TOXICOLOGIC AND CLINICAL APPRAISAL OF BUCLIZINE, A NEW ANTIHISTAMINIC COMPOUND

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The search for histamine antagonists of low toxicity and prolonged activity continues. A new class of antihistaminic preparations has been recently synthesized which, in addition to diethylene diamine (piperazine), has three benzylic rings. One of these compounds is buclizine, 1-p-chlorobenzhydryl-4-p-tertiary butylbenzylpiperazine dihydrochloride; its structural formula is shown in Fig. 1.

In animals, buclizine has been shown to possess marked protective activity against aerosolized and intravenously injected histamine. Although the onset of its action has proved to be relatively slow, the duration of activity is unusually prolonged. For example, it has been shown that 1 mg. per kilogram of the drug administered orally to the guinea pig protected the animal for about sixteen days against the lethal bronchoconstrictor effect of a histamine aerosol. This dose is equivalent to 73 mg. in a man of usual weight, and the persistent action in the guinea pig would lead one to expect very prolonged action in man. Clinical experience does not bear this out, however, as daily doses of 75 mg. or more are well tolerated and appear to have no cumulative effect. This is probably a species difference and deserves further study. In the dog and rat, buclizine is relatively nontoxic, but comparable studies have not been done in the guinea pig.

Preliminary clinical data in normal volunteers and subjects with various allergic states pointed to excellent tolerance for buclizine administered orally. It seemed desirable to determine whether or not these advantageous properties would be evident after long-term administration of the drug and to gather further data on its therapeutic efficacy.

MATERIALS AND METHODS.

Seventy patients were given oral buclizine in the extending period from Dec. 7, 1953, to Dec. 18, 1954. Among the seventy patients, twenty-eight were male and forty-two female; their ages ranged from 9 to 73 years, with an average age of 35 years. Of these patients, forty-two had vasomotor rhinitis (as far as can be determined, there was no evidence of an allergic cause), twenty-two had allergic rhinitis of the perennial variety, and six had urticaria. These conditions lend themselves well to a study of this type, for such patients frequently require daily medication for long periods in an effort to obtain relief. All patients had moderate to severe symptoms and had often failed to obtain relief by other measures, including injections of allergens. The patients who were receiving injections (22 per cent) continued to do so, but were urged to avoid other antihistaminic drugs. Seventy-five milligrams of buclizine per day was prescribed, to be taken in three equally divided doses between arising in the morning and bedtime. Patients were encouraged to take the medication irrespective of "need" unless untoward reactions occurred. In some, the daily dose had to be reduced to 25 or 50 mg. per day, and in children the daily dosage was one-half the adult dose. There was no way of being absolutely certain about the number of days the subjects were on the drug but, based on their statements, the compound was taken orally for from 8 to 233 days, with an average of 93 days. Since the primary purpose of the study was to determine the presence or absence of toxic effects from prolonged administration of the drug, neither a placebo control nor a blind study was attempted.

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Prior to and following the administration of buclizine, urinalyses, van den Bergh reactions, thymol turbidity tests, studies of the hemoglobin levels, and leukocyte and differential counts were obtained in twenty patients: fifteen patients had urinalyses and blood studies; and in fifteen it was possible to record only the urinary findings. These fifteen patients comprised the experimental group. The laboratory procedures were not satisfactorily completed in the remaining twenty patients and, therefore, are not included in this group. The method for the van den Bergh reaction was a modification of that described by Evelyn and Malloy. Bilirubin is converted to a red-violet azobilirubin when treated with Ehrlich’s reagent (diazotized sulfanilic acid). A fifteen-minute reading is obtained in aqueous solution, giving the total direct-reacting bilirubin, and a thirty-minute reading is taken in methyl alcohol solution. This reading constitutes the total bilirubin. The difference between the two readings is a measure of the indirect-reacting bilirubin. The method for thymol turbidity is a modification of that described by MacCullum. Under certain conditions, a turbidity is formed when serum is treated with a buffered thymol solution due to the precipitation of a protein-thymol-phospholipid complex. The density of the turbidity is determined nephelometrically.

Laboratory examinations were repeated at approximately four- to eight-week intervals and in several instances this period had to be extended. All subjects were seen at seven- to fourteen-day intervals over a period of weeks to months, and were observed carefully for the development of possible toxic reactions. The effectiveness of the buclizine in relieving symptoms was noted.

**RESULTS OF LABORATORY STUDIES.**

The fifty patients comprising the experimental group were given oral doses of buclizine daily for an average of approximately four months. One patient took buclizine for 233 days, and none received the drug for less than ten weeks. Of the fifty patients in whom the urinalyses were followed at stated intervals, evidence of renal dysfunction was found in one. This was based both on the absence of significant glycosuria or albuminuria and on examination of centrifuged sediments, which did not reveal abnormal microscopical elements. Although concentration tests were not included, all patients were able, at one time or another, to concentrate urine to a specific gravity of 1,020 or more.

Evaluation of hepatic function in twenty patients was based on the van den Berg reaction and the thymol turbidity test. These examinations were carried out on fasting blood samples. No abnormalities in function, as determined by these two tests, were observed before or during the course of therapy with buclizine.

Of the thirty-three patients in whom hemoglobin determinations and complete blood counts were made periodically, evidence of anemia, leukopenia, or abnormalities of the microscopic picture of the blood was not observed.

**SIDE EFFECTS.**

Of the seventy patients given buclizine, fifty-two (74 per cent) were free from side effects. The reactions in the remaining eighteen (26 per cent) are summarized in Table 1.

