CASE REPORT

Pheochromocytoma crisis induced by glucocorticoids: a report of four cases and review of the literature

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Abstract

Context: Pheochromocytoma crisis (PC) is a rare life-threatening endocrine emergency that may present spontaneously or can be unmasked by 'triggers', including certain medications that provoke the release of catecholamines by tumors. Several isolated cases of PC have been reported after administration of exogenous glucocorticoids; evidence that these drugs cause adverse events in patients with pheochromocytoma is mainly anecdotal.

Patients: We report four cases of PC most likely induced by glucocorticoids and review seven previous reports in the literature linking steroid administration to the development of PC.

Results: In four new cases reported here, glucocorticoid administration was associated with a fatal outcome in one case, a pheochromocytoma multisystem crisis in another, and serious hypertensive crises in two others. Two patients had incidental adrenal masses and were undergoing high-dose dexamethasone suppression tests (DST).

Conclusions: Exogenous glucocorticoids may unpredictably trigger PC. Pheochromocytoma should be included in the differential diagnosis of any patient who develops a hypertensive crisis, cardiac failure, tachycardia, headache, and abdominal or chest pain after receiving exogenous glucocorticoids. Glucocorticoid induced PC is frequently associated with hemorrhagic pheochromocytoma. Although exogenous glucocorticoids cause serious complications unpredictably, they should be avoided or administered only if necessary and with caution in patients with known or suspected pheochromocytoma. During the investigation of incidental adrenal masses, pheochromocytoma should ideally be ruled out before administering glucocorticoids. However, no cases have been reported with 1 mg of dexamethasone when given as a DST in patients with pheochromocytoma; larger doses, as low as 2 mg of dexamethasone, may trigger a PC. A patient with pheochromocytoma presenting as an adrenal incidentaloma may also be at risk if exposed to glucocorticoids given as pre-treatment in case of allergy to contrast media.

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Introduction

Pheochromocytoma crisis (PC) is a rare life-threatening endocrine emergency with a reported mortality as high as 85% (1, 2). Acute and rapidly progressive hemodynamic disturbances result from the actions of high quantities of catecholamines secreted by the tumor and lead to organ failure. PC can present spontaneously, or as a result of 'unmasking' by 'triggers' such as trauma, surgery, anesthesia, and drug therapy.

Many classes of drugs are well known to precipitate adverse reactions, but the evidence linking exogenous glucocorticoids to the unmasking of pheochromocytoma producing serious or fatal reactions is mainly anecdotal or limited to single case reports. We report

four cases of PC possibly induced by glucocorticoids and review seven previous reports and anecdotes in the literature. We discuss possible mechanisms and interactions between glucocorticoids, catecholamines, and pheochromocytoma. Finally, we review clinical management issues regarding the use of dexamethasone suppression tests (DST) in the evaluation of adrenal incidentaloma.

Case reports

The four cases reported here (Table 1) were patients referred for evaluation over a period of 16 months (August, 2005–December, 2006) at three centers: the

Table 1 Clinical characteristics.

