10681

Electrophoresis of Epinephrine into the Skin. Application to the Treatment of Asthma.

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It has been known for many years that epinephrine may be transported by electrophoresis into the skin where it produces its typical blanching in the intact dermis. As far as the writer is aware, this phenomenon has not been applied to the electrical transport of comparatively large quantities of epinephrine into the skin to establish locally in the skin reservoirs of epinephrine for the relief of allergic states. A method of administering epinephrine by electrophoresis to form these reservoirs has now been developed. This technic and its application to the relief of severe asthma form the subject of this paper.

Preparation of the solution: With the current densities needed, solutions of epinephrine hydrochloride were too acid to employ. A solution of epinephrine dihydrogen phosphate between pH 3 and 4 was tentatively adopted. This solution is prepared by simply adding equivalent quantities of epinephrine base and phosphoric acid so that the final concentration of epinephrine itself is 1% (with suitable adjustment of pH).

Quantity transported: This solution contains mainly the ionic species:

$$[\text{Epinephrine}]^+;\ [H]^+;\ [H_2PO_4]^-.$$

Although the electric mobility of H^+ is much greater than either of the other 2 ions, its concentration is comparatively small even at pH 3.0. In the routine method now employed a single treatment lasts 30 minutes (occasionally more) with the current at 0.005 amp. Since 1.0 ampere is one coulomb per sec., approximately 9 coulombs are transported. Assuming that Faraday's laws hold here and that the electric mobility of the epinephrine ion is equal to that of $[H_2PO_4]^-$, it can be readily shown that the epinephrine ion accounts for the passage of approximately 2 coulombs; therefore, more than 2×10^{-5} moles of epinephrine are electrically transported into the skin. Since the molecular weight of epinephrine is near 183, about 4 mg of epinephrine are probably deposited in the skin by the method outlined in a single treatment.

Method of application: The epinephrine solution is applied on

cotton or canton flannel. The area of application (arm or leg) is 30 cm^2. Each area is treated 10 to 15 minutes, 2 to 3 areas being used successively in a single treatment. The blanching usually lasts more than 5 hours without injury to the skin. The rate of absorption from the blanched skin is retarded by the blanching itself. The epinephrine in the blanched areas is apparently pharmacologically active over this period and the epinephrine is slowly released from its depots in the skin. It is our view at present that the absorption rate is between 0.5 to 1.0 mg per hour.

Systemic reactions: The reactions (palpitation, tremor, etc.) observed have (with one exception) been less than those obtained with subcutaneous injection of 5 minims of the 1:1,000 solution. The effect of the electrophoretic administration on the blood pressure has been studied with Dr. M. A. Greene on a control normal group. There was frequently a slight drop (during the first 20 minutes) in the blood pressure which subsequently returned to its normal initial level. These data will be reported separately.

Results in asthma: Only hospitalized patients with severe asthma (in status asthmaticus or bordering thereon) were treated. The usual sedatives were administered, although the typical effects of administering epinephrine to asthmatics were encountered without sedation.

Although the number of patients (10) in this series is too small to anticipate the potentialities of this procedure, the therapeutic results appearing in Table I leave no doubt that the general pharmacological effects of epinephrine in asthma are obtained. In only one of the 10 cases summarized were the asthmatic paroxysms not relieved at least as much as by a therapeutic dose of an aqueous injection of epinephrine. Indeed, in several cases it seemed likely that the epinephrine depots formed in the skin by electrophoresis led to a more prolonged action. This is in keeping with the local effects obtained in the skin discussed in the foregoing. That is, the blanching lasts more than 5 hours. Furthermore, larger doses are administered in this way although the rate of absorption is curtailed. There may be some justification in comparing this method with an intravenous drip of epinephrine solution.

