

CASE REPORT

Stress-induced transient cardiomyopathy due to accidental administration of norepinephrine

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Abstract

A 48-year-old healthy female underwent an uncomplicated right ovariectomy. Relaxation status was checked post-surgery. A train of four of 2 of 4 twitches was scored. At this point, 5000 µg of norepinephrine was erroneously administered instead of 2500 µg neostigmine along with 1000 µg of atropine. The postoperative period was complicated by pulmonary oedema, for which non-invasive mechanical ventilation was initiated in the intensive care unit. A transthoracic echocardiogram TTE revealed a left ventricular ejection fraction of 25%. One month after discharge, control TTE showed normalised systolic cardiac function.

Introduction

Medication errors are still a well-known cause of deaths during anaesthesia^[1] and analysis of errors contributes to patient safety.^[2] A patient with transient cardiomyopathy and pulmonary oedema after accidental administration of 5000 µg of norepinephrine combined with 1000 µg of atropine is presented here. The aim of our report is to highlight the cardiopulmonary effects of this toxic dose of drugs.

Case description

A 48-year-old premenopausal female, American Society of Anesthesiologists (ASA) status 1, underwent an uncomplicated right ovariectomy for ovarian cysts by means of mini laparotomy. Induction (propofol, sufentanil, rocuronium bromide) and maintenance (sevoflurane) of anaesthesia were uneventful. Standard monitoring was used: three-lead electrocardiogram (ECG), pulse oxymetry, and automated non-invasive blood pressure (3-minute interval). The relaxation status was checked post-surgery. A train of four of 2 of 4 twitches was scored. At this point, 5000 µg of norepinephrine were erroneously administered instead of 2500 µg neostigmine along with 1000 µg of atropine. Several seconds later, haemodynamic monitoring revealed a

sinus tachycardia of 170 beats/min and the non-invasive blood pressure measurement failed to obtain a valid pressure. The relaxation status was again checked, yielding an unchanged result. Consequently, a medication administration error was strongly suspected. Recovery of the ampoules used revealed that accidentally an ampoule of norepinephrine (5000 µg/5ml) had been given instead of neostigmine. Altogether, the patient had received 5000 µg norepinephrine and 1000 µg atropine as a bolus. About 6 minutes after the injection a blood pressure of 160/90 mmHg and a heart rate of 120 beats/min were recorded. Sedation with propofol 2 mg/kg/h was continued and the patient was transported to the postoperative care unit.

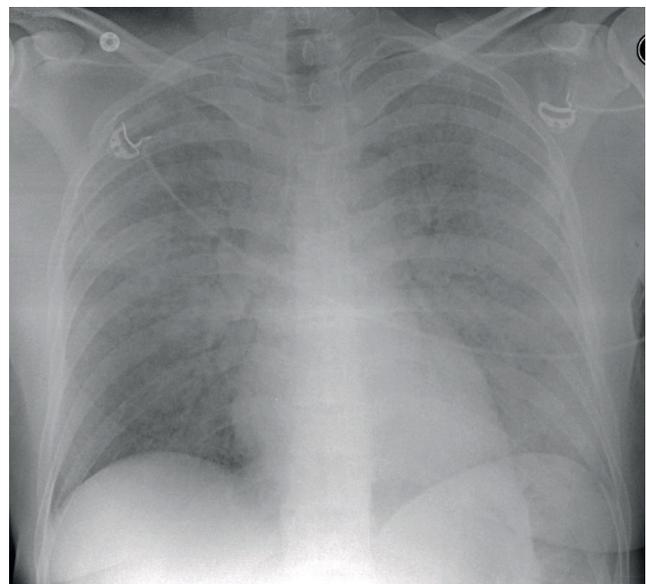


Figure 1a. Chest X-ray taken on ICU admission: acute pulmonary oedema

Forty-five minutes after the incident the remaining muscle relaxation resolved. Her blood pressure was 90/50 mmHg and the ECG showed a normal sinus rhythm of 60 beats/min. After termination of sedation, full recovery of consciousness and neurological function was observed. Subsequent extubation was uneventful. Thirty minutes after extubation, the saturation dropped to 85%. Invasive arterial monitoring was initiated and a blood gas analysis revealed a pH 7.35, pCO₂ 4.8 kPa, pO₂ 6.1 kPa, HCO₃⁻ 19.4 kPa, BE -5.6, Sat O₂ 82%, and lactate 0.8 mmol/l. Auscultation of both lungs revealed crackles and a chest X-ray showed signs of diffuse pulmonary oedema (*figure 1*).