Patient no.	Age (years)	Sex	Steroid, dose/route	Clinical data, complications, outcome	Presenting symptoms	Time to onset (h)
1	26	F	Dexamethasone 2 mg PO QID	PMC: shock; hyperglycemia; pulmonary edema; metabolic acidosis; incidentaloma; <i>fatal</i>	HTN, anxiety, shock	36
2	39	M	Betamethasone 6 mg i.m.	PMC: renal, hepatic, CNS dysfunction; shock, labile BP; hyperthermia; hyperglycemia; IABP; <i>survived</i>	Chest pain HTN, headache, nausea, and vomiting	12
3	27	M	Solu-Medrol 1.5 g i.v.	Hypertensive crisis; metastatic paraganglioma; norepi. secretor; on chemotherapy protocol; <i>survived</i>	Chest, pain, bone pain HTN, nausea, vomiting	8
4	39	F	Dexamethasone 2 mg PO QID	Hypertensive crisis, cardiac ischemia; incidentaloma; <i>survived</i>	Chest pain HTN; headache, nausea, vomiting	5
5 (1973)	69	F	Prednisone 45 mg PO ^a	HTN, recurrent episodes when steroid increased; <i>survived</i>	HTN	N/A
6 (1968)	39	M	Prednisone, hydrocortisone ^a doses: N/A	PMC: HTN, cardiac ischemia, CHF, pulmonary edema, hyperthermia, elevated SGOT; <i>survived</i>	Abdominal pain, palpitation	12
7 (1997)	34	F	Dexamethasone 16 mg route: N/A	Cardiogenic shock; hypotension; cardiac arrest; <i>survived</i>	N & V low B/P	12
8 (1997)	43	F	Prednisone 60 mg route: N/A	'Hemodynamic instability'; low EF, cardiac arrest, (anecdotal case); <i>survived</i>	N/A	N/A
9 (1996)	46	M	'Steroid'	Multisystem illness; (anecdotal case); <i>fatal</i>	Chest pain HTN	'Several'
10 (2004)	44	F	Dexamethasone 2 mg PO TID	Cardiac ischemia, infarction; HTN, abdominal pain, retroperitoneal hemorrhage; <i>survived</i>	Headache, chest pain palpitation	24
11 (2000)	52	M	Dexamethasone dose: N/A intraarticular	Cardiogenic shock; renal insufficiency; IABP, PCPS; <i>survived</i>	Chest pain dyspnea	12

BP, blood pressure; EF, left ventricular ejection fraction; HTN, hypertensive crisis; IABP, intra-aortic balloon pump; i.m., intramuscularly; i.v., intravenously; N/A, information not available; PCPS, percutaneous cardiopulmonary support; PMC, pheochromocytoma multisystem crisis; PO, by mouth; QID, four times daily; TID, three times daily.

^aPrednisone was administered, then 100 mg i.v. hydrocortisone, both caused HTN.

Centre for Postgraduate Medical Education (CPME), Warsaw, Poland (cases 1 and 4); The Methodist Hospital (TMH), Houston, Texas (case 2); and the National Institutes of Health (NIH), Bethesda, Maryland (case 3).

Case 1

A 26-year-old normotensive woman was referred for the evaluation of an incidental adrenal mass. The physical examination, blood pressure (BP), and cortisol levels were normal. An abdominal computed tomography (CT) scan (unenhanced) revealed a 4.2 cm right adrenal mass with high attenuation, 35 Hounsfield units (HU), but with areas of lipid-like density. Adrenocortical carcinoma could not be ruled out by CT scan. A high-dose DST, administering 2 mg orally every 6 h for 2 days, was ordered as per an institutional protocol of the CPME, Warsaw, Poland. The first day was uneventful and the patient remained normotensive and asymptomatic. On the second day of the DST, the patient became weak, anxious, and restless with a BP of 160/110 mmHg and moderate tachycardia. The clinical condition deteriorated rapidly over the next 4 h. The patient developed shock, hyperglycemia, severe metabolic acidosis, and pulmonary edema.

Despite intensive therapy, the patient died 10 h after the onset of symptoms. A 4.5 cm hemorrhagic pheochromocytoma was found at autopsy. The results (collected before the crisis) of two sequential 24-h urinary collections for total metanephrines were: 916 and 1104 µg (ref: 100–1000 µg/24 h).

Case 2

A 39-year-old male patient was completely asymptomatic until December 2005 when he developed a hypertensive crisis followed by congestive heart failure 12 h after 6 mg i.m. betamethasone for airway congestion. No other medication had been given for 8 h prior to the glucocorticoid. After several days in intensive care, the patient's condition stabilized and he was discharged with a diagnosis of viral cardiomyopathy. Pheochromocytoma was not considered in the differential diagnosis during the hospital admission (December 2005).

