

Teaching Point
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Out of the blue

Ajay Dhaygude, Patrick MacDowall, Robert A. Coward and Alexander Woywodt

Renal Unit, Lancashire Teaching Hospitals NHS Foundation Trust, Preston, Lancashire, UK

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Introduction

Episodes of hypotension are common during haemodialysis sessions; they are usually related to volume depletion, presence of cardiac disease or both. Fortunately, severe hypotension with loss of consciousness, disappearance of peripheral pulses and pre-arrest is rare during haemodialysis. Such an event mandates a comprehensive assessment after the patient has been stabilized. We present the interesting case of a 73-year-old patient who was newly started on haemodialysis and sustained a pre-arrest during her fourth haemodialysis session.

Case

A 73-year-old female patient with hypertensive nephrosclerosis was started on haemodialysis via a tunnelled line in July 2008. Her other comorbid conditions included atrial fibrillation and right heart failure with severe pulmonary hypertension (pulmonary artery pressure 83 mmHg) due to pulmonary emboli. Her medication included ramipril 5 mg once daily (OD), bisoprolol 3.75 mg OD (evenings) and sildenafil 25 mg three times daily. Following implantation of her tunnelled line, she underwent three uneventful haemodialysis sessions. The fourth haemodialysis session was started with the patient in good mood and with a blood pressure of 123/71 mmHg. After 8 min of dialysis the patient became unresponsive without peripheral pulse. Dialysis was stopped, and resuscitation was just being initiated when the patient regained consciousness after administration of 1L of fluid. There had been no kinking of any of the tubing. The chest was clear and there was no cardiac murmur; the abdomen was soft. The patient was afebrile. Dialysis was stopped. An electrocardiogram showed no

new changes and troponin T was normal. A bedside ultrasound excluded pleural and pericardial effusion and showed no free intra-abdominal fluid. The inferior vena cava was dilated, in keeping with known right-sided heart failure. Dialysis was discontinued and the patient received oxygen. During that day she made an uneventful recovery. Her C-reactive protein was normal and serum haemoglobin was unchanged. Serum potassium was not elevated. We continued to search for something that was different on the day she had her fourth haemodialysis session and came up with the timing: the uneventful sessions had started at 17.00 p.m., 10.45 a.m. and 15.00 p.m., respectively. The fourth haemodialysis session had been started at 9.00 a.m. We hypothesized that her medication was at fault and ascertained that it had been the only session in close vicinity to sildenafil ingestion (given at 8.00 a.m., lunchtime and 18.00 p.m.). We then tried to schedule all dialysis sessions 3 h after the last sildenafil dose. No further episodes occurred. However, several sessions later the patient was inadvertently called for dialysis again at around 9.00 a.m. and sustained an episode similar to the first although less severe. Sildenafil was stopped entirely, the patient was discharged and no further episodes occurred.

Discussion

This case did not present like a typical case of intra-dialytic hypotension. We therefore reviewed the differential diagnosis of intra-dialytic hypotension [1] (Table 1). Some of those causes, such as those associated with human error and/or technical fault seemed exceedingly unlikely from the beginning. Massive haemolysis can be particularly dangerous and challenging to manage. These incidents are, fortunately, rare in dialysis units in the developed world. Other causes of hypotension, particularly intra-thoracic and intra-abdominal bleeding and pericardial tamponade, were quickly excluded by bedside ultrasound. The remaining causes were excluded with electrocardiogram, normal troponin and normal C-reactive protein. Next, we turned our attention to the main concurrent disease, namely pulmonary hypertension.

Severe pulmonary hypertension is uncommon among haemodialysis patients and the literature is sparse. Notably,

Correspondence and offprint requests to: Alexander Woywodt, Renal Unit, Lancashire Teaching Hospitals NHS Trust, Royal Preston Hospital, Sharoe Green Lane, Preston, PR2 9HT, UK. Tel: +0044-1772-524629; Fax: +0044-1772-523516; E-mail: Mail@Alexander-Woywodt.com

Table 1. Differential diagnosis of hypotension during haemodialysis [1]

