Family Practice Forum

Reserpine: The Maligned Antihypertensive Drug

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During the 1950s reserpine was introduced to physicians in the United States as an effective psychotropic and antihypertensive drug. Within a few years clinicians reported depression and suicide in psychotic and hypertensive patients who had been administered reserpine in dosages of 0.5 to 10 mg/d.[1-4] However, a causal link between reserpine and depression has never been adequately established,[5,6] and recent studies have shown that reserpine in dosages under 0.5 mg is a safe and efficacious antihypertensive medication.[7-9]

A 1971 review of the literature and a 1972 re-evaluation of reserpine and depression by Goodwin and Bunney[6] described the early use of reserpine in a table format, which outlined dosages used (0.25 to 10 mg) and degree of depression diagnosed. The studies from the 1950s had reported an average incidence of depression of 20 percent. Because there was no minimal criteria identification, the clinical criteria the authors used to diagnose depression were not always clear. There was also a considerable difference in the lag period between starting the drug and the appearance of depression (2 weeks to 1 year).[5,6]

In 1958 Ayd[10] described two syndromes that occurred with reserpine in dosages up to 10 mg/d: "Pseudodepression," characterized by a feeling of lassitude and discouragement, and "true depression," which included the symptoms of a major depression. Patients in the first group responded to a decrease in the dose or the discontinuation of

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the drug, but most patients with true depression required electroconvulsive therapy. Prior episodes of depression were in the past medical history of 83 percent of these patients. Thirty-three percent of the recovered patients experienced a subsequent depression that needed treatment. Twenty percent of the recovered patients were back on reserpine in lower doses for hypertension with no problems. The relatives of some patients felt the patients were mildly depressed and unduly worried before seeing their physician for their hypertension. "Until more conclusive evidence is available, it cannot be stated authoritatively that tranquilizers (reserpine and chlorpromazine) per se cause depression."[10]

In a 1960 prospective study by Bernstein and Kaufman,[11] 50 patients on 1 to 5 mg of reserpine per day were interviewed weekly by psychiatrists for 12 to 18 months. Twelve of the 50 complained of being slowed down or overtranquilized. None developed a major depressive episode.

In a 1976 study 231 hospitalized patients were studied prospectively for adverse reactions to reserpine. One hundred forty-seven patients also received diuretics and 78 received other antihypertensive drugs such as methyldopa, guanethidine, hydralazine, and propranolol. (The authors did not record the number of patients that were on reserpine only as a second-step drug.) Adverse reactions were attributed to reserpine in 26 patients, gastrointestinal disturbance in 6, hypotension in 6, and sensitivity reactions in 2. These same adverse reactions have also been noted after using other antihypertensive drugs.[12]

Many practicing physicians have found reserpine to be a good second-step antihypertensive medication. Finnerty et al[7] described reserpine as the second-step drug of choice based on efficacy, convenient dosage, and cost. Channick et al[8] found a chlorthalidone-reserpine combination to be an effective antihypertensive regimen (91 percent with 90 mmHg diastolic blood pressure down from 106.8 mmHg by week 12), ". . . although earlier reports indicated a high incidence of central nervous system side effects to be dose related. In doses required (0.25 to 0.5 mg) to reach goal blood pressure in our patients, there was a low incidence of central nervous system side effects; only one patient (4.5 percent) manifested significant depression." Chlorthalidone-reserpine-treated patients showed a significantly lower incidence of adverse effects than patients treated with hydrochlorothiazide-methyldopa (31 vs 64 percent; $P < 0.02$).[8,9]

Bulpitt and Dollery[13] noted that reserpine in low dosages, with or without mild diuretics, would be justified as the second-step drug of choice because of its good results and the paucity of adverse effects. There was no significant statistical difference in the incidence of depression in patients on different individual drugs (including reserpine, methyldopa, guanethidine, and bethanidine). They concluded that the drugs could not be implicated as the cause of depression in these patients.

An examination and comparison of hypertensive outpatients and nonhypertensive chronically ill outpatients with a mood rating scale at regular intervals for one year by Bant[14] showed an equally high incidence of depression (nearly 50 percent) in both groups. She concluded that illnesses not cured but only controlled by drugs are now assuming greater importance in the cause of depression in chronically ill patients. Most of these episodes of depression seem to be reflections of the illness itself rather than the medication; in comparing the patients on various antihypertensive medications, she found that, "contrary to what might be expected, the more severe depressions occurred in the patients on the adrenergic blockers rather than in those on the reserpine and methyldopa."[15]

In 1978 Schyve et al[16] reviewed the evidence that neuroleptics may increase the risk of breast cancer via their effects on prolactin. Epidemiologic data in three 1974 studies caused concern that reserpine, a potent stimulator of prolactin, increased the incidence of breast cancer.[17-19] The design of the original three studies generated a series of criticism. Subsequent, better controlled epidemiologic studies have uniformly found no association between reserpine use and breast cancer.[20-26] The same critical appraisal of the relationship of reserpine to depression reported during the decade of the 1950s would have avoided the present bias against an effective antihypertensive medication as seen in today's textbooks.[27-30]

The evidence against reserpine comes primarily from retrospective studies of questionable design published during the 1950s. Reserpine dosages over 0.5 mg and the lack of concise criteria for the diagnosis of depression make the conclusions drawn from the data suspect.

Comment

There are three main advantages in using reserpine as a second-step drug: (1) it lowers blood pressure with minimal side effects in dosages less than 0.5 mg; (2) the once-a-day dosage is an important factor in patient adherence to drug regimens[31,32]; and (3) the cost to the patient of one month of propranolol (Inderal) is approximately $14.50, which would purchase approximately one and one-half months' supply of methyldopa (Aldomet) therapy or 9 months of reserpine therapy.[33]

The 15 to 20 percent incidence of depression in the general clinic population is similar to the literature-reported incidence of depression in patients on reserpine. It would appear that the severely depressed patients on reserpine may be responding to pre-existing rather than iatrogenic causes. The effect of chronic disease that is controlled but not cured on the cause of depression adds weight to the idea that rather than reserpine, depression might be an "illness effect."

A prospective study of the efficacy and safety of second-step antihypertensive drugs used in primary care is in order. A protocol can be developed whereby such a study would be carried out in the practicing physician's office.

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