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DICHLORPHENAMIDE IN EMPHYSEMA AND CHRONIC BRONCHIAL ASTHMA

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In the treatment of emphysema partial improvement of lung function can usually be achieved, although the therapeutic possibilities in emphysema are limited. This shows that the impairment of ventilation is not fully irreversible. In the following study we have investigated the effect of the carbonic anhydrase inhibitor dichlorphenamide (dph) on lung function and exercise tolerance in emphysematous states.

METHODS

As a preliminary trial, 46 mostly elderly patients suffering from emphysema or from chronic asthma were given dichlorphenamide (dph), either 100 mg in the morning or 100 b.d. They were asked to continue their other antiasthmatic medication and to report back after 2 weeks. About one third of the patients felt that their breathlessness on exertion had been less while taking the tablets; the others did not notice any change. Some of those who thought they had improved were then changed to placebo tablets. Of these a few thought they were worse again, whilst in others the initial improvement persisted.

The result of this preliminary trial was regarded as equivocal, and since some of the patients had been very emphatic about their improvement, it was decided to study the effect of dph with objective methods.

Besides 13 patients who had reported improvement in the preliminary trial, 22 others were selected. These 35 patients were either typical chronic asthmatics (20), that is their illness had, at an early stage, caused typical nocturnal attacks, or they had a history of emphysema, starting with dyspnoea on exercise, which gradually increased and was complicated by cough (15). In the second type of case unprovoked attacks of dyspnoea typical of asthma were absent until many years after the onset. Patients with cor pulmonale in congestive failure were excluded, for such cases had not improved during the preliminary trial. We were

not able to distinguish the two types of patients except by their history. Also, we could not determine the degree of irreversible emphysema in either group.

17 patients received 50, 100 or 150 mg of dph or a placebo of the same appearance and taste in the morning or in the early afternoon. Some patients also received dph in daily doses from 50 mg to 200 mg for periods of one to several weeks, followed by pauses of similar duration, or followed by periods on placebo tablets. The lung function of the patients was studied by the recorded vital capacity (v.c.) in ml and the peak flow (p.f.) in l/min. These methods have been recently shown to be adequate (*Herxheimer, 1963*). They have, however, limitations when used for positive drug effects, as a normal v.c. or p.f. cannot be improved. An improvement can therefore be measured only when v.c. or p.f. are subnormal. When they approach normal, the improvement gradually becomes smaller and, eventually, nil. In our experiments a greater improvement was to be expected the more reduced the initial v.c. and p.f. were. The v.c. and p.f. were recorded after dph hourly for up to 7 hr and, in some cases, on the following morning. In some of the patients who received daily doses of dph for one to several weeks, these measurements were continued for several mornings after dph had been omitted. The v.c. and the p.f. were determined three or more times at each occasion. The mean of the 3 highest v.c.'s and the highest p.f. were used, but in a few patients v.c. values more than 150 cc below the highest value were omitted when calculating the mean. All patients were carefully trained in the performance of the tests before the experiment was begun, so that a later effect of training could be excluded. In spite of this, not all patients achieved stable results with the p.f.

Placebo experiments were done in exactly the same way as the ordinary experiments. They usually followed the dph experiments. A considerable number of placebo reactors were found, namely 11 out of a total of 35. In some patients arterial pH, buffer base, arterial CO₂ concentration and O₂ saturation were determined by standard methods before and under the influence of dph. In order to study the combined effect of ephedrine and dph, ephedrine (50 or 100 mg) was given in a small number of patients at least one hr before dph, and the lung function recorded after its effect had become evident.

