Retrospective analysis of abnormal 24-h urinary free catecholamine concentration in screening for phaeochromocytoma

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Abstract

Background Patients with hypertension often have increased 24-h excretion of urinary free catecholamines (UFCA) compared with normotensive patients, but the extent to which β-blockade and other antihypertensive agents affect 24-h UFCA concentrations remains unclear. Consequently, many patients with slightly elevated 24-h UFCA concentrations are not adequately investigated for the presence of phaeochromocytoma.

Method We undertook a retrospective study on patients with at least one abnormal 24-h urinary collection of adrenaline (Adr), noradrenaline (NA) or dopamine (DA) between July 1997 and December 1999 to assess these issues.

Results Of the 168 patients identified with raised 24-h UFCA concentrations, 106 with hospital notes were audited. Of the 46 patients whose values were more than twice the upper reference limit, 24 had their result confirmed with a repeat sample and only 10 underwent computed tomography or m-iodobenzylguanidine scanning. Two patients of these 10 had a phaeochromocytoma. We observed that hypertension correlated with significantly increased NA excretion compared with normotensive patients (median value 490 ± 222 nmol per 24 h versus 304 ± 229 nmol per 24 h, $P < 0{\cdot}005$). Patients on β-blockers showed a trend towards significantly increased NA excretion ($P = 0{\cdot}08$).

Conclusions Many patients with abnormal 24-h UFCA excretion are not thoroughly investigated for the presence of phaeochromocytoma. NA concentration is significantly raised above the reference limit for patients with hypertension, and the use of β-blockers showed a trend towards a further elevation in NA concentrations. Care must therefore be taken when interpreting abnormal NA concentrations in patients with hypertension or in those taking β-blockers.

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Introduction

The measurement of 24-h urinary free catecholamines (UFCA) by high-performance liquid chromatography (HPLC) is widely regarded as a sensitive and specific screening test for the presence of phaeochromocytoma. However, studies investigating the effects of β-blockers on 24-h UFCA excretion have produced conflicting results, such as evidence of falsely high metanephrine concentrations with sotalol[1] and falsely low noradrenaline (NA) concentrations with bufuralol, propanolol and labetolol.[2,3] To compound these problems of interpretation, systemic hypertension *per se* has also been shown to be associated with higher catecholamine excretion,[4] and the 24-h UFCA output is a continuum among normotensive and hypertensive populations as well as in those with phaeochromocytoma. Consequently, higher reference limit [NA < 570 nmol per 24 h, adrenaline (Adr) < 120 nmol per 24 h, dopamine (DA) < 3500 nmol per 24 h] based on an in-house study in Nottingham City Hospital (J Wardell, personal communication) were used for abnormal 24-h UFCA results in the hypertensive population (normotensive reference limits: NA < 430 nmol per 24 h, Adr < 70 nmol per 24 h, DA < 2700 nmol per 24 h).

Table 1. Urinary catecholamine excretion (nmol per 24 h) in hypertensives and normotensives

	Hypertensives (n = 85)	Normotensives (n = 21)	P-value
Noradrenaline	490 (222)	304 (229)	0·005
Adrenaline	72 (62)	81 (31)	0·4 (NS)
Dopamine	2057 (1461)	1557 (1116)	0·3 (NS)

Results are expressed as median (± interquartile range). NS, not significant.

Table 2. Catecholamine excretion (nmol per 24 h) in various treatment groups

	No treatment (n = 35)	β-blocker only (n = 17)	Combination treatment, without β-blocker (n = 36)	P-value
Noradrenaline	453 (255)	515 (211)	479 (216)	0·08
Adrenaline	71 (50)	75 (53)	72 (72)	NS
Dopamine	2190 (1651)	2027 (1102)	2046 (1354)	NS

Results are expressed as median (± interquartile range). Patients taking a combination treatment that included a β-blocker were excluded from this study. NS, not significant.

We therefore undertook a retrospective case-note study on patients who had at least one abnormal 24-h urinary collection of free NA, Adr or DA to assess these issues.

Methods

All patients with at least one recorded abnormal 24-h UFCA collected in the pathology department at Kings Mill Centre between July 1997 and December 1999 were identified and their notes were audited. Patients with hypertension (>160/90 mmHg) were further categorized into those who were not on any antihypertensive agents, those who were on β-blocker only and those who were taking a combination of antihypertensive agents (but not β-blocker).

