Mineralocorticoid Hypertension Due to a Nasal Spray Containing 9α-Fluoroprednisolone

FRANCO MANTERO, M.D.
DECIO ARMANINI, M.D.
GIUSEPPE OPOCHER, M.D.
FRANCESCO FALLO, M.D.
Padua, Italy

LORENA SAMPIERI, M.D.
BRUNO CUSPIDI, M.D.
CESARE AMBROSI, M.D.
GIOVANNI FAGLIA, M.D.
Milan, Italy

Reprinted from the September issue

The American Journal of Medicine

A Yorke Medical Journal
Published by Technical Publishing Company,
a Division of Dun-Donnelley Publishing Corporation,
a Dun & Bradstreet Company,
666 Fifth Avenue, New York, New York 10103

Printed in the U.S.A.

eralocorticoid Hypertension Due to a Nasal Spray itaining 9α-Fluoroprednisolone

:O MANTERO, M.D.
ARMANINI, M.D.
PPE OPOCHER, M.D.
:ESCO FALLO, M.D.
Italy

NA SAMPIERI, M.D.
PIDI, M.D.
RE AMBROSI, M.D.
NNI FAGLIA, M.D.
Italy

The finding of hypokalemia and of low plasma renin activity (PRA) in a hypertensive patient suggests a diagnosis of primary hyperaldosteronism. Medications containing compounds with mineralocorticoid-like activity (licorice, carbenexolone) may also cause the same syndrome. Recently, we carried out detailed studies on 10 patients with severe hypertension and hypokalemic alkalosis, suppressed PRA and low aldosterone levels. Plasma levels of cortisol and ACTH were suppressed in most of the cases. Measurement of deoxycorticosterone and corticosterone (and in some patient of 18-hydroxydeoxycorticosterone and 18-hydroxycorticosterone) was not significantly higher than normal. Therapeutic trials of dexamethasone and aminoglutethimide were ineffective. In contrast, spironolactone and amiloride treatment resulted in substantial but incomplete amelioration of both hypertension and hypokalemia. All of the patients share a common history of chronic rhinitis and habitual use of large doses of nasal spray containing 9α-fluoroprednisolone and vasoconstrictor agents. Withdrawal resulted in a complete remission of hypokalemia in one to two weeks in all patients. The hypertension and depressed levels of PRA, aldosterone and cortisol took longer to return to normal, varying from case to case; in all but one patient, the values returned to normal within two months. This report reveals another cause of factitious mineralocorticoid excess which may be considered in the differential diagnosis of hypokalemic hypertensive syndromes.

The finding of hypokalemia and of low plasma renin activity (PRA) in a hypertensive patient, not receiving diuretics, suggests a diagnosis of primary hyperaldosteronism [1]. If aldosterone levels are, however, within normal limits or low, the existence of an excess of other mineralocorticoids may be suspected. Such syndromes include deficiency of 17α-hydroxylase [2], 11β-hydroxylase [3] or 11β-ketoreductase [4], tumors producing deoxycorticosterone (DOC) [5] or corticosterone (B) [6]; and possibly overproduction of 18-hydroxydeoxycorticosterone (18-OH-DOC) [7]. The abuse of substances containing aldosterone-like activity (licorice, carbenexolone) may also cause a similar clinical picture [8,9]. Recently, we found a group of patients with moderate to severe hypertension and marked hypokalemia in whom all these etiologic possibilities were excluded. All patients had a common history of endonasal pathology (chronic allergic rhinitis, septal deviation, partial surgical relief of polyposis), together with the subsequent continued use, for months or even years, of nasal sprays including fluoroprednisolone acetate and vasoconstrictor agents.

Istituto di Semeiotica Medica, Universita
va, Padua; and the Istituto di Clinica Medica
ersita di Milano, Milan, Italy.

This work was
ed in part by a Consiglio Nazionale delle
ne grant (No. 780196604).

Requests for
should be addressed to Dr. Franco Man-
ituto di Semeiotica Medica, Via Ospedale
05, 35100 Padova, Italy.

Manuscript ac-
March 10, 1981.