RESULTS

Single doses of dph considerably increased v.c. and p.f. The percentage increases have been statistically evaluated and are presented in Table 1 and Fig. 1. Table 2 contains the percentage increases of v.c. and p.f. in the placebo experiments of those 17 patients who had a much greater effect from dph than from placebo. Table 1 shows the dph effect in the same patients after subtraction of the placebo effect. It will be seen that in the v.c. of these patients a small but significant positive

TABLE 1

*Percentage increase of v.c. and p.f. after 50, 100 and 150 mg dph
after subtraction of placebo effect.*

Vital capacity				Peak flow			
Dose: 50 mg		100 mg	150 mg	Dose: 50 mg		100 mg	150 mg
$\bar{x}$	8.8	12.8	13.0	$\bar{x}$	13.0	9.7	11.8
n		17		n		17	
ϵ	1.8	2.3	2.2	ϵ	3.2	2.2	3.4
P	<0.01	<0.01	<0.01	P	<0.01	<0.01	<0.01
P_d	$\uparrow$ <0.001	$\uparrow\uparrow$ >0.45	$\uparrow$	P_d	$\uparrow$ >0.3	$\uparrow\uparrow$ >0.3	$\uparrow$

$\bar{x}$ = mean increase in per cent of basal value.

n = number of patients.

e = standard error.

P = level of statistical significance.

P_d = level of statistical significance of differences between individual increases.

TABLE 2

*Percentage increase of v.c. and p.f. of the same patients as in Table 1
after placebo alone.*

Vital capacity		Peak flow	
$\bar{x}$	3.0	$\bar{x}$	6.9
n	17	n	17
e	0.75	e	2.5
P	<0.0025	P	<0.01

TABLE 3

Percentage increase of v.c. and p.f. in 11 placebo reactors after placebo.

Vital capacity		Peak flow	
$\bar{x}$	16.0	$\bar{x}$	20.6
n	11	n	11
e	1.8	e	1.5
P	<0.01	P	<0.01

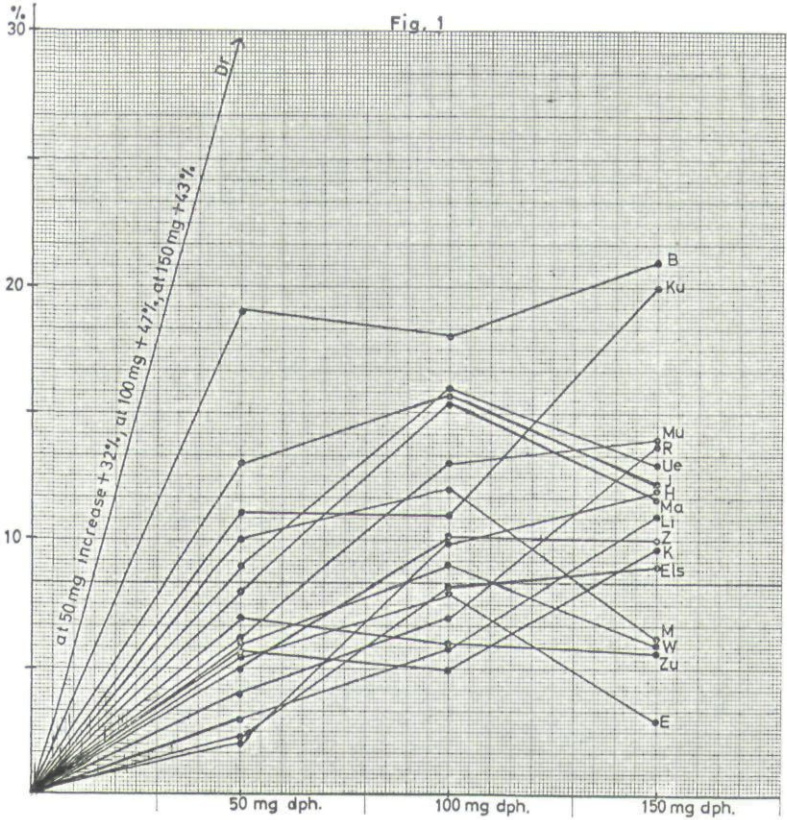


Fig. 1.

Percentage increase (ordinate) of v.c. in 17 patients after 50, 100 and 150 mg dph (abscissa). Placebo values have been subtracted.

placebo effect is present. Nevertheless the effect of dph is much higher and statistically significant. It increases with 50 mg dph by 8.8 per cent and with 100 mg again significantly by 12.8 per cent. There is no further increase with 150 mg. With the p.f. there is no dose-response relationship, but a significant increase with all three doses. The scatter is considerable, and there is no significant difference between the three doses. Table 3 shows the placebo effect in the 11 placebo reactors, and it will be seen that the mean increase is about the same as in the 17 other patients, if their placebo effect (average 3 per cent) is added.

