EVALUATION OF THERAPEUTIC SUBSTANCES EMPLOYED FOR THE RELIEF OF BRONCHOSPASM. VI. AMINOPHYLLINE[1]

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The use of various xanthine derivatives in the management of bronchial asthma was first described by Herrmann and Aynesworth (1) in 1937. They were able to demonstrate definite increases in the vital capacity of patients with bronchial asthma after the intravenous administration of aminophylline. The clinical contributions of Barach (2), Cooke (3), Unger (4), Segal (5) and others amply describe the valuable role played by this medication in the management of patients seriously ill with bronchial asthma.

We have previously described in detail (6–10) the historical development of a technique for evaluation of medications employed in the treatment of bronchial asthma by testing the efficacy of such compounds in preventing the decrease in vital capacity artificially induced in sensitive asthmatic subjects by the administration of suitable bronchospastic agents (histamine, methacholine, or allergens). The exact relationship of the dyspnea and bronchospasm induced by histamine or by methacholine to that occurring in spontaneous bronchial asthma is uncertain. However, since it is probable that only asthmatic or potentially asthmatic individuals respond to these agents by changes in vital capacity (7, 11, 12), this technique of assay in man may be of value. This report will concern itself with the results obtained with theophylline-ethylene diamine (Aminophylline, U.S.P.).

METHODS

A protection study consists of the observation of the decreases in vital capacity produced by the repeated administration of a bronchospastic agent (by any of various routes) before and after a protecting drug is administered. A "control" drop, which should be equal to at least one-quarter of the resting vital capacity, is first established; this drop should preferably exceed 1000 cc. The protecting agent is then administered (by any of various routes) and bronchospasm re-induced at suitable intervals until the effect of the protecting agent disappears. We have devised an equation (1, 2) by which the degree of protection afforded by any given drug at any time may be expressed in percentage:

$$P = \frac{C - E}{C} \times 100,$$

where P represents the degree of protection in percentage, C equals the control drop in vital capacity before the protecting drug is given, and E is the drop produced at any time after the protecting drug has been administered. These data, being independent of vital capacity determinations, may be grouped into averages. Since we have repeatedly encountered individual protection studies which vary greatly from the mean derived from a group of studies, we have computed all our data on the basis of such averages derived from at least four individual protection studies on different subjects.

RESULTS

By means of this technique we have measured the protecting ability of aminophylline, administered by various routes, against the decrease in vital capacity induced by the intravenous or aerosol administration of histamine or of methacholine.

(1) Intravenous aminophylline vs. intravenous histamine and methacholine. After the intravenous injection of 0.5 Gm. of aminophylline in 20 cc. of distilled water, over a period of ten minutes, protection against the bronchospastic effects of histamine[6] and of methacholine[7] was observed immediately. Against histamine, this immediate level was 65 per cent; against methacholine it was only 37 per cent. In view of the many unavoidable

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[6] The preparation used (histamine diphosphate) was kindly supplied by Abbott Laboratories Inc., North Chicago, Illinois.

[7] The preparation used ("mecholyl chloride") was kindly supplied by Merck and Co., Rahway, New Jersey.

errors inherent in any technique of clinical assay, we have considered all protection values below 40 per cent as insignificant. With this figure as a standard, it is apparent that intravenous aminophylline displays a protecting action against methacholine which is just short of being significant. Significant protection against intravenous histamine persisted for two hours and ten minutes

