Intravenous azithromycin as salvage therapy in a patient with Legionnaire's disease

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Abstract

A patient with proven Legionnaire's disease is described whose clinical condition improved with intravenous azithromycin after failure to respond to treatment with erythromycin and rifampicin.

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Infection with *Legionella pneumophila* is a relatively uncommon cause of pneumonia in adults, accounting for 2-6% of cases acquired in the community in the United Kingdom.¹ Erythromycin has been the agent of choice in the treatment of *Legionella* pneumonia, but therapeutic failures have been documented² and antibiotic resistance due to emergence of mutant strains has been demonstrated in vitro.³ Recently, macrolides such as azithromycin have been shown to have superior activity against *L pneumophila* in an animal model of Legionnaire's disease.⁴

We report a case of Legionnaire's disease where intravenous azithromycin was used as salvage therapy in a patient who had not responded to treatment with erythromycin and rifampicin.

Case report

A 38 year old man presented to his general practitioner with a five day history of headache, abdominal pain, and offensive urine following a holiday in France during which he stayed in a hotel. He was treated with cotrimoxazole and subsequently developed a dry cough and exertional dyspnoea.

On admission he was febrile with a temperature of 38.6°C and had signs of consolidation in his right lung. He was treated for suspected pneumonia and pyelonephritis with intravenous Augmentin. The chest radiograph on admission showed extensive consolidation in both lung fields. Biochemical investigations showed a serum sodium concentration of 125 mmol/l.

On the third day, despite initiation of continuous positive airway pressure (table 1) he continued to deteriorate and needed to be intubated and was supported with intermittent positive pressure ventilation and positive end expiratory pressure of 10-15 cm H₂O (fig 1). As Legionnaire's disease was suspected his

antimicrobial treatment was therefore changed to intravenous erythromycin, 1 g six hourly, and cefotaxime, 1 g eight hourly. *Legionella* serogroup 1 antigen was detected in his urine by enzyme linked immunosorbent assay three days later.

Over the following three days he deteriorated so intravenous rifampicin 300 mg daily was added. Total parenteral nutrition was commenced in view of his catabolic state. An elective tracheostomy was performed.

Ten days after admission his renal function deteriorated, his serum creatinine rising to 129 µmol/l and urea to 12.5 mmol/l. Urine biochemical analysis was compatible with established renal failure: urine sodium was 309 mmol/24 hours (normal range 100-250 mmol/24 hours) and urine potassium was within the normal range at 94 mmol/24 hours. In addition, proteinuria of 2 g in 24 hours was observed. There was no evidence of a disseminated intravascular coagulopathy.

Pulmonary artery flotation catheter studies showed that the pulmonary artery pressure was 64/34 mm Hg (normal range 15-30/3-15 mm Hg) and pulmonary capillary wedge pressure was 17 mm Hg (normal range 6-12 mm Hg); cardiac output was 18 l/min (normal 5-5.5 l/min) and systemic vascular resistance was 408 dynes cm⁻⁵ (normal range 900-1200). The elevated pulmonary capillary pressure was attributed to fluid overload and the raised cardiac output, together with a low systemic vascular resistance, were compatible with his sepsis syndrome. Continuous arteriovenous haemofiltration was therefore commenced.

The patient's clinical condition deteriorated further and treatment with intravenous azithromycin was initiated (fig 2). The patient received a dose of 250 mg 12-hourly on the first day followed by a dose of 250 mg once daily for 13 days. After 48 hours of treatment both clinical and radiological improvement were observed (table 1). Erythromycin and rifampicin were discontinued after the first 24 hours of azithromycin therapy.

The patient's renal failure worsened with his serum creatinine stabilising at around 500 µmol/l. Continuous arteriovenous haemodiafiltration was commenced. It is not clear whether azithromycin may have contributed to the impairment of his renal function.

Three weeks after admission the serological tests became positive for *Legionella*, with a

Arterial blood gas analyses

Days after admission	FIO ₂	PaO ₂ (kPa)	PaCO ₂ (kPa)	pH
2	0.3	5.3	4.5	7.52
3	0.5	5.8	4.8	—
6	IPPV started	19.9	—	—
12	0.6	8.9	5.9	7.32
18	0.6	10.1	7.1	7.26
20	Azithromycin started	11.8	5.9	7.35
26	0.35	15.5	4.7	7.4
	Artificial ventilation stopped			

FIO₂ = fractional inspired oxygen; PaCO₂ = arterial oxygen tension; PaCO₂ = arterial carbon dioxide tension; IPPV = intermittent positive pressure ventilation.

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Figure 1 Chest radiograph showing extensive consolidation on the third day when intubation and ventilation was started.

Figure 2 Chest radiograph taken before azithromycin treatment.

titre of 1/512 to serogroup 1 compared with a baseline value of <1/16. Titres to serogroup 6 rose to 1/256.

The patient's clinical condition continued to improve. He required haemodialysis for a further week and was discharged five weeks later, since when he has remained well with normal renal function and a normal chest radiograph.

Discussion

We describe a patient with proven severe *Legionella* pneumonia whose clinical condition improved with intravenous azithromycin. Azithromycin differs structurally from the macrolide erythromycin by the insertion of a methyl substituted nitrogen at position 9a in the lactone ring creating a 15 numbered structure. This modification leads to an extension of the broad spectrum of activity against Gram positive and Gram negative bacteria.⁵ Azithromycin achieves high concentration in different tissues, including lungs, and these concentrations are in excess of the minimal inhibition concentrations against various microorganisms

including *L. pneumophila*⁶ and therefore may explain the improvement in our patient's condition. Quinolones such as ciprofloxacin have also been shown to have activity against *L. pneumophila*.⁷

A definitive diagnosis of Legionnaire's disease may be difficult to establish early in clinical practice as culture of the organism requires the use of multiple selective media and the sensitivity of this method is variable. Direct fluorescent antibody staining of sputum or bronchoalveolar lavage fluid is highly specific and provides a rapid diagnosis but also has a relatively low sensitivity. Detection of soluble *L. pneumophila* antigen in urine by enzyme linked immunosorbent assay overcomes some of the difficulties inherent in these methods; positive results can be obtained within three days of the onset of symptoms as illustrated in our case and this method has a sensitivity of 80%.⁸

Azithromycin has been shown to be as effective as erythromycin and better tolerated in the treatment of atypical pneumonia in adults.⁹ A three day regimen of azithromycin was shown in a single blind study to be as effective clinically and microbiologically as a 10 day regimen of co-amoxiclav in the treatment of acute lower respiratory tract infections.¹⁰

As far as we are aware, this is the first case report where intravenous azithromycin has been used in the treatment of a patient with severe legionellosis. Clinicians should consider this option for critically ill patients in whom standard treatment has failed.

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