Case Report

Novel therapeutic option in hypertensive crisis: sildenafil augments nitroprusside-induced hypotension

Madan M. Bahadur, Vikram D. Aggarwal, Manish Mali and Aseem Thamba

Jaslok Hospital and Research Centre, Nephrology, Mumbai, Maharashtra, India

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Introduction

Sodium nitroprusside (SNP) produces hypotension by increasing nitric oxide-mediated generation of cyclic guanosine monophosphate (cGMP), which causes vasodilatation. On the other hand, sildenafil, a phosphodiesterase type 5 inhibitor (PDE5), increases cGMP by inhibiting its degradation by PDE5. Hence, theoretically, the two should be complementary. We present a case where the two agents were used together to manage a hypertensive crisis. This, to the best of our knowledge, is the first such case report worldwide.

Case

A 15-year-old girl presented with severe headache to a university hospital in Northern India in 2002, and was found to be markedly hypertensive (210/130 mmHg). Tests revealed a serum creatinine of 2.3 mg% and small contracted kidneys, detected by ultrasound. She was initially managed conservatively, but gradually progressed to end-stage renal disease (ESRD). In May 2004, she was started on thrice weekly maintenance haemodialysis. She came to us for a live, related renal transplant in September 2004, at which time her blood pressure (BP) was 130/90 mmHg. She was on atenolol 100 mg, prazocin 10 mg, amlodipine 10 mg and ramipril 10 mg once daily.

On September 19, 2004, she had severe diarrhoea and vomiting, and did not take her medications because of persistent nausea. Later that evening, she had an episode of generalized tonic–clonic convulsions and became mentally obtunded.

When wheeled into the Accident and Emergency Department of Jaslok Hospital, Mumbai, at 11 p.m., she was in a post-ictal confused state without focal neurological signs, and her BP was 220/130 mmHg. A brain computed tomography (CT) scan was normal, confirming hypertensive encephalopathy.

Course in the intensive care unit

A Ryle’s tube was passed via which she received all her BP medications. In addition sublingual nifidipine was given at regular intervals, according to her BP readings, but it was of no sustained benefit. She received prazocin 10 mg tid, atenolol 100 mg bid, amlodipine 10 mg qid and benzozipril 5 mg tid also without much benefit. An SNP drip was started at 5 μg/kg/min, along with arterial BP monitoring. As her BP remained high, the SNP dose was increased to 10 μg/kg/min, and her BP stabilized at 170/110 mmHg at this dosage.

However, rebound hypertension developed whenever we attempted to taper the SNP dose, and it could not be reduced below 5 μg/kg/min. Therefore, intravenous (i.v.) enalapril was added (2.5 mg every 6 h) along with i.v. labetolol (100 mg every 6 h) and as often as required (SOS). Despite the introduction of the centrally acting agent and the angiotensin receptor blocker, her BP remained at ~160/100 mmHg, and thus SNP was continued.

After 48 h of continuous SNP usage at high doses she became drowsy; her SaO2 fell to 92%, suggesting cyanide toxicity. Hence, she was dialysed to remove sodium thiocyanate. Her dry weight as assessed earlier had been 39 kg; her pre-dialysis weight was 37.9 kg, so we removed only 11 of ultrafiltrate, as we suspected renin-mediated hypertension secondary to gastrointestinal losses due to the earlier vomiting and diarrhoea. SNP could be tapered, and was discontinued during dialysis. Her sensorium improved but her BP remained at ~180/110 mmHg. SNP was continued.

Correspondence and offprint requests to: Vikram D. Aggarwal, Jaslok Hospital and Research Centre, Nephrology, Mumbai, Maharashtra, India. Email: akdktr@jaslokhospital.net
Sildenafil augments nitroprusside-induced hypotension

She was now on the following medications: amlodipine (10 mg every 6 h), benazapril (5 mg tds), prazopress XL (10 mg tds), atenolol (100 mg bid), aldomet (500 mg qds), candesartan (10 mg tds), i.v. SNP (5 µg/kg/min), i.v. enalapril (2.5 mg every 6 h), i.v. labetolol (100 mg every 6 h) and SOS. Minoxidil and moxonidine were not available for administration.

She was also simultaneously investigated for other causes of secondary hypertension. Colour Doppler sonograms of her aorta and renal vessels ruled out coarctation or renal artery stenosis. Antinuclear antibody (ANA)/antinuclear cytoplasmic antibody (ANCA) titres were negative, serum cortisol was normal. Urinary vanillylmandelic acid (VMA) levels were not determined, as they would be fallacious in this setting; but a CT scan of her abdomen and chest did not detect an adrenal or ectopic mass; similarly, a metaiodobenzyl guanide scan (MIBG) scan done later was normal.

