

96. Lactic Acidosis Associated with Linezolid Treatment: Cases Notified to the French Pharmacovigilance Network

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Introduction: Linezolid belongs to a new class of antibacterial drugs (oxazolidinones) that may be used to treat gram-positive infections including infections, due to methicillin-resistant *Staphylococcus aureus* (MRSA). Lactic acidosis, besides peripheral neuropathy, has been reported with this drug and may be potentially related to drug-induced mitochondrial dysfunction.

Methods: We report six cases of lactic acidosis associated with linezolid which have been notified to the French Pharmacovigilance Centres network from 2003 to 2005.

Results: This series concerns 3 men and 3 women aged 45-78 treated by linezolid 600mg twice a day. Symptoms associated with lactic acidosis appeared after various durations of treatment (rapidly in one case, more than the maximal recommended duration in 4 weeks in the other cases: 7 to 12 weeks). Therapeutic indications were cutaneous and soft tissues infections in 2 cases, osteo-articular infections in 3 cases and endocarditis in the latter patient. The severity of metabolic acidosis varied largely between the cases (pH values from 7.33 to 6.94). The two cases associated with the more severe acidosis (pH 6.94 and 7.03) were associated with hepatic failure and fatal issue. Clinical and biologic abnormalities improved rapidly after drug withdrawal in the other cases. Thrombopenia and/or anaemia were associated side-effects in 4 cases.

Some data are now available to suggest the role of mitochondrial dysfunction as the mechanism of this side-effect. Palenzuela et al.^[1] analysed clinical and molecular genetic features of patients who developed lactic acidosis while receiving linezolid. They found polymorphisms in mitochondrial RNA which may have contributed to lactic acidosis. Indeed, linezolid binds to mitochondrial ribosomes which have similarities with bacterial ribosomes, the target of this drug on bacteria. Soriano et al.^[2] reported a reduction in enzyme activity for mitochondrial respiratory chain complex II in 3 patients with hyperlactatemia during prolonged course of oral linezolid therapy. In one patient of our series a low level of L-carnitine with high cetonc bodies has been demonstrated.

Conclusion: Lactic acidosis is a severe life-threatening side effect potentially occurring during linezolid therapy. This must be kept into mind in patients developing asthenia, digestive symptoms or other manifestations possibly related to acidosis. Further investigations are necessary to analyse more precisely the effect of linezolid on mitochondrial function.

References

1. Palenzuela L, Hahn NM, Nelson RP, et al. Does linezolid cause lactic acidosis by inhibiting mitochondrial protein synthesis? *Clin Inf Dis* 2005; 40: e113-6
2. Soriano A, Miro O, Mensa J, et al. Mitochondrial toxicity associated with linezolid. *N Engl J Med* 2005; 353: 2305-6