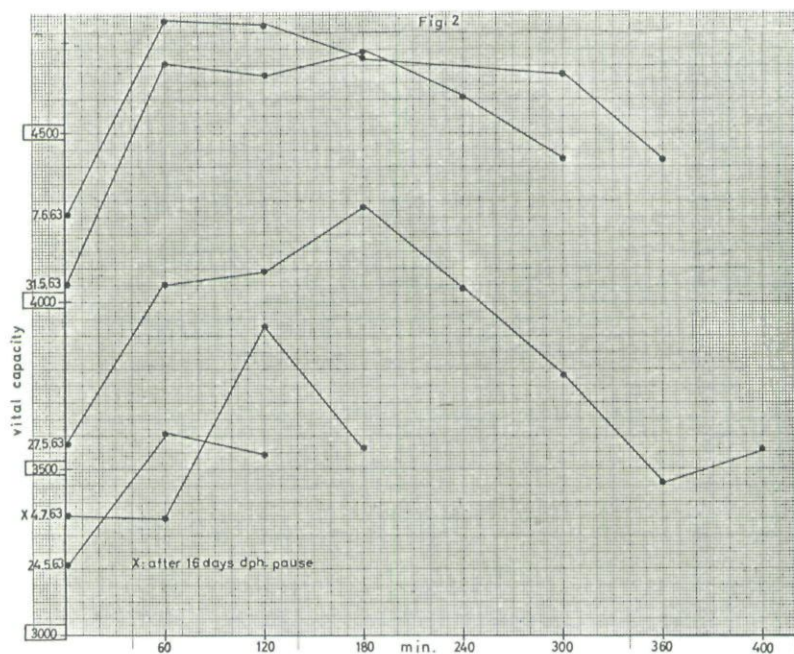


Fig. 2.

Pat. M. Effect of daily administration of 200 mg dph on the v.c. over two weeks. It will be seen that the peak effect is reached between the first and third hour, and that the basal v.c. steadily increases during the 2 weeks. When dph was omitted for 16 days, the basal v.c. fell again. (Ordinate: v.c. and dates of experiments. Abscissa: time in min. of the single experiments).

The dph effect sometimes began within the first hr but reached its peak in most cases after 3 hr, as shown in two representative experiments (Fig. 2 and 3). In some cases (4 out of 8) its effect was at least partly present the following morning (Table 4). With continuing daily doses of dph the basal v.c. began to increase and gradually reached surprisingly high values within 1-2 weeks. This is shown in the v.c. of the patients plotted in Fig. 2 and 3 and in Table 5. This high v.c. persisted for some time when dph was omitted, and fell only gradually, as a rule within 4-7 days, to its original value (Table 5).

With the objective improvement of the lung function, the

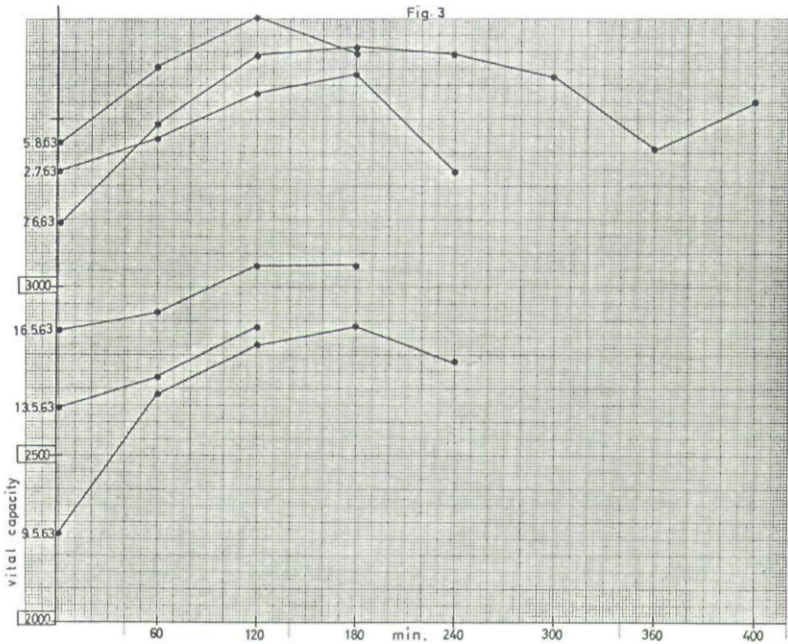


Fig. 3.

