Antihypertensive Drug Side Effects in the Hypertension Detection and Follow-up Program

J. DAVID CURB, KENNETH SCHNEIDER, JAMES O. TAYLOR, MORTON MAXWELL, AND NEIL SHULMAN

SUMMARY The 5485 participants in the Hypertension Detection and Follow-up Program, Stepped-Care group form one of the largest groups to date on which detailed surveillance of long-term antihypertensive therapy and drug side effects has been reported. During a 5-year period, among all hypertensive persons (mild, moderate, and severe combined) who were not taking antihypertensive medications at the beginning of the study and who attended the clinic at least once during the 5-year trial, a total of 9.3% had definite or probable side effects severe enough to cause discontinuation of the drug treatment in question. Less than 1% of active participants required hospitalization for side effects. No death that could be attributed to side effects was detected. Thus, the Hypertension Detection and Follow-up Program data, which have previously demonstrated the beneficial effects of antihypertensive therapy, confirm the relative safety of such therapy.

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KEY WORDS • blood pressure • treatment • adverse reactions • prospective • surveillance • cholesterol • reserpine

THE beneficial effects of drug treatment have been demonstrated in individuals with hypertension.1-3 The adverse effects of antihypertensive medications also have been well documented.6,7 While high blood pressure can be safely treated in most individuals, side effects of drugs are relatively frequent and may have notable effects on quality of life and compliance with the prescribed regimens.

Each possible side effect encountered by a therapist or practitioner is a combination of the patient’s perception, the clinician’s preconceptions, and the actions of the drug. While the Hypertension Detection and Follow-up Program (HDFP) was not designed to study the side effects of drugs in comparison with placebo, its Stepped-Care category does constitute one of the largest cohorts (n = 5485) from which detailed clinical surveillance data on antihypertensive drugs are available. The data presented here represent a description of the experience of the HDFP with antihypertensive drug side effects.

Methods

Data relevant to adverse drug reactions were gathered through a number of methods in the HDFP. These included questions asked in the home annually by nontherapist interviewers, responses elicited by questionnaire in the clinic, information provided by the therapist in the clinic, and information from the laboratory and electrocardiogram (ECG).

In the clinic’s questionnaires, each stepped-care participant was asked at baseline and at each subsequent clinical visit during the first year of the HDFP a set of 12 standard questions relating to nonspecific symptoms often associated with adverse drug side effects.8 These questions and the answers to them were used as an index of the patient’s perceptions of symptoms related to side effects.

Data on clinically detected drug side effects presented in this article are based on summary information on stepped-care participants provided by the HDFP staff therapist or physician on the basis of all available clinical information. Treatment was initiated with a stepped-care protocol using drugs that were approved by the Food and Drug Administration for use at the...
beginning of the trial in 1973, including chlorthalidone in step 1, reserpine or methyldopa in step 2, hydralazine in step 3, guanethidine in step 4, and additional or alternative drugs in step 5. Although this was the standard protocol, maintenance of blood pressure control was the primary goal of HDFP therapy, and when problems such as suspected side effects occurred, the HDFP therapist modified individual regimens as clinically necessary.

During the entire program, discontinuation of treatment with any antihypertensive medication required the completion of special study forms to provide explanation for discontinuation of treatment with that drug; other data were available on routine clinical visit forms. The final classification of each side effect event was based on the central physician’s review of all prior and subsequent clinical data relative to the event, including specific side effect follow-up records. To reduce bias due to past experience with antihypertensive medications and their side effects, all individuals already receiving antihypertensive therapy at entry into the study were excluded from this analysis.

The effect of thiazides on mean serum cholesterol values was examined for all 5 years of the study. The quantification of cholesterol was accomplished using a Technicon SMA 12/60 (TM) multichannel analyzer using the Leibermann-Burchard method in a CDC standardized laboratory. Overall analytical drift was monitored by one-blind and two-unblinded techniques. These three methods revealed a small, random analytical drift that was judged by all committees to be nonsignificant.

### Results

During the year in which the patient symptom questionnaire was administered, 15,076 visits were made to HDFP clinics by stepped-care participants not on antihypertensive medication at baseline. At baseline, before therapy was initiated, 74.8% of these individuals reported at least one of the 12 symptoms. During the first year of therapy, 75.4% reported having at least one of the symptoms during at least one clinical visit. New symptoms (not reported at baseline) were much less frequent in all race and sex groups (14.3% overall): black and white differences were small, but male and female differences were significant ($p<0.05$). Forty-five percent of individuals reporting symptoms during therapy had reported the same symptom before therapy was initiated.

