After subtraction of individual baseline levels the data on urinary 17-OCS (Fig. 6) show a similar response after 0.25 mg. of depot tetracosactrin to that after 50 units of corticotrophin gel, the higher doses of the synthetic preparation again producing a more sustained effect.

Clinical Observations

Reactions with subcutaneous administration of both preparations were not infrequent, occurring in 5 of the 12 cases following depot tetracosactrin and in 2 of 12 cases after corticotrophin gel. In every case reactions took the form of local erythema and pruritus lasting from a few hours to about two days. None was severe. In one instance corticotrophin gel was subsequently continued long-term without difficulty.

The effect of both preparations on disease manifestations did not appear to differ one from the other, apart from duration of response. There is a wide variability of dose-response among individuals to long-acting corticotrophin, so that the numbers in this series are too few to draw significant conclusions regarding the clinical dose relationship between the two preparations. Nevertheless, in every instance in which a significant clinical response to both injections occurred, that following depot tetracosactrin was sustained longer than that following corticotrophin gel.

Discussion

In terms of maximum plasma cortisol concentration Besser *et al.* (1967) concluded that 1 mg. of the synthetic preparation is equivalent to about 80 units of corticotrophin gel, both doses stimulating the adrenal glands maximally, but that the gel must be given twice daily and depot tetracosactrin once daily to maintain stimulation. There can be little doubt that the latter substance has a distinctly greater duration of action. In a dose of 1 mg. adrenal stimulation lasts 48 hours, implying that, in this dosage at least, injections every two days should suffice. In regard to the relative degree of adrenal stimulation, our results suggest that 0.25 mg. of depot tetracosactrin is equivalent to about 50 units of corticotrophin gel by the subcutaneous route.

It is open to question whether the prolonged action of depot tetracosactrin will prove to be an advantage in long-term corticotrophin therapy. Nichols *et al.* (1965) have shown that

corticosteroids administered at night cause a significantly longer suppression of pituitary-adrenal response than administration earlier in the day. There is some evidence (Jasani *et al.*, 1968) that maintenance of the diurnal rhythm of plasma corticosteroid levels is an important factor in retaining normal pituitary-adrenal response.

Clinically, local reactions to depot synthetic corticotrophin may be a problem. Within the very limited experience of this trial erythema and skin irritation were appreciably more frequent with depot tetracosactrin than with gel. No doubt local reactions would be less frequent with intramuscular injection. Such reactions are not to be confused with inactivation of the hormone by antibody formation, which is most unlikely to tetracosactrin (Felber *et al.*, 1966).

In conclusion, it seems fair to state that depot tetracosactrin has a very real place in medical investigation and therapeutics in view of its potency and the convenience of its prolonged action. From these aspects it could replace the use of animal corticotrophin gel. The incidence of local reactions, however, may prove troublesome, and its obliterative effect on the diurnal rhythm of cortisol production is a theoretical disadvantage in long-term therapy.

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Preliminary Communications

Effect on Airways Resistance of Prostaglandin E₁ Given by Aerosol to Healthy and Asthmatic Volunteers

British Medical Journal, 1969, **4**, 723-726

Summary: The forced expiratory volume in one second (F.E.V.₁) was measured in healthy and asthmatic volunteers and the inhalation of prostaglandin E₁ (PGE₁) was compared with that of isoprenaline, using metered aerosols.

In healthy volunteers PGE₁, either as the free acid or the neutral triethanolamine salt, did not affect the F.E.V.₁; the free acid was irritant to the upper respiratory tract. In five out of six asthmatic volunteers with reversible airways obstruction, inhalation of 55 µg of

PGE₁ (triethanolamine salt) produced an increase in F.E.V.₁ comparable in both degree and duration to that produced by an inhalation of 550 µg. of isoprenaline sulphate.

Though the triethanolamine salt was well tolerated in most of the asthmatic subjects studied, in one asthmatic subject this preparation caused coughing and there was a progressive reduction in the F.E.V.₁ associated with bronchospasm.

INTRODUCTION

The prostaglandins have been intensely studied since 1962, when the chemical structure of the first member of this group of naturally occurring fatty acids was determined (Bergström, Ryhage, Samuelsson, and Sjöwall, 1962). Of their pharmaco-

logical properties (Bergström, Carlson, and Weeks, 1968) the effects on bronchial smooth muscle have until recently received little attention. Main (1964) showed that prostaglandin E₁ (PGE₁) relaxes isolated tracheal smooth muscle of the guinea-pig, and Sweatman and Collier (1968) demonstrated that this prostaglandin relaxes isolated human bronchial muscle.

