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THE EFFECT ON THE PULMONARY VENTILATION OF DIFFERENT THEOPHYLLINE DERIVATIVES COMPARED TO ADRENALINE AND ISOPRENALINE

By

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In a previous paper (9) the plasma concentration of three different theophylline derivatives was studied following parenteral, oral and rectal administration. In connection with these studies the authors made the present observations in patients with bronchial asthma on the effect on the pulmonary ventilation after intravenous administration of these derivatives.

Comparable groups of patients were simultaneously studied after subcutaneously injected adrenaline, inhaled isoprenaline and for the comparison parenteral administration of a placebo. Further studies concerning the effects on the pulmonary circulation in patients with induced bronchial asthma after administration of adrenaline and theophylline-derivatives is to be published (7).

MATERIALS AND METHODS

Selection of Patients

162 patients of both sexes were observed. All of them had bronchial asthma (for definition see 3). The patients were selected with great care. The diagnosis had been established for several years, the course of the disease and the general effect of systematic treatment was well known for a long time. All

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patients were hospitalized and at the time these observations were made, in a "steady" asthmatic condition of moderate severity. The patients received no drugs 12 hours prior to the investigations. The patients were divided at random into six groups; one control group, which received placebo injections, and one group for each of the investigated drugs, (Aminophylline, β -hydroxypropyltheophylline, Dihydroxypropyltheophylline, Adrenaline and Isoprenaline). Pertinent data about the patients are seen in Tables 1 and 2. The groups are fully comparable, as there were only minor differences between them as regards sex distribution, age distribution, duration of asthmatic symptoms prior to these investigations, vital capacity, forced expiratory volume in one second and maximal voluntary ventilation at the time of study.

TABLE 1
Clinical Data

Drug group	Total No. of patients	Sex M/F	Age (in year)	Av. Range	Duration of asthma (in year)	Av. Range
T	29	16/13	48	22-73	14	2-32
HPT	48	27/21	47	17-65	18	4-36
DHPT	22	13/9	54	38-74	12	1-29
A	21	11/10	49	23-75	7	1-12
I	23	14/9	47	28-64	19	5-34
Placebo	19	10/9	51	15-67	10	1-21
Total material	162	91/71	49	15-75	14	1-36

For abbreviations see Text.

Dynamic Spirometry Methods

All injections, inhalations and the spirometric procedure were made by one well trained nurse. The spirometric studies were made during the morning hours, in order to avoid diurnal fluctuations (10). A "training" effect could be excluded as all patients previously on several occasions had been examined spirometrically and were familiar with the procedure. A slightly modified Bernstein spirometer was used in the same manner as was earlier described in the evaluation of normal subjects in this hospital (1, 2, 6). From the spiograms the vital capacity (VC), the forced expiratory volume in one second (FEV_{1.0}) and the maximum voluntary ventilation (MVV) were determined. The frequency in MVV was kept around 40 RPM ($m = 41$, range 32-55). The spirometric investigations were made before and after the administration of the drugs. Great care was taken to ensure perfect spiograms. 3-5 determina-

TABLE 2
Spirometric Data

Drug group	VC			FEV _{1.0}			MPV					
	Normal values			Normal values			Normal values					
	Mean	SD		Mean	SD		Mean	SD				
T	2.88	±0.89	3.96	±0.41	1.50	±0.66	2.88	±0.62	52	±22	122	±26
HPT	3.12	±1.03	3.94	±0.79	1.71	±0.77	2.93	±0.66	59	±24	124	±28
DHPT	3.02	±0.81	3.75	±0.66	1.66	±0.59	2.66	±0.57	58	±20	116	±18
A	2.56	±0.67	3.79	±0.62	1.25	±0.78	2.66	±0.81	47	±28	110	±30
I	2.90	±1.13	3.88	±0.61	1.52	±0.84	3.04	±0.76	59	±25	125	±32
Placebo	2.82	±0.56	3.96	±0.53	1.50	±0.50	2.92	±0.39	53	±15	121	±18

VC = vital capacity.

FEV_{1.0} = forced expiratory volume in one second.

MVV = maximal voluntary ventilation.

SD = standard deviation.

tions of $FEV_{1.0}$ were made and the best result of these were used. All volumes are given at ambient temperature and pressure, saturated (ATPS). As normal reference values, data from 1, 2, 6 were used.

Administration of Drugs

All the intravenously given drugs were diluted up to 10 ml and administered according to a previously planned scheme. Neither the nurse nor the patient did know if placebo or an active drug were administered.

