An evaluation of Gay's solution in the treatment of asthma


Forty-three patients with severe asthma were treated with Gay's solution (Powler's solution which contains potassium arsenite, tincture of digitalis, sodium phenobarbital, and potassium iodide). Eight of 25 patients in a pilot uncontrolled study and 13 out of 18 patients on arsenic in a double-blind study were improved. The results of the double blind study were statistically significant at a p < 0.01 level. It is concluded that Gay's solution is effective in the treatment of severe asthma and that this effectiveness is dependent on the presence of arsenic in the mixture. Because of the high incidence of side effects we recommend that it be tried only in refractory cases and that they be followed carefully.

Although good results have been reported1-3 in treating asthma with a mixture of Fowler's solution, tincture of digitalis, sodium phenobarbital, and potassium iodide (Gay's solution), this treatment has not been widely used or accepted. It has been generally assumed that the efficacy and toxicity of the mixture is largely due to the potassium arsenite in the Fowler's solution.

The present study was undertaken because of the dramatic improvement of a patient after a trip to Gulfport, Mississippi, where he received Gay's solution with no other change in his management as far as we could see. The study was conducted in two phases. The first phase involved the use of Gay's solution in 25 patients to familiarize ourselves with its administration and side effects. The second phase involved a double-blind study in 28 patients of mixtures with and without Fowler's solution and with and without the potassium iodide.

METHODS

Phase I study (observations from March, 1961, to July, 1963)

Seventeen clinic and 8 private patients were selected who had chronic and/or typical asthma. Thirteen of the total 25 patients were relatively well but symptomatic on what was considered to be a minimum maintenance dose of alternate day
corticosteroid and full conventional bronchodilator treatment; these are designated Group I. Their corticosteroids were abruptly stopped when Gay's solution was started. The 10 patients of Group II were not doing well on their corticosteroid dosage and ordinarily would have had it increased. They were placed on Gay's solution instead. Group III consisted of 2 patients who were not doing well on full conventional bronchodilator treatment and ordinarily would have been started on corticosteroids. Instead, they were placed on Gay's solution. Thus, in the Phase I study, 23 out of 25 patients were receiving corticosteroid therapy prior to the study and 10 out of 25 were on corticosteroid therapy and Gay's solution concurrently. All Phase I patients were treated with Gay's solution purchased from Dr. Gay.

To be considered improved, patients in Group I had to be as well as or better on the mixture than they had been on their maintenance steroid program. Patients in Group II not only needed to respond to the mixture as well as would have been expected with corticosteroids, but subsequently had to maintain the improvement when their maintenance steroids were stopped. Patients in Group III had to clear up as completely with the mixture as would have been expected with corticosteroids.

**Phase II double-blind study (observations from July, 1963, to March, 1966)**

Seven clinic and 21 private patients were selected for the double-blind phase of the study. Fourteen of these 28 patients were not doing well on their corticosteroid dosage and ordinarily would have had it increased (Group A). Fourteen patients were not doing well on full conventional bronchodilator treatment and ordinarily would have been started on corticosteroids (Group B). Instead, all 28 patients were placed on Gay's solution. Thus, in the Phase II study, 14 out of 28 patients had been and were on corticosteroid therapy at the time they were studied. The mixtures used in the double-blind study were prepared in the hospital pharmacy. The formulas for these mixtures (ADKP* solutions A, B, C, and D) are given in Table I along with the procedure followed in compounding them. Solution A is essentially Gay's solution with only slight modifications made in an attempt to improve the stability of the mixture. The ADKP solution for each patient was determined by lot by the hospital pharmacist at the time the patient first presented a prescription. A log of the ADKP solutions was kept and once a patient was assigned to a group, the same solution was dispensed for each subsequent prescription.

