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CURRENT PRACTICE

Catecholamine measurements in clinical medicine

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Introduction

There are 3 endogenous catecholamines, noradrenaline, adrenaline and dopamine. Noradrenaline is the neurotransmitter in sympathetic nerve endings, while the adrenal medulla secretes mainly adrenaline. The reason for this difference is that adrenaline synthesis from noradrenaline is catalyzed by an enzyme, phenylethanolamine-N-methyltransferase (PNMT), which is absolutely dependent on induction by glucocorticoids (Wurtman and Axelrod, 1966); only in the normal adrenal medulla is there a high local concentration of cortisol due to the portocapillary circulation from cortex to medulla. There is little circulating dopamine, whereas in urine, dopamine is the predominant catecholamine. It is formed within the kidney from circulating DOPA (Brown and Dollery, 1981), but earlier reports that it may have a natriuretic action have not been confirmed (Alexander *et al.*, 1974; Oates *et al.*, 1979).

If the clinical requests for catecholamine analyses received by our laboratory are representative, the overwhelming majority of such analyses are performed for research purposes—usually research related to hypertension and anti-hypertensive drugs. The main non-research reason for requests is, without doubt, as an aid in the diagnosis of phaeochromocytoma, and this will be the principal subject of the review. Before turning to this, other indications or possible indications will be discussed.

Autonomic neuropathy

This condition, after phaeochromocytoma, is the main indication for catecholamine measurements. In normal subjects, plasma noradrenaline concentration rises 2-fold from the supine to standing position. This increase may be exaggerated if orthostatic hypotension is caused by non-neuropathic disease such as salt wasting. In patients with an autonomic neuropathy, there is no postural rise in plasma noradrenaline concentration. The supine plasma noradrenaline concentration provides an indication of the extent of nerve-ending degeneration. In theory, lesions in the afferent nerve, central nervous system (CNS) or preganglionic nerve do not cause any fall in the supine plasma noradrenaline concentration, for instance, in Shy-Drager syndrome. In practice, such theoretical subdivisions disappear with advanced disease, and have not rendered treatment of orthostatic hypotension any less empirical (Ziegler, Lake and Kopin, 1976, 1977). One recent drug which may prove a more 'logical' therapy of this condition is the α_2-receptor antagonist, RX 781094. This increases plasma noradrenaline concentration partly by blocking CNS α-adrenoceptors, and partly by uncoupling the negative feedback loop which exists at sympathetic nerve endings (Langer, 1977). It is, in short, a clonidine 'antidote', and has opposite effects from those of clonidine on noradrenaline release and blood pressure (Clifford, Day and Orwin, 1982).

Treatment of heart failure

One of the commonest pathological causes of raised plasma catecholamine levels is cardiac failure; the levels fall when the failure is treated (Chidsey, Braunwald and Morrow, 1965; Wenting *et al.*, 1983). Salt depletion also elevates catecholamine values, so that, in theory, sequential plasma catecholamine analysis in a heart failure patient might facilitate optimal use of diuretic therapy and avoid excessive desalination (Romoff *et al.*, 1979; Nicholls *et al.*, 1980). I am not aware of any practical experience with such a technique.

Testing compliance with antihypertensive therapy

Many antihypertensive drugs alter plasma noradrenaline concentration. Most extreme are the reduction by clonidine (Dollery *et al.*, 1976; Watkins *et al.*, 1980) and increase by vasodilator drugs such as hydralazine, nifedipine and minoxidil (Murphy *et al.*,

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1982). Indeed, vasodilator drug therapy is the commonest cause of elevated vanillylmandelic acid (VMA) excretion in the hypertension clinic. On the other hand, hospitalization reduces catecholamine release and blood pressure (Hossman, Fitzgerald and Dollery, 1981). This is a confusing factor when trying to assess previous compliance with drug therapy in patients admitted to hospital with poorly controlled hypertension. Since some vasodilator drug has usually been prescribed by the time the step of hospitalization is reached, catecholamine analysis may (to speculate again) differentiate patients whose blood pressure falls in hospital because of previous non-compliance from those in whom blood pressure falls precisely because of hospitalization. In the former group, catecholamine secretion would be expected to rise as a result of re-institution of vasodilator therapy, overriding the effects of hospitalization seen in the latter group.

Parkinsonian patients

Response to L-DOPA therapy is notoriously variable. One cause seems to be variable absorption and/or distribution of the L-DOPA and both the extent and duration of the response to therapy correlates well with the plasma DOPA concentration (Rosser *et al.*, 1980). So in parkinsonian patients' resistant to therapy, it may be worth assessing whether they fail to achieve adequate plasma DOPA levels.