1. *Aminophylline* (theophylline-ethylendiamine = T) was given intravenously. 250 mg (equivalent to 200 mg theophylline) was injected slowly for 3-4 minutes.
2. β -hydroxypropyltheophylline (HPT). 265 mg (equivalent to 200 mg theophylline) was injected exactly as aminophylline.
3. Dihydroxypropyl-theophylline (= DHPT) 282 mg (equivaleant to 200 mg theophylline) was injected exactly as aminophylline.
4. *Adrenaline* (= A) 0.5 cc of a 0.1 per cent solution (0.5 mg) was injected subcutaneously the injection was given at the rate of 0.1 cc per minute.
5. *Isoprenaline* (= I). The Medihalor riker was used. The patient was instructed to inhale deeply three times, each dose was 0.06 mg.
6. *Placebo* injection. 10 ml of a 0.9 per cent NaCl solution was injected intravenously exactly as aminophylline.

Repeated spiograms were made after the administration of the drug, starting with 3-5 forced expirograms in 10-15 minutes. Ten minutes later the MVV was measured.

Statistical Methods

Means and standard deviations of all spirometric data were calculated. The significance of the differences in the spirometric data before and after drug administration was analysed by means of t-test. The level of significance is $P < 0.05$.

RESULTS

The results are summarized in Table 3. It is seen that the correlation between $FEV_{1.0}$ and MVV before and after the administration of the different drugs is very good. The intravenous injection of physiological saline with double-blind technique had no effect on the parameters studied.

DHPT had no effect whatsoever on the pulmonary ventilation.

The experiments disclosed that HPT had a statistically

significant effect on $FEV_{1.0}$ and MVV but no effect on VC.

Aminophylline had a highly significant effect; VC increased by about 8 per cent, $FEV_{1.0}$ by about 17 and MVV by about 16 per cent.

The effects of isoprenaline inhalations and adrenaline injections were also highly significant and of about the same magnitude. VC increased by about 12 and MVV by about 28 per cent. $FEV_{1.0}$ increased by 38 per cent after adrenaline and 26 per cent after isoprenaline.

Adrenaline and isoprenaline gave significantly higher effects than the theophylline-derivatives studied.

DISCUSSION

The symptomatic treatment of the air-way obstruction in bronchial asthma is often multifaceted. Most of the drugs used have both advantages and drawbacks. For a great many years drugs belonging preferably to two different pharmacological groups have been used: the amines (*e.g.* ephedrine, adrenaline, isoprenaline), and the xanthines (*e.g.* theophylline, coffeine, theobromine). Their long and continuous use is indicative of their values but they also have well known side-effect.

In our clinical experience most patients definitely prefer intravenous administration of aminophylline to subcutaneous adrenaline injections or isoprenaline inhalations in the acute asthmatic attack. Our present results, however, indicate that both adrenaline and isoprenaline give a more pronounced effect on the pulmonary ventilation as compared to aminophylline and two closely related drugs. These findings correspond to the results given in another paper (7) which reported the effects of these drugs on the pulmonary ventilation and circulation in some other patients with induced air-way obstruction. We think it is understandable that most patients prefer aminophylline as the administration of adrenaline subcutaneously is often accompanied by a central excitation. As regards the inhalation of isoprenaline the possible effect of this is often highly reduced in severe asthmatic attacks because of

the deficient alveolar ventilation, which may cause difficulties with all types of inhalation (8). Thus in the choice of drug in bronchial asthma the patient usually prefers the drugs with the least drawbacks to the drugs with the most pronounced pharmacological effects.

Statistical data of the kind presented here must be interpreted with great care. For example Simonsson (11) in his extensive work on chronic bronchitis insists on changes of $FEV_{1.0}$ of more than ± 15 per cent before the values can be accepted as significant. If so, only A, I and T have an effect with the doses used in this study. It seems, however, justified to include HPT among this group, as there is a significant correlation between $FEV_{1.0}$ and MVV and because of the statistically significant difference between the results with this drug and the placebo. The absence of clinical effect when administering DHPT could be explained by the fact that this drug gives only about half the plasma concentration of theophylline compared to the other two derivatives if corresponding dosages were given (9). According to Turner-Warwick (12) the therapeutic effect is dependent on the plasma level achieved. According to some authors (4, 5,) the spirometric methods used could aggravate the air-way obstruction of the patients. According to our experiments with this material of patients with moderate obstruction and with the low resistance spirometer used, such aggravation is minimal. The results after placebo injections under double-blind conditions indicate that no significant effect could be recorded even after repeated $FEV_{1.0}$ and MVV.

SUMMARY

162 hospitalized patients with chronic moderate bronchial asthma were selected for study and divided into comparable groups. The pulmonary ventilation was studied with dynamic spirometry before and after the administration of 5 different drugs and placebo.

The most pronounced effect was found after adrenaline

given subcutaneously and after isoprenaline by inhalation. Significant effect was also seen after two of the theophylline-derivatives studied: Aminophylline and β -hydroxypropyl-theophylline in corresponding dosage. Dihydroxypropyltheophylline and the placebo had no effect on the pulmonary ventilation.

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