In Phase II a more subtle system of evaluation was employed. The patients' progress was judged on the basis of (1) the number of attacks they were having, (2) the medicines they required in addition to ADKP, (3) their exercise tolerance, (4) their timed vital capacity, (5) the nature and amount of their sputum, and, finally, (6) their own appraisal of how they were. Patients were classified as improved if, coincidentally with ADKP administration, they improved in the first five variables, whether they felt they were better or unchanged in terms of their own appraisal; or if there was no change in the first

*ADKP stands for the mixture of arsenic, digitalis, potassium iodide (K), and phenobarbital.
**Table I. ADKP solutions used in Phase II study**

<table>
<thead>
<tr>
<th>Solutions</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fowler's solution</td>
<td>44.5 c.c.</td>
</tr>
<tr>
<td>Digitalis tincture</td>
<td>22.2 c.c.</td>
</tr>
<tr>
<td>Sodium phenobarbital</td>
<td>4.33 Gm.</td>
</tr>
<tr>
<td>Potassium iodide</td>
<td>59.5 Gm.</td>
</tr>
<tr>
<td>Saccharin</td>
<td>0.36 Gm.</td>
</tr>
<tr>
<td>Methylparaben</td>
<td>0.8 Gm.</td>
</tr>
<tr>
<td>Propylparaben</td>
<td>0.2 Gm.</td>
</tr>
<tr>
<td>Amaranth solution 1 per cent</td>
<td>2.5 c.c.</td>
</tr>
<tr>
<td>Distilled water qs. to 1,000 c.c.</td>
<td></td>
</tr>
<tr>
<td>B Without Fowler's solution</td>
<td></td>
</tr>
<tr>
<td>C Without Potassium iodide</td>
<td></td>
</tr>
<tr>
<td>D Without Fowler's solution or potassium iodide</td>
<td></td>
</tr>
</tbody>
</table>

Dissolve the sodium phenobarbital, potassium iodide, and saccharin in 250 c.c. of distilled water. Dissolve the parabens in 200 c.c. of hot distilled water and add to the first solution. Add the Fowler's solution to the digitalis tincture and then add the previously prepared aqueous solution to them. Finally, add the amaranth and enough distilled water to make 1,000 c.c. of solution, then refrigerate.

five variables but the patients felt that they were definitely better. Patients were not classified as improved if by any of the six variables they were worse after ADKP treatment.

The double-blind code was broken after 20 patients had been studied in Phase II to judge whether there were any differences between the groups, and if so, how many additional patients would need to be studied to achieve statistical significance at the 0.01 level. ADKP was stopped in the only 2 patients on it at that point. These patients, as well as 1 additional patient who had been in the study earlier, were redrawn when their clinical situation satisfied the conditions for selection for the study again. One of the 3 patients received the same solution both times.

The first 20 patients of Phase II were studied double blind only in relation to the arsenic in the ADKP. The potassium iodide was omitted if there was a previous history suggesting iodide rash or intolerance. The last 11 patients of Phase II were studied double blind in regard to both the arsenic and the iodide.

The arsenic and nonarsenic groups in the Phase II study are closely matched in average age (38 and 43 years, respectively) and in sex (8 out of 18 and 5 out of 11 being males, respectively). The youngest and the oldest patients were 10 and 70 years old.

**General patient management of both studies**

Patients were routinely screened for evidence of allergic factors, chronic infection, major psychological factors, heart failure, pulmonary emboli, hydroxyindole acetic acid secreting tumors, sweat electrolyte abnormalities, collagen disease, serum protein abnormalities, thyroid disease, seizure disorders, and primary adrenal-pituitary insufficiency. Where any of these factors were found, they were treated, and in several instances, where the possibility could not be ruled out, therapeutic trials of appropriate agents were tried and evaluated before Gay's solution was administered. The exacerbations of asthma in patients in both Phase
I and Phase II studies which led to their inclusion in the study were not seasonal or infectious as far as could be determined by the nature of their sputum, white blood count, sputum culture, and, in most cases, an empirical course of tetracycline.