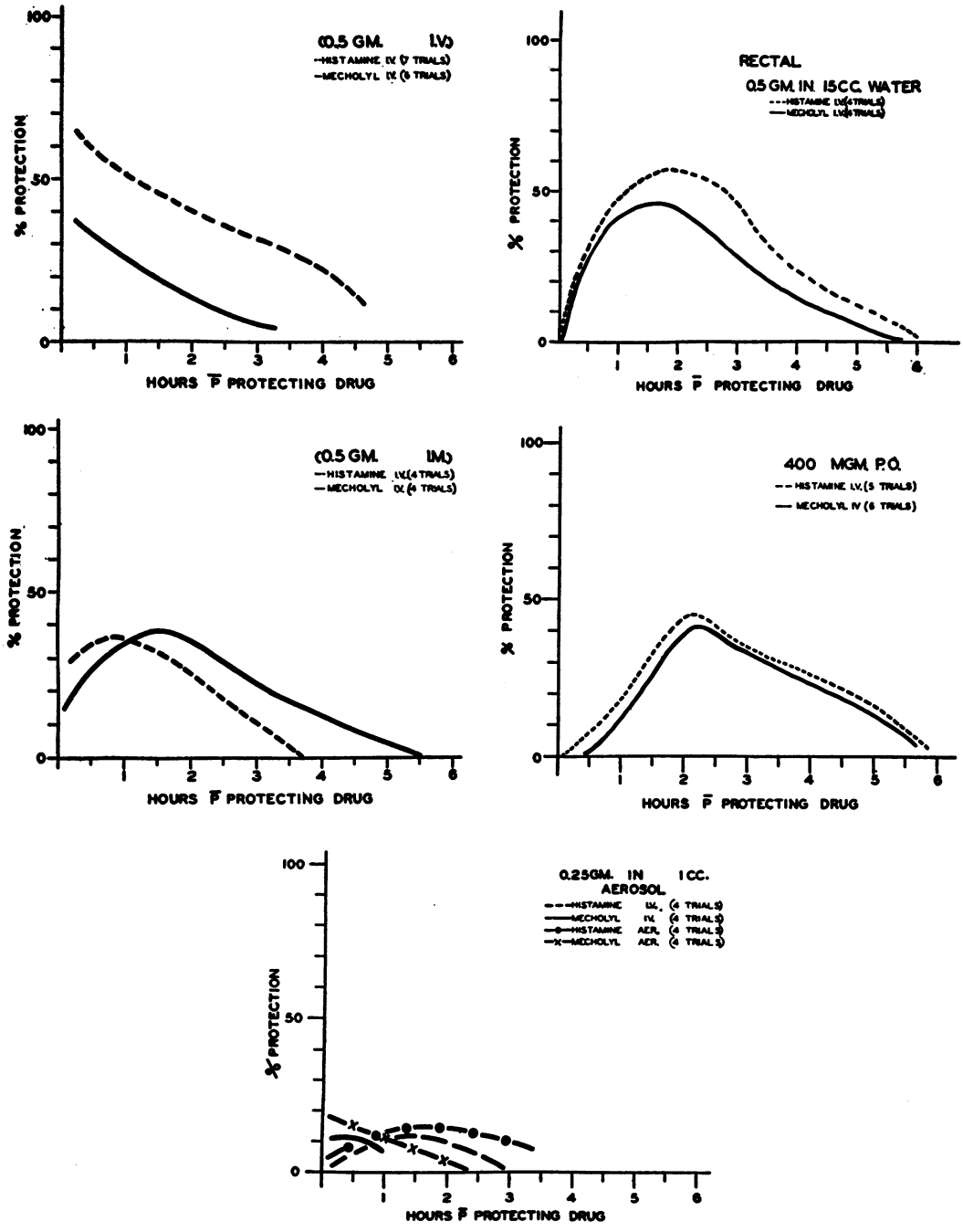

FIG. 1. THE PROTECTING ACTION OF AMINOPHYLLINE, ADMINISTERED BY VARIOUS ROUTES, AGAINST THE DYSPNEA AND BRONCHOSPASM PRODUCED BY HISTAMINE AND METHACHOLINE (REFERRED TO ABOVE AS MECHOLYL)

TABLE I

The relative intensity and duration of the protecting action afforded by aminophylline administered by various routes against the effects of histamine and methacholine (referred to below as mecholyl)

PROTECTING DRUG	BRONCHOCONSTRICTING AGENT: HISTAMINE I.V. — LATENT PERIOD OF DEVELOPMENT OF 40% LEVEL (MIN)	PEAK LEVEL %	PEAK TIME P INJ. (MIN.)	DURATION OF SIGNIFICANT 40% PROTECTION (MIN.)	MECHOLYL I.V. — LATENT PERIOD OF DEVELOPMENT OF 40% LEVEL (MIN.)	PEAK LEVEL %	PEAK TIME P INJ. (MIN.)	DURATION OF SIGNIFICANT 40% PROTECTION (MIN.)
AMINOPHYLLIN 0.5 GM IN 20 CC I.V.	0	65	IMMED.	130	—	37	IMMED.	0
AMINOPHYLLIN 0.5 GM IN 2 CC I.M.	—	36	50	0	—	38	90	0
AMINOPHYLLIN 0.5 GM IN 20CC H2O RECTALLY	45	58	120	150	55	45	105	90
AMINOPHYLLIN 0.4 GM (C.T.) ORALLY	105	45	130	50	130	42	135	20
AMINOPHYLLIN * 0.25 GM IN 1 CC AEROSOL	—	12	75	0	—	12	15	0

COMPARATIVE PROTECTIVE VALUE OF AMINOPHYLLIN ADMINISTERED BY VARIOUS ROUTES AGAINST HISTAMINE AND MECHOLYL-INDUCED DYSPNEA AND BRONCHOSPASM IN ASTHMATIC SUBJECTS.