A case not listed in the table is described by Fig. 1. Note in Fig. 1, which is an illustration of treatment in a very severe case, that on the 2nd, 3rd, and 4th days the patient required very few injections of epinephrine subcutaneously. During this time epinephrine was administered by electrophoresis. Iontophoresis was discontinued on the 5th day when the patient's condition became worse. On the 6th

TABLE I.

Case No.	Sex	Age	No. of treatments administered	Clinical diagnosis	Pharmacologic effects of epinephrine on asthma
1	F	30	5	Constitutional Hypersensitiveness; Infectious Asthma	Obtained
2	F	55	1	Infectious Asthma	"
3	F	21	1	Infectious Asthma	"
4	F	60	4	Essential Hypertension; Congestive Heart Failure; Infectious Asthma	"
5	M	64	1	Atherosclerotic valvular disease; old coronary thrombosis; Acute coronary thrombosis; Infectious Asthma	Obtained partially
6	F	58	9	Infectious Asthma	Obtained
6a (Readmitted)			26		
7	F	45	2 (within 2 hr)	Infectious Asthma	"
8	M	24	6	Infectious Asthma; Psychoneurosis	Not obtained
9	F	38	8	Infectious Asthma; Lung Cyst	Obtained
10	F	58	3	Infectious Asthma; Myocardial Insufficiency	"

day epinephrine was administered by iontophoresis with only partial effect. On the 8th day and 9th day epinephrine in oil showed some slight effect. In this particular instance it seems evident that the pharmacologic effect of epinephrine was very well evident by the electrophoretic method. It should be noted that the care of the patient was not under the jurisdiction of the individual giving the epinephrine by electrophoresis. The nurse in charge of the patient administered epinephrine whenever the patient's condition warranted it. If at any time on the 2nd, 3rd, or 4th day conditions had required epinephrine, the nurse in charge would have given it, irrespective of the fact that epinephrine had been administered by ionto-

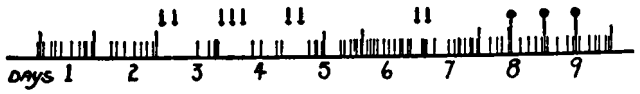

FIG. 1.

Diagram illustrating treatment of Mrs. B., a patient in status asthmaticus, by four different methods of administration of anti-asthmatics. The short vertical bars represent injection of 5 minims of 1:1000 epinephrine hydrochloride subcutaneously. The long vertical bars represent aminophyllin intravenously. The arrows pointing downward are treatments of epinephrine phosphate by electrophoresis. The longest vertical bars (8th and 9th day) surmounted by a closed circle are injections of epinephrine in oil.

phoresis. This, indeed, happened on the 6th day where the patient's condition was much worse and she was not relieved at all by injection of epinephrine and not as much as usual by the electrophoretic technic.

It is the impression of the writer that with further development and analysis of the technic here disclosed, more prolonged and effective action may be obtained than that observed with hypodermic administration.

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10682

Dose-Response Relationship of Androsterone by Direct Application to the Capon's Comb.*

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Fussgänger[1] first discovered that the capon comb is very sensitive to the direct application of dissolved androgen. McCullagh and Osborn[2] use this method for the determination of androgens in the blood of men. Butz and Hall have taken advantage of the sensitivity of this method in a recent study[3] wherein they showed that more of the androgen in bull's urine was found in the "cholestenone" than in the "cholestanone" fraction when the Anchel-Schoenheimer fractionation procedure was applied. None of the above authors has described fully the methods or the dose-response relationship for androsterone.

In an attempt to standardize the conditions in the use of this method and to understand the factors that influence the response, more than nine hundred individual tests have been made over a period of a year and a half. We have reported elsewhere[4] that season, previous use,

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2 McCullagh, D. R., and Osborn, W. O., *J. Biol. Chem.*, 1938, **126**, 299.

3 Butz, L. W., and Hall, S. R., *J. Biol. Chem.*, 1938, **126**, 265.

4 Hall, S. R., and Hunt, John D., *Proc. Am. Physiol. Soc.*, 1939, in press.