Reserpine and Breast Cancer in the Hypertension Detection and Follow-Up Program

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SUMMARY Recent reports on the efficacy of pharmacological management in reducing mortality associated with mild hypertension have enhanced the importance of increasing our knowledge about drug toxicity. The Hypertension Detection and Follow-Up Program (HDFP) provides a convenient setting in which to examine the association reported between reserpine usage and breast cancer. In the intensively treated and followed group (Stepped Care [SC]), the relative breast cancer experience of those who did take reserpine and those who did not was examined. Of 2529 females in SC, 1036 received reserpine, with an average exposure of 1.97 years during 5 years of follow-up. Through extensive investigation, 21 cases of breast cancer were identified. Using a life table regression method of analysis to adjust for actual time of reserpine exposure, race, sex, and medication status at entry, and comparing those who took reserpine with those who did not, the authors calculated a risk ratio of 1.28, with a confidence interval of 0.58 to 2.80. Adjustment for a number of other variables known to have relationships to breast cancer did not appreciably change the results. Thus, with certain precautions, the authors conclude that in this setting there is no indication of the recently postulated association of reserpine and the short-term enhancement of breast tumor growth.

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KEY WORDS • reserpine • breast cancer • hypertension treatment • drug toxicity

RECENTLY released findings of the Hypertension Detection and Follow-Up Program1, 2 and the Australian Trial in Mild Hypertension3 provide evidence of the efficacy of pharmacological treatment of mild hypertension. However, such findings and their potential extension to long-term drug treatment of millions with mild hypertension require that possible long-term toxic effects of antihypertensive drugs be examined.

In 1974, three reports of case-comparison studies suggested an association between a history of reserpine use and the occurrence of breast cancer.4-6 These initial reports raised serious concern and stimulated further studies to support decisions as to whether the use of reserpine as an antihypertensive agent should be continued. Several subsequent case-comparison studies failed to confirm previous observations. Lack of consistency in study results prevented satisfactory resolution of the question.7-18 One major study in animals was conducted under the auspices of the National Cancer Institute; it was reported to the NCI Clearinghouse on Environmental Carcinogens in May, 1979, independently reviewed after extensive critical comment, and finally accepted by the Clearinghouse in February, 1980.17 The findings of this study were interpreted as indicating carcinogenicity for the mammary gland of female mice but not of rats. Thus, inconsistencies in both human and animal studies persist; two recent reviews of the case-comparison studies on reserpine use convey similar impressions.18, 19

In addition to the more readily conducted case-comparison studies, direct estimation of risk in exposed human populations as determined through prospective epidemiologic studies is desirable. Because of the necessary delay and continued exposure characteristic of prospective study designs, as future exposure experience must be acquired, use of existing data sources to conduct a historical-prospec-
tive approach is particularly attractive. One such study has been conducted at the Mayo Clinic. There was no significant excess in the frequency of breast cancer among all women ever exposed to reserpine (450 of 1730 women with hypertension diagnosed after 1954), and fewer cases than expected were observed among those exposed for 1 year or longer (250 of the 450 women ever exposed), relative to the general population.

It is desirable to replicate this single prospective study, but few settings provide the necessary medical follow-up to document both exposure (at least as prescribed and recorded) and outcome. The Hypertension Detection and Follow-up Program (HDFP) offered an opportunity of this kind. In the HDFP, data are available on the intensive follow-up of over 2500 women who were under active treatment for hypertension with a well-documented drug regimen that included reserpine. Periodic examinations, including history, physical and laboratory findings, and documentation of hospitalizations and deaths, provide for ascertainment of breast cancer in this population, as well as information on other factors which, if left uncontrolled, might serve to bias such an analysis. We decided to examine the possible association between the use of reserpine and breast cancer among the HDFP population participants.