PGE₁ and isoprenaline have similar bronchodilator activity when injected intravenously in anaesthetized guinea-pigs, but when given by aerosol PGE₁ is 10 to 100 times more active than isoprenaline (Large, Leswell, and Maxwell, 1969). The bronchodilator effect of PGE₁ was not antagonized by propranolol, a β -adrenergic receptor blocker. These workers found that in the anaesthetized monkey PGE₁ and isoprenaline had no bronchodilator activity when given by aerosol or intravenously.

In the present study the effects of the inhalation of PGE₁ on timed forced expiratory volume has been determined in normal and asthmatic volunteers.

METHODS

All measurements were made with the subject seated. The forced expiratory volume in one second (F.E.V.₁) was measured by a Vitalograph and the blood pressure was measured by a modified mercury sphygmomanometer (Garrow, 1963; Dunne, 1969). The electrocardiogram was monitored continuously and displayed on a large oscilloscope. F.E.V.₁, blood pressure, and pulse rate were taken in duplicate at intervals of not more than 10 minutes and the means calculated.

Healthy Volunteers.—Six healthy volunteers were studied (Table I). None had any history of bronchial asthma.

TABLE I.—Details of Normal Volunteers

No.	Sex	Age	Weight		Vital Capacity (l.)	F.E.V. ₁ (l.)	Current Treatment
			lb.	kg.			
3	M	39	149	67.6	5.5	4.4	None
	M	30	141	64.0	4.5	3.1	None
	M	33	161	73.0	4.9	3.9	None
4	F	29	128	58.1	4.0	3.8	None
5	M	36	178	80.7	4.4	3.9	None
6	M	51	186	84.4	5.3	3.6	None

Asthmatic Volunteers.—Eight asthmatic volunteers were studied (Table II). None of the subjects used a bronchodilator aerosol within four hours of the beginning of an experiment. Oral corticosteroids were taken as usual by Subjects 7 and 11, but otherwise bronchodilator drugs were withheld on the day of the experiment.

TABLE II.—Details of Asthmatic Volunteers

No.	Sex and Age	Weight		Duration of Symptoms (Years)	Vital Capacity (l.)	F.E.V. ₁ (l.)	Current Treatment
		lb.	kg.				
7	M 36	150	68.0	32	2.8	1.2	Oral corticosteroids. Carbimazole. Medihaler Iso aerosol
8	M 22	154	69.9	16	4.8	2.6	Salbutamol aerosol
9	M 22	178	80.7	11	5.8	3.5	Medihaler Iso aerosol
10	F 49	128	58.1	33	2.3	1.2	Frano-Plus tablets. Atropine and isoprenaline aerosol
11	F 28	94	42.6	27	2.4	1.1-1.5	Oral corticosteroids. Frano-Plus tablets. Iso-Brovon aerosol
12	M 26	178	80.7	23	5.5	3.7	Medihaler Iso aerosol
13	F 27	112	51.0	23	1.2	0.5	Isoprenaline and atropine methonitrate aerosol. Oral contraceptives
14	F 51	108	49.0	16	2.2	1.0	Orciprenaline aerosol

All volunteers, both healthy and asthmatic, were persons who by their intelligence and training were able to appreciate the nature of the experiments.

Drugs.—All formulations were supplied in PVC-coated glass bottles of identical appearance fitted with aerosol metering

valves. Metered doses (55 μ l.) consisted of the active principle dissolved in ethyl alcohol, dichlorotetrafluoroethane and dichlorodifluoromethane. PGE₁ was supplied as the free acid and as the triethanolamine salt in concentrations of 0.005, 0.05, and 0.5 mg./ml., delivering single metered doses of 0.275, 2.75, and 27.5 μ g. Isoprenaline sulphate was supplied in a concentration of 5 mg./ml. delivering a dose of 275 μ g. A placebo was also supplied containing only ethyl alcohol and inert propellants.

RESULTS

HEALTHY VOLUNTEERS

Graded doses of PGE₁ (free acid) in the range 0.275–27.5 μ g. were given to all six subjects. There was no change in the F.E.V.₁ or blood pressure following the inhalation, though all three subjects who received 27.5 μ g. noticed slight irritation of the upper respiratory tract.

