EDITORIAL

Impact of commonly used drugs on 24-hour urine metanephrine excretion

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We read with great interest the study by Kokoszka et al[1] published in this issue of *Polish Archives of Internal Medicine*, which evaluated the effect of commonly used drugs on 24-hour excretion of urinary fractionated metanephrines. This widely-used assay was evaluated in a cohort of 1051 patients with adrenal incidentalomas for the screening of pheochromocytoma. The study from the Jagiellonian University Medical College confirms strong influence of commonly used drugs on the urinary excretion of metanephrines. This is an important issue, since we know that there are several comorbidities, and especially drugs, that may interfere with metanephrine determination leading to false-positive results.[2] Remarkably, patients are usually instructed about the foods to avoid 3–4 days before urine collection, even though some studies indicate that amine-rich foods have no relevant effect on free plasma or urine metanephrines.[3] In contrast, no specific recommendations on drugs are provided, even though probably some of them should be withdrawn.

As outlined in the Endocrine Society Clinical Practice Guidelines on pheochromocytomas and paragangliomas (PPGLs), biochemical testing for catecholamine-producing PPGLs is recommended to include measurements of free plasma or fractionated urine metanephrines.[4] One of the most important points to take into account in metanephrine evaluation is the laboratory assay used. It is known that liquid chromatography coupled with mass spectrometry (LC-MS/MS) offers numerous advantages over other analytical methods. Currently, it represents the gold standard for measurements of urine fractionated metanephrines and plasma free metanephrines, including 3-methoxytyramine. LC with electrochemical detection is also a reliable technique for determination of these compounds.[4] As shown by Kin et al,[5] the measurements of urine fractionated metanephrines by MS provide excellent sensitivity (97%) and even higher specificity than the plasma metanephrine measurement (94.2% vs 75.6%; P <0.001) for the diagnosis of pheochromocytoma. Nonetheless, to ensure high diagnostic accuracy, when measuring the 24-hour urinary excretion of fractionated metanephrines, urinary creatinine should be determined to verify completeness of urine collection.[4]

Kokoszka et al[1] found that the patients on β-blockers, calcium channel blockers (CCBs), loop diuretics, α-blockers, nonmetformin antidiabetic drugs (NMADs), and neuroleptics had significantly higher levels of urinary normetanephrine excretion than the patients not using these drugs. On the other hand, the patients treated with thiazide diuretics, metformin, lipid lowering drugs (LLDs), and proton pump inhibitors (PPIs) had similar levels of urinary normetanephrine to the individuals not taking these drugs. It should be considered that phenylethanolamine N-methyltranferase (PNMT) is an enzyme responsible for methylating norepinephrine to epinephrine.[6] Thus, the drugs that decrease PNMT activity, elevate normetanephrine levels. This is the case for β-blockers, CCBs, loop diuretics, neuroleptics, and α1-blockers. The latter also increase concentration of metanephrine due to reflex sympathetic stimulation. The effect of NMADs is unclear, but they are known to decrease metanephrine and increase normetanephrine levels.[7]

Regarding the influence of various drugs on the 24-hour metanephrine excretion, the use of α-blockers resulted in a reflex sympathetic stimulation, which was probably responsible for an increased metanephrine concentration in urine. This dependency should be evaluated in patients with hypertension or benign prostate hyperplasia, since the increase reached 50%. Thus,

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treatment withdrawal could be considered. In contrast, in the patients taking NMADs, antidepressants, or glucocorticosteroids (GCSs), decreased urinary metanephrine excretion was observed. Both NMADs and antidepressants seem to decrease the activity of PNMT.[6,7] The impact of GCSs should be evaluated cautiously, since these drugs stimulate the activity of PNMT,[6] and an increase in urinary metanephrines is expected.

In the study by Kokoszka et al,[1] no differences in the 24-hour excretion of 3-metoxytyramine was observed between the patients taking and not taking the analyzed drugs, except for its lower excretion in the patients treated with levothyroxine (LT4) in the univariate analysis. This finding could be related to the fact that the activity of catechol-O-methyltransferase, which is necessary for 3-metoxytyramine production, is not affected by other drugs.[8] Importantly, according to the multivariate analysis, LT4 did not affect the excretion of any metabolite in urine, which could have been expected, since tyrosine hydroxylation results in increased serum L-3,4-dihydroxyphenylalanine levels.[9]

Nevertheless, the work of Kokoszka et al[1] did not describe the percentage of false-positive results in the patients treated with these interfering drugs. In our opinion, this is a key issue, since if the influence of these drugs is minimal, that is, not leading to excess of metanephrines above the established upper limit of reference, there is probably no need to change the treatment regimen before urine collection. However, if the percentage of false-positive results is high, the most cost-effective approach would be to change the interfering medication, if feasible. Another point to consider is the magnitude of the excess, since when the increase is 3-fold or more above the upper cutoff, the current recommendation is to perform an imaging test, while for mild excess the clonidine suppression test with measurements of plasma normetanephrine is a useful tool for a differential diagnosis of mildly elevated metanephrine levels and true-positive elevations.[4] Diagnostic specificity of 100% with sensitivity of 97% were reported considering a 40% decrease in plasmatic normetanephrine levels after 3 hours of adminstration of clonidine, as compared with baseline levels, as the criteria to differentiate false-positive results and endogenous hypersecretion.[10] Another potential limitation of the study by Kokoszka et al[1] is the fact that most patients are usually treated with several drugs that may affect metanephrine levels, so it is difficult to stablish an isolated effect of each drug in metanephrine concentrations. To clarify this point, the patients treated with a single drug in monotherapy should be evaluated separately. In addition, the authors did not provide information on distribution of different comorbidities, such as renal failure, ischemic stroke or intracerebral hemorrhage, or obstructive sleep apnea (OSA), which can potentially affect plasma and urinary metanephrine and normetanephrine concentrations.[11-13] A recent study evaluating the influence of OSA on the levels of urinary and plasma metanephrines found that 27.9% of OSA patients had elevated levels of plasma and/or urinary metanephrines. In addition, the report described more false-positive results for urinary metanephrines than for plasma metanephrines in these patients (25.4% vs 3%; P <0.001).[13] Thus, information about the prevalence of OSA should be provided when drug interference is evaluated.

ARTICLE INFORMATION

DISCLAIMER The opinions expressed by the author(s) are not necessarily those of the journal editors, Polish Society of Internal Medicine, or publisher.

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