## RESPONSE TO THE LETTERS TO THE EDITOR FROM VAN DER VOORT ET AL. AND VODOVAR AND MÉGARBANE

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To the Editor,

We thank our colleagues Van der Voort et al. for proposing 4-aminopyridine as an alternative treatment for calcium channel antagonist (CCA) intoxication.[1] Our manuscript focused on the most practical treatments.[2] However, apart from the treatments that we discussed, several other treatments have been suggested for CCA overdose, e.g. phosphodiesterase III inhibitors, levosimendan, methylene blue, L-carnitine and 4-aminopyridine.[3] The clinical evidence for these treatments is mostly based upon animal studies and anecdotal human reports. In our opinion, further research is needed to establish the efficacy and safety of these therapies before they can be routinely implemented in the treatment of CCA overdose.

4-Aminopyridine is a mechanistically appealing treatment candidate for CCA overdose. It blocks potassium channels on the cytoplasmic side of the membrane, resulting in depolarisation and opening of voltage-gated calcium channels. Several animal models have shown haemodynamic improvement after 4-aminopyridine administration,[4-9] although severe side effects, such as muscle fasciculation and seizures, were also noted.[6-8] Only few human data are published on the use of 4-aminopyridine in CCA overdose.[10-13] Wilffert et al. describe a patient with amlodipine/lorazepam overdose who haemodynamically improved after administration of a three-hour intravenous infusion with 4-aminopyridine.[13] In a patient with verapamil overdose it was unclear whether the haemodynamic improvement could be attributed to 4-aminopyridine or other treatments.[12] In addition, as Wilffert et al. already mentioned in their manuscript, intravenous preparations of 4-aminopyridine are only sparsely available in Dutch hospital pharmacies.

Phosphodiesterase III inhibitors inhibit the breakdown of cyclic adenosine monophosphate, resulting in increased intracellular calcium concentrations, and improved inotropy.[14] Levosimendan is a calcium sensitiser, showing direct interaction with troponin C in the myofilaments of cardiomyocytes.[15] However, both phosphodiesterase III inhibitors and levosimendan can cause significant vasodilatation, worsening CCA-induced hypotension. Methylene blue inhibits nitric oxide synthase and guanylyl cyclase activity, decreasing the production of cyclic guanosine monophosphate (cGMP). Elevated intracellular cGMP concentrations lead to relaxation of myocardium and vascular smooth muscle. Methylene blue can possibly counteract CCA-induced toxicity by inhibition of excessive production of cGMP.[16] In CCA overdose, the metabolism of cardiac myocytes is switched from free fatty acids to glucose. L-carnitine could positively influence cardiac metabolism, by reversing the metabolism back to free fatty acids.[17,18] The effectiveness of these alternative treatments, including evaluation of adverse effects, should be further explored in order to draw more definite conclusions about their therapeutic value in CCA overdose.

Furthermore, we would also like to thank Vodovar and Mégarbane for proposing and clarifying the role of extracorporeal albumin dialysis (Molecular Adsorbent Recirculating System (MARS)) in CCA overdose.[19] Interestingly, the improvement in haemodynamics is not always accompanied by a substantial removal of toxin by MARS. Several hypotheses are provided that could explain the beneficial effects of MARS in CCA overdose.[19] However, the limited availability of MARS will obstruct general application of this technique. In the Netherlands, only a few university hospitals perform this treatment. An alternative but promising treatment is the use of extracorporeal life support,[20,21] which should be used as a rescue therapy when conventional pharmacological interventions are not sufficiently effective.

### DISCLOSURES

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