UFCA concentrations were measured using reversed-phase HPLC with electrochemical detection. Sample clean-up was achieved using weak cation-exchange chromatography followed by alumina absorption.[5]

The Mann–Whitney *U*-test was used to compare two non-parametric variables and ANOVA was used to compare differences between more than two variables.

Results

Patients' characteristics and investigative outcomes

Between July 1997 and December 1999, 168 patients had at least one abnormal 24-h UFCA result. Of these, 92 (54%), 102 (61%) and 43 (26%) had an abnormal urinary excretion of NA, Adr or DA, respectively. One hundred and six patients whose notes were available were audited. They had a median age of 42 years (range 25–85); 80% were hypertensive and 67% of these were taking antihypertensive agents.

Of the hypertensive patients, 57 (56%) had values exceeding the currently defined hypertensive catecholamine reference limit. Of the 46 (45%) patients with 24-h UFCA values more than twice the upper reference limit, only 24 (52%) had their results confirmed with a repeat sample. Of these 46 patients only 10 underwent computed tomography (CT) scan or *m*-iodobenzylguanidine scan, two of whom had a phaeochromocytoma.

Effect of hypertension and antihypertensive agents on 24-h UFCA

Hypertension was found to be associated with a significantly increased 24-h urinary excretion of NA (but not Adr or DA) compared with the normotensive group ($P < 0{\cdot}005$) (Table 1). Patients on blocker alone or on a combination of antihypertensive agents showed a trend towards significantly increased NA excretion ($P = 0{\cdot}08$) (Table 2). When these two groups were compared individually to the hypertensive group receiving no treatment, they both showed a significant increase in NA excretion but not Adr or DA excretion ($P = 0{\cdot}05$).

Discussion

Twenty-four-hour UFCA output in patients suspected of having phaeochromocytoma is regulated by complex interactions between antihypertensive agents and their haemodynamic effects on endogenous catecholamine excretion. Three clinically relevant observations have emerged from this study.

First, this study highlighted a number of patients in our hospital with raised 24-h UFCA concentrations,

who had not been adequately investigated for the presence of phaeochromocytoma. The reason for this remains speculative and may reflect the diverse speciality and/or experience of investigating physicians. Furthermore, the poor positive predictive value of the 24-h UFCA as a screening for phaeochromocytoma may be a well-recognized fact among general physicians, which may again contribute to these observations. Steps will be taken by our department to improve our 24-h UFCA reporting system to include advice on further investigation and/or referral. In addition, we are also reassessing the methodology of our UFCA measurement and reference limits.

Second, these results show that NA concentrations (but not Adr or DA concentrations) are significantly elevated in patients with hypertension to a concentration beyond the hypertensive reference limit, such that a modification of the currently utilized hypertensive reference limit for NA concentrations may be necessary. Indeed, increasing the upper reference limit may partly ameliorate the problem of false positives, but this needs to be balanced against the risk of false negatives.

Third, our results suggest that the use of β-blockers (in patients with hypertension) may induce a further increase in 24-h urinary NA excretion (but not of Adr or DA) compared with hypertensive patients not receiving any drug treatment. This may be surprising because β-blockers are thought to suppress sympathetic activation and consequently a reflex reduction in endogenous catecholamine excretion.[6] Interestingly, McGrath *et al.*,[7] in a randomized control trial similarly showed that, in postmyocardial infarction patients, urinary catecholamine excretion was consistently high in patients given a β-blocker compared to the placebo group. These apparently contradictory reports of the effect of β-blocker on 24-h UFCA excretion may be partially explained by the dependence of its hypotensive effect on pretreatment plasma renin activity, the latter postulated to be regulated by endogenous catecholamine secretion.[8] It is of note that the use of β-blockers in patients suspected of phaeochromocytoma is indeed inappropriate in the absence of complete α-blockade, but this may, however, be a reflection of inadequate knowledge and/or inadequate suspicion of the referring physicians.

Increased vigilance among physicians is therefore necessary when interpreting abnormal 24-h UFCA results for hypertensive patients who are taking antihypertensive agents. A revised reporting system that includes advice on repeat samples, referrals to appropriate physicians and the use of diagnostic imaging may improve the follow-up of patients with abnormal 24-h UFCA excretion and thus minimize false negative diagnoses.

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