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Maynard Howard Porter
University of Nebraska Medical Center

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It is the purpose of this thesis to review the literature, written in English, on a synthetic sympathomimetic amine named aludrine, which is hailed by its investigators as a new and effective therapeutic drug in relieving the dyspnea of an asthmatic attack. It is claimed that aludrine elicits responses in the body similar to those of epinephrine and that it has a pronounced broncho-dilator action, but a marked peripheral vasodilating action, and a good smooth muscle relaxing ability. (13) This isopropyl modification of epinephrine, racemic 1-(3-4- dihydroxyphenol)-2- isopropylamino-ethanol, has various names: "I.P.A." (Specific Pharmaceutical, Inc.), "Aleudrin" in European literature and "Aludrine" in this country. "Isorenin", now "Isonorin" (Carroll Dunham Smith), "Isuprel" (Winthrop-Stearms, Inc.) and "Norisodrine" (Abbott).

This compound, generally believed of recent discovery, was synthesized prior to 1905, under the direction of Dr. Scheuing in the chemical laboratories of C. H. Boehringer and Son, Igleheim, Germany. (6) The early work of the German experimenters Loewi and Myer

(1905), as well as that of the English investigators, Dakin, and Barger and Dale (1910) showed the sympathomimetic action of a series of N alkyl homologues of epinephrine including the compound isopropyl epinephrine. It was not until World War II that aludrine was first tried clinically by a German, Konzett, who concluded in December 1940 from his studies that the bronchodilator activity of the compound was ten times that of epinephrine alone. From 1940 to 1947 several European investigators reported aludrine to be an effective antiasthmatic when used as a simple spray. It was further claimed that the crises of experimental dyspnea induced in healthy subjects by the use of choline aerosols could be controlled. (4) (8)

In 1947 the publication of the work of Segal and Beakey with isuprel marks the first American report in the literature. They recommended isuprel to be effective in relieving the dyspnea of bronchial asthma by three routes of administration, namely; oxygen aerosolization, subcutaneously and orally. The fourth route of administration, the sublingual, was first reported early in 1949. (9) (15)

Consideration of each of the four routes of administration of aludrine will be taken up separately.

1. Inhalation Therapy.

The value of inhalation therapy can be appreciated if one realizes the tremendous absorptive powers of the surface of the lung whereby an inhaled medication reaches the desired objective without modification and is not dissipated in an extensive circulation which itself may not be functioning properly. With aerosols it is possible to obtain high local concentrations and varying blood levels. Within the past few years this therapy has gained impetus from many new drugs, that is, penicillin aerosol with its ability to treat conditions formerly resistant to treatment. (1) (21)

Aludrine may be administered for oral inhalations; a solution by means of a hand nebulizer, a solution by oxygen-aerosolization, and a preparation in a dust form ("Norisodrin Sulfate" Abbott) may be inhaled from a small plastic dispenser which dispenses 3 to 5 mg. per inhalation. Aludrine sulfate and aludrine hydrochloride solutions 1:100 or 1:200 were used. 0.25 to 1.5 cc. of the solution was used in oxygen aerosol therapy with the oxygen flow of four to five liters being sufficient to aerosolize 1.0 cc. in ten minutes. The usual dosage by hand nebulizer was from three to fifteen inhalations. The dosage has to be individualized.

Segal and Beakey in their first report, on eighty-two ambulatory cases of chronic bronchial asthma treated by inhalation (isuprel-oxygen-aerosol) therapy, stated the response was striking with rapid control of cough and an increase in vital capacity ranging from 0.43 liter to 0.8 liter depending on the degree of bronchospasm, i.e. the greater the bronchospasm present, the greater the increase in vital capacity immediately following a treatment. In addition, expectoration was easier and greater immediately following each inhalation.

Segal and Beakey (20) treated forty hospitalized patients with severe asthma with isuprel by inhalation. Many of these patients were in the severest stage of status asthmaticus and had previously received intensive therapy including infusions of saline or dextrose and saline with aminophylline, epinephrine subcutaneously, aminophyllin by rectum, and phenobarbital without relief. In this notoriously treatment-resistant group, eighty-five per cent obtained gratifying relief from the use of isuprel alone.