In five of the six subjects a comparison was made between PGE₁ (free acid) 55 μ g., isoprenaline sulphate 550 μ g., and placebo. The treatments were administered blind according to an incomplete Latin square. The block consisted of all possible combinations of three treatments allocated randomly. The F.E.V.₁ was unaltered by the inhalation of isoprenaline or placebo, and there was no change in the blood pressure or pulse rate in any of the subjects. Neither inhalation produced any irritation of the upper respiratory tract. After inhalation of the PGE₁ aerosol there was no alteration in the F.E.V.₁, but all five subjects experienced some irritation in the throat and coughed immediately after the inhalation and in the subsequent 5 to 10 minutes. This was associated with an increase of pulse rate of between 10 and 30 beats/minutes and the systolic blood pressure was raised 15 and 19 mm. respectively in two subjects. The diastolic pressures were unchanged and there was no alteration in systolic or diastolic pressures in the other subjects.

The study was repeated with 55 μ g. of the neutral triethanolamine salt of PGE₁. No change in F.E.V.₁ was seen following the inhalation of the triethanolamine salt, and only three of the five subjects noted any irritation of the upper respiratory tract. In two of these the changes in pulse rate and blood pressure were similar to those noted with the free acid; in the third subject there was an increase in pulse rate but no change in blood pressure.

It was therefore decided to use the triethanolamine salt of PGE₁ in studies on asthmatic volunteers.

ASTHMATIC VOLUNTEERS

In preliminary studies six of the eight asthmatic volunteers (Nos. 7–12) were shown to have reversible airways obstruction. Doses of PGE₁ (triethanolamine salt) in the range 2.75 to 27.5 μ g. were given by inhalation to all eight subjects. In most of them there was a 20 to 40% increase in F.E.V.₁, and the total duration of the effect was 15 to 35 minutes. Subjects 13 and 14, who had irreversible airways obstruction, had no change in F.E.V.₁ following the inhalation of 5.5 μ g. Subject 12 found the inhalation of 5.5 μ g. to be irritant and there was a progressive fall in F.E.V.₁, which is referred to below.

COMPARISON OF PGE₁ AND ISOPRENALINE

A comparison was made between PGE₁ (triethanolamine salt) 55 μ g., isoprenaline sulphate 550 μ g., and placebo in five asthmatic subjects (Nos. 7–11). The treatments were administered blind according to the same Latin square, except that

the treatments were re-randomized. The results are shown in Fig. 1 and Table III. In all of the subjects the inhalation of PGE₁ caused an increase in F.E.V.₁ which was comparable in degree and duration to that of isoprenaline. There was no change in the blood pressure, pulse rate, or electrocardiogram in any of the subjects.

FIG. 1.—Record of the changes in F.E.V.₁ in five asthmatic subjects following the inhalation of PGE₁ (triethanolamine salt) 55 µg. (○) and isoprenaline sulphate 550 µg. (●) by metered aerosol. Means and standard error of means are shown. Shaded area represents mean changes in F.E.V.₁ after administration of placebo aerosol ± standard error of mean.

The effect of PGE₁ appeared less rapidly than that of isoprenaline. The effect of isoprenaline was maximal at 3 minutes in four of the five asthmatic subjects. In contrast, PGE₁ produced its maximal effect some 30 minutes after the inhalation, and though F.E.V.₁ levels were maintained for a longer period there appeared to be little difference in the overall duration of the two preparations.

One asthmatic subject (No. 7) received repeated inhalations of 5.5 µg. of PGE₁ (triethanolamine salt) at about 90-minute intervals (five doses). The changes in the F.E.V.₁ were comparable on each occasion and there was no evidence of tachyphylaxis.

TABLE III.—Comparison of Effect of PGE₁ 55 µg. (Triethanolamine Salt) and Isoprenaline 550 µg. on F.E.V.₁ after Aerosol Administration. The F.E.V.₁ Before Inhalation is the Mean of Three Paired Readings Taken at Five-minute Intervals

No.	Isoprenaline 550 µg.					Prostaglandin E ₁ 55 µg.				
	F.E.V. ₁ Before Inhalation	Max. F.E.V. ₁ After Inhalation	Time Max. Effect (min.)	Maximum % Increase	Total Duration Effect (min.)	F.E.V. ₁ Before Inhalation	Max. F.E.V. ₁ After Inhalation	Time Max. Effect (min.)	Maximum % Increase	Total Duration Effect (min.)
7	1.16	1.54	3	33	90	1.23	1.61	13	30	95
8	2.54	3.03	3	19	70	2.68	3.08	13	15	70
9	3.53	3.8	3	7.5	80	3.46	3.9	38	12.5	100
10	1.29	1.65	25	28	130	1.09	1.65	53	51.5	115
11	1.09	1.28	3	17.5	55	1.54	1.71	13	11	50

