IONTOPHORESIS OF PYRIBENZAMINE HYDROCHLORIDE IN PRURITIC DERMATOSES*

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Iontophoresis or ion transfer is based on the ability of a galvanic current to cause an electrophoretic migration of ions through a solution or other system. In the early part of this century, Ledue in France carried out some fundamental and classical experiments in iontophoresis. He showed that drug ions may be introduced through intact skin depending upon their polarity, and may exert a local as well as a systemic effect (1). Ion transfer has been used as a method of treatment in systemic disease and in dermatologic conditions.

In the treatment of many skin eruptions, especially the eczematoid dermatoses, the control of the associated pruritus is often the chief presenting problem. Adequate control of the pruritus very often brings about marked clinical improvement in the objective changes of the itching dermatosis. The disappearance of the lichenification and eczematization can often be attributed largely to the control of the pruritus.

The use of the anti-histaminic drugs has proven efficacious in urticaria, etc. where their effects on the causative mechanism can be readily understood. Although oral administration of benadryl and pyribenzamine have been widely used in the treatment of many dermatoses due to both primary irritants and sensitizers as well as of the diseases often called disseminated and circumscribed neurodermatitis, the results obtained have been beneficial only in a relatively small proportion of the patients. When they have been helpful in improving a dermatitis, the results were thought to be due to diminution of the pruritus (4).

It has been shown that pyribenzamine hydrochloride can be deposited into the skin by means of iontophoresis and can inhibit histamine whealing for 24 hours after its introduction, similar to histamine and other drugs (2–2A). The amount of inhibition is dependent upon the strength of the solution, the length of time of the application of the electrode, and the amperage used.

It would therefore seem logical to use iontophoresis with pyribenzamine hydrochloride to treat dermatologic disorders in which the underlying mechanism was either urticarial in nature, or due to pruritus with a secondary dermatitis due to scratching. Allergic eczematous contact dermatitis as well as dermatitis due to primary irritants is certainly not considered by most authorities to be based on a mechanism in which histamine or histamine-like substances play a

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role. If this is true it seems likely that whatever beneficial effects iontophoresis with pyribenzamine hydrochloride would have in these last named conditions could only be attributed, to the local relief of pruritus. This was indicated by the results obtained in the treatment of fifteen patients with various forms of lichenified pruritic dermatoses reported in this paper.

METHOD

An ordinary iontophoresis apparatus was used. Canton flannel, saturated with the solutions used, was applied to the lesion. The positive electrode, made of aluminum foil, was used to introduce the pyribenzamine into the skin (Abramson, Aaron and Abramson (2, 2A)) and was placed over the flannel. The negative electrode was attached to some other part of the body. The time of the application of the electrode to the skin for each daily treatment was 5 minutes. Where the dermatitis occupied small areas, the electrode and flannel were cut to cover the entire lesion. Where the dermatitis was extensive the electrode was moved from site to site in order that the entire area would have the same allotted time of treatment. The largest electrode used in this study was 225 sq. cms. The current density in all cases was lower than that recommended for safety by Molitor (3). The solution used was 10% pyribenzamine hydrochloride in distilled water. However, 5% pyribenzamine hydrochloride was used in a few cases. The solutions made use of as controls in some of the cases were physiological saline and 2% procaine hydrochloride.