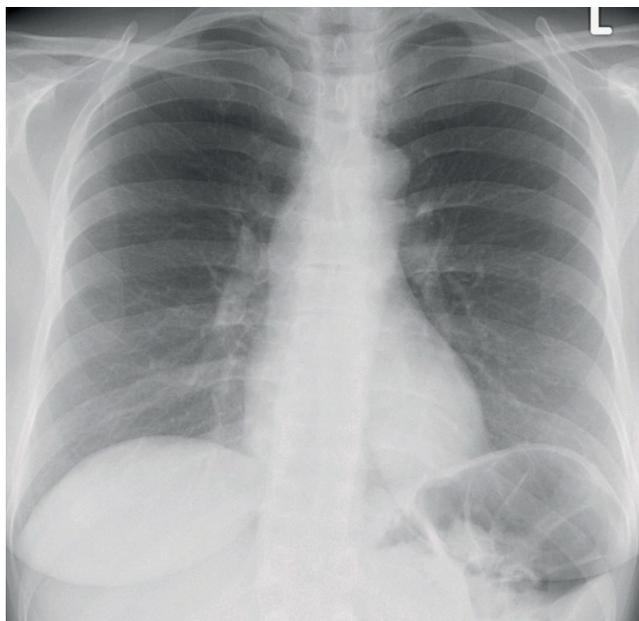


Figure 1b. Chest X-ray taken at discharge: no abnormalities

Pulmonary oedema due to cardiac injury was suspected. A bolus of furosemide (40 mg) was administered and non-invasive mechanical ventilation (NIV) was initiated (positive end-expiratory pressure (PEEP) 5 cmH₂O, inspiratory airway pressure 5 cmH₂O above PEEP, oxygen in air FiO₂ 50%). The intensivists as well as the cardiologist were consulted and the patient was admitted to the intensive care unit (ICU). A transthoracic echocardiogram (TTE) revealed impaired systolic function (a left ventricular ejection fraction (LVEF) of 25%). The most severe regional dysfunction was present in the mid-papillary segments, as shown in *figure 2*. No signs of acute myocardial infarction were found on successive ECGs. Serological markers, however, revealed increased biomarkers: Troponin-T peak value 0.78 µg/l (reference value (ref) <0.01 µg/l) after 8 hours and peak creatine kinase (CK) 259 µg/l (ref 0-480 µg/l), CK-MB isoenzyme 24.1 µg/l (ref <2.9 µg/l), brain natriuretic peptide (NT-proBNP) 61.8 pmol/l (ref <35 pmol/l), and aspartate aminotransferase peak value 54 U/l (ref <45 U/l; this was after 15-20 hours).

Treatment for congestive heart failure was started and was mostly supportive, with diuretics and non-invasive mechanical ventilation (NIV), since there were no signs of severe cardiogenic shock. Fifteen hours after ICU admission, the patient's clinical condition had improved and NIV was stopped. The patient was discharged to the ward 40 hours after the incident.

Two days later cardiac magnetic resonance imaging (CMR) was performed for detection and assessment of the morphology and functional characteristics of the cardiomyopathy. CMR showed improvement in contractility (LVEF 49%), hypokinesia of the mid-papillary anterior segment, and no myocardial oedema or infarction were visible. A coronary angiography to rule out ischaemic heart disease revealed normal coronary arteries. One week after the incident the patient was discharged from the hospital while on furosemide 40 mg, and candesartan 4 mg, all once daily.

One month after discharge, the patient was asymptomatic with normal exercise tolerance. Control TTE and CMR revealed normalisation of the systolic heart function with an LVEF of 65%. All cardiac medication was stopped. No rebound heart failure was observed.

