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COMPARISON BETWEEN EFFECTS
OF SOME AEROSOLS WITH ANTI-ASTHMATIC
EFFECT ON THE AIRFLOW IN ASTHMA
AND EMPHYSEMA

By

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The purpose of this study was: 1. To compare the effect on airflow from two different isoprenaline derivatives given as inhalations alternatively with the De Vilbiss spray or as dose-aerosol. 2. To study the effect from one of these isoprenaline derivatives (alupent) in patients with "obstructive disease" with or without asthmatic symptoms.

Bronchial spasmolytics are widely used in the therapy of bronchial asthma and lung emphysema. Many patients are dependent on sprays, though it is not possible to show any effect objectively, for example, by measuring the airflow, the mixing of air in the lungs or the ventilation-perfusion relationship. The healthy lung tolerates a great deal, as inhalation of vasoconstrictive adrenaline derivatives, but in emphysema, for instance, with reduced pulmonary blood volume, those may possibly be disadvantageous. Our possibilities of estimating the extent of possible lung injury are still limited, in spite of the improved methods available. In our efforts to ascertain the treatment indicated in each case, on the basis of the analysis of the individual case, we are naturally anxious to use all the aids available to us. In practice, however, we are generally still dependent on the usual clinical assessment.

MATERIAL AND METHODS

The effect of alternate isoprenaline and alupent inhalations on the same individuals was studied in 15 asthmatic patients and afterwards alupent was used routinely in about 500 spirometric investigations in patients with various diseases. In the following investigation patients were selected who had primarily been assessed according to clinical and allergological findings on the basis of the consistent observation of their lung status—especially the variability of this status—guided by the clinical status, lung x-ray, composition of the sputum etc. These patients were divided into two classes, those with predominantly bronchial asthma though with no demonstrable specific allergy and those with an even longer history of disturbance of the lung function, in whom the development of emphysema was the principal feature. In these patients a check was carried out with Bernstein spirometry before and after 1–3 weeks symptomatic treatment including ACTH and cortisone. In this check the forced inspiratory volume (FIV) and the forced expiratory volume (FEV) before and after the inhalation of isoprenaline or a new derivate (alupent) were measured.

Alupent (1-(3,5-dehydroxyphenyl)-2-isopropylaminoethanol sulphate) (6) differs from isoprenaline in that in alupent both hydroxy groups are in the meta-meta position, whilst in isoprenaline the hydroxy groups are in the para-meta position. The result of this chemical variation is that alupent is stable in the injection solution (unlike isoprenaline) and that the oral resorption, compared with that of isoprenaline, is fifty times better, due to its stability also in contact with the enzymes in the digestive tract. The improved resorption has largely compensated the weakening of effect found in animal experiments in comparison with isoprenaline, when doses equivalent in weight were administered. In addition, both the animal experiments and the clinical investigations (2, 3, 4, 9, 11) in oral administration showed a considerably longer effect (4–6 hours), compared with isoprenaline and ephedrine. Tachycardia ensues after alupent only following a dose thirteen times greater than that of isoprenaline (intra-muscular injection). Taking LD_{50} (mouse and rat) as a basis, the toxicity of alupent, compared with that of isoprenaline, is considerably less. The positively inotropic and chronotropic effect of alupent was demonstrated in the isolated heart preparation; both quantitatively and qualitatively certain differences from isoprenaline were revealed. Alupent acts somewhat more gently and therefore tachycardial disorders of conduction do not contra-indicate its use.

RESULTS

The effect of alternate isoprenaline and alupent inhalation on the same patient was investigated with the guidance of air-flow, pulse and blood-pressure checks. Then alupent was used routinely in about 500 spirometric investigations on patients at S:t Göran's Hospital. Although its effect on pulse and blood