Complication	Cause	Signs and symptoms other than hypotension	Diagnosis/specific treatment
Air embolism	Human error, technical failure (e.g. broken tubing or line)	Foam in line; neurological signs and symptoms, dyspnoea, shock due to air in right ventricle and decreased cardiac output	Cardiac murmur and air in the extracorporeal circuit/stop dialysis, clamp venous line, position patient head and chest down on the left side
Massive haemolysis	Human error/technical failure (hypotonic/overheated or contaminated dialysate); line kinking between blood pump and downstream circuit	Lumbar and abdominal pain; pancreatitis; dyspnoea, neurological signs and symptoms due to cerebral oedema	No diagnostic test/stop dialysis (never flush blood back to the patient), resume with different machine after technical fault excluded (will have hyperkalaemia!)
Severe hyperkalaemia	Incompliance with diet, long interval and/or inefficient dialysis	'Heavy legs', paraesthesia; sudden asystolic arrest common	Emergency dialysis; i.v. calcium, beta 2 agonists, glucose/insuline, resonium to buy time if dialysis not immediately available
Dysequilibrium syndrome	Overzealous first dialysis in a very ureamic patient	Neurological signs and symptoms due to cerebral oedema, seizures	No diagnostic test/stop dialysis (prevent with short repetitive sessions)
Dialyzer reaction	Cytokine storm, complement activation	Urticaria, pruritus, dyspnoea	No diagnostic test/stopping of dialysis, epinephrine/anti-histamines and steroids if severe; change of dialyzer
Late intra-thoracic bleeding after insertion of tunnelled line [15]	Bleeding from a previously sealed vascular leak	Chest pain	Ultrasound and chest x-ray, drop in haemoglobin/stopping of dialysis, chest drain; surgery if appropriate
Gastrointestinal bleeding or bleeding into abdominal cavity	Intra-dialytic use of heparin precipitates bleed	Coffee-ground vomiting, melaena, abdominal pain	Endoscopy/stop dialysis, transfuse and watch potassium, heparin-free dialysis
Pericardial tamponade	Usually uraemic pericarditis	Chest pain, distended jugular veins, muffled heart sounds	Echocardiography or ultrasound/pericardial drain if severe; heparin-free dialysis
Occult sepsis	Often line infection	Fever, chills	C-reactive protein, blood cultures/identification of focus and antibiotics
Coronary event	Increased myocardial oxygen demand	Chest pain, dyspnoea	Electrocardiogram and troponin/stop dialysis, medical treatment or intervention as appropriate
Valvular heart disease	Usually aortic stenosis	Murmur, chest pain, dyspnoea	Echocardiogram and further investigations/valve replacement, consider PD if high risk for surgery
Pulmonary embolism	Uncommon during haemodialysis	Dyspnoea, chest pain	Electrocardiogram, echocardiography/full anticoagulation, thrombolysis if severe

primary pulmonary hypertension often affects younger or middle-aged female patients, and chronic renal failure is not very prevalent among this age group. Renal failure is usually perceived as a contra-indication to lung or heart–lung transplantation, the definitive treatment for advanced primary pulmonary hypertension, while combined transplantation is only performed in exceptional circumstances. Scleroderma with renal failure comes to mind as a scenario where end-stage renal failure and pulmonary hypertension may coincide but the prognosis of these patients is often dismal and peritoneal dialysis is the preferred treatment option. Finally, one wonders whether thrombectomy of vascular access may be a risk factor for pulmonary hypertension: not so, according to (admittedly small) studies [2]. More recently, studies have emerged to suggest that pulmonary hypertension among patients with end-stage renal disease may

be more common than is usually appreciated, and some authors have proposed that end-stage renal disease itself may play a pathogenic role [3] although it remains unproven. Accordingly, there was not much the literature could offer to handle this case: a PubMed search with the search terms 'dialysis', 'hypotension' and 'pulmonary hypertension' did not yield a single relevant article. We first asked ourselves whether volume depletion might have played a role in the case under discussion. However, neither personal experience nor the literature told us how to gauge the intravascular volume in these patients, given that the width of the inferior cava is obviously unreliable. Finally, we managed to find one case of a dialysis patient with pulmonary hypertension and syncope [4]. Remarkably, this patient did not sustain her episodes during the haemodialysis sessions [4]. Moreover, Havlucic and colleagues reported an improvement in



Fig. 1. The dosette with our patient's medication (left, breakfast medication).

pulmonary artery pressures with dry weight reduction. De-compensation of severe pulmonary hypertension is feared but does not usually recover unless expert treatment is at hand, with right-sided cardiac monitoring and sophisticated drug treatment. These thoughts gave us further confidence that neither volume depletion nor the pulmonary hypertension itself played a crucial role in the case under discussion. We continued to think long and hard as to the cause of pre-arrest in this patient and pondered her medication (Figure 1) although no new drug had been started recently. We excluded bisoprolol, since the drug had also been administered on the days of the uneventful dialysis sessions. We then suspected sildenafil.

