

Hypertension during reduction of long-term steroid therapy in young subjects with asthma

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Corticosteroids can induce hypertension, which reportedly remits as the drug is withdrawn. We studied nine patients with steroid-requiring asthma, aged 9 to 16 years, who had elevated blood pressures during corticosteroid treatment. Unlike in previous studies, all nine patients developed hypertension during corticosteroid reduction. Diastolic blood pressures were 50 to 84 mm Hg during maximum corticosteroid therapy (1 to 4 mg/kg/day); these values were in the normal range for seven of the nine patients and in the high normal range for the other two patients. Maximum diastolic pressures were 100 to 120 mm Hg, 1 to 8 weeks after corticosteroid reduction was started. Hypertension occurred at 0% to 70% of their maximum corticosteroid dose. Corticosteroid reduction was the only medication change. Renal causes of hypertension were excluded. Six patients had levels of renin and aldosterone measured before onset of treatment. All six patients had elevated levels of renin, and five patients had elevated levels of aldosterone. Blood pressure elevations were resistant to diuretic therapy but responded rapidly to angiotensin-converting enzyme inhibitors. Caretakers of subjects with asthma need to be aware that hypertension may occur both during maximum corticosteroid use and during corticosteroid reduction. (J ALLERGY CLIN IMMUNOL 1992;89:816-21.)

Key words: Asthma, steroid reduction, hypertension, angiotensin-converting enzyme inhibitor

Steroid-induced hypertension is a common finding in patients with Cushing's syndrome¹ and is frequently observed in patients taking corticosteroids for a variety of diseases.²⁻⁶ Hypertension in subjects with asthma taking corticosteroids has been studied in detail only in adults in whom the incidence ranges from 10%⁷ to 40%^{8,9} and is highest in patients taking >7.5 mg of prednisone daily.⁹ Corticosteroid-induced hypertension is theorized to be produced by increased

Abbreviations used

BP:	Blood pressure
TAO:	Troleandomycin
MPn:	Methylprednisolone
ACEI:	Angiotensin-converting enzyme inhibitor
q.d.:	Every day
b.i.d.:	Twice daily
q.o.d.:	Every other day
PRA:	Plasma renin activity

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sodium and fluid retention secondary to the mineralocorticoid effect of the steroids,¹⁰ steroid-induced increases in sensitivity to endogenous catecholamines,^{11, 12} and increased production of angiotensinogen.¹³

We report nine children with steroid-requiring asthma who developed hypertension only as their steroids were being reduced. Their severe hypertension developed from 1 to 8 weeks after steroid reduction had been initiated and when steroid doses were 0% to 70% of maximum. The hypertension in these patients was not explained by other medication changes or organic causes.

PATIENTS AND METHODS

Patients

Patients were referred to National Jewish Center for Immunology and Respiratory Medicine for evaluation and treatment of asthma not responsive to outpatient management. All patients had asthma as defined by the American Thoracic Society.¹⁴ The nine patients with hypertension during reduction of long-term steroid therapy were identified during a period of 19 months, from August 1985 to February 1987. The nine patients were receiving the inpatient service during the entire period of observation. During this period, there were 360 total admissions of children with asthma (for lengths of stay of 3 weeks or longer), 6% of whom were black. By comparison with previously collected data on patients admitted to National Jewish Center in the same 5-year period,¹⁵⁻¹⁸ approximately 240 of these patients were receiving oral steroid medications at the time of admission (primarily prednisone), with doses of 26 mg/day,¹⁵ and 6% were black. The patients admitted to the pediatric service had steroid reduction of 64%, on average, during their stays of 3 weeks or longer.¹⁵ Of the 240 patients receiving steroids, a diagnosis of hypertension was made in 28 patients coded at the time of discharge, nine with the characteristics described below. Parents of all patients gave informed consent for participation of their children in the study. The study protocol and informed consent form were approved by the National Jewish Institutional Review Board.