Diagnosis of phaeochromocytoma

It is useful for diagnostic purposes to consider the patients in 2 groups—those with 'large' and those with 'small' phaeochromocytomas. This arbitrary distinction corresponds to the level of catecholamine secretion rather than the anatomical size of the tumour and gives rise to 2 different diagnostic problems. The adrenoceptors in patients with 'large' tumours have been down-regulated by chronic exposure to high circulating catecholamine levels (Greenacre and Conolly, 1978); even a moderate degree of hypertension therefore requires a several-fold elevation of plasma noradrenaline concentration, reflected in urine excretion of noradrenaline or its metabolites. The only diagnostic problem is remembering to consider the diagnosis.

By contrast, the problem with 'small' tumour diagnosis is that the possibility is often entertained in patients with symptoms, signs and perhaps biochemical evidence of catecholamine excess, in only a small fraction of whom the diagnosis proves correct. Clinically, the distinction is usually impossible, although our own experience is that, paradoxically, patients who present with a 'full house' of phaeochromocytoma symptoms rarely or never have a phaeochromocytoma. Biochemically, a more logical approach to diagnosis is possible and usually successful (Causon and Brown, 1982). Firstly, most phaeochromocytomas arise in the adrenal gland and are more readily detected in their early stages by adrenaline than noradrenaline measurement (Brown *et al.*, 1981a). Not only is adrenaline the major adrenomedullary catecholamine, but it does not have to be detected, like noradrenaline, against a background of sympathetic neurone secretion. We estimated that adrenal secretion has to increase 50-fold in order to double plasma noradrenaline concentration, whereas plasma adrenaline is a pure marker of adrenomedullary secretion (Brown *et al.*, 1981b).

Phaeochromocytomas which are part of the Multiple Endocrine Adenoma syndrome are especially amenable to diagnosis by plasma or urine adrenaline estimation before any of the more commonly used biochemical indices (plasma noradrenaline, urine catecholamines, metanephrines or VMA) are abnormal (Stevenson *et al.*, 1981).

However, plasma adrenaline is often increased in patients without phaeochromocytomas by fright or anxiety and only a repeatedly elevated value can be considered suggestive of a tumour (Dimsdale and Moss, 1980). In order to circumvent the need for repeated sampling, a suppression test may be used (Brown and Lewis, 1982). The most convenient is the pentolinium test in which plasma catecholamines are measured before and at 10 and 20 min after an intravenous bolus of 2·5 mg pentolinium, a short-acting ganglion-blocking agent (Brown *et al.*, 1981a). This reduces plasma noradrenaline and adrenaline values into the normal range if their elevation was physiological, since their release is dependent on preganglionic nervous transmission to either sympathetic nerves or the adrenal medulla. Tumour release of catecholamines, on the other hand, is autonomous and unaffected by ganglionic blockade. The 2·5 mg dose of pentolinium has little or no effect on supine blood pressure in either group, and patients are kept supine for 1 hr after the drug injection.

It should be stressed that the pentolinium test is required only for patients with marginal (less than 2-fold) elevations of plasma noradrenaline or adrenaline concentration and only mild hypertension. Most patients with slightly elevated VMA excretion have more severe hypertension that could not be due to a slight elevation of noradrenaline release. Interestingly, if a pentolinium test is performed in these latter patients, many are found to have normal plasma noradrenaline values even before pentolinium administration. Phaeochromocytoma patients tend to have relatively greater elevation of plasma noradrenaline concentration than of VMA excretion. The likely reason for this is that noradrenaline released from a phaeochromocytoma is secreted directly into

the bloodstream, without prior metabolism, whilst noradrenaline released from nerve endings is largely recaptured by, and metabolized in, the nerve endings. Recently, we made use of this fact to develop a single-sample test in which the simultaneous plasma concentrations of noradrenaline and its deaminated metabolite, dihydroxyphenylglycol (DHPG), were measured; the relation of DHPG to noradrenaline is illustrated in Fig. 1. It was shown that DHPG arises mainly in nerve endings and that little is formed from circulating noradrenaline. In 15 patients with phaeochromocytomas, the ratio of noradrenaline to DHPG in plasma was greater than 2, whilst in 16 control patients (patients with an elevated plasma noradrenaline concentration but no tumour) the same ratio was less than 0·5 (Brown, 1983).