LOCAL TOLERANCE

In the studies in asthmatic volunteers slight irritation of the upper respiratory tract was noted with 55 µg. of PGE₁ (triethanolamine salt) by Subjects 10 and 13, but this did not result in any change in the blood pressure or pulse rate. Subject 12, who had previously been shown to have reversible airways obstruction, experienced irritation in the throat and

coughed following the inhalation of 5.5 µg. of PGE₁ (triethanolamine salt). This was associated with a progressive reduction in F.E.V.₁ (Fig. 2); wheezing and bronchospasm were evident when the F.E.V.₁ had fallen to 2.3 l. There was no change in the blood pressure, but the pulse rate was raised 10 beats/minute for 60 minutes. The attack was readily reversed by the inhalation of isoprenaline. The inhalation of PGE₁ (triethanolamine salt) did not cause irritation of the upper respiratory tract in any of the other asthmatic volunteers.

FIG. 2.—Record of the F.E.V.₁ in one asthmatic subject (No. 12) following the administration of PGE₁ (triethanolamine salt) 5.5 µg. (▲), isoprenaline sulphate 550 µg. (○), and placebo (---) by aerosol. At each of the arrows on the right of the figure one inhalation of isoprenaline (275 µg.) was given.

DISCUSSION

Human bronchial smooth muscle is relaxed by PGE₁ and PGE₂ in vitro but contracted by PGF_{2α} (Main, 1964; Sweatman and Collier, 1968), and PGE₁ and PGF_{2α} have been identified in human lung (Änggård, 1965; Karim, Sandler, and Williams, 1967). The function of the prostaglandins in the lung and their relationship to bronchial asthma is unknown. Horton (1969) has speculated that the overproduction of the bronchoconstrictor PGF_{2α} at the expense of the relaxants PGE₁ and PGE₂ might be an explanation for the changes associated with bronchospasm; another suggestion is that prostaglandin E may be converted to prostaglandin F in the lung, though there is no evidence that this occurs in normal biosynthesis. It is also interesting that the lungs can remove prostaglandins rapidly from the circulation (Änggård and Bergström, 1963; Ferreira and Vane, 1967); this may be related to the difference in potency which was observed following the intravenous and aerosol administration of PGE₁ to experimental animals (Large *et al.*, 1969).

The doses of PGE₁ and isoprenaline which were used in the present study were based on the differences in bronchodilator activity when these substances were given by aerosol to experimental animals. Though irritation of the upper respiratory tract was invariable when PGE₁ (free acid) was inhaled by normal volunteers, none of these subjects showed any change in F.E.V.₁. The triethanolamine salt was better tolerated in normal volunteers and had little or no irritant effect in seven asthmatic volunteers. The time course of the progressive reduction in F.E.V.₁ which occurred in the other asthmatic subject following the inhalation of PGE₁ (triethanolamine salt) suggests that the bronchospasm was reflex in origin and secondary to the irritant effect. It seems unlikely that PGE₁ has any direct bronchoconstrictor activity in normal or asthmatic subjects.

There are difficulties in the graphical representation of the results obtained in the asthmatic subjects. Percentage changes,

which are often used to illustrate this type of data, give disproportionately large values in subjects with a low initial F.E.V.₁ and must be corrected to the normal distribution if used for analysis—for example, by a logit transformation (Oldham, 1968). A simple alternative method, which has been used here, is to consider only the actual changes in F.E.V.₁. Neither method is entirely satisfactory, since they cannot allow for variation due to the interesting relation between the severity of the asthma and the degree of response obtainable from the use of bronchodilator aerosols (Hume and Gandevia, 1957; Hume and Rhys Jones, 1961).

These results suggest that the aerosol administration of a naturally occurring substance, prostaglandin E₁, can cause a substantial reduction in airways obstruction in asthmatic subjects. It is probable that this action of PGE₁ is not mediated through the stimulation of sympathetic β -receptors. The relation of the prostaglandins to the function of respiratory smooth muscle obviously merits further investigation.