Evaluation for elevated BP

BPs were obtained routinely on each patient of the inpatient service once a week by auscultation following guidelines of the Second Task Force on Hypertension.¹⁹ BP was measured in the right arm of seated patients who had been at rest for at least 15 minutes before measurement. Diastolic BP was determined by Korotkoff sound 4 in children, aged 3 to 12 years, and by Korotkoff sound 5 in children, aged 13 to 18 years. Higher BPs between the 95th and 99th percentiles were classified as significant hypertension and higher than the 99th percentile associated with symptoms of hypertension as severe hypertension.¹⁹

Evaluation of patients with hypertension during steroid reduction

At the time of their evaluation, all patients were receiving the inpatient service, and their asthma was well controlled. All patients were evaluated for etiologies of hypertension other than corticosteroid administration and reduction. This evaluation consisted of serum creatinine and electrolytes, 24-hour urine collections for creatinine clearance, sodium and protein excretion, as well as urine culture, urinalysis, and technetium-99m diethylenetriamine penta-acetic acid renal scan.¹⁶⁷ For six of the nine children, plasma for measurement of PRA and aldosterone was obtained after 4 hours of recumbancy and 12 hours of fasting before the start of antihypertensive medication. These assays were performed with standard RIA procedures in the clinical laboratory at National Jewish. PRA levels were indexed to 24-hour urine excretion. FVC and FEV₁ were measured at least two times a day.

Case report

The index patient was an 11-year-old black boy admitted for treatment of asthma (patient 1 in Tables I, II, and IV). He had been treated with TAO and MPn for 2½ years. He had had five episodes of respiratory failure requiring mechanical ventilation. The last episode was 1 month before admission. Family history was positive for asthma (father and maternal aunt) and hypertension (mother whose hypertension was well controlled with diuretics alone). Medications on admission included a long-acting theophylline preparation, 250 mg b.i.d., MPn, 32 mg q.o.d., TAO, 250 mg q.o.d., and metaproterenol, 0.3 cc of a 5% solution by nebulization, four times a day. Vital signs were weight, 43.3 kg (85th percentile); height, 124 cm (<5th percentile); heart rate, 100; BP, 120/80 (between 90th and 95th percentiles); FEV₁, 0.76 L (51% predicted); and FVC, 0.95 L (54% predicted). (Lung volumes could not be obtained initially because of poor patient cooperation.) Serum electrolytes, calcium, phosphorous, creatinine, and total protein were normal. Pulmonary functions improved to 100% of predicted within the first week, allowing decreases in steroid dosage starting in the second week. (His initial pulmonary functions may have been decreased because of suboptimal effort, explaining the rapid rise in his pulmonary functions.) All other medications, including his TAO, theophylline, and β -agonist, were kept constant. His MPn was decreased to 18 mg q.o.d. (56% of original dose) without a decline in pulmonary functions. Three weeks after the initial decrease in MPn, he became hypertensive with a BP of 150/120 (>99th percentile), accompanied by frontal headaches and ischemic changes on ECG. Weight at the onset of the hypertension was 42.3 kg (a decrease of 1 kg from admission), and his heart rate was 72. Evaluation of renal function and anatomy was normal (Table II). Although his BP decreased initially with intravenous hydralazine, consistent control was difficult to obtain and required use of multiple antihypertensive drugs (Table I). His BP was well controlled (diastolic BP, <90th percentile) only after 5 weeks of antihypertensive treatment.

The only time this patient's BP was stable during this initial 5-week period was when MPn was increased to 60 mg a day to treat an exacerbation of asthma. When MPn was subsequently decreased to 40 mg a day (67% of the increased dose) (day 31), he again became hypertensive (BP, 170/110). Steroid reduction continued to MPn, 6 mg q.o.d. After 8 weeks of treatment, BP improved and methylglucamine was stopped. After 10 weeks, furosemide and hydralazine were stopped. A repeat ECG at that time was normal. Thirteen weeks after onset of hypertension, he required only spironolactone, 25 mg q.d., and nifedipine, 20 mg b.i.d., to maintain his BP at 100 to 120/70 to 90 (75th to 99th percentiles).

