ischemic strokes while on aspirin; control group consisted of patients with nonrecurrent ischemic strokes while on aspirin.

The aspirin doses used were variable; 7 patients took 100 mg, 68 patients were on 250 mg, 21 patients used 325 mg, and 33 patients took 500 mg aspirin daily. The average period to recurrence according to aspirin doses, shown in Table 1, shows a significant trend toward longer intervals in patients on higher aspirin doses.

ASAF Group Versus a Control Group Matched for Aspirin Dose and Date of First-Ever IS

ASAF patients were younger (72.4±7.4 versus 74.2±7.7 years) and were less often male (89 versus 94 men) than control subjects in whom stroke had not recurred. These differences were small and not statistically significant.

ASAF Group Versus a Control Group Matched for Age, Sex, and Date of First-Ever IS

The distribution of aspirin doses in patients with ASAF and in control subjects is shown in Table 2. There was a trend toward higher frequency of lower doses of aspirin in patients with ASAF (x^2 for trend, 3.5; P=.06).

ASAF Group Versus a Control Group Matched for Age, Sex, Date of First Stroke, and Aspirin Dose

The relative frequencies of the risk factors for stroke showed that the ASAF group had an excess of almost all stroke risk factors. The results of the statistical analysis are shown in Table 3. The differences between ASAF and control groups were statistically significant only for ischemic heart disease and hyperlipidemia.

**Discussion**

In the Stroke Prevention in Atrial Fibrillation I Study,9 it was shown that older patients were often "aspirin nonresponders." However, Sivenius10 concluded that age (above or below 65 years) does not influence the effectiveness of aspirin therapy. We also found that age does not influence the efficacy of aspirin. The proportion of women was greater in the ASAF group than in the control group. Although the difference was not statistically significant, it is consistent with11-14 but not all15-17 previous studies suggesting that aspirin may be less efficacious for secondary stroke prevention in women.

Our study showed a significant trend toward high frequency of ASAF in patients under lower doses of aspirin and a longer period until stroke recurrence in those treated with higher aspirin doses (Table 1). It is consistent with a laboratory study18 in which it was shown that there was a progressive increase in the number of patients with platelet hyperactivity as the aspirin dose decreased.

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Aspirin Failure Group (n=129)</th>
<th>Control Group (n=129)</th>
<th>OR</th>
<th>CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>82</td>
<td>73</td>
<td>63.3</td>
<td>1.34</td>
<td>0.79-2.28</td>
</tr>
<tr>
<td>Ischemic heart disease*</td>
<td>65</td>
<td>40</td>
<td>50.4</td>
<td>2.26</td>
<td>1.32-3.88</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>44</td>
<td>38</td>
<td>34.1</td>
<td>1.24</td>
<td>0.71-2.17</td>
</tr>
<tr>
<td>Smoking</td>
<td>39</td>
<td>34</td>
<td>30.2</td>
<td>1.21</td>
<td>0.68-2.16</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>20</td>
<td>18</td>
<td>15.5</td>
<td>1.13</td>
<td>0.54-2.38</td>
</tr>
<tr>
<td>Hyperlipidemia*</td>
<td>19</td>
<td>8</td>
<td>14.7</td>
<td>2.61</td>
<td>1.03-6.80</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>14</td>
<td>15</td>
<td>10.9</td>
<td>0.93</td>
<td>0.40-2.14</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>8</td>
<td>6</td>
<td>6.2</td>
<td>1.36</td>
<td>0.41-4.56</td>
</tr>
</tbody>
</table>

OR indicates odds ratio; CI, confidence interval.

*Risk factors with statistically significant differences between aspirin failure and control groups by x^2 test.
As expected, hypertension, ischemic heart disease, smoking, diabetes mellitus, and peripheral vascular disease were prevalent both in patients followed after a single stroke without a recurrence and in those with recurrent IS. The control and treatment of these risk factors might influence the success of primary and secondary stroke prevention. Although hyperlipidemia and ischemic heart disease were more common among ASA-F patients, it cannot be concluded that these well-known risk factors necessarily affect the efficacy of aspirin. However, the results do demonstrate that aspirin does not obliterate the excess risk for stroke recurrence associated with ischemic heart disease and hyperlipidemia. These results correspond with previous studies\textsuperscript{7,8}; therefore, patients with ischemic heart disease and hyperlipidemia should be considered for more aggressive forms of therapy, as already suggested by Chyatte and Chen.\textsuperscript{5}

We conclude that neither sex nor age but other unknown causes could influence the efficacy of aspirin; these causes require further clinical and laboratory evaluation.

References
Failure of aspirin treatment after stroke.
N M Bornstein, V G Karepov, B D Aronovich, A Y Gorbulev, T A Treves and A D Korczyn

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