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Azithromycin: cardiovascular deaths

● **Beware risk factors for QT prolongation.**

A US team conducted a cohort study based on a healthcare insurer database in Tennessee. This study compared patients who received a prescription for *azithromycin*, a macrolide antibiotic (347 795 prescriptions) and patients who did not receive an antibiotic (1 391 180 control prescriptions) or patients who were prescribed another antibiotic (1).

Twenty-nine deaths due to cardiovascular causes were recorded in the *azithromycin* group (85.2 per million 5-day treatment periods), including 22 sudden deaths. During 5 days of treatment, patients in the *azithromycin* group had a higher risk of cardiovascular death than controls, with an odds ratio (OR) of 2.88 (95% confidence interval (95%CI) 1.79 to 4.63). The odds ratio for death from any cause was also higher (OR 1.85, 95%CI 1.25 to 2.75). Patients with known cardiovascular risk factors were at higher risk.

There was no increase in the risk of cardiovascular death among patients treated with *amoxicillin* compared to untreated controls. Furthermore, when compared to *amoxicillin*, *azithromycin* was again associated with an increased risk of cardiovascular death (OR 2.49, 95%CI 1.38 to 4.50) and death from any cause (OR 2.02; 95%CI 1.24 to 3.30). The estimated excess of cardiovascular deaths was about 47 per 1 million treatment courses.

Some macrolide antibiotics carry a lower risk of pharmacokinetic interactions than others; this is a marked advantage of *spiramycin*. In contrast, other macrolides such as *telithromycin* have a particularly unfavourable adverse effect profile (2).

All macrolides are known to prolong the QT interval, which increases the risk of cardiac arrhythmia (2). The results of this study confirm that effects initially seen on the electrocardiogram can sometimes have fatal consequences. This risk must be taken into account, particularly in patients with risk factors for QT prolongation (hypokalaemia, co-administered drugs, etc.).

Selected references from Prescrire's literature search.

1- Ray WA et al. "Azithromycin and the risk of cardiovascular death" *N Engl J Med* 2012; **366** (20): 1881-1890.

2- Prescrire Rédaction "16-1-8. Patients sous macrolide" *Rev Prescrire* 2011; **31** (338 suppl. interactions médicamenteuses).

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Saxagliptin and tuberculosis

● **Immunosuppressive effects.**

Like other gliptins used in type 2 diabetes for their hypoglycaemic action, *saxagliptin* has immunosuppressive effects. Gliptins inhibit the enzyme dipeptidyl dipeptidase 4 (DPP-4), and modulate the function of CD26, a similar protein present on the surface of lymphocytes (1). Infections, especially urinary and upper respiratory tract infections, are more frequent in patients taking gliptins than in controls (1).

In 2009, premarketing studies showed no increase in the risk of tuberculosis in patients on *saxagliptin* (1).

In 2010, however, the clinical trials database on *saxagliptin* included 6 cases of tuberculosis among 4959 patients taking *saxagliptin* (0.12%), and none among 2868 controls (2). The difference was not statistically significant but the effect appeared to be dose-dependent (0.71 cases per 1000 patient-years with 2.5 mg/day *saxagliptin*, 1.19 per 1000 with 5 mg, and 1.4 per 1000 with 10 mg).

In the first quarter of 2012, the pharmacovigilance database of the US Food and Drug Administration (FDA) mentioned 5 cases of pulmonary tuberculosis and 5 cases of tuberculous pleural effusion attributable to *saxagliptin* (3).

In practice, it is better not to use these drugs which, despite their effect on blood glucose levels, have no proven clinical benefits.

Selected references from Prescrire's literature search.

1- Prescrire Editorial Staff "Saxagliptin. No more effective than other gliptins, but a high potential for drug" *Prescrire Int* 2011; **20** (113): 33-37.

2- U.S. Food and Drug Administration "Summary review. Kombiglyze XR (saxagliptin/metformin XR fixed-dose combination product)" 28 October 2010. www.fda.gov accessed 16 July 2012: 32 pages.

3- Drugcite "Saxagliptin - Mycobacterial infectious" 2012. www.drugcite.com accessed 16 July 2012: 1 page.

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Corticosteroid injections: serious infections and necrosis

● **Do not endanger patients.**

In 2012, a group of German authors published an analysis of 278 reports of complications associated with corticosteroid injections, collected between 2005 and 2009 by the German system for handling complaints regarding possible medical errors (1).

The adverse effect was an infection in 223 cases, most of which occurred after an intra-articular (42% of cases), paravertebral (19%) or intramuscular (13%) injection.

There were also 55 cases of tissue atrophy, commonly after an intramuscular depot injection, mainly to treat allergy.

73 treatment errors resulted in infection. There were also 24 cases of delayed diagnosis of infection, 18 breaches in aseptic technique, 14 cases in which the interval between injections was too short, etc., as well as 20 failures to inform the patient of the risks.

In one case, a 74-year-old woman who had received lumbar and sacral paravertebral injections for pain underwent 3 operations for abscesses in the paraspinal musculature, a psoas muscle, and the vertebral canal. The partial paralysis of her lower limbs caused by these abscesses slowly resolved.

In another case, an obese 49-year-old woman developed aseptic gluteal necrosis after receiving corticosteroid and *diclofenac* injections. After surgery to remove 500 g of necrotic tissue, an infection developed at the resection site requiring multiple hospitalisations.

The authors pointed out that "*overtreatment is certainly a problem in* […] *medicine in general*" and that "*patients are being endangered where there is no justification for doing so*" (1,2).

Selected references from Prescrire's literature search.

1- Holland C et al. "Septic and aseptic complications of corticosteroid injections: an assessment of 278 cases reviewed by expert commissions and medication boards from 2005 to 2009" *Dtsch Arztebl Int* 2012; **109** (24): 425-430.

2- Prescrire Rédaction "Gonarthrose et corticoïdes intra-articulaires. Peu de résultats probants" *Rev Prescrire* 2006; **26** (274): 521-522.