MATERIAL AND METHODS

Ten patients (nine men and one woman), aged 24 to 67 years, affected with systodiastolic high blood pressure (blood pressure 150/100–235/135 mm Hg) were studied. All of them were hospitalized and showed marked hypokalemia (serum potassium 1.9 to 3.4 meq/liter), alkalosis (pH 7.39 to 7.47), suppressed PRA (0.03 to 0.09 ng/ml/hr) and low aldosterone excretion (1 to 7.6 μg/24 hr). All the patients had a common history of chronic rhinitis and continual use of large doses of nasal sprays containing fluoroprednisolone acetate and vasoconstrictor agents (Table 1). Two preparations have been used: Biorinil®, Farmila SPA, Milan Italy, and Deltarinolo®, Dow-Lepetit, Milan Italy; the composition of which per milliliter is indicated as follows:

Biorinil: 1.0 mg 9α-fluoroprednisolone acetate; 1.0 mg chioroprophenpyridamine sulphate; 1.0 mg tetrahydrazoline hydrochloride; 20 mg kanamicine sulphate, buffered isotonic saline (Bottles of 10 ml).

Deltarinolo: 0.025 mg 9α-fluoroprednisolone acetate; 5 mg ephedrine hydrochloride; 1.25 mg 2,1-naftimetilimidazoline; buffered isotonic saline solution (Bottles 15 ml).

Deltarinolo is widely available, being registered in 45 countries including Austria, Belgium, Brazil, Egypt, Holland, Hungary, Italy, Mexico, Nigeria and Switzerland.

A typical case history of one of the patients is reported here:

CASE REPORT

This patient is a 25 year old man with no family history of hypertension. From the age of 18, he had been diagnosed as having hypertrophy of the turbinates and deviation of the nasal septum. At the age of 21, hypertension and electrocardiographic alterations were found in the course of a preoperative examination for corrective nasal surgery. He was subsequently hospitalized on three separate occasions for investigations of the hypertension. Because of the finding of low serum potassium levels (1.9 to 2.6 meq/liter) and alkalosis (blood pH 7.44), a presumptive diagnosis of hyperaldosteronism was made. PRA was suppressed; however, urinary aldosterone was not increased. Neither spironolactone nor a variety of other hypotensive agents significantly lowered his blood pressure. In October 1977, when the patient was referred to our Clinic, his blood pressure was 170/120 mm Hg and heart rate 84/minute. Physical examination disclosed no abnormalities other than weakness and cardiomegaly. Upon prompting, the patient stated that he had been using a nasal spray (Biorinil), two bottles a week continuously for four years.

The studies designated "during nasal spray self-administration" (period I) and "after 15 days of withdrawal" (period II) were performed while the patients were hospitalized in the Institute of Medical Clinic, University of Milan (Cases 1 through 4) and in the Institute of Semeiotica Medica, University of Padua (Cases 5 through 10).

Student's t test for paired data were employed for comparison of data between different periods.

During hospitalization patients received a diet containing 120 to 150 meq of sodium and 30 to 70 meq of potassium. The studies performed 60 days after withdrawal of the treatment (period III) were carried out in the majority of cases on an outpatient basis. Blood pressure was measured by sphygmomanometer; routinely with the patient supine and when indicated, upright. Serum and urinary electrolytes were measured by flame photometry. PRA was measured by the method of Haber et al. [10] (normal values: recumbent 0.4 to 1.5 ng/ml/hr; standing 0.9 to 2.5 ng/ml/hr) in Cases 1 through 4; and by the method of Stockigt et al. [11] with the boiling step eliminated, using antiserums kindly supplied by Dr. Stockigt, in Cases 5 through 10. Using this method ranges are as follows: recumbent 0.3 to 1 ng/ml/hr; standing 1 to 2.3 ng/ml/hr. In all patients CIS-Sorin kits, Saluggia, Italy, were used to measure plasma ACTH, plasma aldosterone, plasma cortisol, plasma progesterone, plasma 17-OH-progesterone and 24 hours urinary aldosterone (18-glucuronide). Normal ranges for these assays are as follows: plasma ACTH 20 to 100 pg/ml; plasma aldosterone 4 to 12 ng/dl supine, 10 to 30 ng/dl upright; plasma cortisol 5 to 20 μg/dl; plasma progesterone 0.17 to 0.40 ng/ml and 17-hydroxyprogesterone 0.8 to 1.4 ng/ml (male); urinary aldosterone 5 to 15 μg/24