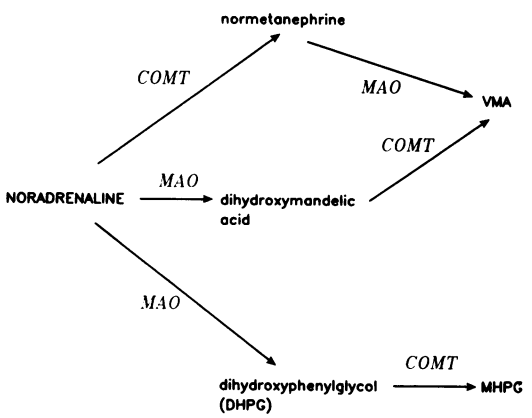

FIG. 1. Simplified diagram of noradrenaline metabolism. MAO = monoamine oxidase; COMT = catechol-O-methyltransferase; MHPG = methyoxyphenylglycol; VMA = vanillyl-mandelic acid. Monoamine oxidase, but not catechol-O-methyltransferase, is present in sympathetic nerve endings as well as in extraneuronal tissue.

Localization of phaeochromocytomas

Most phaeochromocytomas occur in an adrenal gland and cause a high plasma adrenaline concentration, whereas extra-adrenal tumours are almost always pure noradrenaline secretors. Computerized tomographic (CT) scanning is now the method of choice for visualizing the adrenal gland, whether normal or not, and no other investigation is usually required in phaeochromocytoma patients with elevated adrenaline secretion (Stewart *et al.*, 1978). In patients with normal plasma adrenaline values, the tumour is either extra-adrenal or is a large tumour. As discussed earlier, adrenal synthesis is dependent on an intact adrenal porto-capillary system, which is disrupted and eventually outstripped by tumours as they enlarge.

In patients with normal plasma adrenaline values, selective venous sampling is currently the most sensitive and accurate method of localization (Jones *et al.*, 1980; Allison *et al.*, 1983). Since catecholamines are rapidly cleared from the circulation, even a small tumour causes a detectable step-up in noradrenaline concentration if this is measured in a vein draining the tumour. Paradoxically, adrenal tumours can be more difficult to diagnose by sampling, although it is possible for an experienced radiologist to obtain samples from both adrenal veins. The problem is that adrenal blood flow through a phaeochromocytoma is much higher than through a normal gland, so that the higher *amount* of catecholamine secreted may not cause a higher *concentration* in the adrenal vein. The best solution to this problem is provided by measuring both noradrenaline and adrenaline; for a normal gland secretes 5–10 times more adrenaline than noradrenaline, whereas, for the reason discussed above, this ratio is either lower or reversed for glands containing a tumour (Brown *et al.*, 1981a).

Extra-adrenal tumours can often now be detected by radioisotope scanning, using ^{131}I-methyl-iodobenzylguanidine, and we are currently comparing its accuracy and sensitivity with that of selective venous sampling (Sisson *et al.*, 1981). Injection of 1–2 mCi of ^{131}I limits the convenience of the scan, and it does not detect recurrence of a malignant tumour in patients who have undergone previous radiotherapy.

Catecholamine analyses

I have deliberately forborne from recommending particular methodologies. In the diagnosis of the majority of phaeochromocytomas—the 'large' ones—the decision about which catechol or metabolite to measure is less important than adopting one assay and doing it well. It may be suggested that the best vindication for routine screening of all hypertensive patients for phaeochromocytomas is not the pick-up rate (< 1%) but the credibility achieved by a regularly performed assay. Most 'VMA-negative' tumours reflect the impotence of the laboratory, not the tumour!

The pentolinium test and selective venous sampling do, of course, require good plasma catecholamine assays. These should employ either a double-isotope enzymatic technique (Brown and Jenner, 1981) or high performance liquid chromatography with electrochemical detection (Jenner, Brown and Lhoste, 1981). Again the choice is more likely to be determined by the laboratory's other interests and is less important than perfecting whichever assay is chosen. Neither assay is as simple as the radioimmunoassays of most other hormones, and the radioenzymatic assays are much more expensive. Although this limits the number of laboratories performing the

assays, most hospitals can arrange for analysis by a convenient laboratory.

Conclusion

The diagnosis of phaeochromocytoma is the only established clinical use of catecholamine assay. It is a rare tumour; but it justifies great efforts to make the diagnosis because it is both potentially malignant and, on the other hand, one of the few truly curable causes of hypertension. In few other patients can the finding of a tumour bring so much satisfaction.

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