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Medical Memoranda

Circulating Anticoagulant to Factor VIII Associated with Rheumatoid Arthritis

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CASE HISTORY

In October 1968 a 59-year-old woman with seropositive rheumatoid arthritis treated with intermittent steroids developed anaemia, purpura, and occult blood in the stools. There was no previous bleeding tendency, no other relevant medical history, and no family history of a bleeding diathesis.

On examination she was very anaemic but not jaundiced, and mild changes of rheumatoid arthritis showed in her hands and knees. There were pronounced purpuric areas on her arms and legs but the Hess test was negative. Her stools were positive for occult blood, but, apart from a sinus tachycardia (120/min.), physical examination showed no other abnormality.

It was thought that she had bled from the gastrointestinal tract, and that this might have been the result of steroid therapy, salicylate ingestion, or a bleeding diathesis. The last-mentioned factor was confirmed by tests of the clotting mechanism which showed the presence of a circulating anticoagulant. This finding was proved by tests performed by Dr. J. R. O'Brien, who further demonstrated an acquired inhibitor of factor VIII and that the factor VIII assay was less than 1%.

Investigations.—Haemoglobin 34% (5 g./100 ml.); P.C.V. 17%; W.B.C. 11,000/cu. mm., with a normal differential; E.S.R. 28 mm. in the first hour (Wintrobe); blood urea and electrolytes normal; liver function tests normal; latex test for rheumatoid arthritis positive; latex test for lupus erythematosus negative (on three occasions). The L.E. cell phenomenon was not demonstrable on five specimens, occult blood was positive on all specimens of stool, and the direct Coombs test was negative. Chest x-ray barium meal, and barium enema examinations all showed no abnormality. Tests of the clotting mechanism showed: bleeding time four minutes, whole-blood clotting-time 60 minutes, prothrombin index 80%, platelets 500,000, partial thromboplastin time 80 seconds, and antihæmophilic globulin assay less than 1%.

The patient continued to bleed from the gastrointestinal tract and required repeated blood transfusions. On 14 November she was transferred to the Oxford Haemophilia Centre, where laboratory

investigation confirmed the previous findings and showed a whole-blood clotting time of 42 minutes, kaolin cephalin clotting time 119 seconds, prothrombin consumption index 150%, and factor VIII assay 0%. A course of Imuran (azathioprine) 50 mg. b.d., resulted in a slight repeated improvement in the level of the inhibitor.

In mid-December she was transferred back to the Royal Hampshire County Hospital, where she developed a swinging pyrexia and blood cultures grew *Escherichia coli* on two occasions. Azathioprine and prednisolone were stopped and she was started on cephaloridine 1 g. q.d.s., to which the organism was sensitive. She developed hot painful swellings of both knees which contained fluid, and her right calf became indurated and swollen with pitting oedema of the right foot. Fluctuation could not be elicited. It was thought that these swellings could be hæmorrhagic or infective in origin or perhaps both, and on January 3, 1969, she was transferred back to the Oxford Haemophilia Centre for further management. The following day she was given a dose of porcine antihæmophilic globulin and her factor VIII level rose from 15% to 200%. Two days later she was noted to be drowsy and oliguric and her blood urea was 205 mg./100 ml., chloride 100 mEq/l., bicarbonate 8 mEq/l., sodium 138 mEq/l., and potassium 5.2 mEq/l. A diagnosis of acute renal failure was made, the cause of which was not apparent. The severe acidosis was treated with intravenous bicarbonate, following with normal saline.

Two days later her clinical condition had deteriorated: she was stuporous, and her blood urea had risen to 270 mg./100 ml. As her factor VIII level was more than 150% of normal peritoneal dialysis was started, with clinical and biochemical improvement. Urological examination was performed under anaesthesia, but no evidence of obstruction of urinary outflow was found, and the kidneys, pelvis, and ureters were normal.

That evening she suddenly became unwell, was hypotensive, and developed a sinus tachycardia. A rapid infusion of normal saline brought transient improvement. It was thought that she had a further septicaemia in view of her recent instrumentation and infected urine, which was shown to contain *Pseudomonas pyocyanea*, coliform bacilli, and *Streptococcus faecalis*. She was therefore started on ampicillin and Colomycin (colistin sulphate), to which these organisms were sensitive. Blood cultures taken at this time were negative.

Next day the patient again became severely hypotensive and vomited blood. The factor VIII level was still in excess of 100% of normal, and it was felt that she had developed uraemic ulceration