**Side Effects Produced in Seventy Patients by Buclizine.**

<table>
<thead>
<tr>
<th>Reaction</th>
<th>No. of patients affected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>1</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>6</td>
</tr>
<tr>
<td>Headache</td>
<td>1</td>
</tr>
<tr>
<td>Dryness of the mouth</td>
<td>8</td>
</tr>
<tr>
<td>Urticaria « aggravated »</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total side effects</strong></td>
<td>18 (26 per cent)</td>
</tr>
</tbody>
</table>

Of the six patients experiencing drowsiness, in none was it especially troublesome, and complete or almost complete disappearance of the sedative effect followed a decrease in the dose of the drug. All patients except one were able, within a few weeks, to tolerate full doses of the drug. Dryness of the mouth in eight patients was relieved as the dose of the drug was reduced by approximately 50 per cent. In the remaining four patients (16 per cent), the drug was discontinued. These had dizziness, headache, and nausea, and one patient stated that the urticaria for which she was taking the drug became worse. This statement was difficult to assess. Palpitation, insomnia, jitteriness, nervousness, headache, and digestive disturbances were not noted.

**THERAPEUTIC RESPONSE.**

The results were evaluated according to the following criteria: excellent if complete relief of symptoms occurred and lasted for several hours; moderate if relief was greater than 50 per cent and lasted for two or more hours; slight when there was 25 to 50 per cent relief; and no relief when relief was less than 25 per cent or the duration of relief was thirty minutes or less. The degree of relief is shown in Table II. Relief of symptoms, when it occurred, required about forty-five to sixty minutes.

**Table II. — Therapeutic Response to Buclizine.**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>None</th>
<th>Slight</th>
<th>Moderate</th>
<th>Excellent</th>
<th>Total Number of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perennial Allergic Rhinitis</td>
<td>3</td>
<td>4</td>
<td>7</td>
<td>8</td>
<td>22</td>
</tr>
<tr>
<td>Vasomotor Rhinitis</td>
<td>8</td>
<td>7</td>
<td>13</td>
<td>14</td>
<td>42</td>
</tr>
<tr>
<td>Urticaria</td>
<td>1</td>
<td>3</td>
<td>2</td>
<td>6</td>
<td>6</td>
</tr>
</tbody>
</table>

Of twenty-two patients with perennial allergic rhinitis, fifteen (68 per cent) reported moderate to excellent relief of symptoms; in four, relief was slight; and no relief was seen in the remaining three. Relief was moderate to excellent in twenty-seven (64 per cent) of the forty-two patients with vasomotor rhinitis; seven had only slight relief; and no relief was obtained in eight. Five of the six patients with urticaria experienced moderate to excellent relief and in one the symptoms, as stated previously, apparently were intensified. Increasing the dose of buclizine in the patients who failed to obtain more than slight improvement seemed to make little difference in the effectiveness of the drug.

Forty-seven subjects had moderate to excellent relief and in thirty-two this persisted for two to four hours; in eight it was five to eight hours; and in the remaining seven it was ten or more hours.
DISCUSSION.

Clinical experience, including simple studies of the renal, hepatic, and hematologic systems, appears to support animal experimental data showing that the drug can be administered for weeks or months without producing toxic manifestations. In this rather small group of patients, granulocytopenia and anemia were not observed, effects, which, on occasions, have been reported following the use of other histamine-antagonizing agents. An additional feature, aside from toxicity, was the absence of serious side effects. Dryness of the mouth and drowsiness were easily controlled by decreasing the dose of the drug without significant loss of clinical effectiveness. In the majority of instances, these mildly annoying side effects gradually subsided as treatment was continued, to be followed frequently by complete tolerance of full doses of the drug. Excellent tolerance by patients for buclizine was confirmed by another group of investigators, who found a lessened incidence of side reactions when the drug was compared with most other antihistaminic preparations.

Despite the somewhat slower onset of action, buclizine appears, in the majority of cases, to control very satisfactorily the symptoms of perennial allergic rhinitis, vasomotor rhinitis, and urticaria.

The duration of action of the drug deserves comment in view of the discrepancy between experiments in animals and clinical experience. Protection from aerosolized histamine was observed for as long as sixteen days following a single dose of 1 mg. per kilogram in guinea pigs and in similar experiments in another report this protection was observed for four days following a single dose of 2.5 mg. per kilogram. Even this represents prolonged action when the metabolic rate of an animal as small as the guinea pig is taken into account. In this animal, therefore, this prolonged action would lead one to expect a cumulative effect of the drug and the development of toxic manifestations with daily doses of the order given to patients. However, such doses in rats, dogs, and man (75 to 100 mg. daily) do not produce toxic reactions and, furthermore, in most patients clinical effectiveness does not persist for more than a few hours. These observations suggest that the excretion or metabolism of the drug in guinea pigs is different from that of rats, dogs, and man. If this is indeed correct, then we have an example of the part played by species difference in the behavior of drugs.

REFERENCES.


SUMMARY.

1. Buclizine, 1-p-chlorbenzhydryl-4-p-tertiary butylbenzylpiperazine dihydrochloride, a new antihistaminic drug, was administered in seventy patients with allergic and related states, with the majority of these patients under observation for many months.
2. Buclizine, taken orally in doses of 25 to 75 mg. daily for an average of four months, produced no significant abnormalities in the formed blood elements or in hepatic and renal function.
3. In contrast to the prolonged activity of the drug in guinea pigs, the duration of action of comparable dosage in man is relatively short—a point deserving further study.
4. The drug appeared to be effective in relieving the symptoms in the majority of patients with perennial allergic rhinitis, vasomotor rhinitis, and urticaria.