Levosimendan as a Potential Calcium Channel Blocker Antidote – A Systematic Literature Review

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Objective

Calcium channel blockers (CCB) remain amongst the most challenging pharmaceuticals to treat in overdose due to potent toxic effects on the cardiovascular system and are associated with significant morbidity[1]. We performed a systematic literature review to determine whether the myocardial calcium sensitizer levosimendan may have a role in managing CCB poisoning.

Method

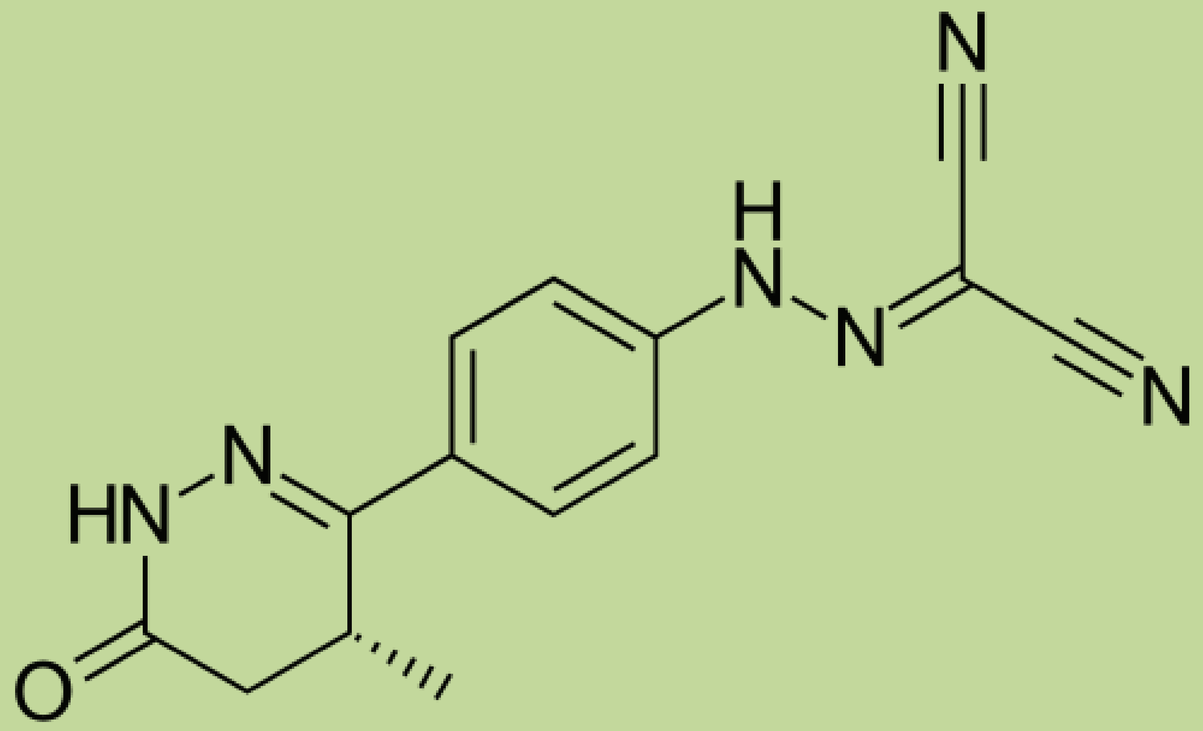
Ovid MEDLINE, Ovid Embase and Google Scholar were interrogated using the following 'exploded' category plus keyword search: (['Levosimendan' or 'Simdax'] and ['calcium channel blocker' or 'verapamil' or 'diltiazem' or 'nifedipine' or 'amlodipine']). In total, 546 relevant entries were retrieved. Entries that did not consider levosimendan in CCB overdose were excluded, resulting in 22 entries for inclusion.

Results

Five papers reported levosimendan use in human (n=6) CCB overdose, four papers reported animal models and 13 entries were classified as correspondence, commentary or existing reviews of levosimendan efficacy.

In human cases, ingested CCBs included amlodipine (n=3; 250 mg, 500 mg, 630 mg), verapamil (n=2; 480 mg, 16,000 mg) and diltiazem (n=1; 3,360 mg). Levosimendan loading doses ranged between 0 - 24 µg/kg via bolus with infusion doses between 0.1 - 0.2 µg/kg/minute. No adverse reactions were reported following levosimendan administration and survival occurred in all patients. Recorded improvements in blood pressure (n=3) were exceeded by improvements in heart rate (n=5), consistent with results from animal models.

In Wistar rat models treated with verapamil no improvement in blood pressure was reported following levosimendan administration, although heart rate increased. In two reports (n=35, n=60) levosimendan was suggested to be detrimental to managing hypotensive shock due to vasodilatory effects, consistent with levosimendan contraindications in therapy. Calcium salts outperformed levosimendan in one report, and a Landrace-pig model showed an improvement of left ventricular pressure over 60 minutes (+38% LV dP/dt, control -31%) in addition to increased survivability.



Discussion

Levosimendan in human CCB poisoning has an optimistic consensus regarding its efficacy based on human data, though reported patients were intensively managed with conventional CCB treatments such as vasopressors, ionotropes, and insulin/dextrose regimes for up to 8 days prior, and often during levosimendan administration.

In controlled animal studies, consensus ranged from improved survivability in Landrace-pigs to increased mortality in Wistar rats, though the latter has been disputed in medical correspondence. Levosimendan requires further reports of its use if it is to be considered as a potential CCB antidote.

References

[1] St-Onge M, Anseeuw K, Mégarbane B, et al. Experts Consensus Recommendations... Critical Care Medicine; 2017;45,3:e306-e315.