During the 5-year follow-up, stepped-care participants made 172,569 clinical visits to the 14 HDFP clinical centers. At the end of the fifth year, 79% of the participants were active in the program. During this period, blood pressures (BP) among the stepped-care participants were reduced, on the average, by 28.7 mm Hg systolic and 17.0 mm Hg diastolic. Of those seen at the fifth annual clinical visit, 74.2% were at or below their blood pressure goal. Among 3844 individuals who were not receiving medications at the beginning of the trial and who remained active participants in it, a total of 1258 participants (32.7%) experienced at least one possible adverse reaction to a medication, which prompted the clinical therapist to discontinue the use of one or more drugs (Table 1); 40% of these individuals had more than one such event. Rates of side effects by baseline blood pressure strata and indications of whether the event was thought to be possibly, probably, or definitely a side effect are shown. Only 9.3% of stepped-care participants were reported to have probable or definite side effects during the 5 years. Such side effects were reported in 8.6% of those with mild hypertension (diastolic BP, 90–104 mm Hg), in 11.0% of those with moderate hypertension (diastolic BP, 105–114 mm Hg), and in 12.0% of those with severe hypertension (diastolic BP, $>115$ mm Hg).

Figure 1 summarizes the percentage of active stepped-care participants experiencing side effects (possible + probable + definite) among active stepped-care participants for each of the 5 years of follow-up by race and sex. During this period, 22.9% of the black women, 26.6% of the black men, 33.7% of the white women, and 40.9% of the white men had drug treatment discontinued because of side effects. There was a decreasing percentage of participants having treatment discontinued because of side effects in all these groups over time, with the rates during the fifth year being less than half those during the first year.

There were few life-threatening side effects, and there were no deaths that could be directly attributed to drug side effects. Only 23 individuals (<1%) were hospitalized for suspected side effects. The frequency of reported side effects was highest in those in the 50- to 59-year-old age group for all HDFP drugs except hydralazine, for which the incidence was greatest in the 40- to 49-year-old group. The incidence of side effects was lowest in the 60- to 69-year-old group for all drugs. Similar patterns were seen when the criteria

<table>
<thead>
<tr>
<th>Baseline BP (mm Hg)</th>
<th>Total active participants</th>
<th>Definite or probable</th>
<th>Possible</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>90–104</td>
<td>2756</td>
<td>236</td>
<td>8.6</td>
<td>642</td>
</tr>
<tr>
<td>105–114</td>
<td>730</td>
<td>80</td>
<td>11.0</td>
<td>157</td>
</tr>
<tr>
<td>&gt;115</td>
<td>358</td>
<td>43</td>
<td>12.0</td>
<td>100</td>
</tr>
<tr>
<td>Total</td>
<td>3844</td>
<td>359</td>
<td>9.3</td>
<td>899</td>
</tr>
</tbody>
</table>

*Participants regularly followed in an HDFP clinic. Modified from Curb et al. with permission.
TABLE 2. Incidence of Selected Adverse Drug Reactions Among Active Participants by Age

