Evaluation of Nitroglycerin in Angina in Patients on Isosorbide Dinitrate

By Wilbert S. Aronow, M.D., and Herman M. Chesluk, M.D.

SUMMARY
Seventeen male patients with angina pectoris due to coronary artery disease who had not received long-acting nitrates for at least 1 mo prior to this study were evaluated in a double-blind crossover study to investigate whether the presence of isosorbide dinitrate interfered with the effective response of exercise-induced angina to nitroglycerin administered sublingually. There was no significant difference in the duration of angina following nitroglycerin whether the patients were on no medication, sublingual placebo or sublingual isosorbide dinitrate. There was no significant difference in the blood pressure, heart rate, product of systolic blood pressure and heart rate, or electrocardiographic response after the complete relief of angina following sublingual nitroglycerin whether the patients were on no medication, sublingual placebo, or sublingual isosorbide dinitrate. These results indicate that long-acting nitrates do not cause any clinical impairment of the effective response of angina pectoris to sublingually administered nitroglycerin.

Additional Indexing Words:
Placebo Coronary artery disease Nitrates

The possibility that chronic administration of long-acting nitrates may lead to cross-over tolerance to nitroglycerin so that nitroglycerin becomes ineffective in the treatment of angina pectoris has been raised by several investigators. Sublingually administered isosorbide dinitrate proved to be no more effective than a sublingually administered placebo in patients with angina pectoris due to coronary artery disease in preventing episodes of angina pectoris requiring nitroglycerin, in improving exercise performance, and in affecting the electrocardiogram at rest and after exercise. During this study, the possibility of clinical ineffectiveness to nitroglycerin developing in patients receiving isosorbide dinitrate sublingually was also investigated and will be reported in this paper.

Methods
The protocol and methodology were as previously described. Seventeen of the 20 male patients, 33 to 56 years of age, with angina pectoris for more than 2 years, completed this double-blind crossover study. None of the patients received any nitrates except for nitroglycerin the month prior to this study.
In addition to the methodology previously described, 0.6 mg of nitroglycerin was administered sublingually to subjects in all exercise studies immediately after the first clinical manifestation of angina following upright exercise on a bicycle ergometer at 60 watts. The time in seconds between the administration of nitroglycerin and the complete relief of pain was measured with a stopwatch. Blood pressures were recorded in the upright position by the same observer with a mercury sphygmomanometer and heart rates with an electrocardiograph following the complete relief of angina in all exercise studies. Electrocardiograms using leads II and V₆ were taken in the upright position immediately after the complete relief of angina in all exercise studies.

From the Cardiology Section, Medical Service, Veterans Administration Hospital, Long Beach, California, and the University of California College of Medicine, Irvine, California.
Address for reprints: Wilbert S. Aronow, M.D., Cardiology Section, Veterans Administration Hospital, 5901 East Seventh Street, Long Beach, California 90801.
Received January 27, 1970; accepted for publication March 30, 1970.

Circulation, Volume XLII, July 1970 61
Table 1

Comparison of Duration of Angina from Onset of Angina to Complete Relief of Angina by Nitroglycerin on No Medication, Placebo, and Drug

<table>
<thead>
<tr>
<th>Case no.</th>
<th>On no medication (sec)</th>
<th>On drug (sec)</th>
<th>On placebo (sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>87 ± 7</td>
<td>90 ± 2</td>
<td>97 ± 18</td>
</tr>
<tr>
<td>2</td>
<td>73 ± 13</td>
<td>65 ± 10</td>
<td>67 ± 6</td>
</tr>
<tr>
<td>3</td>
<td>73 ± 19</td>
<td>69 ± 3</td>
<td>70 ± 4</td>
</tr>
<tr>
<td>4</td>
<td>53 ± 10</td>
<td>58 ± 6</td>
<td>58 ± 7</td>
</tr>
<tr>
<td>5</td>
<td>86 ± 7</td>
<td>98 ± 8</td>
<td>91 ± 6</td>
</tr>
<tr>
<td>6*</td>
<td>87 ± 14</td>
<td>82 ± 6</td>
<td>77 ± 5</td>
</tr>
<tr>
<td>7</td>
<td>65 ± 6</td>
<td>64 ± 6</td>
<td>66 ± 4</td>
</tr>
<tr>
<td>8</td>
<td>68 ± 7</td>
<td>66 ± 6</td>
<td>67 ± 8</td>
</tr>
<tr>
<td>9</td>
<td>102 ± 6</td>
<td>102 ± 6</td>
<td>102 ± 6</td>
</tr>
<tr>
<td>10†</td>
<td>75 ± 4</td>
<td>72 ± 4</td>
<td>72 ± 5</td>
</tr>
<tr>
<td>11</td>
<td>63 ± 6</td>
<td>63 ± 4</td>
<td>60 ± 5</td>
</tr>
<tr>
<td>12</td>
<td>68 ± 5</td>
<td>73 ± 5</td>
<td>71 ± 12</td>
</tr>
<tr>
<td>13</td>
<td>64 ± 5</td>
<td>72 ± 5</td>
<td>67 ± 7</td>
</tr>
<tr>
<td>14</td>
<td>75 ± 4</td>
<td>75 ± 5</td>
<td>82 ± 7</td>
</tr>
<tr>
<td>15</td>
<td>65 ± 6</td>
<td>64 ± 6</td>
<td>62 ± 3</td>
</tr>
<tr>
<td>16†</td>
<td>66 ± 5</td>
<td>70 ± 5</td>
<td>74 ± 4</td>
</tr>
<tr>
<td>17</td>
<td>76 ± 8</td>
<td>74 ± 4</td>
<td>73 ± 5</td>
</tr>
<tr>
<td>Group mean</td>
<td>73 ± 13</td>
<td>76 ± 20</td>
<td>74 ± 14</td>
</tr>
</tbody>
</table>

