LETTERS

Outbreak in meldonium positive laboratory tests: are we missing something?

As clinicians facing the challenges associated with the interpretation of drug concentrations or clinical laboratory measures in our daily practice, the outbreak of adverse analytical findings reported on meldonium makes us wonder if the information on meldonium available to date is sufficient to adequately interpret such findings. An adequate interpretation of a drug concentration requires knowledge of its pharmacokinetic characteristics and profile over time, and this has not been studied fully for meldonium.

Available studies suggest that meldonium is eliminated mainly by the kidneys. Single dose administration showed both linear and non-linear pharmacokinetics with an elimination half-life (t1/2) ranging from 3.6 to 6.6 h.[1–4] Multidose administration (500 mg 3×/day for 13 days) indicated an accumulation of meldonium consecutive to a 70% decrease in its elimination and a t1/2 reaching 15.3 h.[1 2] From these results, it can be expected that the duration over which meldonium can be detected in urine should not exceed 5 days (ie, 7× t1/2). This time frame is, however, only valid if the elimination is linear- or concentration-independent and might only reflect the first rapid elimination phase. The non-linear pharmaokinetic properties of meldonium after multiple dose administration in humans implies that the elimination time may markedly vary depending on individual characteristics and on the level of drug concentrations. In addition, drug accumulation will increase exponentially with the dose level. Furthermore, none of the available pharmacokinetic studies have monitored meldonium concentrations above 24 h after multidose administration. This means its terminal elimination phase has not been fully characterised and means it is impossible to exclude the presence of low concentrations over a prolonged time after chronic use.

This is particularly troublesome when considering the pharmacokinetic characteristics of a chemically very similar endogenous compound, L-carnitine. L-carnitine homeostasis is regulated by a combination of factors including saturable renal tubular reabsorption mediated by the transporter OCTN2.[5] This indicates that the renal filtered L-carnitine is actively reabsorbed into the bloodstream until saturation level occurs, above which urinary loss is increased.[5] L-carnitine has also been associated with a prolonged retention time within the muscles, with a muscle compartment turnover time of 191 h (8.0 days), and a whole body turnover time of 66 days.[5]

Animal data have shown that meldonium competes with L-carnitine for transport via OCTN2.[6] If meldonium mimics L-carnitine pharmacokinetics, the time required to reach its complete elimination after chronic use might be significantly longer than expected and low concentrations could persist over time. Studies with longer follow-ups evaluating the time necessary for complete elimination after prolonged use are needed to adequately interpret the current laboratory findings.

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