

Editorial Comment

Diagnosis of Pheochromocytoma

Reflections on a Controversy

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The optimal evaluation of patients suspected of having a pheochromocytoma remains controversial. The availability of large numbers of hormone assays and the need to exclude with certainty a potentially lethal disorder with an unpredictable course have led to various approaches to biochemical testing.

The quantification of the urinary excretion rate of catecholamine and catecholamine metabolites has been the mainstay of the diagnosis of pheochromocytoma. The most useful urine tests are those that measure concentrations of metanephrines (normetanephrine and metanephrine combined), vanillylmandelic acid (VMA), and free (unconjugated) catecholamines. The 24-hour urine collection is the standard. Nighttime urine collections,¹ 4- to 8-hour urine or single voided urine collections,² and random 1-hour urine specimens³ have been recommended. Each test varies in sensitivity and specificity, with urinary metanephrines having the best sensitivity and specificity.⁴ All are susceptible to chemical interference from drugs, with the measurement of metanephrines being least affected. Thus, assays of urinary metanephrines are adequate to diagnose pheochromocytoma in most patients. This test is readily available and relatively inexpensive.

However, urine collections can be inconvenient, inaccurate, and sometimes impossible in outpatient and even hospital settings. In addition, the pathophysiological significance and interpretation of urine tests are influenced by a number of factors. First, the handling of catecholamines by the kidney is dependent on excretory function.⁵ Intrarenal metabolic conversion, intrarenal release of norepinephrine, and an active renal tubular system for the catecholamines all contribute significantly to total excretion. Second, in pheochromocytoma, the activities of the enzymes involved in catecholamine synthesis (tyrosine hydroxylase, aromatic amino acid decarboxylase, and dopamine β -hydroxylase) are markedly enhanced, whereas the activities of the enzymes involved in catecholamine catabolism, monoamine oxidase, and cathecol-

o-methyltransferase, are reduced.⁶ Thus, excess amounts of newly synthesized norepinephrine that cannot be stored in the filled catecholamine storage vesicles may not be degraded and result in large amounts of circulating norepinephrine with relatively small increases in urinary catecholamine metabolites. These observations may account for the discordant relation among simultaneously measured plasma norepinephrine and epinephrine, urinary metanephrines, and VMA in some patients with pheochromocytoma.⁴ Using measurements in patients with essential hypertension as reference values, we found (Figure 1) that 25 of 43 patients had false-negative results for urinary VMA, whereas only nine had false-negative results for urinary metanephrines. In one patient, all three biochemical measurements were within the range of values in patients with essential hypertension. In another patient, an elevated level of urinary metanephrine was the only biochemical abnormality, and in three patients the only abnormal result was an elevated level of plasma catecholamines. All had sporadic pheochromocytoma; one had metastatic disease.

Precisely executed, the measurement of plasma catecholamines has proved of great diagnostic value in pheochromocytoma. We have found,⁷ as have others,⁸⁻¹⁰ that plasma catecholamine concentrations are invariably increased in the presence of pheochromocytoma whether patients are persistently hypertensive or are normotensive but have paroxysms of hypertension. Besides confirming the diagnosis, the use of plasma catecholamine assays in pheochromocytoma has other unique advantages: 1) it obviates the need for accurate collection of urine specimens, which are often difficult to obtain; 2) it permits the convenient collection of blood specimens during pharmacological testing; and 3) it permits the correlation of spontaneous or provoked changes in catecholamine production with cardiovascular responses.

In this issue, Grossman and coworkers¹¹ report their findings in a prospective study of 113 hypertensive patients (39 with and 74 without the tumor). They found that very high basal levels of catecholamines (i.e., plasma norepinephrine greater than 1,200 pg/ml; plasma epinephrine greater than 276 pg/ml; norepinephrine/dihydroxyphenylethylglycol ratio greater than 1.09; or dihydroxyphenylalanine greater than 7,000 pg/ml) indicated the presence of a pheochromocytoma. However, because of several

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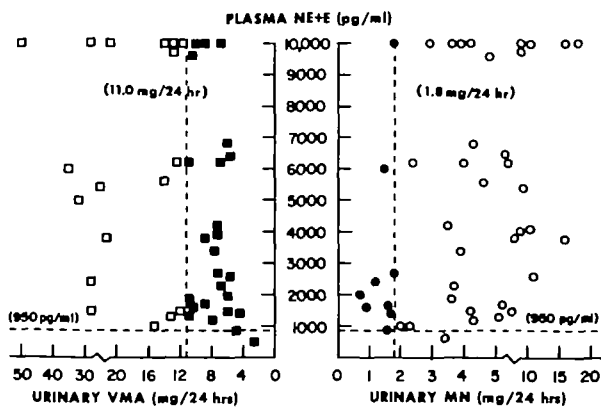