Sildenafil citrate (ViagraTM/RevatioTM, Pfizer) is a potent and selective inhibitor of cGMP-specific phosphodiesterase type 5 (PDE5) (Figure 2). Phosphodiesterases actually come in 11 varieties as described elsewhere [5]. The PDE5 family is responsible for degradation of cGMP in the corpus cavernosum in the penis; hence, inhibition of PDE5 leads to a prolonged effect of NO and increased penile tumescence. However, more recently, the use of phosphodiesterase inhibitors has been advocated in pulmonary hypertension and altitude sickness [6]. In the pulmonary vasculature, nitric oxide is constitutively produced by NO synthase and serves to redirect blood flow to well-ventilated areas [5]. Clinical benefits have been reported first in primary pulmonary hypertension [6]. More recently, its use has been advocated in other forms of pulmonary hypertension as well. Future indications for PDE5 inhibitors may include Raynaud's and ulcers in scleroderma [5].

There is increasing experience with sildenafil in patients with renal impairment [7]. Grossman and colleagues evaluated pharmacokinetics of sildenafil in patients on maintenance haemodialysis. According to them, haemodialysis did not significantly clear either sildenafil or its primary metabolite, UK-103 320 [8]. Seibel and co-workers studied the drug in a placebo-controlled double-blind study in haemodialysis patients and convincingly found it to be efficacious and safe [9].

Side effects of sildenafil in patients on haemodialysis are not often reported. It is worthwhile to remember that

hepatic and renal impairment affect the pharmacokinetics of sildenafil [10]. Accordingly, our patient with end-stage renal disease and hepatic impairment due to right-sided heart failure can be expected to have a shorter time to max than healthy patients and, indeed, the patients in the Grossmann study [8]. Mohamed and colleagues, from our own department, reported a haemodialysis patient with hypotension that was thought to be related to sildenafil in 2000 [11]. The report was disputed [12]. According to Grossmann and co-workers, intra-dialytic hypotension was not observed more frequently when sildenafil was administered before haemodialysis [8]. Of note, in that study sildenafil was administered exactly 2 h prior to dialysis and patients had no cardiac disease. It is worthwhile to think about possible mechanisms. Sildenafil prolongs the effects of NO through inhibiting the degradation of its downstream mediator, cGMP. Incidentally, this is also the basis for the feared interactions between sildenafil and nitrates, drugs that donate nitric oxide. Interestingly, nitric oxide is also involved in intra-dialytic hypotension. Yokokawa and colleagues described markedly elevated production of nitric oxide during hypotensive episodes in haemodialysis patients [13]. In another study, methylene blue, a nitric oxide inhibitor, prevented hypotensive episodes during dialysis [14].

Conclusion

We cannot prove that sildenafil caused the two pre-arrest episodes in the patient under discussion. However, the fact that all other factors, except the timing of sildenafil, were identical during the uneventful sessions supports our theory. All other causes, we believe, were excluded. The involvement of nitric oxide in the pathophysiology of intra-dialytic hypotension provides a possible mechanism for sildenafil-induced hypotension in our patient. Finally, the fact that no more episodes occurred after the drug was stopped gives us further confidence in the interpretation. The majority of dialysis patients who receive sildenafil take the drug as needed for erectile dysfunction. For obvious reasons, these patients will not usually take the