Pat. E. Experiment as in Fig. 2. The patient received 50 to 200 mg dph daily during the period from 9.5.1963 to 5.8.1963.

general wellbeing of the patients and their exercise tolerance improved. It seemed also that the cough improved, although this is only an impression. Two examples were particularly striking. One was a greengrocer aged 65 yrs who had had symptoms and signs of emphysema for 4 yrs. He could not handle his vegetables and at the same time talk to his customers as he was too breathless. His v.c. increased from 3.200 to 4.835 ml under treatment, and he could do a full day's work in his shop without any restrictions. The other patient was a man of 55 yrs with a long history of emphysema, severe breathlessness at the slightest movement and cyanosis. There were signs of cor pulmonale but he was not in failure. At the start of the treatment, he had to be brought from the ward to the laboratory in a wheelchair. After one week, he was able to walk back the 500 yards slowly but unaided. His v.c. had in-

TABLE 4

*Effect of 100 mg dph on v.c. and p.f. after 2-4 hr and 24 hr
(subj. K. 50 mg only).*

Pat.	Basal v. c. basal p. f.	v. c. p. f. % increase after 2-4 hr.	v. c. p. f. % change after 24 hr.
Ue.	2665 130	+ 22 + 22	+ 3 ± 0
L.	2040 115	+ 19 + 21	+ 17 + 20
M.	2900 230	+ 15 + 22	+ 3 + 17
Z.	3125 115	+ 26 + 48	+ 25 + 4
E.	3035 130	+ 14 + 7	+ 5 - 16
Els.	2840 160	+ 12 + 6	+ 4 + 3
K.	2315 120	+ 11 + 25	+ 6 - 12
Dr.	2050 105	+ 47 + 29	+ 11 + 10

creased from 1.400 to 2.600 ml. After another week on placebo tablets he gradually relapsed and complained of more severe dyspnoea and his v.c. fell to 2.150 ml. He maintained, however, that he was still better than before treatment was started. When the placebo treatment was replaced by dph, he quickly improved again.

The side effects we have seen consisted mainly of pins and needles in hands and feet, a symptom frequently seen in alkalosis. As this symptom has also been observed after acetazolamide it is very likely to be related to the loss of CO₂. Most patients found this side effect tolerable, and they were en-

TABLE 5

Vital capacities and peak flow before dichlorphenamide, after a period of daily dichlorphenamide (1×50 — 2×100 mg) and some time after omission.

Pat.	Age	Sex	Before treatment v. c. / p. f.	After continuous daily dph. v. c. / p. f.	After omission of dph v. c. / p. f.
Ell.	59	♂	2265 / 95	3475 / 125 (46)	2675 / 115 (9)
Zu.	64	♂	3345 / 170	4055 / 260 (27)	3115 / 125 (20)
Els.	66	♂	2840 / 160	3335 / 160 (54)	2825 / 145 (22)
H.	39	♀	2095 / 90	2555 / 165 (15)	1940 / 95 (2)
W.	60	♀	1820 / 60	2635 / 90 (10)	2315 / 50 (6)
L.	51	♂	2040 / 115	2560 / 150 (45)	2260 / 150 (4)
Mu.	56	♂	3275 / 125	3765 / 135 (35)	3145 / 105 (7)
R.	64	♂	2870 / 130	3545 / 140 (41)	2945 / 120 (10)
Me.	68	♂	3210 / 125	4260 / 135 (44)	3365 / 100 (20)
Ue.	61	♂	2400 / 120	2950 / 125 (38)	2790 / 150 (25)
Zie.	53	♂	3125 / 115	4120 / 220 (7)	3440 / 135 (8)
Li.	64	♂	1860 / 150	2450 / 190 (7)	1950 / 135 (15)

The figures in brackets give the length in days of the proceeding period without dph.

couraged in this view. Two patients complained of general malaise and weakness, and in them the drug was discontinued. In one patient tolerance developed and in three others no effect of dph was seen.