After 1 year (December 7, 2006), he presented again with chest pain, severe hypertension (240/140 mmHg), headache, nausea, and vomiting 12 h after 6 mg of i.m. betamethasone. He quickly deteriorated, developed cardiogenic shock, and aspirated. The patient had cardiac arrest twice, was successfully resuscitated, and

then developed PC with encephalopathy, progressive renal and hepatic insufficiency, hyperthermia, and hyperglycemia. Abdominal CT revealed a 5 cm complex left adrenal mass. Lab. values: serum-free normetanephrine, 8089 pg/ml (nl: 0–163 pg/ml); metanephrine, 3940 pg/ml (nl: 0–96 pg/ml); plasma norepinephrine, 22 686 pg/ml (nl: 80–520 pg/ml); epinephrine, 8633 pg/ml (nl: 10–200 pg/ml); and dopamine 386 pg/ml (nl: 0–20 pg/ml). The patient underwent emergency open left adrenalectomy. A hemorrhagic pheochromocytoma of 5.5 cm in diameter was excised. Postoperatively, the patient recovered completely.

Case 3

A 27-year-old male with confirmed metastatic pheochromocytoma, evident mainly by multiple bone lesions, was enrolled in an experimental ^{131}I -metaiodobenzylguanidine (MIBG) treatment protocol that included pre-treatment with methylprednisolone. Before starting the protocol, the patient's BP was stable and controlled with medication. The patient received 1.5 g of methylprednisolone i.v. but no MIBG was administered. The vital signs before glucocorticoid administration were normal. After the injection, vital signs were BP: 188/107 mmHg and pulse: 105. After 20 min, the BP and heart rate decreased and the patient was discharged. After 8 h, the patient developed nausea, vomiting, and hypertension with pain in the right chest wall and left hip. Admission vital signs were BP: 189/119 mmHg and pulse: 137. The patient was treated with i.v. antihypertensives and was stabilized. A CT scan of the painful areas of the chest and hip demonstrated a necrotic lesion on the right side of the chest surrounded by fluid (an increase in size by about 20% from the previous findings, 3 months before) and a lesion in the left ischium, which was determined to be significantly larger (by about 40%). Because of this reaction, methylprednisolone was dropped from the protocol and no other patient with metastatic pheochromocytoma received methylprednisolone.

Case 4

A 39-year-old woman was evaluated for an incidental adrenal mass. Past medical history was significant for a 3-year history of hypertension and diabetes mellitus, which developed during her third pregnancy. An abdominal CT scan (unenhanced) revealed a non-homogeneous 6.9 cm left adrenal mass with a high attenuation value of 28–31 HU. High-dose DST was ordered as per an institutional protocol of the CPME, Warsaw, Poland. About 5 h after the first 2 mg high-dose DST, the patient suddenly developed nausea and vomiting, headache, and restlessness in concert with hypertension (BP: 220/120 mmHg), chest pressure, and tachycardia. An electrocardiogram (ECG) revealed tachycardia and signs of anterior wall ischemia. BP and

pulse rate normalized after treatment with a combination of i.v. vasodilators and β -blockers. Lab. values (obtained prior to crisis): total 24-h urinary metanephrines = 2292 $\mu\text{g}/24\text{ h}$ (nl: 100–1000 $\mu\text{g}/24\text{ h}$). A laparoscopic left adrenalectomy was performed 2 weeks after treatment with phenoxybenzamine. Pathologic examination revealed an 8 cm multicystic pheochromocytoma with hemorrhagic foci.

The hypertension and diabetes mellitus ceased and total urinary metanephrines fell to normal after surgery.

Review of cases from the literature To our knowledge, there are seven previously published case reports linking glucocorticoids to a life-threatening PC (Table 2).

Case 5

In 1973, Dagget *et al.* (3) reported that a 69-year-old woman developed severe hypertension after taking 45 mg of prednisone orally daily for 3 days. The hypertension resolved after prednisone was decreased to 5 mg orally, but recurred acutely after one dose of 100 mg of hydrocortisone i.v. After a pheochromocytoma was removed, there were no more episodes of hypertension despite the daily administration of 100 mg of hydrocortisone for 3 days or after 10 mg of daily oral prednisone.

Case 6

In 1968, Page *et al.* (4) reported that a 39-year-old male developed PC after receiving unknown doses of parenteral hydrocortisone, adrenocorticotrophin (ACTH), and oral prednisone. An epinephrine-secreting pheochromocytoma was diagnosed.

