EDITORIAL

On calcium channel antagonist poisoning: towards evidence-based decision making in poisoned patients

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Almost 500 years ago, Paracelsus already stated: *'Sola dosis facit venenum'*. This famous adage underlines a basic principle in the world of toxicology: every substance can be poisonous, as long as the dose is high enough. This fundamental rule still applies in modern times, reflected by the substantial burden of both accidental and intentional poisoning in the US.[1] Also in the Netherlands, an astonishing documented number of 33,700 patients were exposed to toxic substances in 2014, mostly pharmaceutical drugs (56%), followed by household cleaning substances (16%) and food, drinks and stimulants (7%).[2]

In contrast to the current era of evidence-based medicine, many antidotes or treatment strategies in intoxicated patients are solely based on anecdotal reports, case series, animal studies and expert opinions. This is reflected by the absence of clear guidelines and further underlined by the findings of Duineveld and colleagues,[3] who demonstrated considerable variation in the care of intoxicated patients in Dutch hospitals. In a subsequent prospective study, two algorithms to predict the need for treatment in intoxicated patients were implemented in clinical practice, with promising results in terms of good sensitivity and better specificity than routine clinical care.[4] These findings underscore the need for evidence-based practical guidelines, in order to improve clinical care and maximise efficacy.

In the current issue of the Journal, Rietjens and co-workers provide an in-depth overview of the treatment options in calcium channel antagonist (CCA) poisoning, and merge these recommendations into a practical algorithm.[5] Along with 'classical' strategies for detoxification and supportive care (e.g. activated charcoal, calcium, atropine, vasopressors), the relatively new approach to the poisoned patient using hyperinsulinaemia/euglycaemia and intravenous lipid emulsion therapy is highlighted and incorporated in their algorithm.

After the first case report on hyperinsulinaemia/euglycaemia therapy as adjunctive treatment in CCA overdose in humans in 1999, accumulating case reports and case series with beneficial (haemodynamic) effects have been gathered,[6] and similar favourable results have been reported in beta-blocker intoxicated patients treated with hyperinsulinaemia/euglycaemia.[6,7] Based on animal models and increasing clinical experience, the modulatory effects of hyperinsulinaemia/euglycaemia in CCA and beta-blocker poisoning are generally ascribed to their positive inotropic properties, possibly (partly) mediated by enhanced intracellular glucose transport in cardiomyocytes and improved perfusion of the coronary (micro)vasculature.[7] Interestingly, a dose-response effect was observed in a pig model of beta-blocker poisoning, where improved outcome in the pigs treated with high-dose insulin (10 IU/kg/h) was accompanied by a higher cardiac output, as compared with the pigs treated with placebo and 5 IU/kg/h insulin.[8] This shows that not only the dose makes the poison, but in this case the dose also makes the antidote.

The first reports on altered drug concentrations following emulsified fat infusion date back to the 1960s and 1970s,[9] where it was used for reversal of local anaesthetic systemic toxicity. Nevertheless, the full therapeutic potential of intravenous lipid emulsion in ameliorating the toxicity profile of drugs was only recognised by Weinberg and his colleagues in the late 1990s, using a rat model.[10] Ever since, beneficial effects of intravenous lipid emulsion have been described in a wide variety of lipophilic drugs,[9] including CCA and beta-blockers, adding intravenous lipid emulsion to the repertoire of treatment options in the severely intoxicated patient. It must be noted that initiation of intravenous lipid emulsion must be carefully considered for each individual poisoning, as effectiveness is likely to primarily depend on the degree of lipid solubility of the

ingested substance, as exemplified by the opposing effects of intravenous lipid emulsion in metoprolol (relatively hydrophilic) and propranolol (lipophilic) poisoning in animal studies.[11,12]

Both hyperinsulinaemia/euglycaemia and intravenous lipid emulsion are now increasingly being recommended by poison control centres. Nevertheless, clinicians do not always follow these recommendations, possibly due to the fact that they are unfamiliar with these treatment regimens.[13] We hope that the explanation of the underlying pharmacological principles and the detailed dosing regimens provided by Rietjens and co-workers will take away the last scepticism and further stimulate the approachable and adequate use of hyperinsulinaemia/euglycaemia and intravenous lipid emulsion in CCA intoxication. As can be extracted from the flowchart, we would like to point out that hyperinsulinaemia/euglycaemia and intravenous lipid emulsion can, and sometimes must, be combined to optimise clinical outcome in severe CCA poisoning. In cases of refractory shock, extracorporeal life support can be considered a bridge to recovery.