TABLE I **Some Clinical Characteristics and Type and Duration of Treatment with Fluoroprednisolone-Containing Nasal Spray in 10 Hypertensive Patients**

Case No.	Sex and Age (yr)	Blood Pressure (mm Hg)	Disease of the Upper Respiratory Tract	Drug	Fluoroprednisolone* (mg)	Duration Treatment (mo)
1	M, 25	185/115	Hypertrophy of turbinates, nasal septum deviation	BR	30	48
2	M, 25	200/130	Fracture and subsequent nasal septum deviation, chronic rhinitis	BR	60	24
3	M, 37	210/130	Hypertrophy of turbinates, sinusitis	DR	1.3	120
4	M, 46	190/110	Chronic rhinitis, sinusitis	DR	1.3	144
5	M, 27	180/100	Chronic rhinitis	BR	42.5	72
6	M, 43	195/130	Chronic rhinitis	BR	30	72
7	M, 22	170/120	Chronic rhinitis	BR	52.5	24
8	M, 27	140/100	Hypertrophic sinusitis, nasal septum deviation	DR	0.8	174
9	M, 24	150/100	Sinusitis	BR	22.5	24
10	F, 67	235/130	Chronic rhinitis	BR	30	24

NOTE: BR = Biorinil; DR = Deltarinolo.
* Approximate dose per week.

TABLE II Blood Pressure, Serum Electrolytes, Blood pH and Hormonal Parameters in 10 Patients*

Case No.	Period	Blood Pressure Supine (mm Hg)	Blood Pressure Upright (mm Hg)	Sodium (meq/liter)	Potassium (meq/liter)	pH	PRA (ng/ml/hr) Supine	PRA (ng/ml/hr) Upright	AER (μg/24 hr)	ACTH (pg/ml)	Cortisol (μg/100 ml)	17-Keto-steroids (mg/24 hr)	17-Hydroxy-steroids (mg/24 hr)	Free Cortisol (μg/24 hr)
1	I	180/115	175/120	140	2.6	7.44	—	—	7.6	26	5.3	3.4	1.0	—
	II	150/100	140/90	142	3.7	7.33	—	—	7.8	29	6.3	8.8	4.2	—
	III	120/80	120/80	143	4.5	7.38	0.50	0.80	8.6	38	9.2	11.6	4.8	—
2	I	200/130	190/115	145	2.5	7.41	0.05	0.05	2.0	34	15.8	14.3	6.0	—
	II	150/95	145/90	144	3.8	7.40	0.03	0.08	3.0	40	14.0	16.9	5.9	—
	III	130/80	125/75	140	4.2	7.39	0.50	1.00	9.2	40	14.3	14.3	5.0	—
3	I	210/130	210/125	139	3.0	7.43	0.07	0.07	6.0	38	12.0	8.2	4.6	—
	II	170/100	165/95	142	3.7	7.39	0.07	0.09	6.5	35	12.6	9.3	5.4	—
	III	120/80	115/85	139	4.4	7.37	0.73	1.25	10.8	38	14.6	15.5	5.8	—
4	I	190/100	185/115	141	3.0	7.47	0.07	0.09	6.7	25	8.0	11.3	5.2	—
	II	160/105	150/100	145	3.9	7.40	0.08	0.10	7.4	29	9.2	14.5	6.3	—
	III	140/90	135/85	140	4.5	7.38	0.85	1.10	5.9	46	11.8	17.7	7.4	—
5	I	180/110	170/100	147	1.9	7.39	0.07	0.07	1.6	—	1.2	7.4	—	27
	II	120/95	120/90	140	4.3	—	—	0.08	2.7	—	11.5	11.4	—	33
	III	135/80	135/80	145	4.5	—	—	1.10	7.3	—	12.0	10.1	—	52
6	I	195/130	190/130	146	2.5	7.39	0.07	0.07	1.1	35	2.4	9.1	—	72
	II	160/100	155/100	140	4.6	—	—	0.40	5.8	52	12.0	11.0	—	48
	III	140/90	140/90	142	4.3	—	—	0.80	—	51	18.0	9.3	—	102
7	I	170/120	150/120	142	3.4	7.43	0.09	0.11	1.8	25	2.5	8.3	—	74
	II	130/95	130/90	146	4.2	—	—	0.40	1.4	39	18.5	9.3	—	92
	III	120/80	120/80	146	4.6	—	—	—	10.6	—	18.0	—	—	—
8	I	150/100	140/100	143	3.4	7.39	0.07	0.07	1.6	—	15.0	5.0	—	55
	II	120/85	105/80	143	4.6	—	—	0.07	4.7	—	13.5	8.5	—	85
	III	120/80	130/80	141	4.8	—	—	0.90	2.4	102	7.5	8.5	—	45
9	I	150/100	145/100	142	2.3	7.42	0.03	0.03	3.4	25	5.7	11.8	—	—
	II	120/80	120/80	140	4.2	—	—	0.07	2.5	63	9.5	—	—	58
	III	125/80	120/80	142	4.4	—	—	0.30	5.3	59	13.0	12.5	—	32
10	I	235/130	200/110	140	3.4	7.41	0.03	0.03	2.1	—	3.5	3.7	—	54
	II	210/115	210/115	142	4.0	—	—	0.13	3.4	—	—	—	—	63
	III	170/100	170/100	146	4.6	—	—	0.70	—	—	—	—	—	41