Cases 7 and 8

In 1997, Kothari *et al.* (5) described that a 34-year-old female developed congestive heart failure (CHF) after taking oral dexamethasone. After 4 months, a pheochromocytoma was removed. In the same article, there is an anecdotal report of a 43-year-old woman who suffered from cardiac failure and arrest after oral prednisone; she underwent a successful adrenalectomy and removal of a pheochromocytoma.

Case 9

Another anecdotal case was described by Pitcock in Manger's 1996 book (6): a 46-year-old man developed PC 'after receiving an injection of steroid... a pheochromocytoma in the right adrenal gland was found at autopsy.'

Case 10

A case report with an excellent review was published by Brown *et al.* in 2005 (7): a 44-year-old female with

Table 2 Tumor pathology; catecholamines, and metabolites.

Patient no.	Age (years)	Sex	Tumor side	Tumor dimensions	Hemorrhage in tumor	Catecholamine and metabolite levels, preoperative
1	26	F	R	42 mm	Yes	Urinary total metanephrines 916 µg/24 h (ref: 100–1000 µg/24 h)
2	39	M	L	55 mm	Yes	P. free metanephrine: 20 nmol/l (ref: 0–0.49 nmol/l) P. free normetanephrine: 44.2 nmol/l (ref: 0–0.89 nmol/l)
3	27	M	Mets	Metastasis	Probable: increase in size by X-ray	Urinary fractionated catecholamines Norepinephrine: 4700 µg/24 h (ref: <121) Epinephrine: 16 µg/24 h (ref: <24)
4	39	F	L	80 mm	Yes	Urinary total metanephrines 2292 µg/24 h (ref: 100–1000)
5	69	F	R	N/A	N/R	P. epinephrine: 5.4 µg/l (ref: 0–0.2) P. norepinephrine: 1.5 µg/l (ref: 0.5–0.9)
6	39	M	R	30 mm	N/R	Urinary catecholamines (µg/24 h) Epinephrine: 59 µg/24 h (ref: 0–15) Norepinephrine: 60 µg/24 h (ref: 10–100)
7	34	F	R	41 mm 3.7×4.1×2.8 cm (by CT scan)	N/R	Urinary fractionated catecholamines Epinephrine: 160 µg/24 h (ref: 0–20) Norepinephrine: 95 µg/24 h (ref: 15–80)
8	43	F	L	Size not mentioned	N/A	N/A (anecdotal)
9	46	M	R	Size not mentioned	N/A	N/A (anecdotal)
10	44	F	R	68 mm	Yes, plus extensive hemorrhage outside	P. free metanephrine: 13.6 nmol/l (ref: <0.5 nmol/l) P. free normetanephrine: 11.3 nmol/l (ref: <0.9 nmol/l)
11	52	M	R	30 mm (3×3×2 cm)	N/R	Urinary metanephrine: 3310 µg/24 h (ref: 10–300 µg/24 h) Urinary normetanephrine 3310 µg/24 h (ref: 50–400 µg/24 h)

F, female; M, male; R, right side; L, left side; N/A, not available; N/R, not reported.

normal coronaries developed a myocardial infarction and severe hypertension after the administration of dexamethasone. A hemorrhagic pheochromocytoma was resected.

Case 11

Takagi *et al.* (8): reported a 52-year-old male who developed cardiogenic shock and pheochromocytoma multisystem crisis after a dexamethasone injection in the shoulder joint. A pheochromocytoma was found.

Clinical presentation (Table 1) The clinical presentation of steroid-related PC was varied. In 2 out of 11 patients, fatal outcomes were related to the administration of glucocorticoids. Eight patients developed either heart failure or cardiogenic shock, and of these two required mechanical cardiac assist devices to survive. Comprehensive clinical information was not reported in several cases; thus the full extent of adverse reactions is unknown. There were six females and five males, ranging in age from 27 to 69 years old; the severity of complications was divided equally among the sexes. Chest pain, severe hypertension, and headache

were the most common symptoms presented. Two patients received glucocorticoids on separate occasions, and developed crises after each administration. The glucocorticoid-induced PC is a heterogeneous clinical manifestation of pheochromocytoma, associated with high morbidity and mortality.