* Died.
† Unable to tolerate drug.

Results

Table 1 indicates the duration of angina from its onset to its complete relief following nitroglycerin without other medication, with placebo, and with isosorbide dinitrate given sublingually. The mean duration of angina was 73 ± 13 sec without other medication, 76 ± 20 sec with sublingual use of isosorbide dinitrate, and 74 ± 14 sec with sublingual placebo. The significance of the mean difference in exercise performance was evaluated by computation of tests using the t-test for correlated means. There was no significant difference in the mean duration of angina on drug versus no medication, on drug versus placebo, and on placebo versus no medication.

Table 2 indicates the group mean systolic and diastolic blood pressures, heart rate, and product of systolic blood pressure and heart rate immediately following complete relief of angina by nitroglycerin on no medication, sublingual placebo, or sublingual isosorbide dinitrate. There was no significant difference in the group's mean systolic or diastolic blood pressure, heart rate, or product of systolic blood pressure and heart rate on drug versus placebo, on drug versus no medication, and on placebo versus no medication.

There was no significant difference in the electrocardiograms immediately following the complete relief of angina without other medication, with sublingual placebo, or sublingual isosorbide dinitrate.

Discussion

Our patients had stopped exercising at the onset of anginal pain. The mean duration of anginal pain following sublingual administration of 0.6 mg of nitroglycerin to our patients who were sitting motionless on a bicycle ergometer was 74 sec for the three exercise periods. Cowan and his associates5 demonstrated...
strated the presence of beneficial effects caused by nitroglycerin in patients with arteriosclerotic heart disease at 45 sec after sublingual administration of this drug.

Nickerson\(^2\) pointed out that tolerance to the production of headache during chronic administration of long-acting nitrites develops readily and that the possibility of cross tolerance decreasing the effectiveness of nitroglycerin used for treating angina should be investigated. Modell\(^1\) pointed out this possibility and stated that an ineffective long-acting nitrite may possibly make nitroglycerin ineffective. Zelis and Mason\(^3\) found that isosorbide dinitrate reduced the venodilator response to nitroglycerin and indicated that this action may be responsible for vascular tolerance and diminished effectiveness of nitroglycerin during chronic administration of long-acting nitrites.

Our results reveal no significant difference in the duration of anginal pain following sublingual nitroglycerin whether the patients were on no medication or on sublingually administered placebo or isosorbide dinitrate. There was also no significant difference in the blood pressure, heart rate, product of systolic blood pressure and heart rate, and electrocardiographic response after complete relief of angina following sublingual use of nitroglycerin whether the patients were on no medication, sublingual placebo, or sublingual isosorbide dinitrate. These results indicate that long-acting nitrites, which are found to be no more effective than placebo in the experience of the authors, do not cause any clinical impairment of the effectiveness of nitroglycerin given sublingually in relieving angina.

Acknowledgment

The authors wish to express their appreciation to Reed Boswell, Ph.D., for his assistance in the statistical analysis of the data.

References

Evaluation of Nitroglycerin in Angina in Patients on Isosorbide Dinitrate
WILBERT S. ARONOW and HERMAN M. CHESLUK

Circulation. 1970;42:61-63
doi: 10.1161/01.CIR.42.1.61
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1970 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/42/1/61

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation 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 Circulation is online at:
http://circ.ahajournals.org//subscriptions/