Letter to the Editors

Is nitroglycerin effective in treatment of haemoptysis?

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Although interventional regimens have rightly become the gold standard treatment for the control of haemoptysis, medication, especially vasoconstrictor medication, is still routinely administered in the clinic. The vasoconstrictor posterior pituitary hormone is the most commonly prescribed drug for the management of haemoptysis in China. However, vasoconstrictor therapy has various adverse effects, some of which may be severe, and is ineffective in a few patients.

So far there have been no reports of the possible benefits of vasodilator drugs as an alternative for the management of haemoptysis. Here we describe a patient suffering from bronchiectasis, atelectasis and old pulmonary tuberculosis (TB) who was treated with nitroglycerin to examine its possible role in the management of haemoptysis.

In July 2008, a 58-year-old woman presented to our hospital with a 2-year history of recurrent and productive cough with haemoptysis, and a recent relapse. The diagnoses were pulmonary TB in the left upper lobe, cystic (saccular) bronchiectasis, and atelectasis. The patient had been hospitalized many times during the past 2 years. She had recently complained of fever, cough, purulent sputum and haemoptysis (approximately 70 ml of bright red blood) in the past 24 h. There was no chest pain.

The patient had suffered from pulmonary TB for 25 years. Anti-TB therapy had been administered on several occasions, most recently in 2000 and 2003.

Physical examination revealed a temperature of 37.6°C, pulse 84 bpm, respiratory rate of 20 breaths min⁻¹ and blood pressure 140/75 mmHg. Her respiratory pattern was normal. No cyanosis of the lip and the nail beds was seen. There were resonance to percussion, harsh breath sounds, and crackles on auscultation of the left lower lobe. There was sinus rhythm, with no cardiac murmurs.

The results of chest computed tomography scan were old pulmonary TB in two upper lobes (fibrosis, proliferation, and calcification in the foci), atelectasis in left upper lobe, and bronchiectasis in left upper lobe, left lower lobe, and right middle lobe (Figures 1 and 2). White blood cell count was $8.28 \times 10^9 \text{ l}^{-1}$, of which 80.7% were neutrophils. Serum C-reactive protein level was $<1 \text{ mg l}^{-1}$. Erythrocyte

Figure 1

Bronchiectasis in left upper lobe

Figure 2

Bronchiectasis in left upper lobe and left lower lobe

sedimentation rate was 20 mm h⁻¹. Acid-fast stains thrice showed undetectable bacilli in sputum.

The diagnoses were (i) bronchiectasis, (ii) atelectasis, and (iii) old pulmonary TB.

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Imipenem/cilastatin (500 mg) was intravenously administered eight hourly. Daily doses of 2000 mg etamsylate and 400 mg aminomethylbenzoic acid were administered intravenously. Posterior pituitary hormone (vasopressin itself is seldom used in China) at a dosage referenced in a Chinese internal medicine textbook was administered as a continuous intravenous infusion of 2 U h^{-1} for 5 h and then at 0.4 U h^{-1} . Additional dosages of 6 U of the drug were administered subcutaneously twice daily. Haemoptysis persisted and deteriorated at 43 h after start of therapy and the daily volume of bleeding was approximately 150 ml. Since vasopressor therapy should preferably be trialled for no more than 48 h, alternative intervention (such as bronchoscopic treatment or bronchial artery embolization) was considered, but the patient did not accept invasive treatment, for fear of the side-effects of such treatment. The patient also refused transfer to a centre more adequately equipped for invasive treatment. We considered if there were any alternative ways in which to manage her haemoptysis. Vasodilators decrease pulmonary artery pressure, which might aid haemostasis. After informed consent (including informing the patient of the possibility that bleeding could worsen to become overwhelming or even life-threatening), treatment with posterior pituitary hormone was withdrawn and 15 mg nitroglycerin was administered intravenously by infusion pump over 24 h. Haemodynamic and respiratory monitoring was maintained. Blood pressure, heart rate and oxygen saturation remained normal. The volume of expectorated bright red blood decreased in the ensuing 15 h and then the expectoration became old blood, but no further fresh blood. Nitroglycerin was continued at the same dosage by infusion pump for a further 3 days. The expectoration of old blood diminished gradually and then disappeared within this time period.

Despite continuous administration of posterior pituitary hormone over 43 h, this patient's haemoptysis persisted, suggesting that the drug was ineffective. Once nitroglycerin was administered, bleeding stopped within 15 h, suggesting that this effect was not explicable as a spontaneous event or a late effect of the vasoconstrictor, but rather as a beneficial effect of the nitroglycerin.

