Published in final edited form as:

N Engl J Med. 2011 June 9; 364(23): 2268–2270. doi:10.1056/NEJMc1101502#SA1.

Drugs and Pheochromocytoma — Don't Be Fooled by Every Elevated Metanephrine

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To the Editor: A 51-year-old woman presented to our clinic in April 2010 with a 10-year history of hypertension and anxiety. The patient was concerned about pheochromocytoma because her identical twin sister had died at the age of 50 from metastatic pheochromocytoma. Her nephew and two grandsons were known to have mutations in the gene for succinate dehydrogenase subunit B (*SDHB*), which increases the risk of pheochromocytoma and paraganglioma.¹ Genetic analysis confirmed that she carried an *SDHB* mutation and therefore required careful follow-up evaluation. Her plasma normetanephrine level was 651 pg per milliliter (reference range, 0 to 145) — greater than four times the upper reference limit — which is reported to have a very high positive predictive value and 100% specificity for biochemically active pheochromocytoma and paraganglioma² (see the Supplementary Appendix, available with the full text of this letter at NEJM.org). However, she was taking venlafaxine, which may increase metanephrine and catecholamine levels as a result of decreased reuptake of norepinephrine.³

After discussion with her psychiatrist, we instructed her to discontinue the venlafaxine 2 weeks before the next assessment. The patient continued taking losartan, hydrochlorothiazide, and amlodipine. In the clinic, her blood pressure was 133/72 mm Hg, her heart rate was 94 beats per minute, and her physical examination was normal. The plasma normetanephrine level returned to normal at 101 pg per milliliter (reference range [different assay from that referred to earlier], 18 to 112), and the catecholamine and dopamine levels were normal (see the Supplementary Appendix). Thus, we thought that she did not have pheochromocytoma. Four months later, with the patient taking sertraline rather than venlafaxine, her metanephrine and catecholamine levels remained within the normal ranges.

Venlafaxine is more potent than the selective serotonin-reuptake inhibitors (SSRIs) as a norepinephrine reuptake inhibitor,⁴ which could explain the initial elevation in normetanephrine. However, SSRIs also inhibit reuptake of norepinephrine at the nerve terminal, as do tricyclic agents, and these medications should be avoided during the diagnostic evaluation. Other medications and substances may also interfere with the biochemical diagnosis of pheochromocytoma (Fig. 1). Caffeine intake, cigarette smoking, and other sympathomimetic factors may increase catecholamine levels through the

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Disclosure forms provided by the authors are available with the full text of this letter at NEJM.org.

adrenergic receptors and should be discontinued for at least 24 hours before a blood sample is obtained.^{2,5} Conversely, α -adrenergic-receptor blockers and β -adrenergic-receptor blockers may reduce catecholamine-related symptoms and signs and thus mask pheochromocytoma. Monoamine oxidase inhibitors block the conversion of norepinephrine to dihydroxyphenylglycol, resulting in a greater release of norepinephrine.³ Paracetamol or acetaminophen may interfere with high-performance liquid chromatographic assays and should also be avoided before blood sampling.²

This case illustrates that elevated plasma metanephrine levels do not always prove the presence of pheochromocytoma and justify costly imaging studies. Before blood is drawn to measure metanephrine and catecholamine levels, patients should discontinue all medications and substances that could interfere with the results. Furthermore, patients with a genetic predisposition to pheochromocytoma require careful surveillance without the confusing effects of drug-induced elevations of catecholamines and metanephrines.

Acknowledgments

Supported by the intramural program of the Eunice Kennedy Shriver National Institute of Child Health and Human Development.

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Figure 1. Mechanisms of Pharmacologic Interference with Catecholamines and Metanephrines
 Sympathomimetic agents such as ephedrine, amphetamine, caffeine, and nicotine increase the release of norepinephrine and epinephrine. Monoamine oxidase (MAO) inhibitors block the conversion of norepinephrine and epinephrine to dihydroxyphenylglycol (DHPG), leading to increased concentrations and availability of these two catecholamines. Drugs that inhibit norepinephrine and epinephrine reuptake, such as serotonin–norepinephrine reuptake inhibitors (e.g., venlafaxine), “selective” serotonin-reuptake inhibitors, and tricyclic antidepressants, lead to increased concentrations of norepinephrine and epinephrine in the synaptic clefts. The α -adrenergic-receptor blockers and β -adrenergic-receptor blockers reduce the effects of catecholamines on end organs such as the brain, heart, gastrointestinal tract, and others. DOPA denotes dihydroxyphenylalanine.