CLINICAL AND EXPERIMENTAL STUDIES

Case 1

S. B. L., white, male, age 26, a physician who had a history of seasonal rhinitis and asthma. On the extensor surface of the right forearm he had a circumscribed area of so-called neurodermatitis measuring 25 sq. cms., which had been present for 3 months. There was a similar area on the flank. The pruritus was increased by the ingestion of citrus fruit and chocolate. The lesions were so pruritic that the patient scratched them during his sleep. Many ointments had been used without success. Pyribenzamine 300 mgs. taken daily by mouth gave no relief but did cause gastrointestinal upsets. The lesion on the arm was treated by iontophoresis. The flannel and the positive electrode were cut to cover the area. 10% pyribenzamine hydrochloride solution was used. The current density used was 0.16 milliamperes per sq. cm. so that a total of 4 milliamperes was used. Six consecutive daily treatments were given. On the second day the patient reported that the pruritus had subsided enough so that he had not scratched the lesion. During the treatment and for about one hour after the electrode was removed a burning sensation was felt. There was also an increase in the erythema, which lasted about the same length of time. Each day it was observed that the burning sensation and the erythema caused by the iontophoresis of the pyribenzamine decreased in intensity. The inflammation had completely subsided by the sixth day; three weeks later no trace of the lesion could be found. The dermatitis on the flank had not been treated and was still present. No detrimental effects due to pyribenzamine were observed.

Case 2

H. K., white, male, age 41, was admitted to the hospital suffering from the Distinctive Exudative Discoid and Lichenoid Chronic Dermatosis of Sulzberger and Garbe. He had had this condition for 4 months prior to admission. The diagnosis had been confirmed by

biopsy. The main complaint was severe pruritus. It was decided to treat only certain parts of his body with iontophoresis of a 10% solution of pyribenzamine and to observe the effect. A positive electrode and the canton flannel were prepared in such a way as to cover an area 9 cms. square. Areas equal in size to the electrode were treated on the dorsum of the left hand, on the lateral surface of the right arm and on the anterior surface of the left leg. Five milliamperes were used for this electrode. Seven consecutive daily treatments were given. After the first treatment the pruritus and the exudation of the lesions in the treated areas began to subside. With each treatment there was an initial burning and erythema which last for about one hour after removal of the electrode and which decreased in intensity with successive treatment. On the seventh day a distinct difference could easily be observed between the treated and the non-treated areas. The areas of skin which had been treated with pyribenzamine had become smoother because of the disappearance of vesicles and decreased lichenification; the pigmentation remained. In the course of his stay in the hospital the patient experienced a general subsidence of the eruption two weeks after the experiments were begun. However, one week later the dermatitis recurred over the entire body except on the three squares that were treated. It was therefore surmised that there was still a depot of pyribenzamine in the skin. With histamine phosphate in a dilution of 1:10,000 whealing and flaring were produced by iontophoresis in the untreated areas while in the treated areas there was inhibition of the histamine wheal and flare. At this stage an area on the left side of the neck was treated with pyribenzamine and the right side of the neck was treated with physiological saline for 5 consecutive days. The left side of the neck improved while the right side of the neck did not improve appreciably and had only slight relief from the pruritus.

Case 3

I. C., white, male, age 39, came into the hospital with a generalized exfoliative dermatitis. In October 1946 he had been given sulfonamides during an attack of grippe. On the third day of the medication he developed an eruption on the thorax. For this he received a sulfonamide ointment; shortly thereafter the eruption spread to almost the entire skin except for the scalp, palms and soles. The patient was hospitalized elsewhere for three weeks without much improvement and then went home again. When he was admitted to this hospital he had marked generalized exfoliation; the skin was thickened, fissured, and itched intensely (Fig. 1A,B,C). In this case the positive electrode and flannel were cut to cover an area of 225 sq. cms. The left arm, left leg and the face were treated with 10% Pyribenzamine hydrochloride, the right arm with physiological saline and the right leg with procaine hydrochloride 2%. The current used for this electrode was 10 milliamperes as the patient complained of a burning sensation if the amperage was increased. Each area was treated for five minutes daily for seven days. The Pyribenzamine areas produced the most marked burning sensation and flare with the treatment. The pruritus abated quickly in the left limbs but the itching remained in the right limbs, which were treated with control solutions. The scaling gradually disappeared from the treated areas and only slightly from the right side. On the seventh day the areas treated with Pyribenzamine started to become pale and the patient noticed that sweat was present on the skin. His face was treated with Pyribenzamine four times and by the end of seven days was nearly normal.