The medication error was immediately discussed with the patient and her family, and reported to the hospital and national patient safety board (Dutch Health Inspection (IGZ))

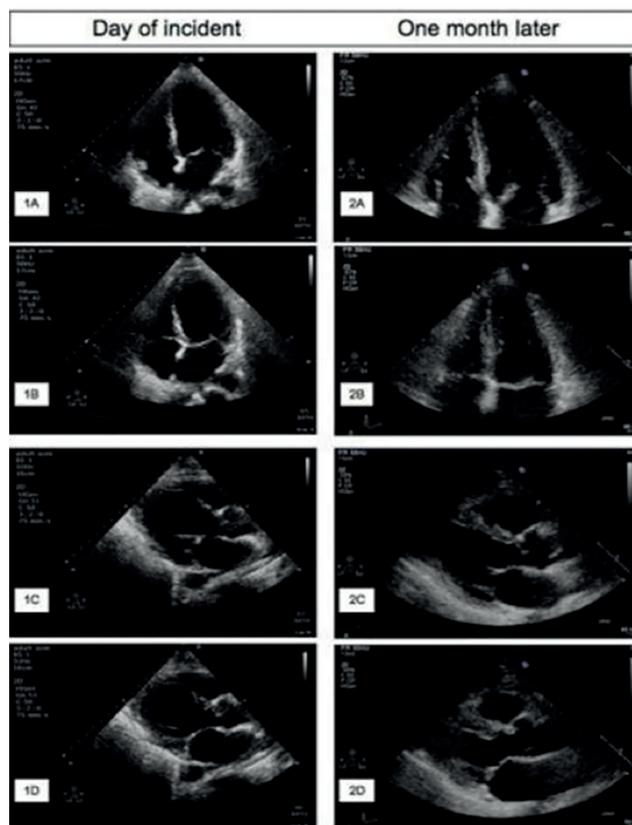


Figure 2. Echocardiography at day of incident (1) and one month later (2). 1A/2A showing apical four-chamber view at end-diastole and 1B/2B at end-systole. 1C/2C showing parasternal long axis view at end-diastole and 1D/2D at end-the systole.

Discussion

We present a rare case of accidental bolus administration of norepinephrine combined with atropine. Stress-induced cardiomyopathy is a relatively uncommon syndrome. A traditional description of stress-induced cardiomyopathy is the following: reversible left ventricular wall motion abnormalities, without significant coronary artery lesion and/or coronary vasospasm.^[3] In 2006 the cardiomyopathies were sub-grouped into two groups: Primary and secondary cardiomyopathies (table 1).^[4] The primary cardiomyopathies were grouped into three groups: Genetic, acquired and mixed. In the process, some stress cardiomyopathy was renamed and reclassified within the subgroup of acquired cardiomyopathies.^[4] Acquired cardiomyopathy occurs in different settings: after acute emotional or physical stress (takotsubo cardiomyopathy, apical ballooning syndrome), left ventricular (LV) dysfunction associated with intracranial haemorrhage, ischaemic stroke and head trauma, and transient LV dysfunction in acute medical illness (sepsis, acute pulmonary illnesses). Secondary cardiomyopathies can have different origins: toxicity (drugs, heavy metals, etc.), endocrine (diabetes mellitus, pheochromocytoma, acromegaly, hypothyroidism, etc.), infiltrative, storage, autoimmune, electrolyte imbalance, etc.^[4] LV dysfunction in pheochromocytoma and with exogenous catecholamine administration are sometimes grouped together.^[5]

Table 1. The 2006 AHA Classification Scheme for Cardiomyopathies with Selected Examples [4]:

Primary cardiomyopathies (predominantly involving the heart)	Secondary cardiomyopathies (with involvement of other organ systems)
Genetic - Hypertrophic Cardiomyopathy - ARVC - Left Ventricular Noncompaction - Storage Disorders: Danon, PRKAG2 - Conduction Defects - Mitochondrial diseases - Ion Channel Disorders: Long-QT, Brugada	<ul style="list-style-type: none"> • Infiltrative: Amyloidosis, Gaucher's • Storage: Hemochromatosis, Fabry's • Toxicity: Drugs, Heavy Metals • Endomyocardial: Loeffler's • Inflammatory: Sarcoidosis • Endocrine: Diabetes, Hyperthyroidism
Mixed - Dilated Cardiomyopathy - Restrictive Cardiomyopathy	<ul style="list-style-type: none"> • Cardiofacial: Noonan Syndrome • Neuromuscular: Muscular Dystrophies • Nutritional: Beriberi, Scurvy • Autoimmune: Lupus, Scleroderma
Acquired - Myocarditis - Stress-Provoked (taka tsubo) - Peripartum - Tachycardia-induced - Infants of diabetic mothers	<ul style="list-style-type: none"> • Electrolyte Imbalance: Hyperkalemia • Therapy: Radiation, Chemotherapy