* Studied during nasal spray containing fluoroprednisolone self-administration (period I), and 15 (period II) and 60 (period III) days after withdrawal of the drug.

TABLE III Basal and Stimulated Levels of PRA, Plasma Aldosterone and Baseline Values of Mineralocorticoids in Seven Hypertensive Patients During Self-Administration of Fluoroprednisolone-Containing Nasal Spray

Case No.	PRA (ng/ml/hr) Supine	PRA (ng/ml/hr) Upright	PRA (ng/ml/hr) After Furosemide	Plasma Aldosterone (ng/100 ml) Supine	Plasma Aldosterone (ng/100 ml) Upright	Plasma Aldosterone (ng/100 ml) After Furosemide	Plasma Aldosterone (ng/100 ml) After ACTH	Deoxycorti-costerone (ng/100 ml)	Corti-costerone (μg/100 ml)	18-hydroxydeoxy-corticosterone (pg/ml)	18-hydroxycorti-costerone (pg/ml)	Proges-terone (ng/ml)	17-hydroxy-progesterone (ng/ml)
1	0.20	0.20	. . .	6.3	5.6	. . .	. . .	3.56	0.20	113	182	0.24	2.50
5	0.07	0.07	0.07	8.0	8.8	3.6	7.6	3.20	0.46	49	43	0.14	0.19
6	0.07	0.07	0.40	3.6	3.6	3.6	3.6	7.10	0.29	105	177	0.74	2.00
7	0.09	0.11	0.31	5.1	5.8	5.8	. . .	2.50	0.23	46	66	0.30	0.10
8	0.07	0.07	0.11	5.8	5.8	6.1	. . .	6.90	—	64	44	—	—
9	0.03	0.03	0.03	8.5	9.7	12.6	—	7.30	0.58	201	106	1.10	0.10
10	0.03	0.03	0.03	9.9	6.4	6.2	—	—	—	59	166	0.14	0.10

TABLE IV Effect of Various Periods of Treatment with Spironolactone or Amiloride in Seven Patients with Spray-Induced Hypokalemic Hypertension*