Type of steroid, dose, and route of administration

Several types of glucocorticoids caused serious reactions; dexamethasone and betamethasone caused the most serious reactions. The route of administration need not be parenteral. Even intraarticular injections may cause severe reactions, as in case 9, although the dose was not mentioned. The smallest documented dose of dexamethasone that induced a crisis was 2 mg administered orally. Prednisone, 5 mg orally daily, did not cause adverse reactions in patient no. 5, but it produced a crisis when increased to 45 mg; 100 mg of i.v. hydrocortisone, a dose equivalent to 20 mg of prednisone, also caused a crisis in the same patient. In some patients (cases 2 and 5), the induction of adverse effects was consistent and reproducible: in patient no. 2, betamethasone, 6 mg i.m., produced severe, life-threatening reactions, on two occasions, a year apart.

Tumor characteristics (Table 2) The pheochromocytoma was hemorrhagic in three cases (1, 2, and 4) and was inferred in case 3 by imaging of known metastasis. In the literature cases, tumor hemorrhage was not specified in five cases, and was absent in one. Tumor size (longest diameter) ranged from 30 to 80 mm and was not always related to clinical severity. Out of 11 tumors, 7 were on the right side and, 3 on the left, and one case involved a metastatic paraganglioma. All patients with pathology reports showing a hemorrhagic pheochromocytoma exhibited high morbidity and mortality.

Fractionated catecholamine/metabolite levels, urinary or plasma, were available in six cases. All six showed elevated levels of both epinephrine, and norepinephrine or their metabolites although epinephrine/metaneprhine levels were predominant.

Discussion

Many drugs can cause adverse reactions in patients with pheochromocytoma (23). Some are well-known, predictable 'triggers', others are less consistent. Our knowledge of many of these inconsistent tumor-related adverse drug reactions comes from anecdotal reports and cases in the literature; the level of evidence is variable. This also applies to the four new cases we report here and to those we review. PC often occurs without specific triggers and could have occurred incidentally or secondary to other uncontrolled variables. Controlled clinical studies that clearly demonstrate the induction of PC by exogenous glucocorticoids are not available, and are unlikely to be forthcoming. With these caveats in mind, the cases suggest that exogenous glucocorticoids may cause severe and even deadly reactions in some patients harboring a pheochromocytoma.

Glucocorticoids are ubiquitously prescribed, for example used as a pre-treatment in patients allergic to contrast dye that is regularly used to image adrenal masses. Glucocorticoids are also used in the DST to evaluate autonomous hormonal secretion by incidental adrenal masses. Thus, under these circumstances, a patient potentially harboring a pheochromocytoma would be exposed to a drug that may be capable of causing lethal complications. The low-dose DST (dexamethasone 1 mg orally at night) has not been associated with PC, but in two of our four cases a high-dose DST was temporally related to the development of PC in one patient and to the death of another. Hence, the institutional protocol at the CPME in Warsaw indicating high-dose DST has now been modified to low-dose DST: dexamethasone 1 mg orally once at night times.

Mechanisms

Adverse drug reactions in pheochromocytoma are usually attributed to the effects of catecholamines, or

other substances, released from the tumor via a variety of mechanisms.

Glucocorticoids are necessary for normal development of the adrenal medulla; they influence catecholamine metabolism, production and release (9), not only in normal chromaffin cells but also in pheochromocytoma cells. In addition, glucocorticoids have important permissive effects on the peripheral vasculature. Thus, it is not surprising that the glucocorticoids may elicit adverse effects in pheochromocytoma.

Glucocorticoids can induce catecholamine synthesis in PC12 pheochromocytoma cell cultures (10), inducing catecholamine biosynthetic enzymes such as: 1) phenylethanolamine *N*-methyltransferase that converts norepinephrine to epinephrine (11, 12); 2) tyrosine hydroxylase, the rate-limiting enzyme in catecholamine biosynthesis (13); and 3) dopamine β -hydroxylase that converts dopamine to norepinephrine (14). Glucocorticoids have also been shown to increase the release of catecholamines from perfused canine adrenal glands (15).

In the cases reported here, there was a time lag of 5–36 h between steroid administration and the development of symptoms. This delayed effect suggests that, unlike other 'triggering' agents, the primary mechanism of glucocorticoid-related PC may not involve the immediate vesicular release of catecholamines. Mechanisms such as inappropriate functioning of regulated secretion, synthesis, and loading of catecholamine granules, followed by massive release, possibly accelerated or caused by tumor necrosis and hemorrhage may be more important.

