Remarkably efficient inhaled antifungal monotherapy for invasive pulmonary aspergillosis

To the Editors:

Voriconazole is a broad-spectrum antifungal agent that is effective against moulds such as *Aspergillus fumigatus*. It inhibits the cytochrome P450-dependent 14-α–lanosterol demethylase, preventing the conversion of lanosterol to ergosterol. This results in the accumulation of toxic methylsterols in the fungal wall and the inhibition of fungal growth [1]. Voriconazole is available as an intravenous infusion solution containing a cyclodextrin molecule (Captisol®; Ligand Pharmaceuticals Inc., La Jolla, CA, USA) to increase its solubility in water [2]. Adverse effects, such as gastrointestinal disorders, visual disturbances and elevated transaminase levels, complicate the use of voriconazole if used systemically. The therapeutic concentration range of voriconazole is from 1 to 5.5 $\mu g \cdot mL^{-1}$ and, although higher concentrations (>5.5 $\mu g \cdot mL^{-1}$) are associated with better clinical outcomes, they are also associated with more severe and less common side-effects, including encephalopathy and hallucinations [1]. Inhaled voriconazole reduces histological manifestations of invasive aspergillosis in rodents [3] and it has been proposed that a favourable lung tissue to plasma concentration ratio is obtained through this route of administration [4]. Consequently, inhaled voriconazole may provide higher concentrations at the site of infection without increasing the risk of systemic side-effects. We present three cases in which life-threatening invasive aspergillosis was treated with systemic voriconazole, but due to unacceptable adverse effects, the treatment had to be withdrawn. With no other conventional treatment options, inhaled voriconazole was administered.

In September 2009, a 66-yr-old, otherwise healthy male was admitted to our Dept of Infectious Diseases due to symptomatic pneumonia that had lasted for 4 weeks. The patient was a previous smoker (40 pack-yrs) and due to brain surgery for an incidental meningioma, he was treated with steroids. Due to complications, he was treated with methylprednisolone (100 mg) for >1 month.

Computed tomography (CT) imaging performed in October 2009 showed marked emphysema, a unilateral abscess and infiltration, but did not suggest lung cancer. Blood samples showed positive *Aspergillus* antigen compatible with invasive *Aspergillus* infection of the lung and oral voriconazole treatment was initiated.

Due to progressive aspergillosis in March 2010, the antimycotic treatment was intensified. Initially, the patient received a combination of antibiotics and antifungal therapy with oral voriconazole and *i.v.* anidulafungin without significant clinical effects. Inhaled amphotericin B was added to the antimycotic treatment but was not tolerated due to nausea, abdominal pain and vomiting.

In May 2010, chest radiography showed a slight lung infiltrate remission and the patient had nearly normalised C-reactive protein. By that time, the patient had developed polyneuropathy and progressive increases in liver enzyme levels. Consequently, antifungal treatment was halted, which normalised liver enzymes but was also associated with a worsened clinical condition and elevated C-reactive protein and leukocytes. Therefore, in July 2010, the patient started monotherapy with inhaled voriconazole at an initial total dose of 40 mg *t.i.d.* that was reduced to 40 mg *b.i.d.* after 2 weeks and was instructed to continue this at home on a daily basis. On inhaled voriconazole, as single therapy for 3 months, the patient recovered completely and could perform normal daily activities. Chest radiography performed in August 2010 showed remission of both the unilateral abscess and the parenchymal infiltration. The treatment was stopped after 6 months and follow-up 6 months later showed no sign of recurrence of the disease.

In September 2009, a 61-yr-old male with interstitial pulmonary fibrosis underwent bilateral lung transplantation. The postoperative period was complicated by graft dysfunction after 9 months.

In April 2010, the patient was admitted due to progressive respiratory insufficiency. Bronchoscopy with bronchoalveolar lavage showed invasive lung aspergillosis. Consequently, the patient started oral voriconazole and *i.v.* anidulafungin treatment but with a clinically insufficient response. Furthermore, elevation of liver enzymes was observed in relation to the treatment. The dose was therefore reduced and inhaled amphotericin B was added. Subsequently, reduced renal function and worsened dyspnoea were observed. At this point, chest radiography showed lung infiltrate progression and pleural effusion, and the patient started inhaled voriconazole with an initial total dose of 40 mg *t.i.d.* that was reduced to 40 mg *b.i.d.* after 2 weeks. A significant clinical response and chest CT remission were seen in July 2010 (fig. 1a and b). There was a slight change in the position of the lesion due to respiration. The maximum diameter of the lesion is shown in both images. 1 month later, the patient was discharged in a good condition and advised to continue with daily inhalations of voriconazole. The patient tolerated this treatment well and without any side-effects or influence on liver enzyme levels or pulmonary function tests. Due to severe graft dysfunction, the patient died 2 months later.