Patients were started on 1 teaspoon of Gay's solution or ADKP 4 times a day, ½ hour before meals and at bedtime. After 4 days the bedtime dose was discontinued. If there was no improvement in the patient's asthma within 10 days, or if increasing difficulty necessitated starting daily steroids before a 10 day trial was completed, the Gay's solution or ADKP was discontinued. If the unsuccessful trial had lasted 4 to 10 days the Gay's solution or ADKP was judged to be ineffective. If the unsuccessful trial was terminated in less than 4 days, it was considered to be an inadequate trial and in some cases Gay's solution or ADKP was retried later, if the conditions for selection of the patient for the study arose again.

If the patients improved during the first 10 days of therapy, they were continued on 3 teaspoons of Gay's solution or ADKP per day for 1 to 3 months. During the Phase I study, if the patients were doing well, their Gay's solution was stopped abruptly after 2 months. If their symptoms recurred, Gay's solution was restarted. Subsequently, they and the patients in the Phase II study, in general, had their doses decreased by 1 teaspoon per day every 1 to 3 months, depending on how well they were.

Initially, patients were seen at least every week. Later, depending on their clinical status and drug therapy, they were seen at 2 to 4 week intervals. At each visit they were questioned and examined by a physician. Timed vital capacities were performed at each visit. White blood counts were done every week for the first month, then every second week while the patients were still on a dosage of 3 teaspoons per day. With decreasing dosage and increasing length of time on the mixtures, counts eventually were done every 6 weeks. Urinalyses were performed regularly at about half the frequency of white blood counts. Stool specimens were checked for occult blood every 1 to 3 months.

RESULTS

Phase I study

Eight out of 25 patients improved dramatically and convincingly or were successfully taken off corticosteroid therapy coincidentally with the administration of Gay's solution. Seven of the 25 developed rashes and 4 of these also had salivary gland swelling and 1, thyroid tenderness and swelling. One patient developed transient leukopenia (3,800 white blood count per cubic millimeter).

Phase II study

The results of the Phase II study are shown in Table II. There is a significant difference between those receiving arsenic and those who did not at the 0.003 probability level with the use of chi-square testing. Similar chi-square testing of those receiving iodide and those who did not in both the double-blind and unblinded studies shows no significant differences between these two groups. Table III, however, which shows the results with each of the four ADKP solu-
Table II. Results of the Phase II study of 31 trials of ADKP solutions in 28 patients, broken down into the results in those receiving arsenic and those who did not

<table>
<thead>
<tr>
<th>Arsenic</th>
<th>Improved*</th>
<th>No effect*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ascorbic</td>
<td>15</td>
<td>5</td>
</tr>
<tr>
<td>No arsenic</td>
<td>2</td>
<td>9</td>
</tr>
</tbody>
</table>

*Probability: p = 0.003.

Table III. Results of the Phase II study of 31 trials of ADKP solutions, in 28 patients broken down into the results with each solution*

<table>
<thead>
<tr>
<th>ADKP-A</th>
<th>ADKP-C</th>
<th>ADKP-B</th>
<th>ADKP-D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arsenic and iodide</td>
<td>Arsenic alone</td>
<td>Iodide alone</td>
<td>Neither</td>
</tr>
<tr>
<td>Improved</td>
<td>11</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Not improved</td>
<td>2</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Per cent improved†</td>
<td>85</td>
<td>57</td>
<td>29</td>
</tr>
</tbody>
</table>

*The number of patients who received each solution is not equal because (1) the first 20 patients studied were not done double blind in respect to the iodide content, and (2) patients were assigned solutions by the actual drawing of lots rather than by a systematically randomized method.

†These percentages are not statistically meaningful but are included to illustrate trends in the data.

ations separately, suggests that the iodide could perhaps have some enhancing effect or even be effective by itself in a small percentage of patients. With the small number of patients involved in the present study, however, no statistically significant iodide effect has been shown.

Three patients developed rashes in the Phase II study which were due to the potassium iodide. Salivary gland swelling occurred three times during the study and disappeared with continued ADKP before the patient's next visit in 2 out of 3 patients. Twice both arsenic and iodide were in the mixture, and one time arsenic was present alone. Gastrointestinal symptoms of nausea, indigestion, and/or diarrhea were the most common side effects in the Phase II study occurring in 6 patients: in 3 out of 14 on arsenic and iodide, in 2 out of 8 on arsenic alone, and in 1 out of 7 on iodide alone.

