Netherlands
The Journal of Medicine

EDITORIAL

Is there still a place for pharmacological testing for phaeochromocytoma?

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Phaeochromocytoma and extra-adrenal paragangliomas are rare catecholamine-producing tumours which, if not timely and properly diagnosed, may result in catastrophic consequences.[1] Definite exclusion or confirmation of the tumour is of utmost clinical importance. For this purpose several biochemical tests are available with those measuring metanephrines as the most accurate ones. Even at a very high prior test probability (for instance 75%), the test of plasma free metanephrines has negative and positive predictive values of nearly 95%.[2] In contrast, at a very low prior test probability of, for instance, 1%, the negative predictive value of plasma free metanephrines approaches 100% but the positive predictive value drops to 6%. Thus, both plasma and urinary metanephrines have a high sensitivity but a limited specificity and this means that they are fraught with a rate of false-positive test results of 20 to 30%, and less then 5% false-negative test results.[2] False-positive results are encountered in patients with slight increments of plasma metanephrines (<4 x the upper reference limit) or of urinary metanephrines (<2 x the upper reference limit) but no phaeochromocytoma. Several causes of false-positive test results such as medications and inappropriate sampling conditions can be dealt with appropriately. Another cause of a false-positive test result, which is more difficult to handle, is an increased secretion of catecholamines or metanephrines that is unrelated to phaeochromocytoma. This applies to several other clinical conditions that are associated with an increased secretion of catecholamines due to an increased sympathetic activity. Conversely, because of a rare false-negative test result, an occasional patient with a phaeochromocytoma may be missed with these tests. False-negative test results may occur in the event of a very small phaeochromocytoma or episodic catecholamine secretion by the tumour.

In the last 60 years several pharmacological tests have been developed to unmask the presence of a phaeochromocytoma. These include glucagon, histamine and tyramine provocation tests, and clonidine and pentolinium suppression tests. The glucagon test and the clonidine test are the most widely used. Despite their use in several studies, abnormal responses of plasma catecholamines are not uniformly defined. Most papers traditionally rely only on the response of plasma norepinephrine levels for both glucagon and clonidine test. More importantly, normal responses of plasma catecholamines to these agents have hardly been assessed in healthy asymptomatic subjects. Finally, only a few small populations of mostly symptomatic patients, who appeared to have no phaeochromocytoma, have been studied as reference populations.

In the current issue, Bisschop *et al.* describe their results of the glucagon and clonidine test in 11 patients with a phaeochromocytoma and in 44 patients in whom a phaeochromocytoma was considered to be excluded.[3] For both tests, plasma norepinephrine responses were used as test outcome. Sensitivity and specificity of the glucagon was 30 and 100%, respectively, whereas the clonidine test was not considered to be diagnostic at all. Although the study sample includes only 11 patients with phaeochromocytoma, the authors should be commended for this prospective clinical study. Based on their findings, the authors conclude that both tests are obsolete and should be abandoned. However, in our opinion, the practical implications of their results are not the same for both tests.

The glucagon test was originally designed by Lawrence in 1967 to unmask a phaeochromocytoma in patients with hypertension.[4] In the earlier years, an excessive blood pressure response to glucagon over that to a cold pressor test was considered diagnostic but later the response of plasma catecholamines (particularly plasma norepinephrine) was used. Since this is a provocation test,

one would expect this test to be performed in patients with normal or only slightly elevated plasma catecholamines. Up to now, several small studies have been carried out with maximal sensitivity of 81%.[5] In contrast, in the current study sensitivity was only 30%. This disparity is probably related to different inclusion criteria (such as inclusion of patients with increased or normal baseline plasma norepinephrine levels, patients with or without genetic predisposition) and different diagnostic criteria. Whatever the reason, it is quite clear, also from previous studies, that the glucagon test lacks sufficient sensitivity to rule out phaeochromocytoma. Taking into account the small risk of side effects (10 to 20% of the patients need phentolamine treatment for excessive blood pressure responses) and irrespective of its excellent specificity, the authors are correct that the glucagon test should be abandoned in clinical practice. Finally, the most definite argument to stop using this test is its redundancy because the sensitivity of basal plasma free metanephrines is already almost optimal, being 97% in patients with a genetic predisposition and 99% in patients with an apparently sporadic phaeochromocytoma.[2]

The findings of the clonidine test in the study by Bisschop *et al*. has a different clinical implication. This test, designed by Bravo in 1981, was introduced to distinguish false-positive test results (for instance due to sympathetic activation) from true-positive test results (patients with phaeochromocytoma).[6] Also for this test, plasma norepinephrine responses have been employed in most studies. Similar to the glucagon test, this test has also been performed in patient cohorts with different baseline plasma norepinephrine levels. Even more importantly, several different diagnostic criteria as test parameter have been used. Some studies used a plasma norepinephrine level of >2.96 nmol/l after clonidine as diagnostic criterion while others used this criterion and/or a plasma norepinephrine response of <50% three hours after clonidine administration. The sensitivities reported in previous studies varied between 97 to 99% while we came to a sensitivity of only 67%.[7] The current study, also using plasma norepinephrine responses, found a sensitivity of only 20% with a specificity of 93%, suggesting that this test lacks diagnostic power altogether. These significant differences are probably due to differences in patient inclusion and in the diagnostic criteria used.

This situation is, however, different when plasma normetanephrine instead of plasma norepinephrine is used as test marker. If plasma normetanephrine is used (failure to suppress defined as a decrease of <40% from basal and a persistent increased basal plasma normetanephrine of >0.60 nmol/l), sensitivity and specificity improve to 96 and 100%, respectively.[7] Similar results have been described both in patients with an apparent sporadic phaeochromocytoma and in those with a genetic syndrome. Thus, while lack of suppression of plasma norepinephrine or normetanephrine both provide strong evidence for phaeochromocytoma, only the suppression of normetanephrine provides reliable evidence that a phaeochromocytoma is not present.

Therefore, in contrast to the glucagon test, which indeed should be omitted from our diagnostic armoury, there is still a place for the clonidine test in patients with slightly elevated baseline plasma metanephrines or catecholamines, provided the response of plasma normetanephrine is used instead of plasma norepinephrine. The improved availability of measurements of plasma metanephrines guarantees that this test can still be used in daily clinical practice.[8]

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