Methods

The HDFP was a multicenter trial designed to investigate benefits of treatment of hypertension in a community-based population. The study population was selected from 14 communities around the United States, generally by formal sampling or full screening from defined census tracts, with varying ethnic and socioeconomic characteristics. Within these communities 158,906 individuals aged 30–69 years were screened for hypertension, and ultimately 10,940 identified hypertensives were enrolled into the treatment program. Half were randomly assigned to a group referred for care to existing community sources (RC) and half to a special treatment group, the Stepped Care (SC) group. Those randomized to the SC were enrolled in special HDFP clinics designed to treat their hypertension in the most efficient and cost effective manner, in accordance with a carefully structured SC approach (table 1). It should be noted that SC therapy included reserpine as its main second-step drug, in combination with the first-step thiazide-like diuretic, chlorthalidone. Completeness of follow-up is suggested by the fact that over 85% of the surviving group attended clinic visits regularly and over 94% of the survivors were seen at the 5th annual follow-up, with less than 0.2% of the SC patients totally lost to follow-up. With respect to reported adherence to the prescribed drug regimens, preliminary analysis indicates as of the end of Year 1 approximately 80% of the participants prescribed reserpine were taking at least 80% of the dosage prescribed. This report concerns the SC participants only.

To examine the association between reserpine and breast cancer in this population, extensive searches were made of hospitalization data and clinic records of annual history and physical examinations. Each participant in whom breast cancer was diagnosed was identified and the date of diagnosis established. It should be noted that detailed information was available on reserpine usage during but not before the program began. Thus, both exposure and outcome as well as other baseline attributes of interest were well documented within the period of participation in HDFP (see table 2).

### Table 1. Stepped Care Drug Protocol

<table>
<thead>
<tr>
<th>Step</th>
<th>Drug(s)</th>
<th>Dosage (mg/day)</th>
<th>Duration* (wks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 1</td>
<td>chlorthalidone†</td>
<td>25–100</td>
<td>12</td>
</tr>
<tr>
<td>Step 2</td>
<td>add reserpine or methyldopa</td>
<td>0.1–0.25</td>
<td>12</td>
</tr>
<tr>
<td>Step 3</td>
<td>add hydralazine</td>
<td>30–200</td>
<td>16</td>
</tr>
<tr>
<td>Step 4</td>
<td>add guanethidine</td>
<td>10–200</td>
<td></td>
</tr>
<tr>
<td>Step 5</td>
<td>add additional agents or substitute</td>
<td>—</td>
<td></td>
</tr>
</tbody>
</table>

*Maximum length of time until advancing to next step if not at goal blood pressure.

†Spironolactone (25 to 100 mg/day) or triamterene (50 to 300 mg/day) were used in addition or alternatively to chlorthalidone when clinically indicated.

### Table 2. Participant Characteristics among 1036 Women Who Took Reserpine and 1493 Who Did Not

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Ever on reserpine (%)</th>
<th>Never on reserpine (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postmenopausal</td>
<td>64.3</td>
<td>68.0</td>
</tr>
<tr>
<td>50 years old or older</td>
<td>52.7</td>
<td>59.0</td>
</tr>
<tr>
<td>Greater than 130% ideal weight</td>
<td>43.6</td>
<td>37.9</td>
</tr>
<tr>
<td>Ever taken antihypertensive medicine</td>
<td>65.8</td>
<td>52.3</td>
</tr>
<tr>
<td>Taking antihypertensive medicine at baseline</td>
<td>37.0</td>
<td>28.4</td>
</tr>
<tr>
<td>Hypertension, 10 years or longer</td>
<td>30.5</td>
<td>22.6</td>
</tr>
<tr>
<td>Birth control pills ever</td>
<td>5.5</td>
<td>5.5</td>
</tr>
<tr>
<td>Black</td>
<td>58.2</td>
<td>49.6</td>
</tr>
<tr>
<td>High school education</td>
<td>44.0</td>
<td>46.5</td>
</tr>
<tr>
<td>Nulliparous</td>
<td>11.0</td>
<td>12.0</td>
</tr>
</tbody>
</table>