Pigmentation occurred in 3 patients in Phase II with prolonged use and generalized dryness of the skin with solar hyperkeratosis in 1 patient. All 3 of these patients were on prolonged therapy. The pigmentation and hyperkeratosis ameliorated while the patients were still on ADKP when the dose was decreased.

Two patients during the Phase II study had unusual illnesses which may or may not have been related to the study. One patient had an episode of acute serum sickness–like illness with leukopenia, rash, diarrhea, and polyarthritis occurring after 4 months of ADKP-A therapy. We have not readministered any of the ingredients in the mixture to explore the possibility that this episode was caused by one of them. A patient with very severe asthma on 80 mg. of prednisone every other day had an episode at work on his third day of ADKP-A therapy,
**Table IV.** A comparison of the results of treatment with arsenic in the Phase I and Phase II patients

<table>
<thead>
<tr>
<th></th>
<th>Improved*</th>
<th>No effect*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preliminary study (Phase I)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Double-blind study (Phase II)</td>
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</tbody>
</table>

*Probability: p = 0.02.

**Table V.** Analysis of the results in the 18 Phase II patients on ADKP with arsenic (A or C)*

<table>
<thead>
<tr>
<th></th>
<th>Improved</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Off</td>
<td>Presumptive</td>
<td>Definite</td>
<td></td>
<td>Off</td>
<td>Definite</td>
</tr>
<tr>
<td>On steroids</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(total = 7)</td>
<td></td>
<td>1</td>
<td>3</td>
<td></td>
<td>3</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>No steroids</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(total = 6)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Two patients who received two trials of arsenic are included only once each.
†See text for definition of these terms.

terminating in a period of unconsciousness and anoxia with permanent anoxic damage to his brain. The event was not witnessed but was not felt to be related to the ADKP therapy.

**Comparison of Phase I and Phase II studies**

Table IV shows a comparison of the Phase I results with the Phase II results.* Over twice as many patients were improved with regard to percentage in the Phase II study, which is a significant difference at the 0.02 probability level. The explanation for this difference probably lies in the difference in design between the two studies. In the Phase I study, only dramatic results were accepted as improvement, and in patients on steroids, Gay's solution was substituted for steroids looking for an all-or-none response. In the Phase II study, because it was done double blind, more subtle responses could be accepted as improvement without fear of the patient's or physician's bias influencing the results.

Table V shows the 18 patients in the Phase II study who received arsenic. Those who responded are divided into those who were on steroids and those who were not. Those on steroids are further broken down into those who could come off and those who could not. The patients not on steroids are divided into those who had a definite response and those whose response was presumptive, as judged by whether the patients demonstrated improvement in all six variables (definite) or not (presumptive). In 2 cases there was evidence of improvement as judged by the objective criteria (1 to 5), although the patients' subjective ap-
praisal was that they were essentially the same. In the one case objective improvement was not measurable, but the patient was convinced he was much improved. If the patients who were able to get off steroids and those giving definite responses are combined, 7 out of 18, or 39 per cent, were improved, which is not significantly different from the 32 per cent incidence of improvement in the Phase I study. As a matter of record, in the cases of the 2 patients who did not receive arsenic but who did improve, one was on steroids but could not come off, and the other had presumptive improvement by the above criteria. If the patients with presumptive improvement are discarded from both groups, the p value for the difference between the arsenic and non-arsenic treated patients is 0.007.

**DISCUSSION**

Although no previous controlled studies have been made of the treatment of asthma with arsenic, there is presumptive evidence of its efficacy both from sources reporting favorably and from those reporting unfavorably on its use. The latter three case reports of toxicity associated with arsenic therapy also clearly report clinical improvement of the patients' asthma with arsenic therapy and difficulty in controlling their asthma after the arsenic was stopped. In another report of toxic effects from arsenic, 1 of the 2 patients restarted arsenic on his own. Although it is not clear in the case report, the patient presumably restarted the arsenic because of a recurrence of his asthma. The present studies substantiate the dramatic effectiveness of arsenic in some patients (approximately one third), as well as less dramatic improvement in others (approximately another one third).