RESULTS

Steroid-withdrawal hypertension

The nine patients who developed severe hypertension during steroid reduction are presented in Tables I and II. In the year before their admission, seven had used steroids daily; one patient, every other day plus

TABLE I. Patients with steroid-reduction hypertension

No.	Steroid dose			BP		Occurred at week into steroid taper	Hypertensive medications
	Max	At BP elevation	% Reduction	At max steroid	Max		
1*	MPn, 32 mg q.o.d.†	MPn, 18 mg q.o.d.†	44	120/84	150/120	4	N,F,CTZ,M
2‡	MPn, 40 mg b.i.d.	MPn, 18 mg q.d.	78	100/50	140/120	7	ACEI
3*	MPn, 25 mg b.i.d.†	MPn, 35 mg q.d.†	30	120/65	150/120	1	N,S,CTZ
4	MPn, 20 mg b.i.d.	None	100	120/80	154/100	0.75	None
5‡	P, 40 mg q.d.	P, 30 mg q.o.d. alt 10 mg q.o.d.	50	114/74	132/106	2	ACEI
6‡	Solmedrol, 30 mg q.i.d.§	P, 30 mg AM 25 mg PM	63	124/76	150/120	1	ACEI
7	MPn, 30 mg b.i.d.	MPn, 30 mg q.d.	50	112/77	138/100	4	ACEI
8	P, 60 mg q.d.	P, 20 mg q.o.d.	83	130/80	150/100	2.5	ACEI
9	MPN, 32 mg b.i.d.	MPN, 56 mg q.o.d.	56	116/70	138/102	0.5	ACEI

Max, Maximum; CTZ, chlorthiazide; F, furosemide; H, hydralazine; M, methylodopa; N, nifedipine; S, spironolactone; P, prednisone. All patients were receiving theophylline and inhaled selective β -agonist.

*Required multiple antihypertensive medications; ACEI not tried.

†Patients receiving TAO, 250 mg q.o.d.

‡Required multiple antihypertensive medications; ACEI started; BP responded; other medication stopped.

§Treatment for status asthmaticus.

||ACEI only with rapid effective response.

TABLE II. Demographics of the nine patients with steroid-reduction hypertension

No.	Age (yr)	Sex	Wt		Ht	
			kg	(percentile)	cm	(percentile)
1	11	M	42	(80)	124	(<5)
2	13	M	49	(60)	133	(<5)
3	13	M	45	(40)	133	(<5)
4	15	M	60	(70)	167	(75)
5	13	M	48	(50)	154	(5)
6	9	M	33	(50)	136	(50)
7	8-1/2	F	56	(>95)	134	(80)
8	16	F	69	(>97)	165	(70)
9	11-1/2	M	56	(95)	138	(5)

several steroid bursts; and one patient, steroid bursts only. Five of the nine patients were black. Six of the nine patients were obese with weight-to-height ratios, >95th percentile. All patients had BP >99th percentile on their entry into the study. BP was normal initially in seven of the nine patients and was only in the high normal range in the other two patients (nos. 1

and 6). Only two patients (1 and 3) had a family history of hypertension.

The hypertension occurred when their asthma was stable; there were no clinical symptoms of asthma, and the FEV₁s and FVCs had not decreased from their best values at the time of maximum steroid use. Eight of the nine patients required treatment for their hypertension. One patient (no. 4) had transient hypertension only, with BP decreasing to the significant range within 24 hours without treatment. This patient was the only one who had not been taking long-term steroids in the year before development of hypertension. Of the eight requiring treatment, five patients required multiple antihypertensive drugs for control. BP in three of the patients (nos. 2, 5, and 6) were refractory to vasodilators and diuretics and became normal only when an ACEI was added to the regimen; medications other than the ACEI were subsequently stopped without an increase in BP.

All eight patients who required treatment for hypertension had headaches when their BPs were >99th percentile. Additional symptoms were noted in two patients. Patient 5 complained of nausea and blurred

vision, and patient 3 had epistaxis. No patient had an abnormal eye examination.

