Catecholamine Measurements in Pheochromocytoma and Neuroblastoma

HERBERT E. SPIEGEL, PH.D.

Clinical Biochemistry Laboratory, Hoffmann-La Roche Inc., Nutley, NJ 07110

ABSTRACT

The metabolic pathways for the catecholamines and their metabolites are presented. Typical urinary metabolite patterns are illustrated for cases of neuroblastoma and pheochromocytoma. Representative methods for performing the analysis of some catecholamine compounds and their metabolites are outlined.

Pheochromocytomas are catecholamine producing tumors derived from chromaffin cells. In these tumors, the biosynthetic and metabolic pathways proceed along the same pathway as in normal catecholamine secreting tissue. This pathway is summarized in figure 1.

Neuroblastoma and ganglioneuromas are other catecholamine secreting tumors. These tumors arise from the neural crest ectoderm and consequently are found wherever sympathetic neural cells are located. The biochemical machinery of these tumors does not permit the conversion of norepinephrine to epinephrine because the cells do not have the enzyme phenylethanolamine N-methyltransferase. Some tumors have recently been shown to be deficient in dopamine beta hydroxylase in tissue culture. Twenty percent of patients with these tumors have elevated homovanillic acid (HVA) and dopamine in their urine but excrete normal levels of vanilmandelic acid (VMA) and normetanephrine. Others have only elevated vanilmandelic acid with all other metabolites excreted within normal limits. Quantitative homovanillic acid determinations are useful to detect the recurrence of tumors after they are surgically removed. Elevated homovanillic acid excretions in patients with pheochromocytoma are usually thought to indicate malignancy. Abnormal catecholamine production in patients with pheochromocytoma is usually reflected in plasma catecholamine levels.

In screening hypertensive patients for pheochromocytoma, urine specimens are assayed for total or free catechols, total or conjugated metanephrines or VMA, depending on the preference of the laboratory. In one study 23 percent of the patients who were found to have pheochromocytoma had VMA excretion rates within normal limits but their excretion rates of the catecholamine were elevated. Patients with pheochromocytoma may also have borderline excretion rates of 6 to 10 μg per hr of catecholamines as can patients who have had surgery or have congestive heart failure. Usually, in patients with pheochromocytoma catecholamine levels of 6 to 10 μg
CATECHOLAMINE MEASUREMENTS IN PHEOCHROMOCYTOMA AND NEUROBLASTOMA

TABLE I

<table>
<thead>
<tr>
<th></th>
<th>Normal µg/hr</th>
<th>Pheochromocytoma µg/hr</th>
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<tbody>
<tr>
<td>Norepi Epi</td>
<td>2.5 ± 0.8</td>
<td>&gt;10*</td>
</tr>
<tr>
<td>Normeta Meta</td>
<td>16 ± 5</td>
<td>&gt;60</td>
</tr>
<tr>
<td>VMA</td>
<td>2.40</td>
<td>&gt;500*</td>
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*Some patients have borderline excretions of 6 to 10 µg per ml.
†Twenty-three percent of patients in normal range.

per hr will exhibit a rise in metanephrines of three to four times the normal level with a VMA only slightly elevated.† Representative urinary metabolite levels for patients with pheochromocytoma and neuroblastoma are depicted in tables I and II.

The urinary profiles of catecholamines and their metabolites in patients with ganglioneuroma and neuroblastoma do not always show a clear pattern. In some patients, norepinephrine and epinephrine, dopamine, VMA and HVA were all elevated. In other patients, only some of the metabolites were high. These selected patients show an elevation in dopamine level most consistently. Correlated with these findings is the observation that dopac is elevated in patients with neuroblastoma. Von Studnitz et al. showed more consistent rises of dopamine than the other catecholamine metabolites particular the metanephrines. The data of Von Studnitz are summarized in table II.

Measurement of abnormal levels of nor-

![Figure 1. Major metabolic pathway of the catecholamine.](image-url)
epinephrine and epinephrine, dopamine, the metanephrines, homovanillic acid and vanilmandelic acid may all be necessary to help confirm a diagnosis of a catecholamine secreting tumor. The literature abounds with methods for the determination of each of these chemical substances. Urinary nor­epinephrine and epinephrine levels may be measured with the method shown in figure 2.10

The DOPA, DA, NE, and E are all assayed by fluorometry after being converted to di and trihydroxy indole derivatives. In figure 3 is shown the fluorescence analysis of urinary HVA.8

In figures 4 and 5 are shown the extrac­tion and spectrophotometric method for VMA and the column and spectrophotometric assay of metanephrines.6,7

This brief survey has not included high voltage electrophoresis methods, paper chromatographic methods or the colorimetric screening procedure now incorporated into a dip stick. All of these latter methods depend on the reaction of diazotized p-nitroaniline forming a purplish color with either VMA, the metanephrines or both. The specificity of the dip stick is questionable; with the possibility of false positives and probably false negatives this test should be used with caution.
References