Case 4

H. S. C., adolescent male, had had atopic dermatitis from infancy. He also had a history of hay fever and asthma. For two weeks prior to treatment both arms were swollen so that he could not bend them. There was much exudation, vesiculation, and pruritus. He was treated with pyribenzamine hydrochloride 10% using an electrode of 225 sq. cms. and 10 milliamperes. He complained of much burning during the first three treatments. There was also some decrease in the edema and exudation early in the treatment. By the end of the fifth treatment the swelling had disappeared, the skin had improved and there was no pruritus. Only pigmentation remained.

Case 5

Mrs. M. M., white, housewife, age 21, had had three areas of chronic circumscribed neurodermatitis on her neck for 6 years. The exciting cause could not be determined. X-ray treatment had cleared the lesions for only a few months. The patient was given 10 consecutive daily treatments with 5% pyribenzamine hydrochloride. Two weeks from the start of the treatment the lesions showed definite improvement.

A total of 15 additional cases of pruritic lichenified eruptions were treated. Every patient received some relief from pruritus during the course of the treatment. In all the cases treated there was clinical improvement and in 10 cases there was complete remission at the end of the treatments or a short while thereafter. One case of pruritus vulvae and pruritus ani was treated with definite although not complete relief of the pruritus. The coexistent dermatitis was improved. One case of chronic circumscribed neurodermatitis of the scrotum was treated with complete relief from the pruritus and marked improvement of the lesions after five consecutive daily treatments. In both of these the duration was six months or more; both noted some relief of the pruritus with the first treatment.

The following experiments were done to study the effect of the iontophoresis of pyribenzamine in the mechanism of allergic and non-allergic dermatitis:

Mrs. P. was contact sensitive to paraphenylenediamine. The lowest dilution to which she was found sensitive by patch test was 1/512 of 1%. Pyribenzamine was introduced into the skin of her arm by iontophoresis with a 10% solution. An electrode 9 sq. cms. in area and a current density of 3 milliamperes was applied for five minutes for two consecutive days; then 2 hours after the electrode was removed the area was patch tested with 1/512 of 1% and 1/128 of 1% paraphenylenediamine which was kept on for 48 hours. Three other normal skin sites were similarly prepared and tested with the same concentrations of the dye. Four other areas were used as controls using physiological saline instead of Pyribenzamine. Forth eight hours after application of 1/128 of 1% paraphenylenediamine, the control sites showed erythema, marked vesiculation and pruritus. In the Pyribenzamine sites the patch tests with the lowest concentration produced no vesiculation or erythema, while the patch test sites with 1/128 of 1% paraphenylenediamine showed moderate erythema and a few vesicles.

Patch tests of 50%, 25% and 10% turpentine diluted in sesame oil produced vesicles on the abdominal skin of 3 guinea pigs after 24 hours.

The size of the vesicles was related to the concentration of the turpentine. Pyribenzamine was introduced by iontophoresis into the abdominal skin of the guinea pigs, using a 10% solution of pyribenzamine hydrochloride. The electrode used was 9 sq. cms. in area and the amperage was 2 milliamperes. Two hours later patch tests with turpentine in the same concentrations were applied. In these areas none of the three concentrations used produced vesicles 24 hours later.

DISCUSSION

A review of our case studies indicates that the iontophoresis of pyribenzamine hydrochloride into the skin is worthy of trial in pruritic dermatitis.

The oral use of histamine antagonists as a therapeutic agent in the treatment of dermatitis has met with varying success. The percentage of successful results in casuistic studies has usually been relatively low (4). The apparent benefit has been considered to consist of alleviation of the pruritus and therefore the subsequent diminution of trauma. Even with high dosage no relief from

pruritus was observed in many cases. In others the dosage was decreased because of detrimental side effects.

