Losartan and amlodipine overdose—Case Report of a patient with anuric renal failure prior to the onset of hypotension

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ABSTRACT
Dihydropyridine calcium channel blockers are generally considered to have lower risk profiles because of their relative lack of negative inotropy when compared to diltiazem and verapamil. Serious toxic effects following a large ingestion of angiotensin receptor blockers (ARBs) are rarely reported. Prerenal renal failure is reported in overdoses of these agents as a result of severe hypotension. We report a case of amlodipine and losartan overdose where anuric renal failure appears to have developed prior to the onset of severe hypotension. We hypothesise that the early anuria observed in our patient is secondary to afferent and efferent renal arteriole dilation in response to profound block of the AT1 receptors.

Cardiovascular drug overdoses are the fifth most common cause of calls to poison centres for adult overdose in the US, and are the second most common causing fatality, with 305 reported deaths in the US in 2011.1

Within this category, calcium channel blocker (CCB) overdoses are well recognised as high-risk toxicological emergencies, and comprise 34% of single substance cardiovascular drug deaths reported to the American Association of Poison Control Centers.1 Of the subclasses of calcium channel blockers, dihydropyridines, such as amlodipine, are generally considered to have lower risk profiles because of their relative lack of negative inotropy when compared to diltiazem and verapamil, however, a few fatal single and polypharmacy ingestions of amlodipine are reported in the literature.3,4

Serious toxic effects following a large ingestion of angiotensin receptor blockers (ARBs) are rarely reported.4 The majority of adults and children remaining asymptomatic, and a minority experiencing mild self-limiting hypotension dizziness and gastrointestinal upset,5 even in large overdose.7 Of >6,500 exposures reported by the National Data Poisons System in 2011, there were no recorded major severity outcomes or deaths.4 There are no reports of anuric renal failure directly attributable to ARB overdose.

In a literature review of EMBASE, OVID and Medline databases (5/5/2015), we identified two previous reports of severe combined calcium channel blocker and angiotensin II receptor blocker overdose. Both focus on management of resultant severe hypotension, which was hypothesised to be the result of synergistic toxicity limiting the effects of both endogenous and exogenous catecholamines. One reports treatment success with hyperinsulinaemia-euglycaemia, the other success with metaraminol after failure of all traditional inotropes, including hyperinsulinaemia-euglycaemia.

We report a case of amlodipine and losartan overdose where anuric renal failure appears to have developed prior to the onset of severe hypotension.

Case report
A 54-year-old Indian woman, weight estimated at 75kg, presented by ambulance...
to the ED at 0145 after an intentional ingestion of 200mg of amlodipine (20 times daily dose) and 2,700g of losartan (27 times maximum daily dose) at 1800 the previous evening. The ambulance was called at the onset of vomiting at 6 hours post ingestion. Past medical history included hypertension, hypothyroidism and hypercholesterolaemia. She had no past psychiatric history.

On ambulance pickup, and prior to any fluid, she was orientated, BP 101/75 (MAP 84), PR 76, RR 18. On arrival to the ED she was alert and orientated with no compromise of airway or breathing. She had a heart rate of 86 and a BP of 90/60 (MAP 70) following 500mls of IV fluid prehospital. Her ECG showed 0.5mm ST depression, inferolaterally.

Initial labs showed acute renal failure with a normal venous blood gas (pH 7.43, bicarbonate 24, lactate 2.0, ionised calcium 1.17, Na 141, K 4.4, Cr 159, Urea 6.2). LFTs and FBC were unremarkable.

An arterial line was inserted, and despite 2L IV fluid, 40mins after arrival to the ED she precipitously dropped her BP to 72/36. She was managed with calcium boluses and an infusion, hyperinsulinaemic euglycaemia (bolus 1 unit/kg and infusion of 1u/kg/hr) and noradrenaline infusion (3mg/hr). She received a number of adrenaline boluses while infusions and central line were prepared.

An IDC was inserted and she was found to be anuric with no urine in the bladder on insertion, suggesting onset of anuria prior to ambulance pickup and deterioration of mean arterial pressure (MAP) to <70.

One hour after arrival to the ED, her venous blood gas showed a progressive metabolic acidosis (pH 7.28, pCO2 4.3, bicarbonate 16, lactate 4.1, ionised calcium 1.13). She was transferred to the Department of Critical Care Medicine, where a dopamine infusion (20mg/hr) was added as chronotropic support. Inotropes were titrated to maintain MAPs >60, however she remained oliguric (20mls in 6 hours) and renal function continued to deteriorate.

On day 2 of admission, she developed progressive respiratory failure, likely secondary to volume overload and required intubation, ventilation and haemofiltration was commenced. Renal function started to improve on day 4, but she required vasopressor support until day 9. She was discharged from hospital 13 days after admission with return to normal renal function.

Discussion

Losartan is an angiotensin II receptor antagonist that is metabolised to an active metabolite E-3174 by the cytochrome P450 system. It acts by competitively inhibiting the binding of angiotensin II at the type 1
angiotensin II receptor (AT1), hence blocking the vasoconstrictive and aldosterone-secreting effects of angiotensin II. Among numerous other effects, angiotensin II causes constriction of the afferent and, to a greater extent, the efferent renal arterioles. We hypothesise that the early anuria observed in our patient was secondary to afferent and efferent renal arteriole dilation in response to profound block of the AT1 receptors. The resultant renal hypoperfusion would be further exacerbated by the peripheral vasodilatation and hypotension resulting from the large amlodipine overdose, and the AT1 blockade would render the normal renin-angiotensin-aldosterone system response to hypotension ineffective.

Following oral ingestion, the peak plasma concentrations of losartan is 1–2 hours and the terminal half-life 6–9 hours. The plasma concentration of amlodipine peaks at approximately 6–8 hours after ingestion with a terminal elimination half-life of 40–50 hours. There is some evidence that severe renal failure leads to higher plasma concentrations and a prolonged half-life. We surmise that the early anuria and renal failure in our patient, presumably as a consequence of the combination of the amlodipine and losartan overdose, would therefore serve to further prolong the toxic effects of the amlodipine, likely accounting for the prolonged hypotension and inotrope dependence observed.

The patient in this case report gave written consent for this case to be published.

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**REFERENCES:**


