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Accidental provocation of phaeochromocytoma: the forgotten hazard of metoclopramide?

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ABSTRACT

The perilous potential of metoclopramide when used inadvertently in patients harbouring phaeochromocytomas goes largely under-recognised. Despite the rarity of phaeochromocytoma, clinicians should exercise caution in the use of metoclopramide among hypertensives and those with labile blood pressures, given the potentially life-threatening crisis it can readily evoke in those with this tumour. We report a series of three patients with phaeochromocytoma who developed acute crises from metoclopramide.

Keywords: catecholamines, dopamine antagonists, hypertensive emergency, metoclopramide, phaeochromocytoma

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INTRODUCTION

Metoclopramide is a dopamine receptor antagonist commonly employed as an antiemetic and endoscopy pre-medication. Serendipitously, the "metoclopramide stimulation test" is a diagnostic test of phaeochromocytoma[1]. Thus, patients with elevated or unstable blood pressures presenting with vomiting or undergoing endoscopy, potentially invite a lethal chemistry of metoclopramide and phaeochromocytoma. Despite previous attempts to highlight this[2-5], clinicians today are generally unaware of this unique contraindication of metoclopramide. We describe three recent encounters with metoclopramide-induced phaeochromocytoma crisis, one occurring in a known phaeochromocytoma while the other two led to the correct diagnosis after acute hypertensive crisis post-metoclopramide.

CASE REPORTS

Case 1

A previously healthy 30-year-old man presented to the emergency department with worsening left hypochondrial pain and vomiting for a day. Past history was non-contributory other than episodic headaches and abdominal pain for several months that was attributed by his family physician to stress. His initial blood pressure was 189/99 mmHg. Shortly after the emergency physician administered metoclopramide 10mg intramuscularly for persistent vomiting, he experienced accentuation of abdominal discomfort associated with a momentary hypertensive spell before collapsing from profound shock refractory to fluids and pressor support that necessitated an intra-aortic balloon pump for resuscitation in the intensive care unit (Fig. 1a). 2-D echocardiography demonstrated global hypokinesia with ejection fraction (LVEF) of 20%.

Phaeochromocytoma was suspected and investigated. Urinary catecholamines and metanephrines were 1,567 nmol/day (normal range 89-582) and 25,996 nmol/day (normal range 1,000-3,500, respectively. Abdominal magnetic resonance (MR) imaging revealed a 6.0 x 9.3cm mass in the left para-aortic region inferior to the renal artery that had high signal intensity on T2-weighted sequences (Fig. 1b). Three weeks after phenoxybenzamine therapy, his LVEF normalised to 58% and his blood pressure stabilised sufficiently for surgery. Tumour histology showed chromogranin and synaptophysin, consistent with a catecholamine-secreting paraganglioma.

Case 2

A previously healthy 27-year-old man re-presented to the emergency department, within a month following his first presentation to us, with acute abdominal pain and vomiting for five hours. The initial impression was acute gastroenteritis with dehydration. Baseline blood pressure was 73/46 mmHg, but spontaneously increased to 156/88 mmHg. It soared to 190/100 mmHg about 25 minutes after the emergency physician administered intravenous metoclopramide 10 mg for vomiting. After his blood pressure settled spontaneously to 90/60 mmHg, he was transferred to the ward. Because of persistent vomiting, another 10mg of metoclopramide given in the ward, resulting in severe headache, diaphoresis and palpitations within 15 minutes. Fundoscopy showed bilateral papilloedema. His

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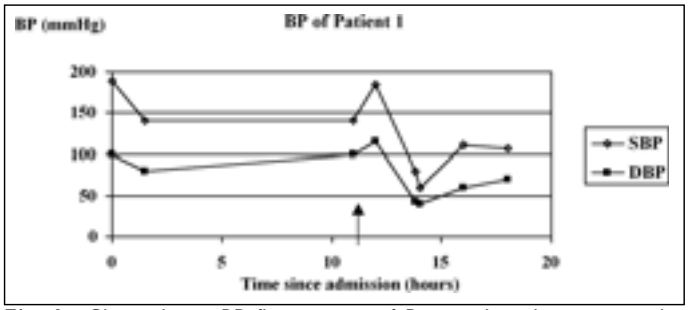

Fig. 1a Chart shows BP fluctuations of Patient 1 with intramuscular metoclopramide 10mg as denoted by arrow. SBP: systolic blood pressure, DBP: diastolic blood pressure.