FIGURE 1. Scatterplot showing comparison of simultaneously measured indexes of catecholamine production in 43 patients with surgically confirmed pheochromocytoma. Horizontal broken lines represent the 95% upper confidence limits of values for urinary vanillylmandelic acid (VMA) (i.e., 11 mg/24 hr) and urinary metanephrines (MN) (i.e., 1.8 mg/24 hr) in 30 subjects with essential hypertension. NE+E, norepinephrine plus epinephrine. Solid symbols denote false-negative tests. Reprinted with permission.⁴

false-negative results, the overall sensitivity was only 77% but overall specificity was 99%. Basal plasma norepinephrine plus epinephrine was less sensitive than metanephrines (72% versus 86%) but equally as sensitive as VMA and more specific (99%) than either metanephrines (86%) or VMA (83%). These findings lend support to our contention⁴ that the simultaneous determination of plasma norepinephrine plus epinephrine and urinary metanephrines should suffice to detect most cases of pheochromocytoma.

The diagnostic dilemma in the workup of pheochromocytoma is to separate pheochromocytoma patients who harbor tumors with relatively low levels of biosynthetic activity from nonpheochromocytoma patients with a secondarily activated sympathetic nervous system. Pharmacological tests are designed to either provoke secretion by a pheochromocytoma or to suppress excessive activity of the sympathetic nervous system.

A provocative test is usually used when the clinical findings are highly suggestive of pheochromocytoma but catecholamine production is 1,000 pg/ml or less and blood pressure is only slightly increased (160/100 mm Hg or less). The glucagon stimulation test is widely used because it has few side effects.¹² Glucagon is given as an intravenous bolus dose of 1.0–2.0 mg after determination of the patient's pressor response to a cold pressure test. A positive glucagon test requires a clear increase (at least threefold or over 2,000 pg/ml in plasma catecholamines) 1–3 minutes after drug administration. A simultaneous increase in blood pressure of at least 20/15 mm Hg above the pressor response to a cold pressor test is desirable but not essential.

In patients with or without hypertension, the demonstration of moderate increases in plasma catecholamines (between 1,000 and 2,000 pg/ml) indicates that a suppression test should be used. The clonidine suppression test¹³ uses the ability of clonidine, a centrally acting α -adrenergic agonist, to suppress the release of neurogenically mediated catecholamine release. The test is based on the principle that normal increases in plasma catecholamines are mediated through activation of the sympathetic nervous system. In patients with pheochromocytoma the increases result, however, from the diffusion of excess catecholamines from the tumor into the circulation, bypassing normal storage and release mechanisms. Therefore, clonidine should not be expected to suppress the release of catecholamines in patients with pheochromocytoma.

Experience over the years indicates these tests to be safe and free of significant side effects with proper patient preparation.

In their article, Grossman and coworkers¹¹ also assessed the sensitivity and specificity of glucagon stimulation and clonidine suppression tests using previously published criteria.⁴ They found that the glucagon test alone had high specificity (100%) but low sensitivity (81%). On the other hand, the clonidine suppression test had high sensitivity (97%) but low specificity (67%). The results indicate that combined glucagon stimulation and clonidine suppression tests can be a useful tool in the definitive diagnosis of pheochromocytoma.

However, as demonstrated from this and another study,¹⁴ the clonidine suppression test may give false-positive results when performed on patients with normal resting plasma catecholamines. Unlike the authors,¹¹ who recommend performing the clonidine suppression test after a negative glucagon stimulation in patients with normal resting plasma catecholamines, we reserve the clonidine suppression test for patients with resting plasma catecholamines ranging from 1,000 to 2,000 pg/ml. Further, based on the principle of "utilizing tests for proper indications" it would not be possible to perform pharmacological testing during one outpatient visit since one would have no prior knowledge of basal test results.