Case No.	Treatment	Blood pressure (mm Hg)		Potassium (meq/liter)	
		Before	After	Before	After
1	Spironolactone, 200 mg/day 2 mo	185/115	160/100	2.4	3.3
5	Amiloride, 20 mg/day 1 mo	185/120	160/90	2.4	3.8
6	Spironolactone, 300 mg/day, 6 mo	205/135	160/100	2.5	4.9
7	Spironolactone, 300 mg/day, 2 mo	220/145	140/90	2.5	4.2
8	Spironolactone, 400 mg/day, 2 wk	200/130	130/80	2.7	4.5
9	Spironolactone, 300 mg/day 2 wk	160/105	140/95	3.3	4.5
10	Spironolactone, 300 mg/day 1 wk	260/120	200/100	2.8	3.8

* During these therapeutic trials all patients were self-administering the spray.

hr. Urinary free cortisol was measured by radioimmunoassay [12], with normal range 30 to 150 μg/24 hr. Plasma deoxycorticosterone was measured by radioimmunoassay [13] after chromatographic step, with normal values of 5 to 15 ng/dl. Plasma corticosterone [14] was similarly measured by radioimmunoassay, using an antiserum from the Endocrine Science (normal range 250 to 1500 ng/dl). Radioimmunoassay [15] was used for measurement of plasma 18-hydroxydeoxycorticosterone as the lactone (normal values 37 to 75 pg/dl); 18-hydroxycorticosterone (kindly performed by Dr. C.R.W. Edwards and V. Martin, St. Bartholomew's Hospital, London) was similarly measured by radioimmunoassay [16], with normal range of 60 to 160 pg/ml. Hydroxycorticosteroids were measured by the Silber Porter method [17] and 17-ketosteroids by the Drekter method [18] (normal values respectively 3 to 8 and 8 to 25 mg/24 hr). Plasma hormones were measured in samples drawn after overnight recumbency; PRA and aldosterone were also measured after patients had been in an upright position for 2 hours. When patients were studied as outpatients, samples were drawn after 1 hour of recumbency.

The PRA and aldosterone levels were measured after a furosemide test (40 mg e.v., blood sampling at 0 to 60 minutes) in six patients. The urinary steroids profile analysis was performed by gas-chromatography [18] (kindly performed by Dr. J. Honour, Clinical Research Center, Harrow, England).

Two patients were treated with dexamethasone, 2 mg/day for 10 days, associated with metyrapone 3 g/day for five days. An additional therapeutic trial was performed with aminoglutethimide, 750 mg/day for seven days. Seven patients were treated with spironolactone (100 to 400 mg/day for one week to six months) or amiloride (20 mg/day for one month). During each period of therapeutic trial, blood pressure and serum potassium were monitored.

RESULTS

As shown in **Tables I, II and III,** blood pressure was high in all cases with values ranging from 150/100 to 220/130 mm Hg (mean 186 ± 8/117 ± 3 mm Hg), serum potassium was low with values between 1.9 and 3.4 meq/liter (mean 2.8 ± 0.1 meq/liter), PRA was suppressed (mean 0.06 ng/ml/hr) and unresponsive to orthostasis or the administration of furosemide. Aldosterone was either at the lowest limit of the normal range, or clearly suppressed below normal levels (mean 3.3 μg/24 hr); in no case could aldosterone levels be stimulated with furosemide or ACTH. Other mineralocorticoid levels, including deoxycorticosterone, corticosterone, 18-hydroxydeoxycorticosterone and 18-hydroxycorticosterone were within normal limits in those subjects in whom measurements were taken. Plasma cortisol, urinary free cortisol and urinary hydroxycorticosteroids levels were within normal limits or low (mean plasma cortisol was 7.5 ± 1.8 μg/dl). In all cases plasma ACTH levels were within normal limits or low. Levels of progesterone, 17-hydroxyprogesterone and urinary 17-ketosteroids were low or within normal limits in those cases in which they were measured. These data would appear to rule out any currently described syndrome of endocrine hypertension, with the exception of that described in children by New et al. [4] characterized by 11β-ketoreductase deficiency. In three patients (Cases 1, 5 and 6), an analysis of the urinary steroid profile was performed by gas chromatography [19]. In all the patients, urinary metabolites of cortisol were low; there was however, no alteration of the THE:THF ratio, thus excluding an 11β-reductase deficiency. The THDOC level was within normal limits.