* AMINOPHYLLIN AEROSOL ALSO EXHIBITED NO SIGNIFICANT PROTECTION AGAINST THE EFFECTS OF HISTAMINE AND MECHOLYL AEROSOLS

(Figure 1, Table I). The lesser degree of protection displayed against the effects of intravenous methacholine was of shorter duration as well.

(*2*) *Intramuscular aminophylline vs. intravenous histamine and methacholine.* Administration of 0.5 Gm. of aminophylline in 2 cc. of distilled water intramuscularly in the gluteal region led to protection against the decrease in vital capacity induced by the intravenous administration of histamine and methacholine which never quite achieved significant levels (Figure 1, Table I). In this case, as in the case of intravenous aminophylline and methacholine, the maximum protecting levels were just below our arbitrary level of significance, being 36 per cent in the case of intramuscular aminophylline against histamine, and 38 per cent against methacholine. These peak levels were reached after a considerable delay (50 minutes for histamine, 90 minutes for methacholine) and were maintained for comparatively brief intervals.

(*3*) *Rectal solution of aminophylline vs. histamine and methacholine.* A solution of aminophylline containing 0.5 Gm. in 15 cc. of distilled water was instilled rectally by means of a Dakin syringe and a well-lubricated No. 12 Fr. urethral catheter. Aminophylline so administered resulted in significant protection (above 40 per cent) against the bronchospastic effects of intravenous histamine for two and one-half hours and against intravenous methacholine for one and one-half hours. This occurred after delays of 45 and 55 minutes respectively, presumably incident to absorption. After the rectal administration of 0.5 Gm. of aminophylline, a peak level of 58 per cent protection against histamine was attained in two hours; 45 per cent protection against methacholine was attained in one and three-quarters hours (Figure 1 and Table I).

(*4*) *Oral aminophylline vs. intravenous histamine and methacholine.* Orally administered aminophylline in the form of two compressed tablets of 0.2 Gm. each yielded protection to a lesser degree against the decrease in vital capacity produced by subsequently administered intravenous histamine and methacholine. Barely significant peak values of 45 and 42 per cent against histamine and methacholine respectively were obtained (Figure 1 and Table I). Significant protection (40 per cent) was attained only after a delay of one and three-quarters hours in the case of histamine, and two hours and ten minutes in the case of methacholine. With histamine, the duration of significant protection was only 50 minutes; with methacholine, 20 minutes.

(*5*) *Aerosol aminophylline vs. aerosol and intravenous histamine and methacholine.* The relative ease of aerosol administration of small quantities of concentrated solutions of adrenergic agents has led us to investigate the properties of an aerosol produced with the standard Vaponefrin nebulizer from a 25 per cent solution of aminophylline. The disagreeable taste of this preparation may be partially masked by the addition of a drop or two of spirits of peppermint. We first investigated the protecting action of six inhalations of such a mist, produced with hand-bulb nebulization, but

were unable to demonstrate any protecting action against the bronchospastic effects of subsequently administered histamine or methacholine, the latter being given both intravenously and as an aerosol. We then nebulized 0.25 Gm. of aminophylline in 1.0 cc. of distilled water employing the Vaponefrin nebulizer with oxygen flows, using the intermittent Y-tube occlusion technique. This procedure is time-consuming and the aerosol is irritating to the pharynx and trachea. No significant protection could be demonstrated (Figure 1 and Table I). Peak protection values in all instances reached only 12 to 17 per cent.

(*6*) *Direct comparison of various routes.* The striking disparity in protection obtained after the administration of aminophylline via various routes led us to compare the antihistaminic potency of aminophylline in each of the five routes employed. In two subjects, R. L. and J. S., aminophylline was administered on successive visits to the laboratory via each of the five routes employed, so that a more direct comparison between these methods of administration might be made (Figure 2). It is apparent from these curves that in both cases optimum antihistaminic activity appeared after the rectal administration of a solution containing 0.5 Gm. of aminophylline. In these two individuals intravenous and intramuscular administration were of essentially equal activity; the intravenous route, however, has the advantage of immediate action. Orally administered aminophylline in a slightly smaller dose was definitely less effective than intravenous or intramuscular medication. Aerosol aminophylline was, as previously noted, totally ineffective.

DISCUSSION

In contrast to the data obtained by similar examination of the protecting ability of various adrenergic agents (10) against the decrease in vital capacity produced by intravenous injections of histamine and methacholine, it is apparent that aminophylline must exert its bronchospasmolytic action in a different manner. Such anti-asthmatic drugs as the sympathomimetic amines have a rapid, intense protecting action in minute doses, whereas the effect of aminophylline is milder and more prolonged and the dose employed is many times greater. In dosage and in the time sequence of its protecting action, aminophylline approaches more closely the antihistaminic drugs (blocking agents), data on which will be presented elsewhere (13).