Marked diuresis was noticed only in two patients, and in those only initially. When ephedrine was given before dph, the v.c. increased as expected. When now at the peak of the ephedrine effect which, from previous experience, was assumed to be reached after 60 min., dph was given, a further increase of v.c. occurred (Table 6). Isoprenaline aerosol (2 per cent) also increased the v.c. after dph, if the individual maximum v.c. had not been reached before.

TABLE 6
Combined effects of ephedrine and dichlorphenamide.

Pat.	Basal v. c.	Dose of ephedrine	v. c.	Dose of dph.	v. c.
	basal p. f.		p. f. after 60 min. (increase in %)		after 2-4 hr. (further increase in % of basal value)
R.	2870	50 mg	3000 + 5	150 mg	3235 + 13
	130		135 + 4		135 + 4
Els.	2935	100 mg	3245 + 11	100 mg	3395 + 12
	145		150 + 3		175 + 20
Zu.	3640	100 mg	3605 ± 0	100 mg	3945 + 8
	175		180 + 3		190 + 9
	3560	100 mg	3640 + 2	150 mg	3875 + 8
	170		215 + 26		200 + 18
Mi.	2345	50 mg	2895 + 23	100 mg	3350 + 43
	170		230 + 35		280 + 65
K.	3495	50 mg	3670 + 5	100 mg	3950 + 13
	130		135 + 4		155 + 20
Jae.	1705	100 mg	1840 + 8	75 mg	2100 + 23
	85		60 — 29		85 ± 0
Bl.	935	75 mg	1390 + 48	50 mg	1610 + 61
	75		70 — 7		70 — 7

The results of the metabolic investigations are shown in Table 7. The pH decreased in all patients under dph, in some slightly. CO₂ concentration and bufferbase fell sharply, as expected; O₂ saturation varied little, except in one case.

DISCUSSION

Dph has been known since 1958 (*Thompson, Richardson & Wingo*) and has been studied by numerous authors since 1960. Most of them have investigated the metabolic action of dph and its action as carbonic anhydrase inhibitor. Some of these

TABLE 7
*Arterial pH and blood gas values in 7 patients before and after 7 days
 of 150 mg dph daily in 2 divided doses.*

Pat.	pH		CO ₂ concentration vol. %		Buffer base mEq		Art. O ₂ saturation in %	
	Dph. before after		Dph. before after		Dph. before after		Dph. before after	
We.	7.440	7.352	51.30	38.30	48.0	41.6	96	93
Zu.	7.455	7.341	48.23	41.85	49.9	43.0	93	92
Blu.	7.360	7.290	50.90	42.9	47.9	42.5	92	84.5*
Li.	7.360	7.312	52.4	43.2	48.0	43.5	89	90
Dr.	7.420	7.310	47.57	34.40	46.7	39.0	97	95
Jae.	7.410	7.304	47.8	36.33	48.2	41.9	91	92
Me.	7.300	7.299	41.44	36.9	42.4	40.0	94	93

* This value is possibly erroneous.

authors seem more concerned with the action of the substance against the metabolic acidosis than with the lung function of the patients (*Sadoul, Robert, Saunier, Pham & Lacoste, 1962*). Some of them note the increased effort tolerance, greater feeling of wellbeing or less dyspnoea (*Ahuja, 1961, Christensen, 1962, Mann, 1963*). These authors report such improvement in altogether 34 of 60 patients. *Simpson (1961 and 1962)* has stressed the great symptomatic improvement. He found a general increase of the FEV₁ by 25 per cent, whilst the cCO₂ fell by 5–15 vol. per cent. *Naimark, Brodovsky & Cherniack (1960)* also studied lung function, but their results were less spectacular. They noted improved effort tolerance in all but one patient.

