

Urinary excretion of epinephrine and norepinephrine in asthmatic children

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Urinary excretion rates of free epinephrine and norepinephrine were measured in children with chronic asthma: (1) during asymptomatic periods, (2) during the stress of asthmatic symptoms, and (3) in response to insulin-induced hypoglycemia. Epinephrine excretion was significantly higher in asymptomatic asthmatic children than in normal children whose urines were collected at home under minimum stress. Urinary epinephrine and norepinephrine excretion rates did not change significantly when children were symptomatic with asthma. Conversely, there was a seven- to tenfold increase in epinephrine excretion after insulin-induced hypoglycemia. In conjunction with the mobilization of endogenous hormones (cortisol and epinephrine), children who were moderately symptomatic with asthma at the beginning of the insulin test had spontaneous relief of asthma. It was concluded that children with asthma are capable of responding normally to certain stresses, but during episodes of mild or moderately severe asthma they do not mobilize sufficient quantities of the endogenous hormones which might help to relieve symptoms.

Although adrenergic agents are widely used in the treatment of asthma, there is very little information about the availability of endogenous catecholamines in asthmatic patients. Several investigators have suggested that asthmatic patients excrete reduced quantities of catecholamines in the basal state and have minimal increases in epinephrine excretion during symptomatic periods.¹⁻³ It has also been observed that, in comparison with normal subjects, patients with mild, asymptomatic asthma have diminished urinary catecholamine responses to psychologic stress.^{1, 2} These reports raise the possibility that clinical asthma might be associated with diminished availability of endogenous catecholamines. In this study we have further examined this possibility by measuring the excretion of urinary free epinephrine and norepinephrine in asthmatic children who were asymptomatic and in children who were symptomatic with asthma. Results were compared with the catecholamine responses of asthmatic children after insulin-induced hypoglycemia.⁴

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MATERIALS AND METHODS

Subjects

The asthmatic children (mean age 11 years, range 8 to 15) were resident patients of the Children's Asthma Research Institute and Hospital (CARIH). Control urines were obtained from the normal children (mean age 10.5 years, range 5 to 18) of CARIH staff members. All urines were obtained by voiding. Subjects were hydrated orally to enhance urine flow and to permit complete emptying of the bladder at the beginning and termination of the collection period. The times of the day and the duration of each urine collection were noted.

Control specimens

Timed urine specimens from normal children were collected by the parents at home. Control urine specimens from asthmatic children were obtained in the CARIH dormitories or in the hospital when children were seen for routine examinations. The urines of asthmatic children were obtained when history and physical examination revealed that the patients were free from asthma and had taken no medications (oral or aerosol bronchodilators, theophylline compounds) for at least 4 hours. Some of the children were on corticosteroid treatment (prednisone on alternate days) and had received this medication on the day of the urine collection. Most of the control urine specimens from normal and asthmatic children were obtained after school hours, during the afternoon or early evening. In a few instances specimens were obtained during the morning. The average duration of the urine collection period in both groups was 90 minutes.

Asthma specimens

Urine specimens were obtained when children presented for treatment of acute symptoms or when asthmatic symptoms recurred while children were in the hospital after treatment of a previous severe episode. The patients were in moderate distress at the time of the urine collection but had not received regular medications or acute oral or aerosol bronchodilator therapy for at least 3 hours. None of the children included in this report had received parenteral epinephrine or aminophylline for at least 10 hours. Some of the children received corticosteroid treatment on the day of the urine collection. When children presented with symptoms, they were hydrated orally, asked to void, and the second urine specimen collected prior to the administration of any therapy other than nebulized isotonic saline (which was given with intermittent positive pressure). Alternatively, if the child could not tolerate postponement of treatment until completion of the urine collection, the specimen was discarded. For comparison with data in control subjects, most of the asthma specimens were obtained during the afternoon or early evening. No specimens were obtained at night or during the first hours after arousal from sleep (when catechol excretion values may be low). The average duration of the urine collection period was 55 minutes.