Haemoptysis is the most common complication observed in bronchiectasis, pulmonary TB and lung cancer. An algorithm for the management of haemostasis incorporates bronchoscopic treatment, bronchial artery embolization, surgical management and therapy with coagulation factors, antifibrinolytic agents and vasopressin [1–4]. Invasive management requires appropriate equipment, expertise and facilities, while drug therapy is not cheap, so that both are difficult to establish in small hospitals or developing countries. Surgical management, apart from the technical requirements, has relatively narrow indications and so drug therapy (especially vasoconstrictor therapy) is extensively used because of its convenience. Posterior pituitary hormone is of interest to Chinese clini-

cians because of its confirmed efficacy and low cost, but it has limitations. Caution is advised in patients with coexistent coronary artery disease or hypertension [2]. A few patients are actually unresponsive to the regimen. In the present case the patient's haemoptysis progressed despite being given known effective dosages of the agent. We speculate that this might reflect abnormally high blood pressure induced by the vasoconstrictor causing increased returned blood volume and pulmonary artery pressure, thus impeding coagulation, and/or distortion of the lung tissue by repeated tuberculous infection, causing vascular deformation and a limited response to vasoconstrictor.

The nitric oxide donor drugs nitroglycerin and sodium nitroprusside have been used clinically during the past 30 years to produce systemic and pulmonary vasodilation [5]. Under normal physiological conditions, the endothelium maintains a low pulmonary vascular resistance by producing two potent vasodilators: an endothelium-derived relaxing factor, which is nitric oxide, and prostacyclin [6]. Traditional therapeutic interventions for pulmonary arterial hypertension include the use of intravenous vasodilators [7] such as nitroglycerin. Nitroglycerin is metabolized to nitric oxide, which produces smooth muscle relaxation in the vascular endothelial cells, thereby causing vasodilation. Puikuan *et al.* [8] reported that inhalation of nebulized nitroglycerin was able markedly to attenuate pulmonary artery pressure induced by high pulmonary blood flow (through an aortocaval shunt) in rats. Sidi *et al.* [9] showed that an infusion of low-dose nitroglycerin ($1 \mu\text{g kg}^{-1}$) showed a selective pulmonary vasodilatory effect during ethanol-induced pulmonary vasoconstriction in pigs. Yurtseven's study [10] has demonstrated the efficacy of inhaled nitroglycerin in reducing pulmonary arterial hypertension in adult patients undergoing mitral valve replacement surgery. Goyal *et al.* [11] reported that inhaled nitroglycerin significantly decreases systolic, diastolic and mean pulmonary artery pressure as well as the pulmonary vascular resistance index in children with congenital heart disease.

The principal pharmacological action of nitroglycerin is relaxation of vascular smooth muscle. Nitroglycerin influences the preload, rather than the afterload, of the cardiovascular system. Dilation of the veins promotes peripheral pooling of blood (mimicking exsanguination) and decreases venous return to the heart, thereby reducing pulmonary blood flow and facilitating the formation of local blood clots. Nitroglycerin is able to reduce pulmonary artery pressure and, to some extent, systemic blood pressure (including bronchial arterial pressure), which may also facilitate haemostasis. On the basis of the preceding rationale and given that the patient in this report had not responded to posterior pituitary hormone therapy, nitroglycerin was administered and appeared to have an unprecedented and encouraging effect in managing the haemoptysis. The daily dosages were based on those used for the control of coronary artery disease and heart failure. We were unable to identify any previous report that a

vasodilator may be effective for haemoptysis in the NCBI database.

Our patient did not display any unwanted effects of the use of nitroglycerin, but there is potential for such unwanted effects were the treatment to be used more widely. Tolerance to the cardiovascular effects of nitrates has been reported. Adverse reactions to nitroglycerin are generally dose-related, and almost all of these reactions are the result of nitroglycerin's activity as a vasodilator [12, 13]. Headache, which may be severe, is the most commonly reported side-effect. Hypotension occurs infrequently, but may be more likely in cases of right ventricular or inferior wall infarction, and in some patients it may be severe enough to warrant discontinuation of therapy. Lightheadedness, bradycardia, reflex tachycardia, syncope, crescendo angina (may be due to a local 'steal phenomenon' or venous pooling), pedal oedema and rebound hypertension have been reported but are uncommon. Nitroglycerin may induce vasodilation in poorly ventilated areas of the lung, which may result in hypoxaemia. Extremely rarely, ordinary doses of organic nitrates have caused methaemoglobinaemia in seemingly normal patients. Nitrate ions liberated during metabolism of nitroglycerin can oxidize haemoglobin into methaemoglobin.

Nitroglycerin may be a novel, effective and inexpensive agent for the management of haemoptysis, especially in patients with coexistent coronary artery disease or hypertension, in patients in whom vasoconstrictor is ineffective, and especially in small hospitals or developing countries. It should be used with caution so as not to induce severe hypotension or hypoxaemia. The rationale for using a vasodilator in patients with haemoptysis exists, but a randomized, controlled, multicentre cohort study of the use of nitroglycerin for the control of haemoptysis is warranted to confirm the efficacy and safety of the drug.

Posterior pituitary hormone was ineffective in our patient. However, nitroglycerin appeared to show unprecedented and encouraging activity in suppressing haemoptysis. This is the first report that a vasodilator can affect haemoptysis.

Competing interests

None to declare.

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