Seven patients were treated for periods of varying duration with spironolactone or amiloride. In all cases such treatment brought serum potassium up to normal, and reduced blood pressure; in only one case, however, was the blood pressure normalized (**Table IV**). In two cases, treatment with dexamethasone, aminoglutethimide and metyrapone produced no significant changes

in serum potassium or blood pressure. In four cases (Cases 1, 2, 5 and 6), clinical and laboratory studies, and therapeutic trials were carried out before it became apparent that the patients were taking the preparation. The chance discovery of a bottle of nasal spray on the bedside table of one of these patients prompted enquiry. Fifteen days after withdrawal (period II), blood pressure levels fell to varying degrees depending on the case (mean 149 ± 9/97 ± 3 mm Hg, $p < 0.01$). Complete normalization occurred in two cases; in seven cases there were significant reductions in both systolic and diastolic pressure, which however, persisted above the normal levels. Blood pressure remained unchanged in one case. In contrast, there was a prompt return of plasma potassium to within the normal range (mean 4.1 ± 0.5 meq/liter, $p < 0.01$), albeit at the lower limit of the normal in four cases. Concomitantly the previously noted metabolic alkalosis was resolved. Sixty days after the withdrawal of the nasal spray (period III), normalization of the blood pressure was observed in all but one patient, to a mean of 132 ± 4.9/84 ± 2.2 mm Hg, $p < 0.01$). Serum potassium was normal (mean 4.4 ± 0.5 meq/liter, $p < 0.01$). PRA had increased towards normal (mean 0.7 ng/ml/hr, $p < 0.01$) and response to orthostasis reappeared. Urinary aldosterone excretion returned to normal (mean 7.5 ± 1 μg/24 hr, $p < 0.05$), as did cortisol and ACTH in those cases in which levels had previously been low.

COMMENTS

All of the patients studied showed typical stigmata of hypermineralocorticoidism; particular features were arterial hypertension and hypokalemia. Levels of mineralocorticoids, both major (aldosterone) and minor (deoxycorticosterone, 18-hydroxydeoxycorticosterone, corticosterone) were either within normal limits or suppressed. The patients were not eating licorice nor were they being treated with antiulcer drugs containing carbenoxolone. Several of the patients had previously been hospitalized for prolonged periods and had been subjected to numerous invasive examinations (renal arteriography, renal and adrenal scans). One patient, in whom arteriography showed an abnormal adrenal image suggestive of a unilateral adenoma, was even subjected to adrenalectomy. Postoperatively the diagnosis of adenoma could not be confirmed, and the clinical syndrome remained essentially unchanged. The first two patients we studied in depth underwent similar investigations and protracted therapeutic trials of dexamethasone, aminoglutethimide and metyrapone in an attempt to exclude various uncommon causes of hypermineralocorticoidism. All these studies gave negative results; only with spironolactone and amiloride did we succeed in modifying the clinical picture, correcting the hypokalemia and significantly reducing blood pressure. The finding of a relatively specific effect of spironolactone and amiloride thus suggested a probable mineralocorticoid genesis of the syndrome. The chance discovery that two patients were using a nasal spray containing a synthetic corticosteroid (fluoroprednisolone acetate) led us to suspect that a similar etiology might underly other unexplained causes of hypermineralocorticoidism. All the patients had a common history of endonasal pathology (previous operations, allergic rhinitis). With this background, the patients had become so used to taking vasoconstrictive/anti-inflammatory nasal preparations that they no longer considered them "drugs," and so omitted them from the history. Only a specifically directed question allowed us to pinpoint analogous cases; many such cases have been subsequently discovered and are not included in the present study. Most of the patients used a preparation containing tetrahydrazolyne and fluoroprednisolone acetate (Biorinil); others used a compound containing ephedrine and 9α-fluoroprednisolone acetate (Deltarinolo). The fluoroprednisolone contained in the first preparation was identified as 9α-fluoroprednisolone [20], the identical steroid to that in the second preparation, but present in concentrations 40 times greater. The mineralocorticoid potence of 9α-fluoroprednisolone was confirmed as being equivalent to that of aldosterone [20]. Thus, if most patients used up to four bottles of nasal spray a week for years, corresponding to a daily quantity of from one (in the case of Deltarinolo) to 40 (Biorinil) times that of normal daily secretion of aldosterone, it seems clear that symptoms of hypermineralocorticoidism present in the patients were due to the presence of this steroid.