In September 1997, a 37-yr-old female with Eisenmenger's syndrome underwent heart and bilateral lung transplantation. There were no operative or immediate post-operative complications. 1 yr after the operation, the patient's forced expiratory volume in 1 s (FEV1) was 2.7 L and her forced vital capacity was 3.4 L. The patient's lung function decreased to an FEV1 of 2.0 L in 2002 and further to 1.3 L in 2005. Azithromycin treatment was introduced in 2008 for bronchiolitis obliterans syndrome. In 2010, the patient's FEV1 was 1.1 L and in 2011, three sputum samples showed *A. fumigatus*. Thus, treatment

FIGURE 1. High-resolution computed tomography images a) before and b) after 5 weeks of treatment with inhaled voriconazole. Between the two images, there was a slight change in the position of the lesion due to respiration. The maximum diameter of the lesion is shown in both images. c) Particle size of the aerosolised voriconazole.

with oral voriconazole (200 mg *b.i.d.*) was initiated. After a few weeks, blurred vision and vomiting started. The dose was reduced but the symptoms continued. The medication was changed to posaconazole but after 2 weeks, the treatment was stopped due to adverse reactions, including tiredness, constipation, mental depression and elevated liver enzymes. After 1 week, side-effects had disappeared and inhalation of voriconazole (40 mg·day^{-1}) was started. After 2 months, the patient's FEV1 had increased to 1.4 L, galactomannan antigen in blood had decreased from 4.4 to <0.5 and two sputum cultures showed no evidence of *Aspergillus*.

In all cases, aerosolised voriconazole was prepared as follows. The dry powder formulation of voriconazole (200 mg) for *i.v.* use was diluted in 20 mL of water and 4 mL, equivalent to 40 mg, was nebulised using a well-known and validated jet nebuliser (Sidestream®; Philips Respironics, Pittsburgh, PA, USA). The nebuliser was driven by a compressor (Portaneb; Medic-Aid, Pagham, UK) at a flow rate of 8 L·min^{-1}. Nebulisation lasted 15 min with the patient breathing quietly with their spontaneous breathing pattern. No breath holding was used and no specific precautions such as fume hoods were taken in order to reduce exhausted voriconazole aerosol.

The aerosol particle size was characterised using a seven-stage Anderson cascade impactor (Copley Scientific, Nottingham, UK), showing a mass median aerodynamic diameter of 2.4 µm (geometric standard deviation 1.5 µm) (fig. 1c). Finally, 93% of the particles were in the fine-particle fraction (<5 µm) and were thus considered in the respirable range.

To our knowledge, this is the first report on the successful administration of inhaled voriconazole for life-threatening invasive aspergillosis after the failure or withdrawal of conventional treatment regimes due to adverse effects.

After *i.v.* administration, voriconazole distributes well into tissues, including the lungs [5, 6], liver and brain [6]. Studies in rats have shown higher concentrations of voriconazole in wet lung tissue than in plasma after inhalation [4, 7], but it is unknown how voriconazole is distributed to other tissues after inhalation. The daily dose used (40 mg *t.i.d.*/40 mg *q.d.*) in our cases was lower than the usual dose for oral administration. Analysis of the aerosol showed very favourable characteristics with >90% of the particles in the respirable range, favouring peripheral lung deposition [8]. Therefore, we hypothesise that delivery directly to the lungs resulted in high local concentrations and effective inhibition of fungal growth, while systemic concentrations and side-effects were reduced.

Elevated liver enzymes returned to normal levels during inhalation therapy. Also, there were no local side-effects attributed to the inhalational route of administration. Thus, inhaled voriconazole seems to be safe and well tolerated.

Nebulisation was performed with the hospital's standard nebuliser without attempts to control the respiratory pattern of the patients. Use of a breath-actuated nebuliser, as opposed to continuous nebulisation, might have reduced waste of the medication and, thus, might reduce the cost of this expensive treatment. Lung deposition was not determined but is expected to be high due to a favourable fine particle fraction of 93%. Targeting the respiratory pattern would probably increase the pulmonary deposition since high tidal volumes and low inspiratory flow rates increase lung deposition [9]. Use of other more efficient nebulisers, such as mesh nebulisers, would also be expected to increase lung deposition and reduce nebulisation time, and should be pursued in future trials.