Evaluation for an etiology of hypertension

In all patients, steroids were the only medication change; no changes were made in theophylline dosages or use of the β_2 -agonists. Theophylline levels were therapeutic in all patients both before and during the hypertension. No patient had significant weight gain at the onset of hypertension. All patients had normal serum electrolyte and creatinine levels, normal urinalyses on several occasions, and 24-hour urine creatinine clearances and protein excretion, and urinary fractional excretion of sodium was low. Renal anatomy was studied in the first six patients in this series: five had normal technetium-99m diethylene-triamine penta-acetic acid renal scans, and one patient had a normal hypertensive intravenous pyelogram. ECGs were normal in all patients except for two patients who had transient abnormalities when they were hypertensive. Patient 1 had evidence of ischemia and patient 6 had evidence of left ventricular strain; results of echocardiograms were normal in both. The ECGs in both patients became normal within 1 week after treatment for hypertension was initiated.

In contrast to the remainder of the workup, PRA was elevated in all six patients studied (Table III). Five of these patients also had elevated aldosterone levels; patient 9 had a high normal level. Three patients had repeat renin and aldosterone levels when they became normotensive and their antihypertensive medications had been stopped; in all three patients, the repeat levels were normal.

Status of hypertension at follow-up

The first six patients were contacted 4 to 8 months after the initial hypertension episode to determine the status of their BP and medication requirements (Table IV). Only patient 1 still required antihypertensive medications; 8 months after the onset of hypertension, his BP was stable receiving nifedipine only.

DISCUSSION

Earlier investigations have demonstrated a relationship between high-dose corticosteroid therapy and hypertension.^{1,2} The nine cases presented here indicate that hypertension can also occur as steroids are tapered. The hypertension in these nine cases was not accounted for by known mechanisms of corticosteroid-induced hypertension. Steroid-induced increases in sensitivity to endogenous catecholamines,^{11,12} and increased hepatic production of angiotensinogen¹³

TABLE III. Renin and aldosterone evaluation in patients with steroid-reduction hypertension*

Patients	PRA (ng/ml/hr)	Aldosterone (3-10 ng/dl)
4	7.5 (0.3-1.3)†	21
5	5.0 (1.4-2.8)	17
6	12 (0.15-2.3)	24
7	16 (4.1-7.7)	12
8	4.5 (0.15-2.3)	33
9	5.3 (0.3-1.3)	9.6

*All renin and aldosterone levels were drawn after at least 12 hours of fasting and 4 hours of recumbency.

†Normal ranges of PRA were indexed to 24-hour urine sodium excretion.

would have remitted as steroids were reduced; increased sodium and fluid retention¹⁰ were not present. (No patient had significant weight gain.) Exacerbation of asthma and changes in the use of β_2 -agonists or theophylline were excluded as possible causes of hypertension in all cases. The roles of the type of steroid used (methylprednisolone in seven of the nine cases) and the rate of steroid withdrawal need to be considered in future studies.

The nine patients with steroid-reduction hypertension are a very small subgroup of children with steroid-requiring asthma, representing only nine of 240 children receiving oral steroid medication when they were admitted to National Jewish Center for control of asthma during the interval of their presentation. On average, all children admitted had steroids reduced to approximately the same degree as observed for the patients with steroid-reduction hypertension. A group of 103 patients discharged from September 1983 to February 1985, just before the presentation of these patients, had steroid reduction of 64%,¹⁵ compared with 61% for the patients with steroid-reduction hypertension. Nineteen other patients receiving steroids admitted during the same interval as the group with steroid-reduction hypertension had a diagnosis of hypertension coded at discharge, but none had severe hypertension accompanied by headache or other symptoms. The incidence of blacks among the patients with steroid-reduction hypertension, 56%, is much

TABLE IV. Status of hypertension at follow-up

Patients	Time after initial episode (mo)	BP	Hypertensive medication	Steroid medication
1	8	100-120/70-90 (90%-99% percentile)	N, 10 mg t.i.d.	MPn, 20 mg q.o.d. TAO, 250 q.o.d.
2	8	105/65 (nl)	None	MPn, 25 mg q.o.d.
3	8	110/60 (nl)	None	MPn, 8 mg q.o.d.
4	7	110/70 (nl)	None	None
5	4	100/70 (nl)	None	P, 10 mg q.o.d.
6	7	102/68 (nl)	None	Mpn, 20 mg q.o.d.