Number per year

| Clinic visits | 7.4 | 5.7 |
| Physician visits | 12.0 | 11.0 |
| Hospitalizations | 0.18 | 0.19 |
Due to the progressive steps of the treatment regimen, it was inappropriate to simply classify individuals into two groups, those who received reserpine during the study and those who did not. Since participants in SC were first placed in Step 1 (chlorothalidone and/or spironolactone or triamterene) and only weeks to months later (if not at goal blood pressure) were they advanced to Step 2 (e.g., chlorothalidone plus reserpine) (table 1), a classification of "on reserpine vs not on reserpine" would lead to a bias known as "length bias sampling," which refers to unequal sampling due to time differences in exposure. The primary statistical analysis we chose, instead, takes into account the time relations in changes in treatment status. This method, referred to as life table regression with time dependent covariates, allows the treatment (on reserpine or not on reserpine) to be assigned during the period of observation so that only the time beyond onset of treatment with reserpine is incorporated into the analysis and comparisons are made with participants at that time who were not on reserpine. The method also adjusts for variables such as age and race while comparing the treatment groups.

As shown in table 3, 1036 of the 2529 female participants in the HDFP Stepped Care treatment program received reserpine for an average of 1.97 years and were at risk for 3994 person-years after first exposure. In most of these individuals, reserpine use was initiated prior to the first reports of its possible association with breast cancer in 1974; 659 received reserpine for more than 1 year. The duration of follow-up for all women in these analyses was 5 years.

An extensive review of all participants in the HDFP revealed that 21 SC participants had been newly diagnosed as having breast cancer at some time during the 5 years.

The method of life table regression analysis cited above was used to test the hypothesis that women who took reserpine were at no excess risk of developing breast cancer. In this analysis each woman was assigned to reserpine therapy only after being placed on reserpine during the course of the HDFP. Table 4 shows results of the regression analysis for the comparison between those women who took reserpine at some time during the study and those who never did. The relative risk adjusted for age, race, and whether

<table>
<thead>
<tr>
<th>Time taking reserpine</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of women</td>
<td>Mean yrs taking reserpine</td>
<td>Mean yrs follow-up after initial prescription</td>
<td>Person yrs at risk</td>
<td>No. of breast cancer cases</td>
</tr>
<tr>
<td>Ever</td>
<td>1036</td>
<td>1.97</td>
<td>3.86</td>
<td>3994</td>
<td>7</td>
</tr>
<tr>
<td>1 year or more</td>
<td>659</td>
<td>2.85</td>
<td>4.04</td>
<td>2662</td>
<td>14</td>
</tr>
<tr>
<td>Never</td>
<td>1493</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>14</td>
</tr>
<tr>
<td>Total</td>
<td>2529</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>21</td>
</tr>
</tbody>
</table>

Results

Table 2 presents the percentages of women who took reserpine and those who did not with respect to some of the factors reported to be associated with breast cancer. Women who were postmenopausal and those over 50 years of age were more common among those who did not take reserpine than those who did. Factors such as obesity, history of hypertension, use of antihypertensive medications, and being black were more frequent among those who took reserpine than those who did not. These factors would be expected to be more common in a group requiring Step 2 therapy. The comparative frequencies of other attributes between the two groups were not greatly different. It should be noted that the two groups were similar with regard to the three factors that reflect clinical contact: activity in the program, mean hospitalizations per year, and mean physician visits per year, and thus bias in ascertainment of breast cancer is unlikely.