Gay and Long studied forty-eight patients using hand nebulizers with isuprel 1:200 on a symptomatic basis. Mild asthma required but a single course of three to five inhalations, while severe asthma called

for repeated courses of from six to eight inhalations. It was noted consistently, however, that the duration of the relief produced was inversely proportional to the severity of the asthma. Response to the optimum dosage of about six inhalations began in two to three minutes and reached its maximum in about five minutes. Only two patients, out of the forty-eight studied, having severe asthma failed to obtain some benefit from inhaled aludrine mist and the incidence of side effects were only four per cent. Aludrine in this form greatly facilitated the liquefaction and excretion of sputum in chronic asthma.

Lowell, Curry and Schiller report that thirty patients using hand nebulizers to dispense aludrine gave corroborative evidence that the drug was very effective in relieving mild or moderately severe asthma and appears to be the most effective agent available for self-medication. However, in severe and prolonged attacks of asthma, the drug was far less satisfactory (three obtained no relief). In certain cases other medications were required. With recovery aludrine was again effective in the control of milder attacks. Mild side effects were noted in two patients.

In thirty-eight cases of bronchial asthma Maietta

used neo-synephrine hydrochloride 1:100 and isuprel hydrochloride 1:100 as separate aerosols. Neo-synephrine was employed in 1.0 cc. and isuprel in 0.5 cc. doses. Usually one or two treatments daily for several days were found to be effective. Aerosolization of these preparations in status asthmaticus has been a life-saving measure. A total of 235 vasoconstricting aerosol treatments were given with uniformly excellent results. This combination may be what is needed to combat bronchial edema which is probably one of the chief reasons for aludrine to be less effective in treating the more severe or long standing asthmatic attacks. Aludrine is inefficient in constricting blood vessels and therefore is inefficient against bronchial edema unless used with a vasoconstrictor.

Krasno, Grossman, and Ivy investigated the use of norisodrine dust by inhalation. In their hands they found that the drug gave complete relief in twenty-four asthmatics. This drug was given in conjunction with some other suitable symptomatic drug. They observed mild side reactions in four of twenty-four patients.

2. Sublingual Therapy.

Sublingual tablets of aludrine are recommended

for use as an adjunct to inhalation therapy. When the acute attack has been successfully treated by inhalations the sublingual route is of value in aborting further attacks. Sublingual tablets used alone are also of value in the treatment of mild cases of asthma. (15)

The most generally effective dose is 15 mg., although some patients may require only 10 mg. or less. The dosage chosen should be based on the response of the individual patient since side reactions such as palpitation frequently occur even when the dosage is only 5 mg. above that of the patient's tolerance. The tablets are allowed to disintegrate under the tongue. Until absorption has taken place, patients are instructed not to swallow saliva. Treatment should not be repeated more often than every three or four hours, or more than three times daily. (9)

Lowell, Curry and Schiller observed thirteen patients receiving the drug by this route for relief of symptoms at home. Three patients who were suffering from mild asthma stated that they had obtained excellent relief after taking one or two tablets. Five patients had asthma of moderate severity, two of which stated that the drug was without effect and the remaining three obtained relief of very short duration even with doses

as large as 50 mg. in two hours. The five remaining patients who had severe asthma denied benefit with similar doses.

Lipman studied twenty-three patients, nine mild to moderate while thirteen patients were classified as severe. Twelve patients out of this total were completely relieved of one or more attacks within five to thirty minutes by one 5.0 mg. sublingual tablet of isuprel, the relief persisting from one-half hour to several days at a time. Eight patients received only partial relief. Three patients were not at all relieved. Out of the twenty-three patients fourteen had mild to severe side reactions.