Response to insulin-induced hypoglycemia

The details of our protocol and some of our observations of the responses to insulin-induced hypoglycemia in asthmatic children have been described in previous reports.⁴⁻⁷ Studies were performed in the morning while children were at bed rest and fasting and had no medication for at least 12 hours. Two 60 minute timed urine specimens were obtained during the control period before administration of insulin. After insulin (0.1 U. per kilogram, given intravenously), consecutive, timed urine specimens were obtained for an additional 2 to 3 hours. The catecholamine responses during the postinsulin period were based on average excretion rates during the first 60 to 120 minutes after insulin. The mean duration of the postinsulin specimen was 99 minutes.⁴

Analysis of specimens

Urine specimens were collected into bottles containing sodium metabisulfite and immediately refrigerated. As soon as possible the volume was measured and an aliquot was stored

TABLE I. Urinary excretion of free epinephrine in normal children and in symptomatic and asymptomatic children with asthma

Group	No.	Epinephrine excretion (ng./min. $\pm$ S.D.)	Comparison with normal
Normal control	16	2.7 $\pm$ 1.3	
Asymptomatic asthma			
On steroid	13	4.6 $\pm$ 3.2	p < 0.05
Off steroid	16	5.2 $\pm$ 2.0	p < 0.001
Total	29	4.9 $\pm$ 2.6	p < 0.001
Symptomatic asthma			
On steroid	18	7.2 $\pm$ 4.9	p = 0.003
Off steroid	18	6.0 $\pm$ 2.9	p < 0.001
Total	36	6.6 $\pm$ 4.0	p < 0.001
Comparison of symptomatic versus asymptomatic asthmatic groups, p > 0.1 (not significant). Comparison of steroid-treated versus untreated groups, p > 0.1 (not significant).			

in the freezer (-10° C.). Urinary free epinephrine and norepinephrine were measured by a modification of the fluorometric trihydroxyindole method of Anton and Sayre.^{8,9} This procedure oxidizes the catecholamines at 2 different pH values and permits separate determination of the 2 amines. The analytic procedure is minimally influenced by the concentration of the urine⁸⁻¹⁰ (but specimens were obtained after hydration to reduce errors in voiding). The rate of catecholamine excretion is not influenced by differences in urine flow.¹⁰ Duplicate determinations as well as repetitive analyses in our laboratory agreed within less than 10 per cent. All results were expressed as average excretion rates (nanograms per minute). The catecholamine values were not corrected for loss during extraction and elution (average recovery = 80 per cent). Standard statistical methods were used to evaluate data.¹¹

RESULTS

Table I shows the mean rates of urinary free epinephrine excretion in normal control subjects and in asthmatic children. Epinephrine excretion was significantly lower in the normal children than in asthmatic patients (p < 0.001). When children were symptomatic with asthma, the mean rate of epinephrine excretion did not differ from that observed in asymptomatic patients (p > 0.1). There were no significant differences in the epinephrine excretion rates of corticosteroid-treated and untreated children.

Mean urinary excretion rates of free norepinephrine in normal control subjects and in asthmatic children are shown in Table II. Norepinephrine excretion was similar in all study groups. Although slightly higher norepinephrine excretion rates were observed when children were symptomatic with asthma, the excretion rates were not significantly elevated above those of either the asymptomatic asthmatic patients or the normal control subjects. There were no significant differences in the norepinephrine excretion rates of corticosteroid-treated and untreated asthmatic children.

Table III compares the catecholamine excretion rates during asthmatic symptoms with the responses of asthmatic children to insulin-induced hypoglycemia. Before insulin, epinephrine excretion was similar to the rates observed in the symptomatic as well as asymptomatic groups; mean norepinephrine excretion was similar to that of the asymptomatic patients. After insulin there was a marked (seven- to tenfold) increase in epinephrine excretion rate

TABLE II. Urinary excretion of free norepinephrine in normal children and in symptomatic and asymptomatic children with asthma

Group	No.	Norepinephrine excretion (ng./min. $\pm$ S.D.)	Comparison with normal
Normal control	16	14.4 $\pm$ 7.1	
Asymptomatic asthma			
On steroid	13	16.2 $\pm$ 6.2	p > 0.4
Off steroid	16	15.5 $\pm$ 5.3	p > 0.6
Total	29	15.9 $\pm$ 5.6	p > 0.4
Symptomatic asthma			
On steroid	14	19.2 $\pm$ 7.6	p > 0.05
Off steroid	18	18.4 $\pm$ 9.0	p > 0.1
Total	32	18.5 $\pm$ 8.6	p > 0.1

Comparison between all asymptomatic versus all symptomatic asthmatic patients, p > 0.1 (not significant). Subgroups, on and off steroid, symptomatic versus asymptomatic (not significant).