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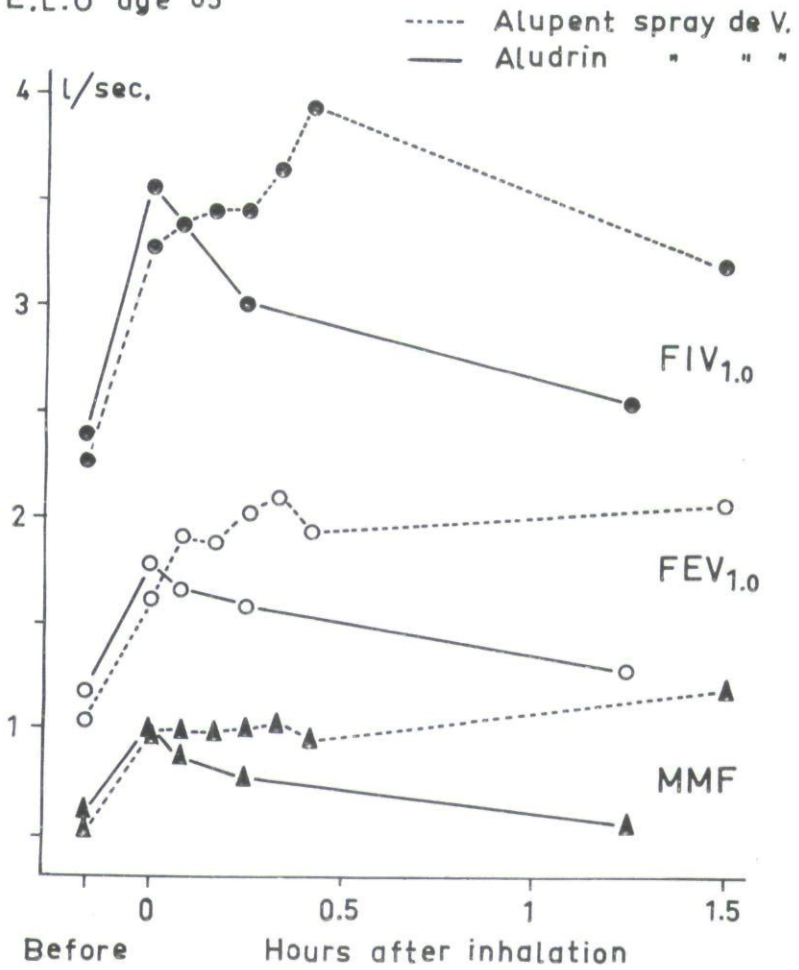


Fig. 1.

Duration of effect after the inhalation of isoprenaline or alupent. Individual example from 15 comparative examinations in asthma patients. FIV_{1.0} = forced inspiratory volume in 1 sec. FEV_{1.0} = forced expiratory volume in 1 sec. MMF = maximal mid-expiratory flow.

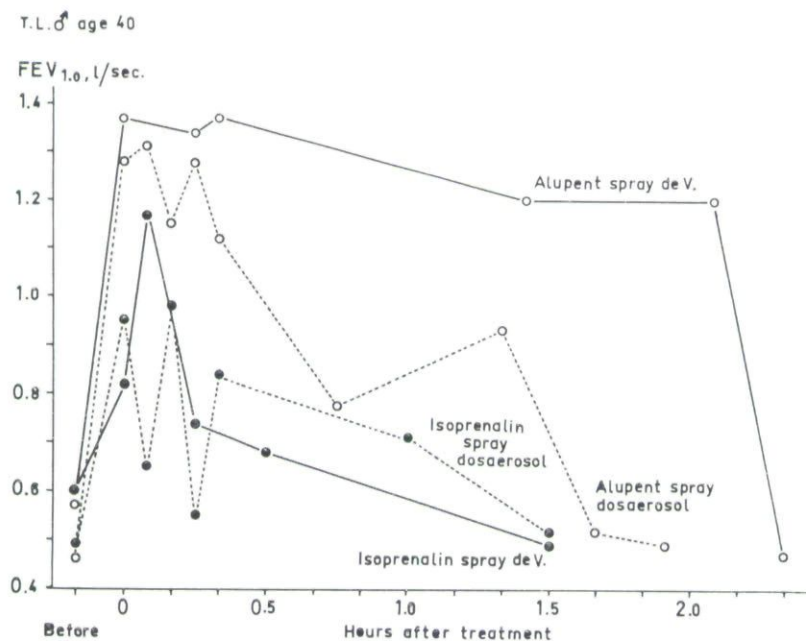


Fig. 2.

Duration of effect after inhalation of alupent with the De Vilbiss spray or with the alupent dose-aerosol and of isoprenaline by the same methods of administration. Typical individual example from 10 comparative examinations. Patient with relatively severe respiratory complaints. FEV_{1.0} = forced expiratory volume in 1 sec.

pressure was insignificant, the improvement in airflow values was comparable throughout with that from isoprenaline. Side effects in the form of transitory palpitations or slight tremor—usually without tachycardia—were observed in 3 per cent of these cases.