Then what is the most cost-effective diagnostic approach to pheochromocytoma? The first step is to determine whether one is excluding or confirming the diagnosis. Exclusion demands sensitive tests; confirmation demands specific tests. In practice, biochemical testing has been used more often to exclude the possibility of pheochromocytoma than to confirm it. And because the benefits of treatment are enormous and the risks of missing the diagnosis are incalculable, diagnostic testing for pheochromocytoma demands a high degree of sensitivity. From this and other studies,⁴ it would appear that a precisely executed measurement of plasma catecholamines under resting conditions combined with either a clonidine suppression or a glucagon stimulation test provides the most cost-effective diagnostic approach to exclud-

ing pheochromocytoma in patients who are suspected to have the disease (see Table 5 of the article). If necessary a 24-hour urine collection for the measurement of metanephrines may be obtained for further corroboration.

Finally, the pretreatment evaluation for patients with pheochromocytoma calls for careful inquiry, painstaking observation, scientific testing, and prudent judgment. Laboratory testing should complement clinical judgment rather than replace it. Our ability to diagnose and treat pheochromocytoma has been enhanced by striking advances in our knowledge of human catecholamine metabolism, by the development of specific and sensitive chemical techniques for assaying catecholamines in biological fluids, and by advances in noninvasive localization techniques. Debate over the relative merits of these various tests will continue, and the availability of tests and expertise in any given center will dictate the nature of investigation in an individual patient. However, it seems likely that if it is reliably carried out, any test will serve as well as another provided the investigator is aware of the limitations and pitfalls of some of the diagnostic tests.

References

- Ganguly A, Henry DP, Yune HY, Pratt JH, Grim CE, Donohue JP, Weinberger MH: Diagnosis and localization of pheochromocytoma: Detection by measurement of urinary norepinephrine excretion during sleep, plasma norepinephrine concentration and computerized axial tomography (CT-scan). *Am J Med* 1979;67:21-26
- Kaplan NM, Kramer NJ, Holland OB, Sheps SG, Gomez-Sanchez C: Single-voided urine metanephrine assays in screening for pheochromocytoma. *Arch Intern Med* 1977;137:190-193
- Oishi S, Sasaki M, Ohno M, Sato T: Urinary normetanephrine and metanephrine measured by radioimmunoassay for the diagnosis of pheochromocytoma: Utility of 24-hour and random 1-hour urine determinations. *J Clin Endocrinol Metab* 1988;67:614-618
- Bravo EL, Gifford RW Jr: Pheochromocytoma: Diagnosis, localization and management. *N Engl J Med* 1984;311:1298-1303
- Baines AD, Craan AA, Chan W, Morgunov N: Tubular secretion and metabolism of dopamine, norepinephrine, methoxytyramine and normetanephrine by the rat kidney. *J Pharmacol Exp Ther* 1979;208:144-147
- Jarrott B, Louis WJ: Abnormalities in enzymes involved in catecholamine synthesis and catabolism in pheochromocytoma. *Clin Sci Mol Med* 1977;53:529-535
- Bravo EL, Tarazi RC, Gifford RW Jr, Stewart BH: Circulating and urinary catecholamines in pheochromocytoma: Diagnostic and pathophysiologic implications. *N Engl J Med* 1979;301:682-686
- Engelman K, Portnoy B, Sjoerdsma A: Plasma catecholamine concentration in patients with hypertension. *Circ Res* 1970;27(suppl 1):I-141-I-145
- Geffen LB, Rush RA, Louis WJ, Doyle AE: Plasma catecholamine and dopamine- β -hydroxylase amounts in pheochromocytoma. *Clin Sci* 1973;44:421-424
- Cryer PE: Pheochromocytoma and autonomic dysfunction. *Arch Intern Med* 1977;137:783-787
- Grossman E, Goldstein DS, Hoffman A, Keiser HA: Glucagon and clonidine testing in the diagnosis of pheochromocytoma. *Hypertension* 1991;17:733-741
- Lawrence AM: Glucagon provocative test for pheochromocytoma. *Ann Intern Med* 1967;66:1092-1096
- Bravo EL, Tarazi RC, Fouad FM, Vidt DG, Gifford RW Jr: Clonidine suppression test: A useful aid in the diagnosis of pheochromocytoma. *N Engl J Med* 1981;305:623-626
- Elliot WJ, Murphy MB: Reduced specificity of the clonidine suppression test in patients with normal plasma catecholamine levels. *Am J Med* 1988;84:419-424

KEY WORDS • pheochromocytoma • catecholamines • glucagon • clonidine