Recently ointments containing histamine antagonists for use in dermatitis have been under study. The results were not satisfactory in most instances. Wet dressings of histamine antagonists have been used by Friedlander (5); the poor result was attributed to insufficient absorption. It has not been possible in every case to know if a beneficial concentration or quantity of the antagonist has penetrated and remained in the epidermis. Most of the patients in our series had taken histamine antagonists orally in high doses with no relief of the pruritus. The itching diminished greatly in intensity and the lesions healed only when pyribenzamine was directly introduced into the skin. This may be merely the indirect result of controlling the pruritus and eliminating the trauma of scratching. Undoubtedly trauma is an important factor in the development and prolongation of many cases of dermatitis. However, the results of local and oral treatment necessarily raise the question of whether pyribenzamine also antagonizes the mechanism of the dermatitis directly. If this is the case, then the beneficial effect may be the resultant of 4 factors: the amount of pyribenzamine in the skin, the ability of pyribenazimine to antagonize the mechanism instigated by the exciting factor, the amount of exciting factor in contact with the subject and site, and the sensitivity of the subject and site to the exciting factor.

It was noticed that in all the patients who were treated by iontophoreses, the flare and irritation that occurred with the initial treatment decreased in intensity with each subsequent treatment.

Friedlander and Feinberg (7) have shown that the wheal produced by the scratch method using a mixture of ragweed antigen and histamine in the skin of a ragweed-sensitive patient was inhibited by the addition of an anti-histaminic drug to the mixture. Pyribenzamine was previously introduced by Aaron and Abramson (2A) into the skin of ragweed sensitive patients by iontophoresis using a 10% solution of pyribenzamine hydrochloride and a current amperage of 2 milliamperes for an electrode 9 sp. cms. in area for five minutes. Over such an area the wheal produced by the scratch method using ragweed antigen was then found to be inhibited.

By means of dyes Rein has shown that positively charged ions can penetrate into the corium (8). The amount of pyribenzamine that is deposited into the skin during an iontophoretic treatment is unknown. The quantity that is absorbed, the rate of absorption, and the rate of excretion has not been completely worked out as yet. A 10% concentration of pyribenzamine hydrochloride introduced into the skin for three minutes will almost completely inhibit the whealing caused by the introduction of a 1:10,000 dilution of histamine 24 hours later. It is significant, therefore, that an appreciable amount is deposited into the skin. In Case 2 it was noted that the inhibition of the histamine wheal was present three weeks after the iontophoresis of pyribenzamine. It seems that very little pyribenzamine reaches the circulation at once and the depot is formed as described previously for histamine (2). It would appear from this observation that a deposit of pyribenzamine is produced in the skin. However,

this length of time is unusual for a deposit to remain. There should be a gradual decrease. Some other factors or factor, perhaps a change in the mechanism of reactivity, must account for this phenomenon.

The length of time that relief is obtained after the treatment will depend on a number of factors. The beneficial effect will be prolonged if the amount of pyribenzamine deposited is large. This is probably related to the strength of the solution, the current density and the number of applications used. If the exciting factor is removed the lesions are likely to remain healed.

Considering all clinical and experimental observations made in this study it is felt that the results obtained cannot be said solely to be due to a drug that just antagonizes histamine. It appears that more than this takes place; the drug when introduced into the local skin lesion by iontophoresis directly inhibits the mechanism responsible for dermatitis.

This method has the advantages that it is easy to apply, it simplifies nursing care, and does not entail the use of dangerous vasomotor drugs.

New technics will be studied for the treatment of generalized dermatitis by means of iontophoretic baths. We have used such a bath in treating two cases of neurodermatitis of the hands. Before reporting these observations, excretion and toxicity determinations will be done.

SUMMARY

1. The results of the iontophoresis of pyribenzamine hydrochloride in several types of dermatitis associated with pruritus are presented.

2. The good results obtained both in the control of the pruritus and in the regression of the skin lesions warrant further trial of this therapeutic procedure.

3. Clinical and experimental evidence including the original studies of R. L. Mayer (6) seem to indicate that pyribenzamine plays a direct role in inhibiting dermatologic reactions due to primary irritants as well as allergens, which is independent of its anti-histamine action.

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