The administration of aminophylline solution by rectum has been extensively popularized in recent years (2). We have long been aware of the powerful bronchospasmolytic action of such medication in the management of patients with severe asthma. This impression is amply borne out by these studies, in which rectally administered

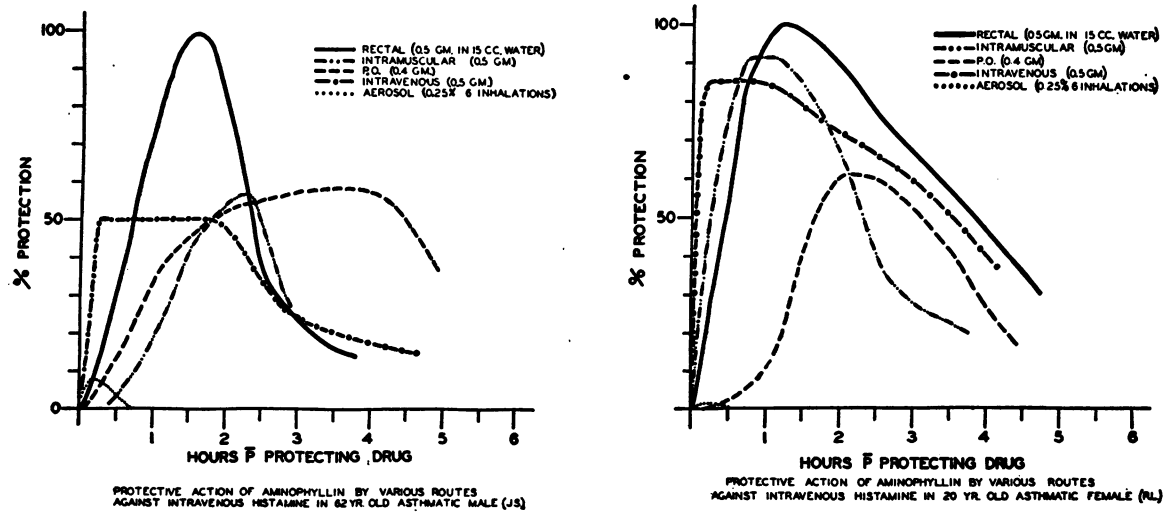

FIG. 2. THE COMPARATIVE PROTECTING ACTION OF AMINOPHYLLINE ADMINISTERED BY EACH OF FIVE ROUTES TO TWO ASTHMATIC PATIENTS AGAINST THE DYSPNEA AND BRONCHOSPASM PRODUCED BY HISTAMINE AND METHACHOLINE (REFERRED TO ABOVE AS MECHOLYL)

aminophylline exhibits a protecting action equal or superior to all other routes, if the 45 to 60 minute absorption delay time is not objectionable. As absorption after oral administration is slower and as the period of significant protection is shorter, this route can have only limited value. Intramuscular aminophylline made a poor showing, one not entirely unexpected in the light of clinical experience. Were the pain usually attendant upon such an injection not already a sufficient deterrent to its clinical use, the lack of significant protecting ability should discourage dependence upon this route. It is our feeling that rectally administered aminophylline solution affords the patient a potent means for relief of asthmatic bronchospasm; moreover, the ease of self-administration of the rectal solution is, of course, an even more important factor. Where maximal immediate effect is essential, the intravenous administration remains the route of choice.

SUMMARY

1. The protecting ability of aminophylline, administered by various routes, against the dyspnea and bronchospasm produced by the administration of histamine and methacholine by various routes is presented.

2. The intravenous administration of 0.5 Gm. of aminophylline results in immediate protection against the bronchospastic effects of histamine and methacholine; the protection against histamine, which is definitely of significant degree, persists for two hours and ten minutes. Protection against methacholine falls below an arbitrary limit of significance.

3. Rectal administration of a solution of 0.5 Gm. of aminophylline yields a degree of protection against the dyspnea and bronchospasm produced by intravenous histamine and methacholine equal or superior to that produced by intravenous injection of the same dose of the drug. There is a 45 to 60 minute delay incident to absorption from the rectal mucosa, whereas the effects of the drug are apparent immediately following intravenous injection.

4. Aminophylline given intramuscularly (0.5 Gm.) is relatively ineffective in counteracting the bronchospastic effects of intravenous histamine and methacholine.

5. The oral administration of 0.4 Gm. of aminophylline results in relatively low degrees of protection as compared to that obtained with the rectal route. Significant protection appears only after a long delay and persists for an extremely short period of time.

6. Aminophylline in the form of an aerosol mist is almost totally ineffective in preventing the dyspnea and bronchospasm produced by intravenous or aerosol administration of histamine or of methacholine.

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