Comment on "A severe linezolid-induced rhabdomyolysis and lactic acidosis in Leigh syndrome"

Dear Editor,

Primiano and Servidei describe a patient with Leigh syndrome caused by a pathogenic *MT-ND5* variant who was admitted to ICU "for supportive treatment for medical complications after surgery of thyroid cancer". We are told that she developed a methicillin resistant staphylococcal aureus (MRSA) pneumonia, that she had a normal lactate level in blood and a slightly elevated creatine kinase (CK). No information was provided about her general medical condition, the possibility of multi-organ involvement secondary to MRSA infection, what other drugs had been given and for how long, whether she had muscular rigidity and an elevated temperature or her pre-ICU renal function. After two doses, and thus approximately 12 hours later, she developed "severe muscle pain, tachycardia, nausea, vomiting and tachypnea, quickly followed by severe muscle weakness resulting in flaccid quadriplegia". Her CK rose to 146,000 (we are not told her myoglobin) and her renal function deteriorated to the point of requiring dialysis.

The authors conclude that linezolid was the cause of this patient's rhabdomyolysis and suggest avoidance of the drug in anyone with impaired mitochondrial function. While we agree that linezolid must be considered as a potential cause, we feel the data presented are insufficient to confirm this suggestion. Important information about the premorbid condition, particularly renal function, the specific reasons for admission to the ICU, the time line of events and all other drugs used is lacking. MRSA pneumonia itself has a high morbidity (including multiple organ failure) and mortality and the choice of linezolid clearly shows the seriousness of the clinical condition.

Concerning our recommendations, we would point out that the Delphi method attempts to elicit and process value judgments and works by repeated evaluation and discussion until consensus is reached. Strong consensus is predefined as ≥70% agreement amongst panelists. Based on the available evidence, we felt there were no good reasons for not using linezolid in the appropriate clinical setting and we therefore wrote - *If indicated, linezolid could be used in mitochondrial disease, with careful lactate monitoring, particularly in children and other patients with pre-existent lactic acidaemia*.

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We agree that personalizing drug prescription in mitochondrial disease is essential. It is not possible, however, to predict idiosyncratic reactions that can occur with any and indeed all drugs. This case report highlights how difficult it is to assign causality in complex clinical situations. Specific mitochondrial disease related drug toxicity describes a recurrent adverse event in multiple patients that is NOT SEEN in those without mitochondrial disease.

Linezolid is an excellent drug for treating MRSA and VRE organisms. It is frequently used in the ICU where crtically unwell patients, including those with mitochondrial disease, will be admitted. Based on the available evidence, we still suggest the cautious use of linezolid in the appropriate clinical setting and with blood lactate monitoring. This report requires confirmation and until that is forthcoming good medical practice must remain the guiding principle.

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