Ramipril poisoning rescued by naloxone and terlipressin

Sir,

Ramipril, an angiotensin-converting enzyme (ACE) inhibitor with extensive tissue distribution, is commonly used in the treatment of left ventricular dysfunction secondary to hypertension, congestive cardiac failure, post myocardial infarction, and prophylaxis in high cardiovascular risk subjects. Commonly described adverse effects of the drug are hypotension, hyperkalemia, cough, rashes, angioedema, dysguesia, and teratogenecity. We report a case of ramipril poisoning presented with severe hypotension and cardiovascular collapses (lowering arteriolar resistance) with hypothermia successfully managed with terlipressin and naloxone.

A 17-year-old girl presented in a collapsed state in our emergency department (ED) 2 hours after consuming 20 tablets of ramipril to commit suicide (her father was on ramipril treatment). She was referred with oxygen and dopamine 20 μg/kg/min. Her pulse and blood pressure were not recordable. Other examinations showed consciousness 7/15 (GCS), cold extremities, respiration 45/min, heart rate 140/min. She was intubated immediately and put on mechanical ventilation. Fluid resuscitation was initiated along with gastric lavage. Norepinephrine was added with dopamine. With dose of 0.5 μg/kg/min noradrenaline her blood pressure (BP) was 60/30 mmHg. Immediate arterial blood gas analysis (femoral art) showed severe metabolic acidosis and lactic acidosis and hyperkalemia. Electrolytes disturbances and acidosis correction were attempted. After primary resuscitation she was shifted to intensive care unit (ICU). Here, invasive monitoring such as central venous cannulation, arterial blood pressure monitoring suggested cardiogenic shock. Portable echocardiography (Micro Maxx Sonosite) with a 2-5 MHZ probe demonstrated severe left ventricular (LV) dysfunction (EF =25%). No kissing sign in LV in short axis mid papillary view, inferior vena cava 1.9 cm. After starting dobutamine 5-10 μg/kg/min contractility slightly improved but BP didn't picked up. After consultation with a cardiologist we started terlipressin (Terlip, Samarth Pharma Pvt Ltd, Mumbai, India) 1 mg bolus followed by 4-6 hourly. Naloxone (Nex, Neon Laboratories, Mumbai, India) 400 μg bolus followed by 100 μg/hour infusion was also added. Within 1 hour of bolus terlipressin her BP picked up and we decided to continue it. Naloxone was stopped after 6 hours. Blood investigation revealed cardiac troponin negative, BNP 356 pg/ml (normal value 100 pg/ml), severe acidosis, hyperkalemia, elevated alkaline phosphate 780 U/ml, INR 3.5. Airway examination with video laryngoscope failed to reveal any angioedema or laryngeal edema. Differential white cells count failed to show any eosinophilia and serum IgE level was within normal limits. She had no history of hypothyroidism. Her temperature improved by forced air warming device. She became hemodynamically stable but developed acute

kidney injury (AKI) and hepatic dysfunction. Continuous renal replacement therapy (CRRT) was started in view of acidosis, hyperkalemia, and AKI. Hepatic dysfunction was managed with vitamin K and fresh frozen plasma. Inotropic support started tapering on the second day. On the third day, inotropes and vasopressor were stopped. Repeated echocardiography showed improvement systolic function (EF 45-50%). Hepatic functions started improving as well. She was extubated on day 5 and transfer out to ward on day 8. Subsequently, she was discharged from the hospital.

Ramipril is usually used to improve left ventricular systolic function by reducing preload, after load and ventricular remodeling and shown long-term benefit in congestive cardiac failure, initially started with low dose. Angiotensin II increases force of myocardial contraction by promoting Ca^{2+} influx and may increase heart rate by enhancing sympathetic activity. Here acute large dose of ramipril produced cardiac depression by reducing its function. In human body, vascular tone is maintained by renin angiotensin system (RAS), sympathetic nervous system, and vasopressin system. In this particular case, poisoning with hypothermia depressed sympathetic system and ramipril blocked the RAS pathway. The only system left to maintain vascular tone is the vasopressin system. So we decided to start long-acting vasopressin analog terlipressin. Boccara *et al.* have shown that terlipressin is effective in treating refractory hypotension in perioperative period in patients chronically treated by ACE inhibitors.[1] This long-acting synthetic analog of vasopressin has a half-life of 6 hour with a higher selectivity for vascular receptors without deleterious cardiac effects as compared with vasopressin.[2] Aldosterone promotes excretion of potassium. ACE inhibitors decrease the release of aldosterone, potassium accumulation presents clinically significant hyperkalemia. ACE inhibitors may inhibit the metabolism of enkephalins and augment their opioid action which includes lowering of blood pressure. Thus, use of naloxone, an opioid receptor antagonist has been justified.[3]

To conclude, in ACE inhibitors over dose or poisoning catecholamine resistance shock is common. Here, terlipressin and naloxone could be use as rescue measures.

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