Together with the animal experiments reporting on both the effectiveness [3] and tolerability [7] of inhaled voriconazole, our three cases suggest that the safety and therapeutic potential of inhaled voriconazole therapy are promising and should be investigated in future controlled trials.

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Screening for diabetes mellitus in patients with OSAS: a case for glycosylated haemoglobin

To the Editors:

Obstructive sleep apnoea syndrome (OSAS) is a highly prevalent disorder, associated with decreased quality of life, increased risk of road traffic accidents, and increased cardiovascular morbidity and mortality [1]. OSAS also appears to independently predict metabolic dysfunction, with a growing body of evidence suggesting that sleep disordered breathing may be an independent driver of insulin resistance and dysglycaemia [2]. Indeed, a particularly intimate relationship exists between obesity and the development of OSAS and type 2 diabetes mellitus (T2DM): in the Sleep Heart Health Study over half of the diabetic subjects studied had some degree of sleep disordered breathing, while 23.8% had a respiratory disturbance index in the moderate or severe range [3]. Similarly, up to 40% of subjects with OSAS are diabetic at diagnosis [4]. Identification of subjects with T2DM allows the introduction of appropriate treatment to reduce cardiovascular morbidity and diabetes-related mortality.

While screening for T2DM has conventionally utilised either fasting plasma glucose (FPG) measurement or performance of an oral glucose tolerance test (OGTT), glycosylated haemoglobin (HbA1c) measurement has recently been approved as a stand-alone diagnostic test for T2DM by the American Diabetes Association (ADA) [5]. Furthermore, emerging data suggests HbA1c is an independent predictor of both the development of T2DM and long-term cardiovascular mortality in non-diabetic subjects [6]. Hence, measurement of HbA1c in OSAS patients not only facilitates screening for T2DM but may also allow identification of subjects at risk of subsequent metabolic and cardiovascular morbidity. We sought to assess the comparative utility of FPG and HbA1c in the identification of subjects with T2DM and impaired glucose tolerance (IGT) in a cohort with newly diagnosed OSAS.

We prospectively assessed consecutive subjects with newly diagnosed OSAS attending our sleep laboratory (St Vincent's University Hospital, Dublin, Ireland). Patients were excluded if they had a previous diagnosis of T2DM based on the medical history as reported by the patient, or the use of oral hypoglycaemic medications or insulin. Bloods were drawn in the morning following an overnight fast. Measurements of HbA1c and FPG were compared in the diagnosis of T2DM and IGT. HbA1c of $\geqslant 6.5\%$ was considered consistent with T2DM as per ADA guidelines, while a level of 6–6.5% was considered analogous to IGT, in keeping with recent evidence. FPG of $\geqslant 7$ mmol·L^{-1} (126 mg·dL^{-1}) or 5.6–6.9 mmol·L^{-1} (100–125 mg·dL^{-1}) were considered consistent with T2DM and IGT, respectively. Fisher's exact test was used for statistical comparisons, with a p-value of <0.05 considered significant.

269 individuals were evaluated. 23 (8.5%) had an antecedent diagnosis of T2DM, and were excluded from the analysis. Of the remaining 246 subjects, the majority were male, <65 yrs of age and obese. 39.7% had severe OSAS, with an overall mean apnoea/hypopnoea index (AHI) of 32.2 events·h^{-1}. Patient characteristics are summarised in table 1. 29 (12%) subjects had HbA1c of $>6.5\%$, consistent with a diagnosis of T2DM. Only 14 (5.5%) of the patients were identified as diabetic using FPG (p=0.025 for comparison) (fig. 1). 66 (27%) subjects had HbA1c of 6–6.5%, indicative of increased cardiovascular risk and predictive of future diabetes. FPG identified only 31(13%) individuals with IGT (p=0.0001 for comparison). Conversely, FPG identified one (0.4%) diabetic subject and 17 (6.9%) additional individuals with IGT not identified by use of HbA1c alone. Patients with T2DM or IGT were older (mean age 51.9 *versus* 47.1 yrs), more obese (mean body mass index (BMI) 36.3 *versus* 33.6 kg·m^{-2}), and had more severe OSAS (mean AHI 40.3 *versus* 29.2 events·h^{-1}) than those without. No significant sex differences were observed.

HbA1c has only recently been recommended as an appropriate stand-alone diagnostic test for T2DM by the most recent report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus [7]. Its diagnostic utility had been questioned prior to this report, principally due to a lack of assay standardisation, leading to inter-centre variability, but recent years have seen the implementation of rigorous standardisation *via* the National Glycohemoglobin Standardization