Since there was a clear exogenous trigger in our case - overdose of norepinephrine - and there was no ST-segment elevation nor T-wave inversion, our patient does not fulfil all the criteria for takotsubo cardiomyopathy.^[5]

Gianni et al. reported a detailed systematic review of case reports and cohort studies, concerning apical ballooning syndrome or takotsubo cardiomyopathy, with a total of 286 patients. As in other studies, prognosis was generally excellent

with full recovery within days to weeks. The in-hospital mortality was 1.1% and only 3.5% of the patients suffered from a recurrence.^[6] The pathophysiology of catecholamine-induced cardiomyopathy is multi-factorial.

The myocardial alterations are similar in all species including humans. Several pathophysiological theories are discussed.^[7,8]

Coronary vasoconstriction: catecholamines have been shown to induce vasospasm resulting in hypoxia at the myocardial level. This significant rise in coronary artery resistance occurs minutes after starting a norepinephrine infusion in conscious dogs.^[9]

Calcium overload: an excess of norepinephrine also influences intracellular calcium levels. The permeability of the sarcolemma membrane is changed resulting in an elevated intracellular calcium level. This has a direct toxic effect on the cell and causes necrosis.^[8-10]

Free radical formation: cytotoxic free radicals from catecholamines could be involved in the genesis of myocyte damage.^[11-14]

Hyper-contraction theory: After administration of high doses of isoproterenol (a synthetic catecholamine that stimulates beta 1 and beta 2 adrenergic receptors), characteristic changes of hyper-contraction of myofilaments with formation of contraction bands, disorganisation and fragmentation of myofibrils are described.^[8]

Fatty acid toxicity: catecholamines increase plasma free fatty acid levels by stimulating the mobilisation of lipids from adipose tissue.^[10] Thus, myocardial lipid accumulation can result in cardiomyocyte apoptosis, destroying cell and mitochondrial membranes.^[15,16]

The resulting pulmonary effects of catecholamines are almost exclusively derived from animal studies. Rassler and colleagues investigated catecholamine-induced pulmonary oedema and pleural effusion in rats using continuous intravenous infusion of norepinephrine and separate α - or β -adrenergic stimulation.^[17]

The α -adrenergic treatment caused severe alveolar oedema associated with IL-6 activation in serum and diffuse pulmonary inflammation.^[18,19] In contrast, pure β -adrenergic stimulation induced interstitial but not alveolar oedema and focal inflammation without IL-6 activation. Rassler et al. concluded that haemodynamic effects causing an increase in pulmonary capillary pressure are considered to be the initial factors in the pathogenesis of pulmonary oedema.^[17] Other conditions associated with sympathetic activation such as high altitude pulmonary oedema and pulmonary oedema in patients with pheochromocytoma support this hypothesis.^[20,21] Besides the above-mentioned causes of pulmonary oedema, pulmonary oedema could be secondary to the left ventricular failure.^[22]

Take home messages of this case report are:

1. Unless there is obviously a quick recovery from a single shot overdose of norepinephrine, patients need to be monitored for

some time to exclude cardiac and pulmonary complications, for instance pulmonary oedema.

2. The prognosis of a single shot overdose of norepinephrine seems to be good in premenopausal healthy female patients, in contrast to other stress cardiomyopathies.
3. In this case, as in other cases of stress cardiomyopathy, supportive therapies seem to be advisable.^[5]
4. During the work-up of stress cardiomyopathy, other diagnoses, such as coronary diseases, should be excluded.^[5]

Conclusion

This rare case of accidental norepinephrine overdose, combined with atropine, illustrates the potential for development of stress cardiomyopathy with pulmonary oedema. As with most of the other cases of stress cardiomyopathy, our patient made a full recovery.

Disclosures

Patient gave oral permission for publication of her case. The included case report is completely anonymous.

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