Unexpected outcome (positive or negative) including adverse drug reactions

Flash pulmonary oedema: a rare but serious side effect of quinine sulphate

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Summary

A 54-year-old woman with a background of psoriatic arthritis but no cardiac history was admitted with acute pulmonary oedema (November 2007) which required invasive ventilation and inotropic support. Investigations including ECG, transthoracic and transoesophageal echocardiography, coronary angiography, renal ultrasound and renal magnetic resonance angiography, cardiac MRI and urinary catecholamines were normal. Due to the lack of precipitant, the authors assumed this was due to nabumetone (a non-steroidal anti-inflammatory drug (NSAID)) which was stopped. A second similar episode (August 2008) was temporally associated with a depo steroid injection, although no NSAID was given. Steroids have subsequently been restricted. However, she was admitted again with pulmonary oedema (April 2010) despite not taking NSAIDs or steroids. At that stage, she advised us that she had been taking quinine sulphate on an as required basis and had taken oral doses before each episode of pulmonary oedema which the authors now believe to have been the precipitant.

BACKGROUND

Quinine is a cinchona alkaloid used primarily for the treatment of *Plasmodium falciparum* malaria. It is also used for the treatment of nocturnal leg cramps as it increases the refractory period of skeletal muscles and reduces the excitability of the motor endplate. The association between quinine and pulmonary oedema has been reported in two previous case reports.^{1 2} Pulmonary oedema is a well recognised complication of acute *P falciparum* malaria occurring in 9–21% of patients^{3 4} and it is therefore reasonable to hypothesise that some of these episodes may have been caused by treatment with quinine rather than as a complication of malaria. I decided to write up this case to enhance awareness of the association of pulmonary oedema with quinine sulphate and because of the severity of pulmonary oedema in this patient requiring invasive respiratory and inotropic support.

CASE PRESENTATION

A 54-year-old woman presented with a background of psoriatic arthritis but had no prior cardiac history. She was initially admitted in November 2007 with a 2-day history of progressive dyspnoea on exertion and an acute episode of paroxysmal nocturnal dyspnoea. She had not experienced any chest pain and had been on a short course of regular nabumetone (a non-steroidal anti-inflammatory medication) and a depo steroid injection before admission. On arrival in the accident and emergency department, she was pyrexial (temperature 38°C), hypotensive (blood pressure 89/49 mm Hg), tachycardic (pulse 110 bpm) and hypoxic (SaO₂ 84% on room air, 94% on 10 litres O₂). Cardiovascular examination revealed normal heart sounds with no murmurs, the jugular venous pressure was not elevated and there was no peripheral oedema. Chest

auscultation revealed coarse inspiratory crackles throughout and a respiratory rate of 22 breaths per minute.

INVESTIGATIONS

- ▶ Bloods: normal full blood count, urea and electrolytes, liver function tests, C reactive protein 8, negative blood cultures.
- ▶ Troponin T: 0.056 (normal range <0.01).
- ▶ Arterial blood gas on 15 litres O₂ via reservoir mask: pH 7.31, pCO₂ 5.3 kPa, pO₂ 8.8 kPa, HCO₃⁻ 20, base excess – 5.8, SaO₂ 91% – severe respiratory acidosis and hypoxia.
- ▶ ECG: sinus tachycardia 110 bpm with no significant ST changes.
- ▶ Chest x-ray: florid pulmonary oedema with normal cardiac size.
- ▶ Transthoracic and transoesophageal echo: normal biventricular systolic function with no significant valvular pathology.
- ▶ Coronary angiography: normal coronary arteries
- ▶ Abdominal ultrasound: diffuse fatty infiltration of the liver. Normal sized kidneys with no evidence of hydronephrosis or ureteric obstruction.
- ▶ MR renal angiogram: no evidence of significant renal artery stenosis.
- ▶ Cardiac MRI: normal.
- ▶ Urinary catecholamines: normal.

DIFFERENTIAL DIAGNOSIS

Cardiogenic versus non-cardiogenic pulmonary oedema.

TREATMENT

The patient was formally intubated and ventilated and transferred to intensive treatment unit. Intravenous furosemide boluses were given followed by an infusion at 5

mg/h. Intravenous dobutamine and then norepinephrine were given for inotropic support. She was started on bisoprolol and perindopril (after renal artery stenosis had been excluded) with dose titration for empirical treatment of cardiac failure in the absence of other identifiable causes of pulmonary oedema. Nabumetone and depo steroid injection were discontinued. Extensive investigations to establish the cause in view of the severity of the episode were unhelpful.

OUTCOME AND FOLLOW-UP

Further hospital admissions with acute pulmonary oedema (August 2008 and April 2010) which did not require invasive or non-invasive ventilation and responded to conventional treatment with intravenous diuretics and nitrates. The patient then reported that she had been taking quinine sulphate for nocturnal leg cramps on an as required basis and had taken oral doses prior to each episode of pulmonary oedema. This has now been discontinued and she has not had any further episodes to date.

DISCUSSION

There have been 11 other reported cases of pulmonary oedema associated with quinine sulphate^{1 2 5} in the absence of other cardiogenic and non-cardiogenic aetiologies. The mean age of the 11 patients was 57 years (range 35–78 years) and the male to female ratio was 5:6. Quinine sulphate had been taken orally by all 11 patients and had been taken on an as required basis by four patients where a direct causal relationship could be established with the onset of pulmonary oedema. The length of time between ingestion of quinine and onset of pulmonary oedema ranged from 30 min to 24 h. The recognised cardiovascular side effects published in the British National Formulary and ToxBase include QTc prolongation, ventricular tachyarrhythmias

including torsades de pointes and heart block. Importantly, pulmonary oedema is not included and we strongly believe that this should be added to ensure that physicians are aware of this potentially life threatening adverse effect.

Learning points

- ▶ Flash pulmonary oedema is a rare but potentially life threatening side effect of quinine sulphate.
- ▶ Flash pulmonary oedema is a medical emergency which requires prompt assessment and treatment with intravenous diuretics, glyceryl trinitrate, opioids and non-invasive/invasive ventilation depending on its severity.
- ▶ Investigation of the cause of pulmonary oedema should focus on both cardiogenic and non-cardiogenic aetiologies including bilateral renal artery stenosis and pheochromocytoma.

Competing interests None.

Patient consent Obtained.

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