<table>
<thead>
<tr>
<th>Reserpine</th>
<th>Race (black or white)</th>
<th>Age (30 to 69 yrs at entry)</th>
<th>Baseline medications*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta</td>
<td>Standard deviation</td>
<td>Z = Beta / SD</td>
<td>Relative risk (e^)</td>
</tr>
<tr>
<td>0.247</td>
<td>0.392</td>
<td>0.63</td>
<td>1.28</td>
</tr>
<tr>
<td>-0.879</td>
<td>0.493</td>
<td>-1.78</td>
<td></td>
</tr>
<tr>
<td>0.998</td>
<td>0.565</td>
<td>1.77</td>
<td></td>
</tr>
<tr>
<td>0.254</td>
<td>0.487</td>
<td>0.52</td>
<td></td>
</tr>
</tbody>
</table>

On or off medication at entry.
the participant was under treatment for hypertension at the time of randomization was 1.28. Because this was a prospective investigation of the relationship between breast cancer and reserpine, with the period of follow-up yielding only 21 cases of breast cancer, it was important to investigate the impact of sample size on the variability of the estimate of the relative risk. This was carried out by computing the 95% confidence limits for the estimate of the relative risk. The distance between the upper and lower limits reflects the variability in the estimate of the relative risk for this study. The limits are 0.58 to 2.80. With further adjustment for additional variables such as percent ideal weight, parity, pre/post menopause status, and history of hypertension, the results were similar (relative risk 1.30 vs 1.28).

To take into account exposure to health care as a factor that could differentially affect the ascertainment of breast cancer, we included the number of physician visits during each year period as a time-dependent covariate. This factor had very little effect on the relative risk (1.27 vs 1.28), consistent with the between-group balance of such variables shown in table 2.

In summary, we found little evidence of association between the use of reserpine and the incidence of breast cancer.

Discussion

The relatively short follow-up period of five years in HDFP does preclude, at this time, any attempt to examine long-term reserpine use for a possible association with breast cancer, as has been suggested by Williams et al. The HDFP data do, however, allow one to examine the question of reserpine enhancement of tumor growth and stimulation of already present carcinomas, as has been postulated by Armstrong et al. If, as they suggested, reserpine acts as an agent that simply accelerates the course of the disease or brings out latent or inapparent disease, one might expect to see the relationship developing in those who had been exposed to the drug relatively recently. The accurate drug histories and close follow-up available in the HDFP make this a very suitable population in which to examine this type of relationship. There is no support for such a relationship in the HDFP.

A randomized controlled clinical trial would provide the most definitive answer to the question of association between reserpine and breast cancer. However, since such a trial would be logistically difficult; use of data sets, such as the one described here, to identify those at risk and follow them through their detailed case histories provides an alternative approach to examine the question. The relatively complete research protocol records of HDFP are undoubtedly superior to those in most patient care circumstances or to a simple recall by patient, relative, or physician. The number of relatively noncompliant participants was small, and most were interviewed yearly by HDFP staff for their drug and health histories. In addition, the analytical technique we used allowed adjustment for actual length of time on the drug.

Information may be lacking regarding some potentially biasing factors. Breast cancer histology was often not recorded in the material available to us. Also, it should be realized that the HDFP was not designed to test effects specifically attributable to single drugs. All women were, of course, diagnosed as having hypertension, and most were taking other drugs, especially chlorthalidone. Complete pretrial drug histories were not available, although an adjustment made concerning whether the patient was under treatment for hypertension at the time of randomization partially corrected for this.

A number of other factors shown in other studies to be possibly related to breast cancer were found to be comparable among those with and without a history of reserpine ingestion during the trial. Notably, this includes medical contacts, which Mack et al. consider to be an important source of bias. Many potentially biasing factors were adjusted for in the life table regression analysis, and, although due to the small number of breast cancer cases we must be cautious in our interpretation, the resultant relative risk estimate was not greatly changed. The ability to ascertain such biasing factors during the prospective follow-up of the HDFP population was certainly better than found in most retrospective and case-control settings. Thus, with certain precautions, we may conclude that in this setting there is little indication of an association of reserpine ingestion and the short-term enhancement of breast tumor growth. Follow-up is, however, continuing.

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