TABLE III. Comparison of urinary catecholamine responses to symptomatic asthma and to insulin-induced hypoglycemia in asthmatic children

Group	No.	Epinephrine excretion (ng./min. $\pm$ S.D.)	Norepinephrine excretion (ng./min. $\pm$ S.D.)
Asymptomatic	29	4.9 $\pm$ 2.6	15.9 $\pm$ 5.6
Symptomatic	36	6.6 $\pm$ 4.0	18.5 $\pm$ 8.6
Before insulin	41	5.3 $\pm$ 2.8	14.2 $\pm$ 5.9
After insulin	41	44.9 $\pm$ 22.0	20.0 $\pm$ 6.5

Epinephrine excretion before versus after insulin: p < 0.001. Norepinephrine excretion before versus after insulin: p < 0.001. Epinephrine excretion before insulin versus symptomatic and asymptomatic groups: p > 0.5 and p > 0.1, respectively; after insulin, p < 0.001. Norepinephrine before insulin versus asymptomatic: p > 0.2; versus symptomatic: p < 0.02. Norepinephrine after insulin versus asymptomatic: p < 0.01; versus symptomatic: p > 0.3.

(p < 0.001). Norepinephrine also increased after insulin (p < 0.001); the mean excretion rate was similar to that of symptomatic patients (p > 0.3) but was significantly higher than that of the asymptomatic group (p < 0.01). As described in detail elsewhere,⁴ corticosteroid treatment had minimal influence on the catecholamine responses to induced hypoglycemia.

The epinephrine response to induced hypoglycemia in asthmatic children was strikingly different from the epinephrine response to asthmatic symptoms. Additionally, a very interesting clinical effect was observed during the hypoglycemia studies. Since many of the tests were performed in conjunction with reduction and withdrawal of long-term corticosteroid therapy and since morning medications were withheld for the purpose of the test,^{4,5} children were occasionally symptomatic with asthma at the beginning of the study. A very striking observation was that the asthma cleared during the hypoglycemia test and that children remained asymptomatic for a period afterward. During almost 200 tests of the response to induced hypoglycemia in children with chronic asthma, no asthmatic episodes occurred during the test procedure. This observation contrasts markedly with our experience with asthmatic children during a variety of other investigations in which tests were often interrupted by the development of asthmatic symptoms.

DISCUSSION

The free epinephrine and norepinephrine excretion rates which we observed in asymptomatic asthmatic children were similar to those reported by a number of investigators who have studied normal children^{12, 13} and adults^{10, 14-16} in relatively nonstressful laboratory settings. The epinephrine results in our normal children were significantly lower than those of asthmatic patients and were also lower than those reported in most studies.

There are 2 factors which may have contributed to the observed differences between our normal and asthmatic groups. One was that in this study the urines of normal children were obtained by the parents at home in an attempt to measure normal catecholamine excretion rates in children under minimum stress; conversely, the urines of asthmatic children were obtained in a hospital environment. It is possible that the differences in epinephrine excretion reflect differing degrees of psychologic stress in the 2 groups. A second factor which cannot be excluded is that previous medications in the asthmatic children may have contributed to the catecholamine measurements or altered the metabolism of endogenous catecholamines.

In the population of asthmatic patients available for study, medication could not be withheld for a prolonged period. Therefore, most of the urine specimens in asthmatic children were obtained within a few hours after administration of ephedrine and/or theophylline compounds. Addition of those compounds to urine specimens, however, did not alter the catecholamine measurements.^{8, 9} Also, there were no differences in the epinephrine excretion of the symptomatic or asymptomatic children and the patients studied 12 hours after previous medication (control period of insulin-tolerance test). Urines of children who received epinephrine within the previous 10 hours were excluded from this study because of our observation (unpublished) that the urinary epinephrine values are elevated for several hours after parenteral administration. Urines of children who received isoproterenol (aerosol) within 3 hours were also excluded because this compound can influence urinary measurements.^{8, 9} Inhaled medication, however, usually has only a small effect on the urinary catecholamines.^{17, 18}

When the asthmatic children were symptomatic, epinephrine and norepinephrine were minimally elevated above the excretion rates during symptom-free periods. Other investigators have also observed the poor epinephrine responses to asthmatic symptoms but have suggested that norepinephrine or its metabolite, normetanephrine, increases during asthma.^{2, 3} In our study norepinephrine increased slightly during symptoms, but the excretion rates did not differ significantly from those of normal control subjects or asymptomatic asthmatic patients.