N, nifedipine; nl, normal; P, prednisone; t.i.d., three times a day.

higher than in patients referred to National Jewish Center, 6%,¹⁵ suggesting that blacks may be more prone to this form of hypertension than whites.

The steroid-reduction hypertension was difficult to control with conventional therapy. Diuretics were inefficient in reducing BP, even though aldosterone was elevated. In addition, the patients did not respond to vasodilators. However, ACEIs were effective in all six of the patients who received this drug. Three patients were controlled with an ACEI only. Since this study ended, we have observed an additional three patients who developed hypertension during reduction of steroids. All patients responded quickly to ACEIs.

Elevations of both renin (PRA) and aldosterone were a consistent feature in the patients with steroid-reduction hypertension. Based on the results in the three patients who had normal levels when their BPs had returned to normal, the increases in PRA and aldosterone appear to be transient and not related to the asthma itself or its treatment. A prospective study will be required to confirm the relationship between steroid-reduction hypertension and abnormalities in the renin-aldosterone system.

It is important for medical personnel caring for patients with asthma to be aware that hypertension can occur, not only as the steroids are being administered, but also as steroids are being reduced. In this study, hypertension was observed only with reduction of oral steroids. Hypertension during reduction of high-dose inhaled steroids was not observed; during the era of this study, high-dose inhaled steroids were used relatively infrequently in our institution. We recommend that BP be measured at each office visit to monitor clinical status during steroid reduction. BP should also be checked if there is appearance of clinical signs or symptoms that may suggest hypertension, such as headaches. Additional studies are required to determine the frequency of steroid-reduction hypertension in children receiving steroids for asthma (especially in relation to the incidence of hypertension during

maximal steroid use) and to determine if steroid-reduction hypertension occurs in adults and in patients without asthma receiving steroids for other diseases.

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Activated T-lymphocytes and eosinophils in the bronchial mucosa in isocyanate-induced asthma

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We have studied the phenotype and activation status of leukocytes in the bronchial mucosa in patients with isocyanate-induced asthma. Fiberoptic bronchial biopsy specimens were obtained from nine subjects with occupational (five toluene- and four methylene diisocyanate-sensitive) asthma, 10 subjects with extrinsic asthma, and 12 nonatopic healthy control subjects. Bronchial biopsy specimens were examined by immunohistology with a panel of monoclonal antibodies and the alkaline phosphatase-antialkaline phosphatase method. There was a significant increase in the number of CD25⁺ cells (interleukin-2 receptor-bearing cells, presumed "activated" T-lymphocytes; $p < 0.01$) in isocyanate-induced asthma compared with that of control subjects. There were also significant increases in major basic protein (BMK-13)-positive ($p < 0.02$) and EG2-positive ($p < 0.01$) cells that represent total and "activated" eosinophil cationic protein-secreting eosinophils, respectively. In agreement with our previous findings, CD25⁺ ($p < 0.01$), BMK-13 ($p < 0.03$), and EG2⁺ ($p < 0.01$) cells were also elevated in extrinsic asthma. No significant differences were observed in the numbers of T-lymphocyte phenotypic markers (CD3, CD4, and CD8) between subjects with asthma (isocyanate-induced and extrinsic) and control subjects. Similarly, no significant differences in immunostaining for neutrophil elastase (neutrophils) or CD68 (macrophages) were observed. The results suggest that isocyanate-induced occupational asthma and atopic (extrinsic) asthma have a similar pattern of inflammatory cell infiltrate. The results support the view that T-lymphocyte activation and eosinophil recruitment may be important in asthma of diverse etiology. (J ALLERGY CLIN IMMUNOL 1992;89:821-9.)

Key words: Eosinophils, T-lymphocytes, neutrophils, macrophages, bronchial biopsies, subjects with asthma, isocyanates

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