Some patients complained of an irritating cough with the alupent inhalation. Heart catheterizations in some cases showed that from alupent inhalation no clear change in stroke volume or vascular resistance in the lungs of healthy patients ensued (5). A spirometric comparison between isoprenaline and alupent showed that, as regards efficaciousness, both preparations are equivalent. The initial effect is approximately the same with both substances; the maximal effect of alupent often

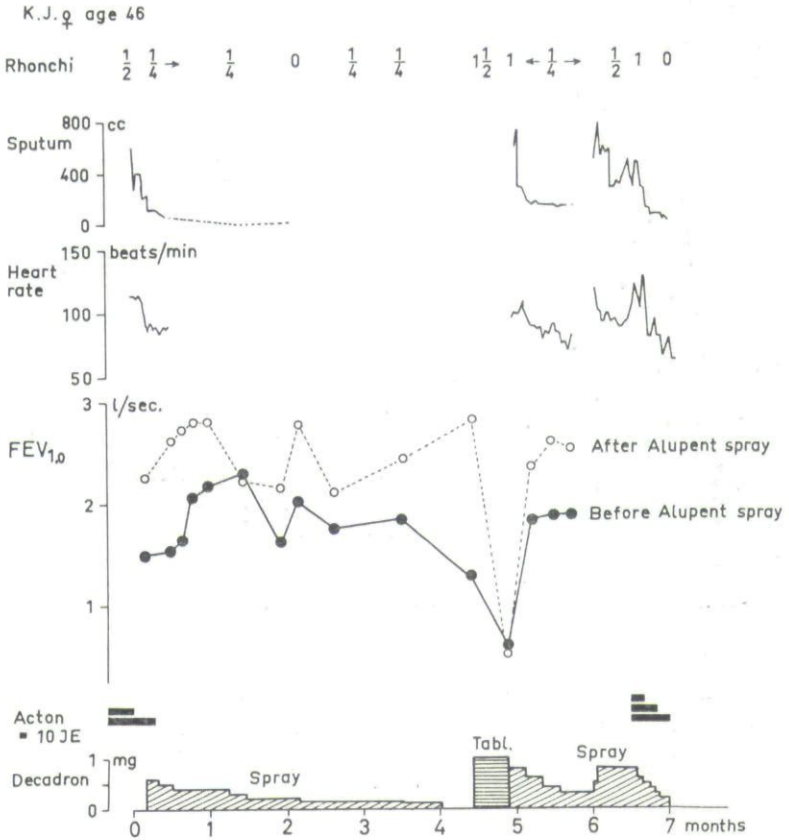


Fig. 3.

Typical individual example from 57 cases. The treatment with dexamethasone inhalations was studied in relation to other different forms of treatment. FEV_{1,0} = forced expiratory volume in 1 sec. Rhonchi = expiratory wheezing, graded 0-3.

occurs somewhat later than with isoprenaline and the duration of the effect of alupent is longer than that of isoprenaline (inhalation).

For the inhalation the compressed-air-driven De Vilbiss spray (15 breaths of a 2 per cent alupent solution) or the alupent dose-aerosol (750 gamma of alupent per breath) were used in turn on the same patient, alternating with isoprenaline in equivalent doses and sprays. Both methods of applying

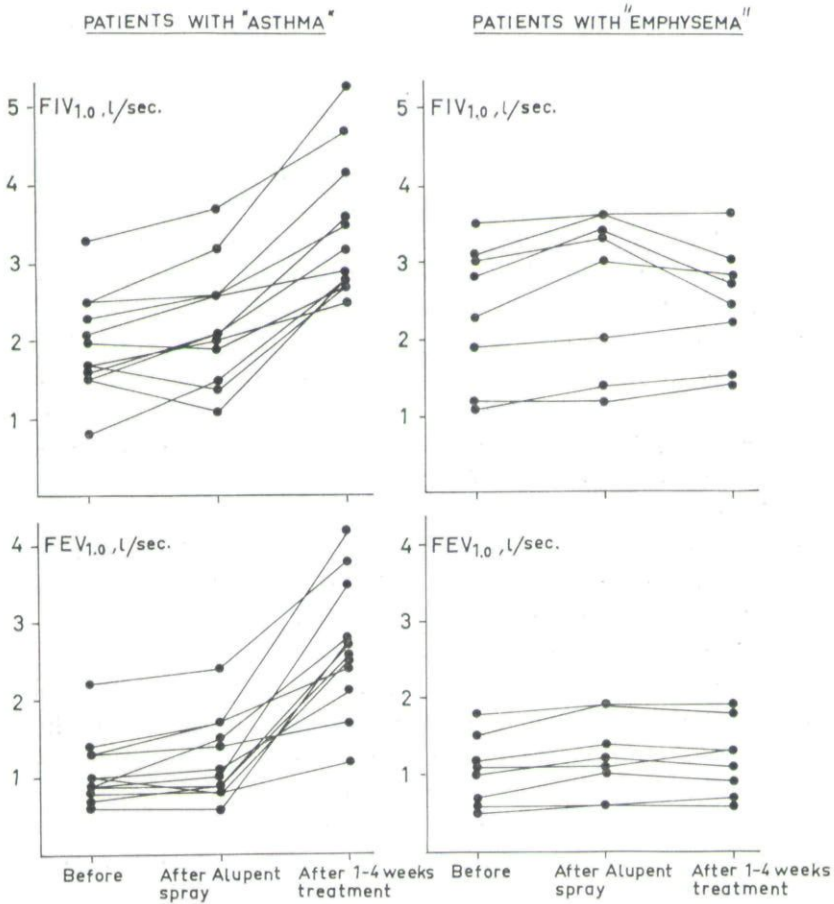


Fig. 4.