In contrast to the minimal change in epinephrine excretion during asthmatic symptoms, there was a marked increase in the epinephrine excretion rate after induction of insulin hypoglycemia. The epinephrine responses to hypoglycemia in our asthmatic children were entirely comparable to those observed by numerous investigators in normal individuals.^{12, 19-21} Moreover, the epinephrine excretion rates were comparable to those observed in asthmatic children during the first 1 to 2 hours after subcutaneous administration of 100 to 150 μ g of

epinephrine (0.1 to 0.15 ml. of a 1:1,000 solution) (unpublished observations). It has also been reported that the excretion of epinephrine in an asthmatic patient was similar to the response of a normal subject after administration of bacterial endotoxin.²² These observations indicate that asthmatic patients have the capacity to mobilize large amounts of epinephrine, at least under certain conditions, and raise the interesting question of why this does not occur in response to the "stress" of asthmatic symptoms. This question is particularly pertinent since animal studies have shown that hypoxia and the associated changes in P_{CO_2} normally evoke release as well as enhanced synthesis of catecholamines.^{23, 24} Perhaps, as may be the case in relation to psychologic stress,¹ there is an abnormality in the neurogenic signal for release of endogenous hormone. Alternatively, metabolic events associated with asthma may cause interference with the normal pathways for synthesis and release of hormones.

We have previously observed that there is also a discrepancy between plasma cortisol responses to asthma and to induced hypoglycemia.^{6, 25} Asthmatic children who were not receiving corticosteroids responded to hypoglycemia with a twofold increase in plasma cortisol concentration.⁶ However, when similar children (who were not receiving corticosteroids) were symptomatic with asthma, plasma cortisol concentrations increased minimally (2 μ g per 100 ml.) above the values observed at corresponding times of the day when the same children were asymptomatic.²⁵

The provocative observation that patients with moderate symptoms were able to clear their asthma spontaneously in conjunction with the mobilization of endogenous hormones after hypoglycemia suggests the possibility that defective mobilization of endogenous hormone in response to asthmatic symptoms may contribute to the disease process. These observations also suggest that it may be possible to promote endogenous hormonal release by other stimuli during the presence of asthmatic symptoms. It is of interest that the beneficial effects of insulin for the relief of asthmatic symptoms have been observed previously. In 1936, Wegierko²⁶ reported that patients who were markedly symptomatic with asthma had relief of symptoms after subcutaneous administration of insulin. After a 4 hour period of hypoglycemia (blood glucose concentration 40 mg. per 100 ml.), symptomatic improvement continued for an additional 10 to 18 hours. In the present study, the exact duration of clinical improvement after hypoglycemia was not documented since children were given their usual medications about 4 hours after the administration of insulin. However, in conjunction with the above report, our observations indicate that asthmatic patients can relieve their symptoms spontaneously, when they mobilize endogenous hormones.

In recent years considerable evidence has accrued that asthmatic patients may have an abnormality in peripheral tissue responsiveness to administered epinephrine, secondary to blockade or reduced function of the beta adrenergic receptors.²⁷⁻²⁹ Some of the data obtained in this laboratory are compatible with the above theory.⁷ We have found that despite mobilization of endogenous hormone after induced hypoglycemia,⁴⁻⁷ asthmatic patients have an abnormal delay in recovery of the blood glucose concentration which mirrors the responses observed in normal subjects after administration of a beta adrenergic antago-

nist.^{7, 30} These observations suggest that certain tissues in the asthmatic patient may respond abnormally to endogenous epinephrine. However, our results also suggest that during episodes of mild or moderate asthma patients do not mobilize sufficient quantities of the endogenous hormones (epinephrine, cortisol) which might help to relieve symptoms.

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