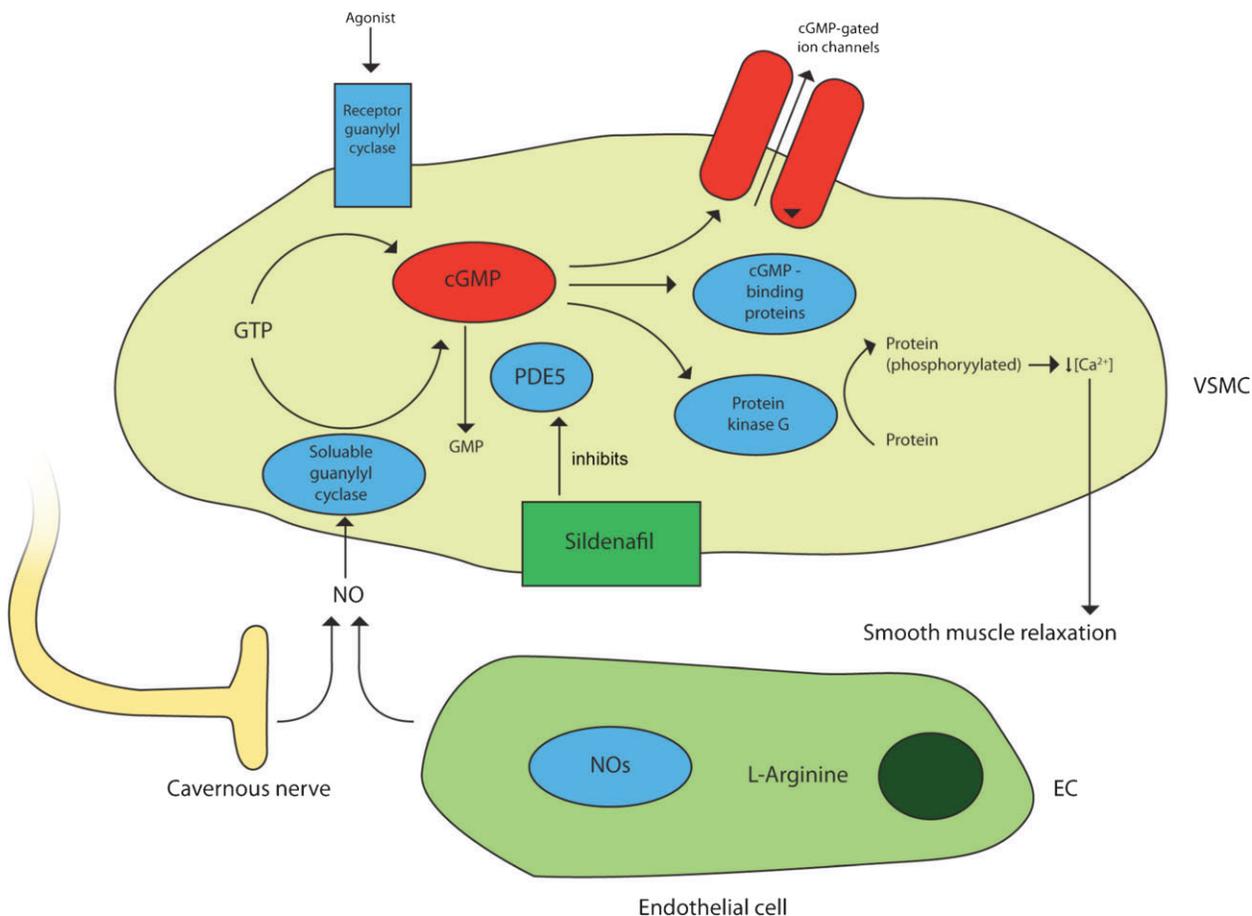


Fig. 2. The nitric oxide/cGMP/phosphodiesterase pathway. Note that phosphodiesterase 5 (PDE5) is crucial for the breakdown of cyclic guanosine monophosphate (cGMP), which eventually leads to the relaxation of vascular smooth muscle cells (VSMC). Smooth muscle relaxation is in part mediated via protein kinase G (PKG) activation and subsequent reductions in intracellular calcium levels. PDE5 is the target for sildenafil and other PDE5 inhibitors. PDE5 inhibitors inhibit the breakdown of cGMP and thereby prolong and increase vascular smooth muscle relaxation. cGMP, cyclic guanosine monophosphate; GMP, guanosine monophosphate; GTP, guanosine triphosphate; NO, nitric oxide; NOs, nitric oxide synthase; EC, endothelial cell; VSMC, vascular smooth muscle cell; PDE5, phosphodiesterase type 5.

drug shortly before haemodialysis. This case provided a good opportunity to remember the differential diagnosis of severe intra-dialytic hypotension and serves as a cautionary tale in the occasional dialysis patient who receives sildenafil for pulmonary hypertension. We believe that in these patients sildenafil should not be given prior to dialysis or best avoided altogether.

Teaching points

- (i) Hypotension is common during haemodialysis and related to ultrafiltration and cardiac disease. However, a variety of sinister causes occur as well.
- (ii) Sildenafil is an inhibitor of type 5 phosphodiesterase and is used in erectile dysfunction, pulmonary hypertension and altitude sickness.
- (iii) Sildenafil causes vasodilation through prolonging the effect of cGMP, a crucial downstream mediator in the NO pathway. This affects not only endothelial cells in target organs but also the systemic circulation.

Hence hypotension is a major side effect of all type 5 phosphodiesterase inhibitors.

- (iv) Pharmacodynamic data suggest a peak effect of sildenafil between 1 and 3 h after ingestion with shorter time to max in renal and hepatic impairment.
- (v) In patients with pulmonary hypertension on haemodialysis, sildenafil should be used with caution and probably avoided immediately prior to haemodialysis.

Conflict of interest statement. A.W. has given one speech for Pfizer followed by a £350 donation by Pfizer UK to the Preston Renal Unit. The other authors report no conflict of interest.

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