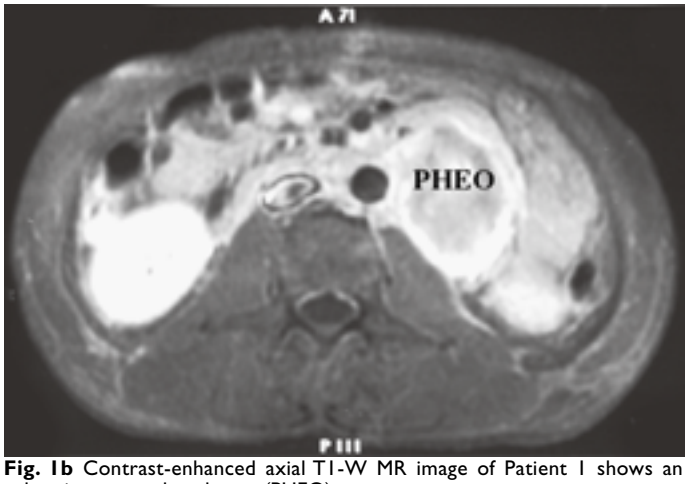

Fig. 1b Contrast-enhanced axial T1-W MR image of Patient 1 shows an enhancing extra-adrenal mass (PHEO).

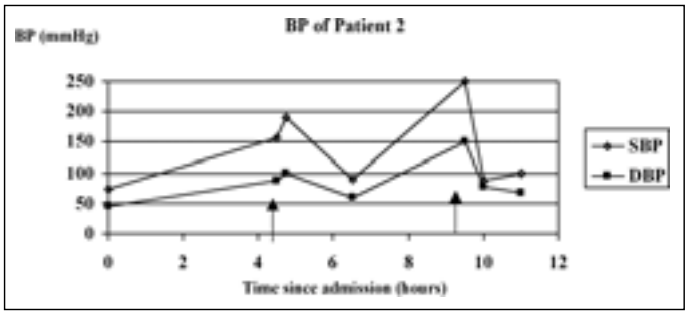

Fig. 2a Chart shows BP fluctuations of Patient 2 with two doses of intravenous metoclopramide 10mg as denoted by arrows. SBP: systolic blood pressure, DBP: diastolic blood pressure.

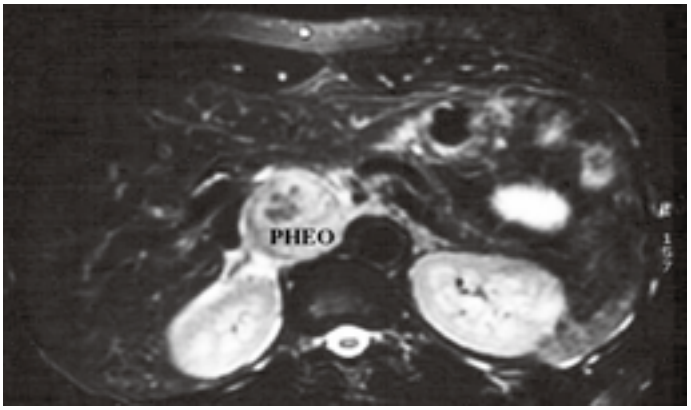

Fig. 2b Axial T2-W MR image of Patient 2 shows a right adrenal tumour (PHEO) that is hyperintense.

recumbent blood pressure peaked sharply at 250/150 mmHg (Fig. 2a).

With hindsight of his first presentation one month earlier, phaeochromocytoma was strongly suspected at that point, and further supported by episodic dizziness and palpitations in his systemic review. Plasma adrenaline was 293 pg/mL (normal range 4-67) and noradrenaline was 16,387 pg/mL (normal range 95-446). Urinary catecholamines and metanephrines measured 15,097 nmol/day and 36,251 nmol/day, respectively. Abdominal MR imaging showed a right adrenal mass that measured 2.8 x 3.1 cm and had hyperintense T2 signal intensity (Fig. 2b). After phenoxybenzamine blockade, he underwent right adrenalectomy, and immunohistochemistry confirmed phaeochromocytoma.

Case 3

A 61-year-old woman presented with paroxysmal spells of headaches, palpitations and drastically labile blood pressures between 70/40 to 300/160 mmHg. She had long-standing type 2 diabetes mellitus and hypertension from a right adrenal phaeochromocytoma diagnosed three years ago. Plasma catecholamines then showed massively elevated adrenaline of 3,324 pg/mL and noradrenaline of 6,187 pg/mL. Urinary catecholamines and metanephrines were impressively raised to 4,774 nmol/day and 71,828 nmol/day, respectively. The diagnosis of phaeochromocytoma was unequivocal. Abdominal MR imaging localised a T2-hyperintense mixed cystic right adrenal mass measuring 6.4 x 7.1 cm (Fig. 3a). Unfortunately, she refused surgery and defaulted phenoxybenzamine and follow-up.