As the patient’s BP remained uncontrolled despite the above medications, and cyanide toxicity from the SNP drip loomed on the horizon again, we decided to proceed with bilateral surgical nephrectomy. On September 24, 2004, she was dialysed and, thankfully, had an uneventful nephrectomy. Her BP decreased to 150/90 mmHg during anaesthesia and in the immediate post-operative period, allowing the dose of SNP to be reduced to 1 µg/kg/min.

However, her BP gradually climbed back to 200/120 mmHg requiring elevation of the dose of SNP to 5 µg/kg/min. The patient was now anephric, and had recently survived major surgery. All groups of antihypertensives were being used at their maximum doses, and yet 24 h after surgery we still could not taper her SNP dosage to below 2 µg/kg/min.

We carried out an extensive literature search and, based on an experimental model proposed by Yoo et al. [1], decided to use sildenafil as a nitroprusside-sparing agent. Written informed consent was obtained from the patient’s parents, to whom we explained all the risks involved, and approval was received from the local ethics committee.

On September 25, 2004, at 2.30 p.m. her BP was 210/120 mmHg, with the dose of SNP at 2 µg/kg/min. At this time 50 mg of powdered sildenafil was administered via the Ryle’s tube. Her BP dropped dramatically to 140/80 mmHg within 30 min. Therefore, SNP was quickly tapered off and discontinued to prevent any further precipitous fall of BP.

Further course in the ward

The patient’s BP gradually rose to 180/100 mmHg over the next 6 h, but this elevation did not require the administration of SNP and could be managed with oral antihypertensives. We gave her sildenafil 50 mg once daily over the next 2 days, when her BP exceeded 200/120 mmHg, in addition to her seven other antihypertensive drugs. The response of her BP was definite, but not as dramatic as when administered SNP; it dropped by an average of 20 mmHg systolic and 10 mmHg diastolic. The patient’s haemogram, liver profile, electrolytes, calcium, phosphorus and bicarbonate values were not affected by sildenafil. The antihypertensive drugs she required for the control of her BP could be gradually decreased to the previous levels; and 2 weeks later she was discharged with a BP of 130/90 mmHg.

Discussion

SNP is cleared from the circulation by an intraerythrocytic reaction with haemoglobin. Each molecule of SNP produces one molecule of cyanmethaemoglobin and four cyanide ions. Thiosulphate binds the cyanide ions, forming thiocyanate, which is filtered out by the kidneys. With normal renal function, cyanide toxicity is much more real. Therefore, any drug that augments SNP action, reducing its required dose, would be welcome.

Medina et al. [2] experimented with segments of coronary, internal mammary and radial arteries, and forearm veins by exposing them to sildenafil, zaprinast and SNP in an organ bath chamber. Isometric tension measurements revealed that sildenafil not only caused concentration-dependent relaxation of these vessels but also augmented the effect of SNP. Meanwhile, Inoue et al. [3] using T-1032 (a new PDE5 inhibitor) on anaesthetized rats concluded that it had a different vasodilatory action from that of an NO donor or a calcium channel antagonist, which act principally by reducing the mean circulatory filling pressure. Recently, Yoo et al. set up an experiment in mongrel dogs specifically to investigate if sildenafil can reduce the dose of nitrous vasodilators given deliberately to induce hypotension [1]. They showed that the magnitudes of the falls of arterial BP and systemic vascular resistance caused by SNP were augmented by sildenafil, whereas those caused by nitroglycerine (NTG) were not.

Interestingly, unlike sildenafil, neither SNP nor NTG alone altered plasma cGMP concentrations; however, the increased cGMP levels seen with sildenafil were augmented by SNP but not by NTG. It was suggested that the potentiation of SNP-induced hypotension by sildenafil may be related to an augmentation of the pool of cGMP in the blood. In human newborns, sildenafil has produced rewarding results in persistent pulmonary hypertension. In a randomized double-blind trial in adults with primary pulmonary hypertension, it improved exercise tolerance, cardiac index and quality of life, although the fall in pulmonary hypertension was not significant [4].
We rationalized the use of sildenafil to augment the action of SNP in our patient based on the above experimental evidence. We had exhausted all possible and available therapies, including bilateral nephrectomy, for the control of a hypertensive crisis. It may be argued that the resultant normotension achieved was due to the delayed effect of nephrectomy, as renin levels take some time to fall. It may also be reasoned that the course of BP under the administration of a large number of drugs, associated with dialysis, is unpredictable. Therefore, the attribution of the decrease of BP solely to the complementary effect of sildenafil could be questioned, although there are clinical and theoretical arguments in favour of that attribution. However, the fact that the fall of our patient’s BP was so dramatic, and over a short period of 30 min, and that it increased again later, though to a lesser extent, suggest a complementary effect.

We therefore propose that sildenafil augments the hypotensive effect of SNP. The addition of sildenafil can reduce the dose of SNP required. This is of special relevance for patients with renal failure in hypertensive crisis who are on SNP, and in whom cyanide toxicity is a possibility. The confirmation of this effect in a few more cases is required before it can be recommended for routine use.

Conflict of interest statement. None declared.

References

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