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Neuropsychological effects of macrolides

● **Pharmacovigilance data collected from several European countries show that macrolides can provoke neuropsychological adverse effects such as hallucinations, delirium, manic episodes and sometimes depression, in both adults and children. These effects seem to be rare and are reversible on macrolide withdrawal.**

● **In practice, keep in mind that if neuropsychological disorders can be attributed to macrolides, treatment should be halted.**

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The principal adverse effects of *erythromycin* are gastrointestinal disorders, reversible ototoxicity and cardiac arrhythmia. Other potential problems including liver damage, pancreatic disorders, cutaneous reactions are less frequent (1). Neuropsychological disorders such as confusion, hallucinations and manic episodes have also been reported with *erythromycin* (2,3). This review is based on European pharmacovigilance data and focuses on the neuropsychological disorders caused by macrolides in general.

Clarithromycin: mania and hallucinations. Acute psychotic episodes, delirium, hallucinations and manic episodes have been reported with *clarithromycin* (2,3). In June 2008, a Spanish pharmacovigilance bulletin reported that the Spanish pharmacovigilance database included 9 manic episodes in patients treated with *clarithromycin* (4). The 7 women and 2 men were aged 45 to 73 years and had no prior psychiatric history. In 4 cases, the manic episode was the only reported adverse effect, while the other 5 patients also had hallucinations, delirium, depressive syndromes, confusion, insomnia, neurotic disorders, abnormal thinking or nightmares.

In 5 cases, the manic episode occurred within 48 hours after *clarithromycin* initiation. The problems resolved in 1 to 12 days in the 8 patients whose outcome was known.

An Italian pharmacovigilance bulletin reported that in 2008 the Italian pharmacovigilance database contained 15 reports of hallucinations in patients treated with *clarithromycin* (5).

Telithromycin: confusion and hallucinations. In response to our request for information, the European Medicines Agency (EMA) sent us a review of adverse effects linked to *telithromycin*. Reports recorded in the European pharmacovigilance database between marketing authorisation (in July 2001) and 9 January 2008 included 38 cases of confusion (13 serious cases) and 27 cases of hallucination (**a**)(6).

A variety of macrolides implicated. In 2000, the Belgian Pharmacovigilance Centre reported that 14 cases of neuropsychological adverse effects linked to *azithromycin*, *clarithromycin*, *dirithromycin* and *roxithromycin* had been received between 1995 and 2000. Four cases involved children under 10 years of age. The adverse effects included dizziness, nightmares, hallucinations, agitation and anxiety. The effects occurred on treatment initiation in 10 cases, and on the first day of treatment in 7 cases. The patients whose outcome was known all recovered (7).

In practice. When a patient presents with recent-onset neuropsychological disorders, it is important to bear in mind the possible role of a drug, including non-psychotropic drugs, particularly macrolides.

It is better to avoid exposing patients to these types of adverse effects when the risk-benefit balance of the drug in question is clearly unfavourable, as is the case with *telithromycin*.

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a- Telithromycin is no more effective than other macrolides but carries a risk of particularly severe adverse effects. After re-examining the available data in 2006 and 2007, the European Medicines Agency restricted the indications of Ketek° to second-line use, for safety reasons. In addition, the SPC recommends taking Ketek° at bedtime, because of a risk of visual disorders and loss of consciousness (refs 8-10).

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