During a recent hospitalisation for hypoglycaemia contributed by anorexia and vomiting, her baseline blood pressure was 153/129 mmHg. This settled spontaneously to 115/70 mmHg in the ward. Following euglycaemia, she was continued on dextrose infusion as her emesis persisted. This led one of her doctors to administer intravenous metoclopramide 10 mg unwittingly despite a documented history of phaeochromocytoma. She abruptly developed hypertensive crisis with headache, palpitations and profuse diaphoresis as blood pressure escalated to 270/130 mmHg with sinus tachycardia of 165/min within 30 minutes requiring urgent stabilisation in the intensive care unit (Fig. 3b). Her blood pressure was controlled after five days with phenoxybenzamine and diltiazem.

DISCUSSION

Phaeochromocytoma is a rare endocrine disorder that may deceptively masquerade conditions commonly

Table 1. Factors that can precipitate phaeochromocytoma hypertensive crisis.

Drugs/Chemicals	Dopamine (D2) antagonists: 1. Metoclopramide 2. Droperidol Opiates: 1. Morphine 2. Fentanyl Blockers of catecholamine re-uptake: 1. Cocaine 2. Tricyclic antidepressants Sympathetomimetic amines: 1. Amphetamine 2. Tyramine 3. Decongestants General anaesthetic agents: 1. Atarcurium 2. Pancuronium Hormones: 1. Glucagon 2. ACTH Other drugs: 1. Phenothiazines 2. Histamine 3. Radiographic contrast media – (esp. ionic and intra-arterially)
Situations/Manoeuvres	Changes in tumour blood flow due to: 1. Deep/vigorous abdominal palpation 2. CT-guided biopsy (inadvertently) 3. Sexual intercourse (vaginally sited lesions) 4. Micturition (for bladder sited tumours) Physical stress 1. Surgery 2. Falls 3. Trauma – (eg. motor vehicular accidents) 4. Hypoglycaemia

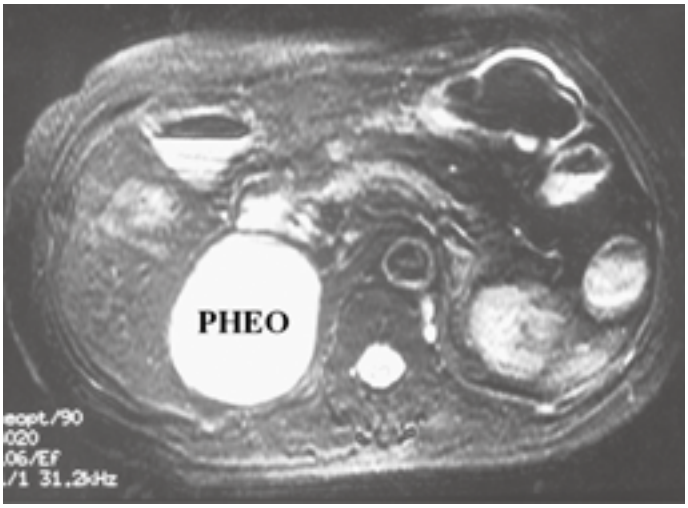

Fig. 3a Axial T2-W MR image of Patient 3 shows a right adrenal tumour (PHEO) that is markedly hyperintense.

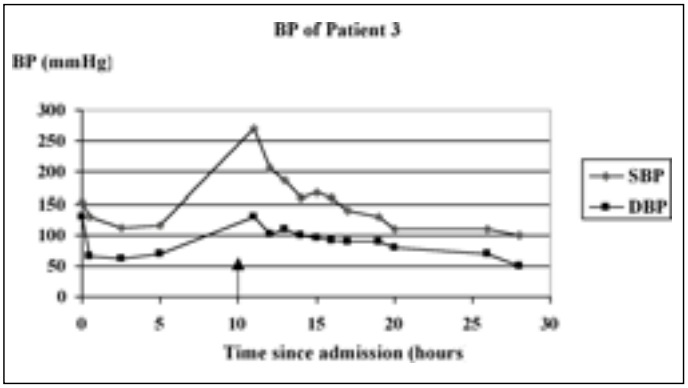

Fig. 3b Chart shows BP fluctuations of Patient 3 with intravenous metoclopramide 10mg as denoted by arrow. SBP: systolic blood pressure, DBP: diastolic blood pressure.

encountered by clinicians, given its protean manifestations[6]. The striking temporal relation of these three crises implicates metoclopramide as the etiologic factor. Dopamine type-2 (D2) receptors are presynaptic on sympathetic nerve endings and stimulation inhibits release of catecholamines and ganglion transmission. Metoclopramide accentuates noradrenaline release via presynaptic type 2-dopamine receptor blockade, and it may thus act as a potent pharmacological trigger of severe hypercatecholaminemia in the presence of phaeochromocytoma[4]. In this regard, one of the mechanisms that metoclopramide is postulated to release massive quantities of catecholamines, is intricately linked to the unique disposal of excess bioamine hormones by the body.