Another factor may involve the peripheral vasculature: glucocorticoids, through receptors in endothelial and smooth muscle cells, regulate vascular reactivity by potentiating the effects of catecholamines. Glucocorticoids suppress production of the endothelial-derived vasodilators, nitric oxide and prostacyclin by down-regulation of enzyme expression and activity. The effect on vascular smooth muscle is of two types: 1) a receptor-independent response, which can occur in min, requires high concentrations of cortisol, is more pronounced for epinephrine, and may be mediated by inhibition of catechol-*O*-methyltransferase; 2) a receptor-dependent response that is more prolonged and is due to the glucocorticoids' genomic transcription effects, via various mechanisms among others those regulating Ca^{2+} homeostasis-dependent smooth muscle reactivity (16). The potentiation of the actions of catecholamines on the peripheral vasculature and heart by glucocorticoids is likely to be an important factor in the clinical presentation of PC.

The administration of exogenous steroids to normal adrenal medulla would not be expected to greatly affect catecholamine production or release since the normal adrenal medulla is already exposed to high concentrations of glucocorticoids (9, 12). However, in pheochromocytoma, normal anatomic relationships and

regulatory functions are lost: tumors may not be completely surrounded by adrenal cortex, and micro-vascular anatomy is surely altered. Thus, normal neural and paracrine control of catecholamine production and release is lost (6). Pheochromocytomas are heterogeneous tumors and express different secretor phenotypes and membrane receptors depending on their genetic origin and state of differentiation. Abnormal regulation and expression of various genes can be induced by dexamethasone in human-derived pheochromocytoma cells (17). Some tumors, for example, can even change phenotype over time from an ACTH-producing non-catecholamine-secreting tumor to a catecholamine-producing pheochromocytoma (18). Pheochromocytomas that secrete massive amounts of catecholamines on exposure to glucocorticoids may thus represent a specific tumor phenotype expressing altered glucocorticoid receptors and secretory patterns. This is purely speculative and needs to be investigated further. It is of interest that the majority of these tumors (Table 2) showed secretion of both epinephrine and norepinephrine, which may not only be important in the clinical presentation but also may shed some light on the secretory phenotype.

Tumor necrosis or hemorrhage is clearly important in the pathogenesis of the glucocorticoid-induced PC (Table 2). Tumor necrosis may be responsible for massive outpouring of catecholamines into the circulation and an end result of catecholamine-induced hypertensive vasculopathy. In this series of patients, the most severe forms of PC occurred when the long-acting glucocorticoids, dexamethasone, or betamethasone were administered. Glucocorticoid-induced catecholamine release and increased peripheral vascular reactivity followed by hypertensive vasculopathy, tumor necrosis, and massive release of catecholamines could repeat itself in a cyclical fashion in the presence of long-acting glucocorticoids causing irreversible end-organ damage.

Glucocorticoids, pheochromocytoma, and the incidental adrenal mass

Two of our cases (1 and 4) represent the first reports in the literature of PC related to, and apparently triggered by, a high-dose DST used during the diagnostic investigation of an adrenal incidentaloma. High-dose DST was being used as part of an institutional protocol at the Center for Postgraduate Medical Education, Warsaw, Poland.

Incidentalomas are one of the most prevalent of human tumors, present in up to 8.7% in some autopsy series. (19) In a review of a large number of studies, the etiology of incidentaloma was: adenoma 41%, metastasis 19%, adrenocortical carcinoma 10%, myolipoma 9%, and pheochromocytoma 8%, with the remainder being mostly benign lesions such as cysts (20).