When forty-seven patients of a study of the different routes of aludrine therapy by Gay and Long, were asked to state their preference between the aludrine linguet and the common antiasthmatic tablet combining aminophylline, phenobarbital and ephedrine (which was used routinely prior to the aludrine study), they chose the later combination in a ratio of three to one. The reason most often given for this choice was the ability of the aminophylline-phenobarbital-ephedrine combination to relieve asthma of severity not appreciably benefited by the aludrine linguet, the

greater duration of relief and the relative absence of unpleasant side effects attending the use of the aminophylline-phenobarbital-ephedrine tablets. All agreed, however, that the linguet afforded the quickest relief and that its greatest usefulness was in the prompt abortion of asthma of a mild degree. Only one patient in twenty-five, with mild asthma, failed to obtain relief using the sublinguet as instructed. Patients suffering from attacks of moderate severity reported less favorable, only seven out of sixteen obtaining moderate to marked relief, three mild relief and six of the sixteen no relief at all. Six patients experiencing frequent paroxysms of severe asthma obtained no relief with repeated use of sublinguets.

Sublingual absorption of 10 mg. pellets is the second method of choice for administrating aludrine because of its convenience, speed of action and the fact the patient can discard all undissolved drug in the event of serious side effects. The sublinguet is of greatest value in the early abortion of mild asthma. It is of less benefit in moderate asthma and of no benefit in severe asthma. It causes mild and fleeting side actions in thirty-three per cent of users. (9)

3. Subcutaneous Therapy.

The 1:1000 dilution of aludrine by the subcutaneous route was studied by Segal and Beakey. Their dosage varied from 0.25 to 0.75 cc., with 0.25 cc. appearing to give the best relief for dyspnea with the least side effects. There was an average increase of 1.18 liters in eighteen vital capacities taken, the smallest increase being 0.4 liters and the largest 2.6 liters. In their second report 0.25 to 0.5 cc. of the 1:5000 and 0.5 cc. to 1.0 cc. of the 1:10,000 dilutions were used. Although fewer side effects were noted and a moderate transient improvement was usually seen, the results were not as dramatic as those with the 1:1000 dilution. The latter appears to be most effective in the initial active treatment of the very ill asthmatic who needs hospitalization.

Gay and Long using doses of 0.1 cc. to 0.5 cc. of 1:1000 aludrine in ten patients during paroxysms of severe asthma observed prompt and dramatic relief in eight of the patients, but every patient receiving this concentration experienced side effects of moderate to marked degree, in some instances sufficiently alarming to preclude the continued use of the drug in a strength of 1:1000. All injections thereafter in their

study were 0.3 to 0.5 cc. of a 1:5000 dilution being repeated as warranted. With this dosage only seventeen of forty-one patients (forty-one per cent) experienced side effects, and in no instance were these of a nature or degree sufficient to render the dosage unsafe or impractical.

It was believed that aludrine sulfate 1:5000 in doses of 0.3 cc. to 0.5 cc. given subcutaneously generally gave a therapeutic effect equivalent to that produced by 0.3 cc. to 0.5 cc. of epinephrine 1:1000 given intra-muscularly. Except for the fact that aludrine appeared to have a slightly more rapid onset of action, Gay and Long did not find it significantly superior to epinephrine for use by injection. On five occasions, however, they obtained favorable response to aludrine in patients who failed to receive further asthmadilator action from repeated injections of epinephrine (which corroborated observations of Segal and Beakey in eleven epinephrine fast patients) and they felt that a trial of aludrine is indicated in any patient in the so-called epinephrine-fast states. No fastness to aludrine has as yet been reported.

The onset of action of aludrine given subcutaneously was apparent in one to three minutes, and its maximum

subjective and objective effects generally occurred from five to seven minutes after injection. As with the other methods of administration, the duration of benefit varied inversely with the severity and duration of the asthma. The milder attacks were relieved completely and the patient would report freedom from wheezing for hours to days. Relief afforded the asthma of greater severity and longer standing generally faded in twelve to fifteen minutes and recourse to repeated injection or supplemental treatment was necessary. (9)

4. Oral Therapy.

Segal and Beakey treated nine patients with oral aludrine in conjunction with hand-bulb inhalations. Most of these patients felt that the drug taken orally was not as effective as by inhalations. Dosages ranged from 50 to 120 mg. in divided doses daily, being a wide variation in both therapeutic response and incidence of side actions among patients. In most cases the results were equivocal and they concluded that oral aludrine may have a place in the management of the chronic asthmatic who wheezes daily but rarely has a severe attack. Its action appears to be too slow to warrant its use in the acute stage of asthma.