The effect of this compound on sodium and potassium balance was recognized 20 years ago [21]. At that time it was recognized that the compound should not be used in the treatment of rheumatic and allergic diseases [22]. Despite these findings, this compound has been included—often in high doses—in drugs that are widely distributed. A similar case of hypokalemic hypertension in a patient using nose drops containing fluoroprednisolone and ephedrine has previously been described by Ambruster et al. [23]. In addition, the steroid exibited ACTH-suppressive activity [24], as indicated by the levels of both cortisol and ACTH demonstrated by our patients using such preparation. No patients, however, showed clinical signs of classic glucocorticoid excess. Withdrawal from the drug was followed by a rapid normalization of serum potassium in 10 to 15 days, whereas in most cases blood pressure levels took rather longer to return to normal. Persistence of suppressed PRA levels may indicate residual sodium retention and/or volume expansion. An alternative explanation is that long-term suppression of PRA could be a reflexion of a "disuse" atrophy of the juxtaglomerular system.

Persistence of hypertension for more than two weeks

after withdrawal of the compound could also be due to the long-term vasoconstrictive effect of vasoactive amines in the preparations on vessels sensitized by sodium excess. Supporting this possibility is the incomplete antihypertensive response obtained with aldosterone antagonists. Syndromes of iatrogenic hypertension caused by abuse of ophthalmic drops and nasal inhalations containing sympathomimetic amines have been described [25]. Demonstration of the relationship between the syndrome and use of the nasal spray, led to the discovery of numerous other cases [26,27]. Thus, it is clear that a history taken from a hypertensive patient must include specific questioning concerning use of topical drugs (nasal drops, creams, and the like). In addition, it is clear that these patients, on occasion, developed a true dependence on these drugs, rendering the situation even more complicated. in such cases it may be difficult to convince a patient to discontinue the treatment and thus to demonstrate that hypertension is drug-related. In summary, prompt identification of such cases is important not only for the well-being of the patient, but also to avoid the long and often invasive investigations that such apparently complex clinical situations require. It is also obvious that 9α-fluoroprednisolone should not be used in anti-inflammatory preparations, given its powerful mineralocorticoid activity which is similar to that of aldosterone.

ACKNOWLEDGMENT

The technical assistance of Tiziana Luzzi Rizzoni, Francesco Pedini and Paola Masarotto is gratefully acknowledged. We thank Drs. Stanley Ulick and John Funder for their suggestions and criticism.