The efficacy of inorganic arsenic in asthma is based on empirical observations, and an analysis of the patients who were improved gives no clue as to the mechanism of its action. An antimicrobial effect was one hypothetical mechanism of action which was considered. A few observations on the arsenic concentration of sputum and saliva showed arsenic to be more concentrated in sputum (approximately fourfold), but the level reached (up to 0.016 mg. per cent) was not bactericidal in vitro to organisms commonly found in the sputum of patients with asthma.

Wenzel and Rosenberg have found that a single dose of arsenic significantly diminished the response of guinea pigs to aerosolized histamine without protecting them from anaphylactic shock, aerosolized acetylcholine, or injected physostigmine. Their further studies in vitro with seventeen compounds that theoretically affect the functioning of sulfhydryl-containing enzymes showed that arsenic, khellin, and pipcritone reduced the response of isolated guinea pig ileum to histamine and acetylcholine, whereas the other thirteen agents did not. Although these findings suggest that the mechanism of action of arsenic in asthma may be elucidated by in vitro studies, presently no clear-cut mechanism is evident.

There is a much wider literature on the toxicity of arsenicals. The literature was reviewed by Vallee, Ulmer, and Wacker in 1960, and, although further case reports have appeared, these reports have confirmed rather than altered the
earlier literature. A more recent review by Schroeder and Balassal\textsuperscript{11} emphasizes the ubiquitous and innocuous nature of naturally occurring arsenicals (as contrasted to the trivalent inorganic form used medicinally in Fowler’s or Gay’s solutions), and the most recent review of arsenicals by Frost\textsuperscript{12} suggests that there are not only optimum nutritional levels for some arsenicals but possibly therapeutic uses in dental health and lead and selenium toxicity as well.

There have been 12 cases of medicinal arsenic poisoning in asthmatic patients reported since 1950 in the English literature involving cutaneous reactions\textsuperscript{2, 5, 7, 13, 14} toxic hepatitis\textsuperscript{4-6, 14} toxic retinopathy\textsuperscript{15} and hemorrhagic encephalopathy.\textsuperscript{16} There are 12 additional cases of medicinal poisoning reported in patients treated for other conditions\textsuperscript{17-20} with inorganic arsenic, as well as 3 additional patients treated with organic arsenicals.\textsuperscript{21-25} The last 3 patients all had central nervous system toxicity predominantly. Half of the 12 nonasthmatic, inorganic arsenic–treated patients were reported because they developed cancer of the lung\textsuperscript{19} and skin.\textsuperscript{18, 20} The latter were accompanied by multiple keratoses and in some cases multiple intra-epidermal epithelioma or carcinoma, which in the older literature was associated with inorganic arsenicals. The recent reviews of Vallee and colleagues,\textsuperscript{10} Schroeder and Balassa,\textsuperscript{11} and Frost\textsuperscript{12} emphasize the tenuous ground of the association.

Gay’s\textsuperscript{2} survey of 1,128 patients treated 2 to 7\textsuperscript{1/2} years with potassium arsenite–containing solutions is the most extensive reported experience in asthma. He reported a 30 per cent incidence of reactions to arsenic and a 35 per cent incidence of reactions to the iodide usually present in the mixture. Only 1 patient appeared to have a serious reaction (i.e., exfoliation) from arsenic. This is the only patient from Dr. Gay’s series who is included in the 12 cases of medicinal arsenic poisoning in asthmatic patients. Eighty per cent of Gay’s 1,128 patients were greatly improved and only 5 per cent were unimproved.

The next largest reported experience is by Hansen-Pruss,\textsuperscript{19} in which he reported 17 cases who were “Gay treatment” failures. Four of the 17 had mild to severe cutaneous and/or hepatic toxicity attributed to the arsenic.