In our investigations we have taken the metabolic action of dph for granted, as it has been confirmed by many authors, and concentrated our attention on the objective and subjective improvement of lung function. In many patients the subjective improvement was of a degree which could not have been achieved by any other means at our disposal, but in some it was less than could have been expected from the increase in lung function. The great advantage of the drug in the many positive cases was its long duration of action which may last

up to 24 hr, and the persistence of the improvement for several days after omission of the drug.

A high percentage of objective improvements has also been described by *Simpson* (1961, 1962), *Thompson* (1961) and *Mann* (1963). Our series seems so far to be the largest series in which the drug has been tried systematically, and our results confirm the findings of these authors. Compared with the result of our preliminary trial, in whom only one third of the patients reported improvement, our present results appear more favourable. The explanation of this discrepancy is that we have not taken into the definite trial patients who in the preliminary trial were sure that the tablets did not help them. Thus in the first 13 subjects in the definite trial a positive result could be expected. The later additions had no preliminary trial but were selected on their history, which was that of uncomplicated chronic emphysema or chronic bronchial asthma. Our favourable result can therefore be attributed to the type of patient we have used. It is interesting to note that the percentage of placebo reactors was about 31 per cent, about the same as has been reported in other blind trials (*Beecher*, 1955).

Only those 11 patients who had pronounced placebo reactions were termed placebo reactors, and we have not used them in dose-response investigations. Of our 17 other patients, whose positive response we have described in detail, 7 showed not the slightest placebo reaction. The remaining 10 had mild placebo reactions with a v.c. increase between 2 per cent and 9 per cent. In these 10 patients the dph effect was much higher than the placebo effect, and we have, therefore, used these patients in our dose-response investigations. In these patients we have subtracted the placebo effect from the dph effect in our evaluation. This should represent the genuine drug effect.

We were surprised at the degree of improvement in lung function in the placebo reactors which sometimes even exceeded the improvement in the other patients. It may be that a purely suggestive factor has been involved in the "placebo" reaction because of a technical fault in the arrangement of our experi-

ments. In most of the placebo reactors the dph was given at first, producing improvement, and the placebo on a later day. It could be possible that in these patients a genuinely positive dph effect in the first experiment has acted as a suggestive factor and thus increased the placebo effect in the subsequent experiment.

In some typical placebo reactors a positive long term effect of dph was noted. If they were given placebo tablets for one or two weeks, they reported improvement for the first week but then they reported increasing complaints, and their lung function deteriorated. When, at this point, placebo was replaced by dph, subjective and objective improvement returned. Thus it seems that the placebo effect cannot be maintained for long periods but can only be reproduced for short intervals.

The great scatter of the peak flow values has been disappointing. It confirms our view (*Stresemann*, 1963) that this method is difficult to use in patients, who cannot be trained successfully in its practice. In our patients the individual values varied a great deal. This individual variation naturally lead to the great scatter described in Tables 1-3 and this is probably the reason why a dose-response relationship cannot be shown in our peak flow values.

We cannot explain the effect of dph on lung function. As *Naimark et al.* (1960) have pointed out, it may have a dual action, on the kidneys and on the respiratory centre, but its mode of action is unknown. We think that our results justify its use in carefully selected patients with emphysema or chronic asthma, without cor pulmonale. As an average starting dose we suggest 100-150 mg/day in two equal doses. If possible, lung function should be assessed by a simple test before and after 3-4 hr. When ephedrine is used in addition, there would be a fair chance of lasting improvement with this regime. We are convinced that the use of dph promises real therapeutic progress in patients in whom poor exercise tolerance has been the main complaint.

SUMMARY

1. In a single blind study the carbonic anhydrase inhibitor dichlorphenamide increased vital capacity and peak flow in many patients with emphysema and chronic bronchial asthma.
2. The exercise tolerance of these patients also improved, and this improvement lasted for 4-7 days after the drug had been discontinued.
3. Tolerance developed in one patient, and in 3 of a total of 35 patients investigated no effect of dichlorphenamide was seen. In 2 patients the drug was omitted because of side effects. 11 patients were placebo reactors.
4. The antiasthmatic effect of ephedrine and isoprenaline was independent of, that is, additive to the effect of dichlorphenamide.
5. A frequent side effect was paraesthesiae in hands and feet.

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