Patients who, according to the clinical assessment, belonged predominantly to the asthma or emphysema groups, although, after the initial inhalations, the expiratory flow (FEV_{1,0}) was not improved. After periods of treatment which varied in individual patients between 1 and 4 weeks, the FEV_{1,0} and FIV_{1,0} improved in the asthma but not in the emphysema group.

alupent produced almost the same results. Only in cases of severe asthma was the De Vilbiss spray preferable (additive effect of repeated small inhalations?).

The patients selected for long-term treatment received the usual symptomatics and corticosteroids during the treatment.

Cortisone was always administered by inhalation (dexamethasone phosphate). This treatment has been critically tested by us in the last two years on 57 patients with chronic asthma, emphysema, etc. (7).

In many cases this form of cortisone treatment is of value per se or as a complement to oral or parenteral steroid treatment. Our hope of reducing the daily dose of steroids through the local effect (inhalation) on the bronchial mucous membrane and thereby of avoiding the side effects of the oral steroid treatment was been fulfilled in several cases. Side effects in the form of increased susceptibility to bronchial infection—which we feared—could not be observed, as far as was indicated by repeated x-ray checks on the thorax, sedimentation-rate tests, analysis of sputum etc.

The patients selected for continuous treatment with steroids and prolonged observation were clinically assessed as follows:

1. Predominantly irreversible disorders of the emphysema type (no signs of allergy, no eosinophilia in blood or sputum, typical anamnesis, x-ray findings).
2. Predominantly reversible disorders of the bronchial asthma type. Cases were particularly selected in which the $FEV_{1,0}$ had not improved after a single inhalation of isoprenaline or alupent (measured with the Bernstein spirometer).

The asthma group showed good improvement after treatment with the bronchial spasmolytics and the dexamethasone inhalations.

In the emphysema group, when no improvement could be obtained cortisone was given per os: when necessary, this group was treated with antibiotics and in addition ACTH injections were administered. In spite of this massive therapy, no improvement observable in the respiratory flow occurred in these patients.

In many asthma patients a certain improvement in the inspiratory flow ($FIV_{1,0}$) could already be observed after the first use of alupent. We regard this as a sign of reversibility which could be recorded earlier on the inspiratory than on the expiratory flow.

DISCUSSION AND SUMMARY

An isoprenaline derivate "alupent" was shown after alternate inhalations in 15 asthmatic patients to have an effect on airflow comparabel to that of isoprenaline. The effect from alupent inhalation had a longer duration than isoprenaline. Used routinely in about 500 spirometric investigations alupent showed few side effects and no significant changes in pulse or blood pressure. In patients with reduced central blood volume, as for instance in emphysema, inhalations of vasoconstrictive drugs may possibly be disadvantageous. For that reason and also because of the risk for a postconstrictive reactive vasodilation the drug of choice theoretically should be one with bronchial spasmolysis but without or with little vasoconstrictive effect. Nevertheless it must be of importance to have the opportunity of using different drugs for inhalation therapy in order to avoid side effects.

Many patients are dependent on sprays though the objective effect is not measurable. In order to study the validity of the clinical diagnoses asthma and emphysema and to study in such cases the effect of alupent inhalations before and after long term treatment two groups of patients were investigated.

1) Patients in whom predominantly reversible changes of the asthma type had been diagnosed after clinical and allergological studies and 2) Patients in whom chronically irreversible disorders with emphysema predominated. All patients were examined before and during 1-3 weeks symptomatic treatment including ACTH and cortisone by measurements of the inspiratory and expiratory flow in the Bernstein spirometer. In the asthma group cases were selected which showed no improvement in $FEV_{1,0}$ at the first Bernstein examination after inhalation of isoprenaline or alupent. Cortisone was often used with advantage in the form of a dexamethasone spray. In spite of equivalent treatment in the asthma and emphysema groups, only a slight improvement in the airflow values occurred in the cases which showed a predominant emphysema from the clinical picture, in contrast to the cases of pre-

dominant asthma, in which a distinct improvement was to be noted. In many asthma cases it was possible to perceive reversibility in the inspiratory flow even at the first measurement.

In observing respiratory disease with eventual reversible features, repeated measurements of the respiratory flow and both the inspiratory and the expiratory flow are of value. The clinically assessed diagnoses asthma or emphysema could be confirmed with repeated studies after treatment.

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