

# DELIRIUM IN THE ELDERLY RESULTING FROM AZITHROMYCIN THERAPY

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## BACKGROUND

Azithromycin, a semi-synthetic azalide antibiotic, is a macrolide that thus far has not shared the neuropsychiatric side effects of other macrolides such as erythromycin and clarithromycin.

## METHODS

We now report significant delirium associated with conventional dosing of azithromycin in two geriatric patients who were being treated for lower respiratory tract infection.

## RESULTS

The onset of delirium was apparent within 72 hours of initiating azithromycin therapy and lasted 48 to 72 hours after discontinuing treatment with the drug.

## CONCLUSIONS

In contrast to the adverse central nervous system symptoms associated with clarithromycin, those induced by azithromycin seem to take longer to resolve, perhaps based upon the longer elimination half-life of the latter antimicrobial, particularly in geriatric women. © 2003 Elsevier Inc. All rights reserved.

## KEY WORDS

*Azithromycin, community acquired pneumonia, delirium, adverse drug reaction.*

Nightingale in 1995 [13], and our group in 1996, [6] reported patients with acute and at times dramatic psychoses associated with clarithromycin therapy. Since then, several other authors have recorded similar observations [9,11,12,14,15,17]. Further adverse central nervous system (CNS) effects due to other macrolides were anticipated, since both erythromycin and clarithromycin were associated with adverse CNS responses including delirium and loss of hearing likely due to effects on the central auditory pathways [3].

Azithromycin is a semisynthetic azalide antibi-

otic that is distinguished from other macrolides by the addition of nitrogen at position 9a of the lactone ring. This structural modification leads to improved tissue penetration, resistance to acid degradation, and a prolonged half-life compared to other macrolides [1]. Although only very low concentrations of azithromycin can be detected in spinal fluid in the absence of inflamed meninges (<0.01 ug/mL), the American Hospital Formulary Service (AHFS) Drug Information report of 2001 notes adverse CNS effects of azithromycin in about 1% of adults including dizziness, vertigo, somnolence, headache, asthenia, aggressive reaction, anxiety, paresthesias, and seizures [1]. However, neither serious psychotic events nor delirium have been reported. We have now seen two hospitalized, elderly patients with acute delirium associated with azithromycin treatment of community acquired pneumonia.

## CASE REPORTS

### CASE 1

A 78-year-old White male, retired Ph.D. nutritionist was hospitalized with low-grade fever, productive cough and dyspnea. His past medical history indicated known arteriosclerotic heart disease with a previous coronary artery by-pass procedure, peripheral vascular disease and non-insulin dependent diabetes mellitus. Physical examination revealed crackles over the right lateral chest and absent pulses below both femoral arteries. A chest X-ray revealed a right middle lobe infiltrate. Blood and sputum cultures failed to grow any pathogens.

On admission, after all cultures were obtained, the patient was empirically placed on ceftriaxone, 1 g IV daily and azithromycin 500 mg initially followed by 250 mg orally daily.

On the third hospital day, the patient began to experience visual hallucinations and vividly recalled having dinner with his doctors at their homes. Twenty-four hours later the azithromycin

*Trade names:* azithromycin, Zithromax; ceftriaxone, Rocephin; clarithromycin, Biaxin; erythromycin, Ery-tab, others.

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was stopped but his other medications continued. Over the next 72 hours his visual hallucinations resolved.

## CASE 2

An 88-year-old retired, female vaudeville dancer with known chronic myelomonocytic leukemia and spinal stenosis entered the hospital with a dry cough, fever, and dyspnea. On physical examination crackles were audible at the right base and a chest X-ray revealed a right lower lobe infiltrate. After blood cultures were drawn, she was begun on ceftriaxone, 1 g IV daily and 500 mg of azithromycin initially followed by 250 mg orally daily. On the fourth hospital day, the patient became confused and had visual hallucinations with paranoia that the nurses were trying to confine her in a remote area of the hospital. Azithromycin was discontinued and within 24 hours the visual hallucinations resolved, but she did not lose the confusion and paranoia for another 2 days.

## DISCUSSION

Gleason et al [10] reported that mortality was approximately 25% less among in-patients with community acquired pneumonia when the initial empiric antimicrobial regimen combined a 3<sup>rd</sup> generation cephalosporin with a macrolide compared with a cephalosporin alone, and additional studies show a 15% reduction in mortality when antimicrobials are initiated within 8 hours of hospitalization [2]. Thus, early treatment with two agents is a most effective regimen in hospitalized patients with community acquired pneumonia. Because community acquired pneumonia affects nearly six million people annually in the USA, and about two million persons require hospitalization with a case fatality rate of 14% [7,8], adverse reactions to this regimen take on serious consequences. Infection and death are common among the elderly.

Azithromycin is distributed into most bodily tissues and fluids after oral or IV administration. It is rapidly accumulated within cells [1]. Only very low concentrations of azithromycin (<0.01 ug/mL) have been detected in CSF in the absence of inflamed meninges [1], but intracerebral concentrations are unknown. The same may be said of other macrolides such as erythromycin and clarithromycin [6]. Thirty years elapsed before CNS side effects of erythromycin were recognized. That clarithromycin and azithromycin enters the CNS appears certain, because both drugs in combination with py-

rimethamine appear to be effective antimicrobials in the management of cerebral toxoplasmosis [1].

Thus, in addition to ototoxicity [16] only two instances of CNS symptoms have been described with azithromycin. One patient, a 79-year-old male, developed a progressive mental change in association with an azithromycin hypersensitivity syndrome [5], and a 50-year-old male developed disorientation and lethargy in association with hyponatremia because of inappropriate antidiuretic hormone secretion [4].

The two patients with delirium associated with azithromycin therapy described in this communication developed psychiatric symptoms within 60 and 84 hours, respectively, after the initiation of azithromycin therapy, with these symptoms resolving within 48 to 72 hours. When one compares the time of onset of mania because of clarithromycin to delirium associated with azithromycin, both are similar, averaging 72 hours. However, whereas symptoms disappeared within 24 hours after discontinuation of clarithromycin, at least 48 to 72 hours elapsed before the delirium associated with azithromycin therapy disappeared. Most likely the slower resolution of symptoms associated with azithromycin relate to the longer terminal elimination half-life of the drug, which averages 68 hours in adults and 55 hours in children [1]. In addition, peak plasma levels are often 30% to 50% higher in geriatric female patients (60-85 years old) [1], when compared to younger adults. This has not been seen in men of a similar geriatric age group. The pharmacokinetic differences between clarithromycin and azithromycin may explain the longer duration of psychiatric symptoms with the latter drug and perhaps predict a higher frequency of such adverse reactions in geriatric female patients.

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“**A** diversity is the first path to truth.”

—GEORGE GORDON, LORD BYRON, *DON JUAN*