REFERENCES

1. Conn JW: The evolution of primary aldosteronism. Harvey Lect 1966/67. 62: 257–291.
2. Biglieri EG, Herron MA, Brust M: 17-hydroxylation deficiency in man. J Clin Invest 1966; 45: 1945–1954.
3. Baulieu EE, Phillon F, Migeon CJ. In: Einsestein AB, ed. The adrenal cortex. London: J. & A. Churchill, Ltd. 1967; 553.
4. New MI, Bradlow L, Fishman J, et al.: Deficiency of cortisol 11β-reductase. A new metabolic defect. Pediatr Res 1976; 12: 416.
5. Brown JJ, Ferris JB, Fraser R, et al.: Apparently isolated excess deoxycorticosterone in hypertension: a variant of the mineralocorticoid excess syndrome. Lancet 1972; 2: 243–247.
6. Fraser R, James WTH, Landon J, et al.: Clinical and biochemical studies of a patient with a corticosterone-secreting tumor. Lancet 1968; 2: 1116–1120.
7. Melby JC, Dale SL, Wilson TE: 18-hydroxycorticosterone in human hypertension. Circ Res 1971; 28 and 29 (suppl II): 143–52.
8. Conn JW, Rovner DR, Cohen EL: Licorice-induced pseudoaidosteronism. JAMA 1968; 205: 492–496.
9. Turpie AG, Thompson TJ: Carbenexolone sodium in the treatment of gastric ulcer with special reference to side effects. Gut 1956; 6: 591–594.
10. Haber E, Koerner T, Page B, et al.: Application of a radioimmunoassay for angiotensin to the physiologic measurement of the plasma renin activity in normal human subject. J Clin Endocrinol Metab 1969; 29: 1349–1359.
11. Stockigt JR, Collins RD, Biglieri EG: Determination of plasma renin concentration by angiotensin I immunoassay: diagnostic import of a precise measurement of subnormal renin in hyperaldosteronism. Circ Res 1971; 28; 175–180.
12. Boscaro M, Karbowiak I, Mantero F: Free cortisol radioimmunoassay. La Ricerca 1978; 3: 169–178.
13. Mantero F, Sonino N, Masarotto P: Plasma deoxycorticosterone radioimmunoassay: method and clinical applications. J Nucl Biol Med 1975; 19: 186–194.
14. Mantero F, Armanini D, Opocher G, et al.: Dosaggi radioimmunologici di attività plasmatica della renina, aldosterone urinario, aldosterone, desossicorticosterone e corticosterone plasmatici nella ipertensione arteriosa. Atti II Convegno su "Metodi Radioimmunologici in Endocrinologia." Milano 19–21 Maggio 1976; 201–213.
15. Edwards CRW, Skrabal F, Martin VI, et al.: Plasma 18-deoxycorticosterone (18OHDOC) and 18-hydroxycorticosterone (18OHB) in patients with different types of hypertension. Abstracts of the 60th Meeting of the Endocrinology Society. June 14–15, 1978; 201.
16. Martin VI, Edwards CRW, Biglieri EG, et al.: The development and application of a radioimmunoassay for 18-hydroxycorticosterone. Steroids 1975; 26: 591–604.
17. Silber RH, Porter CC: The determination of 17-21-deoxy-20-ketosteroids in urine and plasma. J Biol Chem 1954; 210: 923–932.
18. Drekter IJ, Heisler A, Scism GR, et al.: The determination of urinary steroids. The preparation of pigment free and simplified procedure for estimation of total 17-ketosteroids. J Clin Endocrinol Metab 1952; 12: 55–65.
19. Shackleton CHL, Honour JW: Simultaneous estimation of urinary steroids by semi-automated gas chromatography. Investigation of neonatal infants and children with abnormal steroid synthesis. Clin Chim Acta 1976; 69: 267–283.
20. Funder JW, Adam WR, Mantero F et al.: The etiology of a syndrome of mineralocorticoid excess: a steroid containing nasal spray. J Clin Endocrinol Metab 1979; 49: 842–846.
21. Thorn GW, Renold AE, Morse WI, et al.: Highly potent adrenal cortical steroids. Structure and biological acitvity. Ann Intern Med 1955; 43: 979–1000.
22. Fried J, Borman A: Synthetic derivatives of cortical hormones. In: Harris RS, Narrian GF, Thimman KV, eds. Vitamins and hormones: advances in research and applications, vol 16. New York: Academic Press, 333–335.
23. Ambruster H, Vetter W, Reck G, et al.: Severe arterial hypertension caused by abuse of a topical mineralocorticoid. Int J Pharmacol 1975; 12: 170–173.
24. De Gennes L, Bricaire H, Baulieu EE: Inhibition de l'hypersecretion des corticosteroids au cours d'une syndrome de Cushing par le 9 fluoro dehydrocortisol. Presse Med 1956; 64: 1855–1857.
25. Wilenski A: Acute systemic hypertension after conjuctival instillation of phenylephrine hydrochloride. Am J Opthalmol 1973; 76: 156–157.
26. Mantero F, Armanini D, Opocher G, et al.: Pseudoaldosteronismo privitivo da istillazione endonasale di fluoroprednisolone. Atti XVI Congresso Società Italiana di Endocrinologia. Torino/Saint Vincent 17–20. Maggio; 1978; C120.
27. Mantero F, Faglia G, Adam WR, et al.: A new syndrome of factitious mineralocorticoid excess. Abstracts of the 6th Annual Meeting of the Endocrine Society. Anaheim; 1979; 279.