Kaplan found that the use of aludrine by mouth led to side reactions that precluded its use.

Gay and Long concluded from their series of thirty-six patients that the routine use of aludrine by mouth is impractical because of the high incidence of side effects (seventy-five per cent) with use of the minimum effective dose of 15 mg. In general, the relief afforded does not justify the unpleasant symptoms associated with its administration. Aside from untoward reactions noted their therapeutic results were as follows: eighty-three per cent of all patients with mild asthma reported moderate to marked relief following 15 mg. of aludrine taken at the onset of the attack. Those patients who allowed their asthma to go unabated and those experiencing severe asthma rapidly after onset failed to obtain significant benefit from 15 mg. of aludrine so resort was made to epinephrine by inhalation or injection, aminophylline, oxygen, etc.

Those patients helped by oral medications reported relief in twenty to thirty minutes with durations ranging from one to four hours. As with the linguets, many mild attacks aborted early completely subsided for twenty-four or more hours.

Cardiovascular - Aludrine Effect.

Six studies of the blood pressure and pulse change

in five normal individuals were done by Segal and Beakey. The systolic pressure showed an average increase of 13 mm. of mercury with the inhalatory route (1:200) and 22 mm. with the subcutaneous route (0.33 cc. of 1:1000). The pulse pressure showed an average increase of 16 mm. of mercury with inhalation and 39 mm. with subcutaneous injection. The pulse increased an average of eighteen and fifty beats per minute with inhalatory and subcutaneous routes, respectively. This compares with Blumgart's studies in ten normal subjects to whom 0.5 to 1.0 cc. of 1:1000 solution of epinephrine was given subcutaneously. He found an average rise in the systolic pressure of 39 mm. of mercury, an average increase in pulse pressure of 48 mm. of mercury and an average increase in the pulse rate of sixteen beats per minute.

In fifteen asthmatic patients of Gay and Long, 0.1 to 0.5 cc. of 1:1000 aludrine given subcutaneously caused pulse rates to increase to 108 - 176 per minute, one and a half to two minutes after administration. (Thirty-two patients of Segal and Beakey had a pulse jump to 119 - 151 per minute). The greater increases were from 0.3 to 0.5 cc. doses. With doses of 0.1 cc. and 0.2 cc. the rate returned to pre-injection level

within fifteen minutes, while with 0.3 to 0.5 cc. the tachycardia persisted from thirty minutes to sixty minutes. Most of the patients reported palpitation of varying degree in association with their tachycardia.

While Segal and Beakey reported the average pulse pressure increase with 0.1 - 0.5 cc. of 1:1000 aludrine subcutaneously on thirty-two patients to be 10 mm. of mercury, stating that this increase was due almost entirely to a lowering of the diastolic phase, only three patients out of fifteen in the Gay and Long series responded in this manner, but the diastolic fall was to a 20 to 30 mm. level. Ten of the fifteen patients had a systolic rise from 10 to 30 mm. and a diastolic fall of 10 to 30 mm., while two patients experienced precipitate falls in both systolic and diastolic to levels of shock within three minutes after injection. In all patients the degree and duration of blood pressure changes were in close correlation to the tachycardia produced.

The fluctuations in blood pressure in asthmatics, that is, the variation in the systolic and diastolic readings in inspiration and expiration were effectively abolished or markedly decreased, especially when the bronchospasm was greatest, were first observed by Segal

and Beakey.

Electrocardiograms were taken on six patients before and after the administration of 0.1 cc. of aludrine 1:1000 (9). Five of these tracings revealed the development of tachycardia following injection of the drug. There was no disturbance of rhythm. With the exception of the tachycardia, two of the six tracings remained essentially the same. The other four records showed significant positive findings of coronary insufficiency. It was further observed that such changes occurred in one patient without a significant coincident increase in heart rate, indicating that the S-T segment and T wave changes were not necessarily the result of concomitant tachycardia. Gay and Long were of the opinion that the action of aludrine in these observations was not one of coronary artery constriction but of decided increase in the force of myocardial contraction and a resulting demand for more oxygen, which is not met.