Under physiological conditions, it has been demonstrated that excess noradrenaline is recycled via direct uptake-1 (neuronal) and uptake-2 (extraneuronal) processes to inactivate circulating catecholamines[7]. In the former, excess noradrenaline released at the synaptic clefts and those from the circulation, including those secreted by phaeochromocytomas, is transported into the cytoplasm of the sympathetic neurons by an axonal membrane molecular pump that is energy-requiring, saturable, steroselective and sodium-dependent. This intra-neuronal pool of noradrenaline can in turn be taken up into secretory vesicles by specific carriers for re-utilisation or deaminated by monoamine oxidase. In contrast, the uptake-2 process plays a role in plasma clearance of circulating catecholamines by trafficking noradrenaline into the peripheral extra-neuronal effector tissues post-synaptically for catabolism via catechol-O-methyltransferases into O-methylated derivatives. As such, metoclopramide could conceivably precipitate a retrograde catecholamine surge from sympathetic reservoirs "supersaturated" by uptake-1 of excess phaeochromocytoma-derived catecholamines back into the circulation.

Of clinical importance is the fact that the axonal uptake-1 pump is blocked by such pharmacological agents as cocaine, amphetamine, tricyclic antidepressants and phenothiazines. This implies that such agents can also trigger a flood of catecholamines into the bloodstream, and are indeed listed under known precipitants of pheochromocytoma hypertensive crisis (Table I). Metoclopramide has also been shown to directly stimulate catecholamine release from the tumour itself[8]. D2-dopamine receptors on phaeochromocytoma probably mediate this action[9]. This could represent yet another way that metoclopramide can trigger a hypertensive crisis in patients harbouring phaeochromocytomas. However, the exact molecular mechanisms are complex and remain speculative at best.

Stimuli-evoking adrenergic responses, such as hypoglycaemia in the last patient, may trigger catecholamine release. Glucagon secreted during hypoglycaemia could stimulate the phaeochromocytoma and account for her initial elevated blood pressure[10]. But metoclopramide was held to be the main culprit as her hypertensive crisis occurred during euglycaemia. Abdominal pain in the first two patients probably resulted from vasospasm-induced mesenteric ischaemia, but tumour rupture or haemorrhage should also be considered. Abdominal palpation can itself pose a potential hazard if performed too vigorously on a large phaeochromocytoma, and that could have contributed to the hypertensive crisis in the first patient. Finally, phaeochromocytoma patients can develop profound hypotension in the course of a hypertensive crisis that is both diagnostically and therapeutically challenging, and hence deserve some comments here. Notably, those with noradrenaline-secreting tumours are highly vasoconstricted and therefore have reduced blood volumes that manifest clinically as orthostatic hypotension. Any further compromise in their volume status can therefore lead to haemodynamic collapse.

Another crucial factor is that relating to adrenomedullin that could be co-secreted during a phaeochromocytoma crisis. Adrenomedullin is one of the most potent vasodilators known, and is present in large amounts in certain phaeochromocytomas[11]. This can provoke very labile blood pressures depending on the ratio of the levels of vasoconstrictors to vasodilators prevalent at the time of the crisis. In retrospect, the first patient had suffered a full-blown catastrophic phaeochromocytoma multisystem crisis with refractory hypotension despite a catecholamine storm due to catecholamine-induced cardiomyopathy and adrenergic receptors down-regulation and desensitisation from prolonged catecholamine exposure.

Although phaeochromocytoma is uncommon in the hypertensive population, clinicians should be mindful of that possibility before administering metoclopramide in patients with hypertension. We also advocate doctors to exercise similar precautions in anyone with labile blood pressure prior to prescribing metoclopramide. In summary, though metoclopramide remains a useful antiemetic and endoscopic pre-medication, we hope these three cases would serve as a timely reminder to the practising physician of this potential hidden danger of metoclopramide and other similar dopamine antagonists.

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