The incidence of pheochromocytoma is about 5% in the group of incidentalomas reported by Young in 2000

(21). In a series of 1111 patients reported from Poland, the incidence was 3%, but has risen to 4% since the publication of that original report (22). Significant side effects of high-dose DST had not been observed, until the two cases described here, despite its use in about half of the patients eventually diagnosed with pheochromocytoma. Adverse reactions to dexamethasone or other glucocorticoids may therefore occur only in a limited proportion of patients with pheochromocytoma. This presumably reflects the heterogeneous nature of these tumors and is consistent with the variability of adverse reactions to other drugs (e.g., tricyclic antidepressants, dopamine receptor antagonists, sympathomimetics, glucagon) and stimuli or procedures (e.g., exercise, childbirth, surgical anesthesia) with more established risks for patients with pheochromocytoma (23).

Conclusions

Exogenous glucocorticoids may inconsistently cause severe and even deadly reactions in patients with pheochromocytoma. These reactions are often associated with hemorrhage in the pheochromocytoma; the exact mechanism is unclear. The release of catecholamines can be massive.

Glucocorticoids should be avoided, or administered with vigilance, in patients with a potential diagnosis of pheochromocytoma. In patients with an adrenal incidentaloma and imaging characteristics compatible with a chromaffin tumor, pheochromocytoma should ideally be ruled out first, using the most sensitive biochemical diagnostic test available (24, 25) before administering the glucocorticoids. If a cortisol suppression test is nonetheless deemed necessary before ruling out pheochromocytoma, a low-dose DST (1 mg given PO at 2200 h) should be used; no cases of PC have been reported with this dose. Clinicians should be cautious with higher doses of dexamethasone in patients at risk.

Care must also be exercised in patients with undiagnosed adrenal masses compatible with pheochromocytoma, who are allergic to contrast media (26, 27). If these patients are undergoing diagnostic imaging studies, glucocorticoids are usually included as pre-treatment and could trigger a dangerous reaction.

A PC should be suspected and included in the differential diagnosis in any patient who develops severe hypertension, hemodynamic instability, chest pain, and headache several hours after receiving glucocorticoids.

The glucocorticoid-related adverse reactions in patients with pheochromocytoma may take hours to develop and are associated with elevated morbidity and mortality. Once symptomatic, patients can decompensate very quickly; prompt diagnosis and intensive treatment are essential to prevent death or serious complications.