Although the abovementioned interventions can be life-saving, especially in patients in whom the ingested drug is known, it must be emphasised that a standardised evaluation following the well-known ABCDE paradigm remains the cornerstone in intoxicated patients. Clinical clues, usually clustered in toxidromes (e.g. confusion, mydriasis, urinary retention/dry mouth, hyperthermia and dry skin in anticholinerg syndrome), might give direction in the possibly intoxicated patient.

In line with the recommendations for the treatment of CCA poisoning by Rietjens and colleagues, we strongly advocate further development of evidence-based national guidelines for other frequently (intentionally) ingested toxic substances. Given the relatively low incidence of (severe) intoxications, we believe that national collaboration is of utmost importance.

REFERENCES

1. Mowry JB, Spyker DA, Brooks DE, McMillan N, Schauben JL. 2014 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 32nd Annual Report. Clin Toxicol (Phila). 2015;53:962-1147.
2. Mulder-Spijkerboer HN, Kan AA, van Velzen AG, van Riel AJHP, Meulenbelt J, de Vries I. Acute vergiftigingen bij mens en dier. NVIC-Jaaroverzicht 2014. Utrecht: Universitair Medisch Centrum Utrecht; 2015.
3. Duineveld C, Vroegop M, Schouren L, et al. Acute intoxications: differences in management between six Dutch hospitals. Clin Toxicol (Phila). 2012;50:120-8.
4. Ambrosius RG, Vroegop MP, Jansman FG, et al. Acute intoxication patients presenting to an emergency department in The Netherlands: admit or not? Prospective testing of two algorithms. Emerg Med J. 2012;29:467-72.
5. Rietjens SJ, de Lange DW, Donker DW, Meulenbelt J. Practical recommendations for calcium channel antagonist poisoning. Neth J Med. 2016;2:60-7.
6. Graudins A, Lee HM, Druda D. Calcium channel antagonist and beta-blocker overdose: antidotes and adjunct therapies. Br J Clin Pharmacol. 2015 Sep 7. doi: 10.1111/bcp.12763. [Epub ahead of print.
7. Engebretsen KM, Kaczmarek KM, Morgan J, Holger JS. High-dose insulin therapy in beta-blocker and calcium channel-blocker poisoning. Clin Toxicol (Phila). 2011;49:277-83.
8. Cole JB, Stellpflug SJ, Ellsworth H, et al. A blinded, randomized, controlled trial of three doses of high-dose insulin in poison-induced cardiogenic shock. Clin Toxicol (Phila). 2013;51:201-7.
9. Cave G, Harvey M, Graudins A. Intravenous lipid emulsion as antidote: a summary of published human experience. Emerg Med Australas. 2011;23:123-41.
10. Weinberg GL, VadeBoncouer T, Ramaraju GA, Garcia-Amaro MF, Cwik MJ. Pretreatment or resuscitation with a lipid infusion shifts the dose-response to bupivacaine-induced asystole in rats. Anesthesiology. 1998;88:1071-5.
11. Harvey MG, Cave GR. Intralipid infusion ameliorates propranolol-induced hypotension in rabbits. J Med Toxicol. 2008;4:71-6.
12. Browne A, Harvey M, Cave G. Intravenous lipid emulsion does not augment blood pressure recovery in a rabbit model of metoprolol toxicity. J Med Toxicol. 2010;6:373-8.
13. Darracq MA, Thornton SL, Do HM, Bok D, Clark RF, Cantrell FL. Utilization of hyperinsulinemia euglycemia and intravenous fat emulsion following poison center recommendations. J Med Toxicol. 2013;9:226-30.