<table>
<thead>
<tr>
<th>Adverse reaction</th>
<th>30–39 Rate/100</th>
<th>40–49 Rate/100</th>
<th>50–59 Rate/100</th>
<th>60–69 Rate/100</th>
<th>Total Rate/100</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angina</td>
<td>3</td>
<td>0.5</td>
<td>9</td>
<td>0.0</td>
<td>10</td>
</tr>
<tr>
<td>Arrhythmias</td>
<td>3</td>
<td>0.5</td>
<td>12</td>
<td>1.0</td>
<td>15</td>
</tr>
<tr>
<td>Hypertension/orthostasis</td>
<td>15</td>
<td>2.3</td>
<td>23</td>
<td>2.0</td>
<td>20</td>
</tr>
<tr>
<td>Micon Gl</td>
<td>38</td>
<td>5.7</td>
<td>78</td>
<td>6.7</td>
<td>93</td>
</tr>
<tr>
<td>Peptic ulcer/GI bleeding</td>
<td>0</td>
<td>0.0</td>
<td>6</td>
<td>0.5</td>
<td>9</td>
</tr>
<tr>
<td>Liver abnormalities</td>
<td>7</td>
<td>1.1</td>
<td>6</td>
<td>0.5</td>
<td>8</td>
</tr>
<tr>
<td>Arthritis/arthralgias</td>
<td>8</td>
<td>1.2</td>
<td>10</td>
<td>0.9</td>
<td>8</td>
</tr>
<tr>
<td>Muscle cramping</td>
<td>5</td>
<td>0.8</td>
<td>6</td>
<td>1.4</td>
<td>19</td>
</tr>
<tr>
<td>Lupus/flu syndrome</td>
<td>3</td>
<td>0.5</td>
<td>5</td>
<td>0.4</td>
<td>6</td>
</tr>
<tr>
<td>Dermatitis</td>
<td>17</td>
<td>2.6</td>
<td>37</td>
<td>3.2</td>
<td>46</td>
</tr>
<tr>
<td>Asthma</td>
<td>1</td>
<td>0.2</td>
<td>4</td>
<td>0.3</td>
<td>0</td>
</tr>
<tr>
<td>Nasal stuffiness</td>
<td>22</td>
<td>3.4</td>
<td>40</td>
<td>3.4</td>
<td>30</td>
</tr>
<tr>
<td>Sexual</td>
<td>43</td>
<td>6.6</td>
<td>61</td>
<td>5.2</td>
<td>70</td>
</tr>
<tr>
<td>Depression</td>
<td>28</td>
<td>4.3</td>
<td>58</td>
<td>5.0</td>
<td>40</td>
</tr>
<tr>
<td>Nightmares</td>
<td>19</td>
<td>2.9</td>
<td>36</td>
<td>3.1</td>
<td>28</td>
</tr>
<tr>
<td>Other psychiatric</td>
<td>3</td>
<td>0.5</td>
<td>5</td>
<td>0.4</td>
<td>1</td>
</tr>
<tr>
<td>Dizziness/syncope</td>
<td>28</td>
<td>2.0</td>
<td>51</td>
<td>4.4</td>
<td>57</td>
</tr>
<tr>
<td>Headache</td>
<td>20</td>
<td>3.1</td>
<td>22</td>
<td>0.6</td>
<td>15</td>
</tr>
<tr>
<td>Lethargy</td>
<td>32</td>
<td>4.9</td>
<td>59</td>
<td>5.1</td>
<td>56</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>46</td>
<td>7.1</td>
<td>96</td>
<td>8.3</td>
<td>74</td>
</tr>
<tr>
<td>Weakness</td>
<td>19</td>
<td>2.9</td>
<td>41</td>
<td>3.5</td>
<td>47</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>13</td>
<td>2.0</td>
<td>21</td>
<td>1.8</td>
<td>17</td>
</tr>
<tr>
<td>Gout/hyperuricemia</td>
<td>5</td>
<td>0.8</td>
<td>16</td>
<td>1.4</td>
<td>22</td>
</tr>
<tr>
<td>Diabetes/hyperglycemia</td>
<td>5</td>
<td>0.8</td>
<td>18</td>
<td>1.6</td>
<td>27</td>
</tr>
<tr>
<td>Gynecomastia</td>
<td>10</td>
<td>1.5</td>
<td>16</td>
<td>1.4</td>
<td>31</td>
</tr>
<tr>
<td>Hypercalcemia</td>
<td>2</td>
<td>0.3</td>
<td>2</td>
<td>0.2</td>
<td>3</td>
</tr>
</tbody>
</table>

Total                             | 207            | 31.9           | 406            | 34.8           | 436            | 35.1           | 209            | 26.6           | 258             | 32.7           |

Modified from Curb et al.8 with permission.
thought to cause such problems. Only six females dis-
tinued medications because of sexually related
drug side effects.

Figure 2 shows the data on the annual changes in
serum cholesterol during 5 years for thiazide-treated
stepped-care participants. In order to use all chole-
tsterol data available on each patient, the cholesterol values
for every annual visit and cholesterol checks per-
formed 6 months before or after each annual visit were
averaged to give the yearly mean serum cholesterol
concentration. Because patients were seen every 4
months, the yearly value for each patient was usually
an average of two or three determinations. Among
those taking chlorthalidone or thiazides alone or in
combination with reserpine or methyldopa for the en-
tire 5-year period, cholesterol at the first year increased
by 4 mg/dl, followed by a continuous decline amount-
ing to 9 mg/dl at the fourth year, and is stable at the
fifth year. Similar trends were noted in all race, sex,
and age groups. Among those treated with a similar
regimen, an increase in serum cholesterol during the
initial 6-month period was also noted.

Analyses designed to examine the possibility that
the findings were due to a cohort effect suggest that
even though the number of participants decreased from
year to year, a selection process, if it were operative,
did not result in different cholesterol values for those
patients on longer-term therapy.

Discussion

Because of the absence of a blinded-placebo group
in the HDFP, the findings reported here must be con-
sidered as the results of a study of clinical surveillance
for drug side effects and not as a controlled clinical
trial for comparing those taking drugs and those not
taking them. The data presented do indicate, however,
that the number of individuals who report side effect-
like complaints at the beginning of a program, while
not on antihypertensive medication, is substantial
(74.8%).