One would surmise that patients who have serious toxic reactions or who are treatment failures would tend to drop out of Gay’s sight, particularly during the first 2 years of treatment before they qualified for inclusion in his series. Similarly, one would predict that such patients with treatment failure or acute toxic reactions would tend to turn up in a clinic like Hansen-Pruss’ relatively soon after trying Gay’s solution for a short time. It is of interest that 16 out of 17 of Hansen-Pruss’ patients were treated with Gay’s solution for less than 2 years and 10 out of the 17 showed up within 6 months after trying Gay’s solution.

One might infer from such considerations of natural selection that the number of treatment failures and serious toxic reactions is higher than Gay would realize, and that the incidence of toxic reaction and treatment failures is less than Hansen-Pruss and others, who report a toxic reaction, but who do not use potassium arsenite in their practices, would realize. In fact, Hansen-Pruss confesses surprise that “not only the American medical literature, but also the foreign literature has so few articles dealing with the injurious effects of inorganic arsenic upon the human body” in view of the fact that, “as Fowler’s
solution, or as part of many other formulas, inorganic arsenic has been used extensively in this country."¹³ Neither of these two series, however, singly or combined, with or without the additional 1 and 2 patient case reports, allows us to get accurate estimates of the efficacy and toxicity of inorganic arsenic treatment in patients with asthma.

There are two additional factors which cloud the issue when trying to get an accurate assessment of these two vital variables of therapy in asthma. First, the selection of patients for therapy undoubtedly will influence the results, particularly with an agent which is not universally effective. Eighty per cent of Gay's patients are treatment failures from elsewhere, which is quite a selection process in itself. Our subjects were a very select, intractable group of asthmatic patients. Most were on steroids (there was a difference between Phase I and Phase II in this respect) and the etiology of their asthma was unknown. By contrast to the patients we studied, 3 of the 4 patients reported in detail in Hansen-Pruss' series responded "nicely" to "routine anti-asthmatic treatment."

Second, the dose of arsenic and the method of its compounding may effect the therapeutic and toxic results. Gay has pointed out²¹ that in the cases in which cutaneous¹⁷ and encephalopathic¹⁶ complications had been reported, the arsenic concentrations used were three to eleven times that of his formulation.²

The other ingredients and the pH effect the stability of the mixture and may conceivably influence the absorption, fate, and excretion of the arsenic. Studies by Joseph Vona, M.S., and Gerald Bowman, B.S., Peter Bent Brigham Hospital pharmacists, have shown that an easily dispersible precipitate usually forms after the solution has sat overnight in the refrigerator. The amount of the precipitate is influenced by the quality of the distilled water used and by the presence of the digitalis, phenobarbital, parabens, and potassium iodide. Our experience with giving patients prescriptions for their local pharmacist to compound has been that the resultant product is quite variable in color, taste, amount of precipitate, and the presence of crystals and/or filament-like foreign material in the solution. Whether this variability is important clinically is not known. Until more information is available about the intricacies of compounding and their possible clinical significance it would perhaps be best to follow the procedure for compounding outlined in Table I.

Based on our own experience reported here, as well as that reported in the literature, we would make the following recommendations for the use of Gay's solution in patients with asthma until further information becomes available:

1. Gay's solution should be reserved for trial in those patients with asthma which cannot be well controlled by conventional treatment, short of corticosteroids. (1) The physician should discuss with the druggist the importance of careful compounding and the advisability of making up small batches so that it is less than 90 days old when dispensed. The physician should follow the patient carefully for signs and symptoms of efficacy and toxicity. If there is doubt about the efficacy, the mixture should not be continued. If toxicity occurs, the dosage should be decreased or the mixture stopped, depending on the circumstances. Used in this way, Gay's solution may be the treatment of choice in
approximately one third of the patients with difficult-to-manage, intractable asthma.

We would like to thank Dr. F. D. Gay for his helpful comments, suggestions, and cooperation, Dr. Jane Worcester for her advice on statistical matters, and Mrs. Angela J. Keefe, R.N., for her professional assistance.

REFERENCES