Spurious diagnosis of phaeochromocytoma due to drug induced symptoms and abnormal investigation results

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Phaeochromocytomas are rare catecholamine secreting tumours of the chromaffin cells of the embryonic neural crest. They are associated with high cardiovascular morbidity and mortality. When suspected on clinical grounds it is essential to confirm or refute the diagnosis by measurement of urinary and plasma metadrenaline levels.[1] Prior exclusion of drugs known to increase the levels of these metabolites avoids false positive results.

Case History

A 70 year old female was referred for confirmation of a putative diagnosis of phaeochromocytoma based on clinical features (hypertension and tachycardia) and raised urine and plasma normetadrenaline levels (Table 1). Metadrenaline levels were normal. Review of her records confirmed that:-

1) The onset of tachycardia coincided with commencing treatment with nortriptyline 6 years earlier for symptoms of irritable bowel syndrome.
2) In addition to nortriptyline 75mg od she had been taking bisoprolol 7.5mg od, ramipril 5mg od and ivabradine 7.5mg bd at the time of the investigations rendering the results unreliable.

The referring anaesthetist was concerned by the risk of precipitating a phaeochromocytoma crisis at induction of anaesthesia for planned hiatus hernia surgery. Further investigations off treatment with nortriptyline, bisoprolol and ramipril (all known to raise metadrenaline levels) were therefore performed. She remained on ivabradine. Urine and plasma normetadrenaline levels remained elevated and a clonidine test was positive (Table 2). Her long standing tachycardia resolved. Suspicion that ivabradine might be causing spurious results led to repeat investigations off treatment. Plasma normetadrenaline levels became normal and a clonidine test negative (Table 3). Re-exposure to ivabradine resulted in further abnormal levels of plasma normetadrenaline (Table 4). Metadrenaline levels were normal throughout all investigations.

Investigations and results

Table 1: Investigations prior to referral on nortriptyline, bisoprolol, ramipril and ivabradine

Urine normetadrenaline / 24 hours	5.22, 4.71 and 4.91 µmol (<4.40)
Plasma normetadrenaline	2504.9 pmol/L and 2398.8 pmol/L (<1180)

Table 2: Investigations off nortriptyline, bisoprolol and ramipril

Urine normetadrenaline / 24 hours	5.92 and 4.80 µmol
Plasma normetadrenaline supine	1261.3 pmol/L and 1658.7 pmol/L
Plasma normetadrenaline standing	1735.7 pmol/L and 2503.7 pmol/L

Clonidine test:

Plasma normetadrenaline pre clonidine standing	2628 pmol/L
Plasma normetadrenaline pre clonidine supine	2640 pmol/L
Plasma normetadrenaline post clonidine supine	1482 pmol/L

Table 3: Clonidine test off ivabradine

Plasma normetadrenaline pre clonidine standing	1470 pmol/L
Plasma normetadrenaline pre clonidine supine	1170 pmol/L
Plasma normetadrenaline post clonidine supine	618.3 pmol/L

Table 4: Investigations on re-exposure to ivabradine

Plasma normetadrenaline standing	1730.0 pmol/L
Plasma normetadrenaline supine (30 min)	1498.8 pmol/L
Plasma normetadrenaline supine (60 min)	1600.2 pmol/L
Plasma normetadrenaline supine (120 min)	1621.4 pmol/L

Discussion

We concluded:-

1) The tachycardia component of the clinical suspicion of phaeochromocytoma was due to side-effect of nortriptyline.
2) The spuriously positive biochemical results were partially due to drugs already known to elevate metadrenaline levels ie. nortriptyline, bisoprolol, ramipril.
3) Ivabradine, an inhibitor of the I_f "funny" current of the sinoatrial node had also contributed to the spurious results. We believe this is the first report of ivabradine having this effect. The mechanism of the effect is not obvious.

The anaesthetist was reassured and the patient underwent uncomplicated general anaesthesia for her surgery.

References

1. Lenders, J.W.M., Duh. Q-Y., Eisenhofer, A-P G-R., et al (2014). Pheochromocytoma and Paraganglioma: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 99(6): 1915-1942.

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