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References

- Browsers FM, Lenders JWM, Eisenhofer G & Pacak K. Pheochromocytoma as an Endocrine Emergency. *Reviews in Endocrine and Metabolic Disorders*, 2003 **4** 121–128.
- Sauvage MR, Tulasne PA & Arnaud JP. Hypertensive accident in a surgical patient with unsuspected pheochromocytoma. *Anesthesia and Analgesia* 1979 **36** 155–158.
- Daggett P & Franks S. Steroid responsiveness in pheochromocytoma. *BMJ* 1977 **1** 84.
- Page LB, Raker JW & Berberich FR. Pheochromocytoma with predominant epinephrine secretion. *American Journal of Medicine* 1969 **47** 648–652.
- Kothari SN & Kiskin WA. Dexamethasone-induced congestive heart failure in a patient with dilated cardiomyopathy caused by occult pheochromocytoma. *Surgery* 1998 **123** 102–105.
- Manger WM & Gifford RW. *Clinical and Experimental Pheochromocytoma*, p. 144 Cambridge, MA: Blackwell Science, 1996.
- Brown H, Goldberg PA, Selter JG, Cabin HS, Marieb NJ, Udelsman R & Setaro JF. Hemorrhagic pheochromocytoma associated with systemic corticosteroid therapy and presenting as myocardial infarction with severe hypertension. *Journal of Clinical Endocrinology and Metabolism* 2005 **90** 563–569.
- Takagi S, Miyazaki S, Fujii T, Daikoku S, Sutani Y, Morii I, Yasuda S, Goto Y & Nonogi H. Dexamethasone-induced cardiogenic shock rescued by percutaneous cardiopulmonary support (PCPS) in a patient with pheochromocytoma. *Japanese Circulation Journal* 2000 **64** 785–788.
- Ehrhart-Bornstein M, Hinson JP, Bornstein S, Scherbaum WA & Vinson GP. Intraadrenal interactions in the regulation of adrenocortical steroidogenesis. *Endocrine Reviews* 1998 **19** 101–143.
- Tischler AS, Perlman RL, Mortse GM & Sheard BE. Glucocorticoids increase catecholamine synthesis and storage in PC12 pheochromocytoma cell cultures. *Journal of Neurochemistry* 1983 **40** 364–370.
- Udelsman R & Holbrook NJ. Endocrine and molecular responses to surgical stress. *Current Problems in Surgery* 1994 **31** 653–720.
- Wurtman RJ. Control of epinephrine synthesis in the adrenal medulla by the adrenal cortex: hormonal specificity and dose-response curves. *Endocrinology* 1966 **79** 608–614.
- Goodman R, Edgar D, Thoenen H, Wechsler W & Herschman H. Glucocorticoid induction of tyrosine hydroxylase in a continuous cell line of rat pheochromocytoma. *Journal of Cell Biology* 1978 **78** R1–R7.
- Weiner N & Blaschko H. Adrenal gland endocrinology. In *Endocrinology: Adrenal Gland*, Eds G Sayers & AD Smith, Washington, DC: American Physiology Society, 1975.
- Critchley JA, Henderrson CG, Moffat LE, Ungar A, Waite J & West CP. Proceedings: the release of catecholamines from perfused canine adrenal glands by corticoglucocorticoids. *Journal of Physiology* 1976 **254** 30P–31P.
- Shumei Y & Lubo Z. Glucocorticoids and vascular reactivity. *Current Vascular Pharmacology* 2004 **2** 1–12.
- Liu J, Heikkila P, Voutilainen R, Karonen SL & Kahri AI. Pheochromocytoma expressing adrenocorticotropin and corticotrophin-releasing hormone; regulation by glucocorticoids and nerve growth fac-tor. *European Journal of Endocrinology* 1994 **131** 221–228.
- Van Dam PS, Van Gils A, Canninga-van Dijk MR, De Koning EJP, Hofland LJ & De Herder WW. Sequential ACTH and catecholamine secretion in a phaeochromocytoma. *European Journal of Endocrinology* 2002 **147** 201–206.
- Hedeland H, Ostberg G & Hokfelt B. On the prevalence of adrenocortical adenomas in an autopsy material in relation to hypertension and diabetes. *Acta Medica Scandinavica* 1968 **184** 211–214.
- Mansmann G, Lau J, Balk E, Rothberg M, Miyachi Y & Bornstein S. The clinically inapparent adrenal mass: update in diagnosis and management. *Endocrine Reviews* 2004 **25** 309–340.
- Young WF Jr. Management approaches to adrenal incidentalomas: a view from Rochester, Minnesota. *Endocrinology and Metabolism Clinics of North America* 2000 **29** 159–185.
- Kasperlik-Zaluska AA, Roslonowska E, Slowinska-Szrednicka J et al. 1111 Patients with adrenal incidentalomas observed at a single endocrinological center: incidence of chromaffin tumors. *Annals of New York Academy of Sciences* 2006 **1073** 38–46.
- Eisenhofer G, Rivers G, Rosas AL, Quezado Z, Manger WM & Pacak K. Adverse drug reactions in patients with phaeochromocytoma: incidence, pre-vention and management. *Drug Safety* 2007 **30** 1031–1062.
- Lenders JW, Pacak K, Walthers MM, Linehan WM, Mannelli M, Friberg P, Keiser HR, Goldstein DS & Eisenhofer G. Biochemical diagnosis of pheochromocytoma: which test is best? *JAMA* 2002 **287** 1427–1434.
- Sawka AM, Jaeschke R, Singh RJ & Young WF. A comparison of biochemical tests for pheochromocytoma: measurement of fractionated plasma metanephrines compared with the combination of 24-hour urinary metanephrines and catecholamines. *Journal of Clinical Endocrinology and Metabolism* 2003 **88** 553–558.
- Bessell-Browne R & O'Malley ME. CT of pheochromocytoma and Paraganglioma: risk of adverse reactions with i.v. administration of nonionic contrast material. *American Journal of Roentgenology* 2007 **188** 970–974.
- Mukherjee JJ, Peppercorn PD, Reznick RH, Patel V, Kallsas G, Besser M & Grossman AB. Pheochromocytoma: effect of nonionic contrast medium in CT on circulating catecholamine levels. *Radiology* 1997 **202** 227–231.

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