Electrocardiograms were then taken on six patients before and after the injection of 0.3 cc. of 1:5000 aludrine subcutaneously. The alterations observed with this dosage were proportionately of less degree than those found with the 1:1000 strength. These

further observations of the ability of aludrine in 1:5000 concentration to effect significantly cardiac function strengthened Gay's and Long's belief in its potential danger if not routinely given in small doses and to selected persons. Dosage up to 0.5 cc. of a 1:5000 concentration constitutes a safe range when the size of the dose is governed by the age and size of the patient, his tolerance to sympathomimetics stimulants and the severity of his asthma.

Blood Sugars.

No constant or significant changes in blood sugars concentration was found in six patients whose blood sugar levels were determined before and fifteen minutes after subcutaneous administration of 0.3 cc. of aludrine 1:5000 (9).

Side Effects.

The inhalatory route was generally very benign as far as undesirable side effects were concerned. Most patients had no reactions. The few that experienced reactions complained of slight nervousness and palpitations which wore off quickly. While the incidence was relatively high (thirty-three per cent in Gay and Long's studies) with sublingual therapy, the palpitations were usually mild and fleeting. The

more serious reactions - marked palpitations being the most outstanding - were seen from the subcutaneous route, especially if the 1:1000 dilution was used in doses of 0.5 cc. or more. The drug in dilutions of 1:5000 reduced the incidence of subjective symptoms by more than half and showed such dosage to be reasonable and safe if care is taken in selection of patients. All authors but Segal and Beakey agreed that the high incidence and severity of side effects of the oral route of administration precluded its use. "While reduction in the size of the oral dose lessened the severity and duration of the side effects it made no significant difference in their incidence." (9)

The incidence of subjective side effects varied with the method of administration as in the tabulation from Gay and Long.

Method and Dose	Percentage
Sublingual, 10 mg.	33
Oral, 25 - 50 mg.	80
Oral, 15 mg.	75
Inhalation, 1:200	4
Subcutaneous, 1:1000	100
Subcutaneous, 1:5000	41

The side effects observed are given in the accompanying list in their decreasing order of frequency from Gay and Long.

Side-Effect	Percentage of all Side-Effects
1. Palpitation	90
2. Nausea	19
3. Headache	17
4. Nervousness	16
5. Tremor	14
6. Dizziness	13
7. Precordial Ache	9
8. Weakness	7
9. Sweating	7
10. Anginal Pain	3
11. Epigastric Pain	3
12. Vomiting	3
13. Tinnitus	3
14. Flushing of Face	1
15. Diarrhea	1

Aludrine displayed no damaging effect on the blood picture of ten patients using it orally for prolonged periods. (9)

No cumulative effects have been reported.

Conclusion.

Since the majority of sympathomimetic drugs now in use for the symptomatic relief of asthma are associated with a relatively high incidence of undesirable side reactions, current efforts in the development of new anti-asthmatic drugs are being directed toward the symthesis of bronchodilator substances which lack strong vasopressor action and central nervous system stimulating effects. One recent development along these lines is aludrine, which has a great bronchodilator effect and less of a pressor effect than epinephrine. This compound, however, also presents certain limitations in its clinical use. Its oral action is questionable, and when injected it is frequently accompanied by a profound stimulation of the heart and occasionally a precipitous fall in blood pressure. It will find its greatest use through inhalation therapy for it generally affords some relief in asthma of all severity with an incidence of side effects of only four per cent. Sublingual absorption of tablets of aludrine is the second method of choice because of its convenience, speed of action and its value in the early abortion of mild asthma. Aludrine may be of value in the treatment of epinephrine-fast patients.

It will be accepted as one of the better sympathomimetic drugs for the symptomatic relief of bronchial asthma.

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