The frequency of possible drug side effects severe
enough to cause discontinuation of drug therapy in the
HDFP is consistent with clinical experience in the
treatment of hypertension. There are, however, few
well-documented reports of the long-term occurrence
of side effects of antihypertensive therapy. In the
HDFP, although relatively standard drug regimens
were encouraged, blood pressure lowering and, thus,
compliance to the drug regimen took precedence over
the particular medications used. Therapists and physi-
cians were sensitive to actual, potential, and patient-
perceived side effects of the drugs that might affect
compliance, and they would discontinue use of a medica-
tion when a side effect was possible, if it were be-
lieved such an action would help to keep the patient
under active treatment. The HDFP analysis has also
shown that specific questions about patient perceptions
of nonspecific side effect–like symptoms will result in
at least one positive response in most patients at some
time during therapy. The situation is similar to that
faced by the clinician who often has similar goals in his
practice, and the data presented here should approxi-
mate what would be seen by such a practitioner.

Of some interest is the fact that side effects were not
reported more frequently in the older patients than in
the younger individuals. This observation tends to
agree with earlier reports from the European Working
Party on High Blood Pressure Study in the Elderly10
regarding the relative safety of treating hypertension in
older patients.

In several short-term studies, thiazide diuretics have
been associated with an increase in serum cholesterol
and triglyceride levels in normal and hypertensive pa-
tients.11-14 Most of these investigations involved acute
treatment with a duration of 1 year or less.

Two investigations for a longer period than 1 year,
the Framingham Study15 and the Oslo clinical trial,16
reported there was no change in cholesterol levels in
hypertensive patients receiving diuretics for 2 years or
more. Others, including the Multiple Risk Factor In-
tervention Trial (MRFIT) group, have indicated a pos-
sible long-term increase in serum cholesterol.17-19

Thus, there are inconsistent results regarding the
effects of diuretics on serum cholesterol when admin-
istered for a short period of time versus over several
years. The HDFP results indicate a short-term increase
(1 year) followed by a long-term absolute decrease
in serum cholesterol among chlorthalidone-treated
participants.

Immediately after publication of the MRFIT re-
sults,20 which postulated a possible adverse effect for the
"special intervention" group with hypertension and
resting ECG abnormalities at baseline, the HDFP Co-
operative Research Group undertook extensive data
analyses on this subject. The basic aim of these further
analyses of the HDFP data was to determine whether in
a cohort selected to resemble MRFIT participants the
HDFP results would replicate those reported by
MRFIT.

With respect to the mortality experience for HDFP
participants with resting ECG abnormalities at base-
line, the trend of the mortality from all causes (i.e., the
HDFP primary end point) was in favor of stepped-care
treatment of mild hypertension. In other words, for both cardiovascular and total mortality, the stepped-care group with and without ECG abnormalities at baseline experienced a more favorable outcome than the referred-care group. In these respects, therefore, the HDFP and MRFTT findings are not concordant. For a much smaller and more restrictive MRFTT-like subgroup of white males with small numbers of events, coronary heart disease rates are higher in the stepped-care group with ECG abnormalities. This is not true for similarly selected groups of blacks or women.

The subgroup of the HDFP cohort that is most comparable to the MRFTT cohort is small, as is the number of events, hence, variability in the estimates of treatment differences could be substantial. It should be kept in mind that the HDFP and the MRFTT programs had fundamental design differences that make direct comparisons more difficult. The HDFP was a community-based sample, whereas the MRFTT participants were volunteers derived from many sources and were successfully qualified in accordance with a relatively complex algorithm. MRFTT cause of death is based on committee review of all records and interview data, whereas HDFP cause of death is based on a single nosologist’s coding of the death certificates. Substantial differences in the type of events, such as coronary heart disease, included might be anticipated. Therefore, it is significant to note that the HDFP data do not indicate a consistent problem with stepped-care therapy for persons with mild hypertension and with resting ECG abnormalities as was suggested by MRFTT data. Detailed data and a more extensive discussion of this issue are presented elsewhere.

In general, no new or unexpected trends in side effects of the drugs used in the HDFP were noted in this study. Follow-up for long-term drug toxicity has been limited, but an analysis of the HDFP 5-year data regarding the possibility of a relationship between serpine use and breast tumor growth failed to show evidence of such an association. Although there was a high incidence of perceived side effects, the majority of those events reported were relatively mild, and few contributed to significant morbidity. Thus, the HDFP data, which have previously demonstrated the beneficial effects of vigorous antihypertensive treatment, also affirm the relative safety of antihypertensive therapy.

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