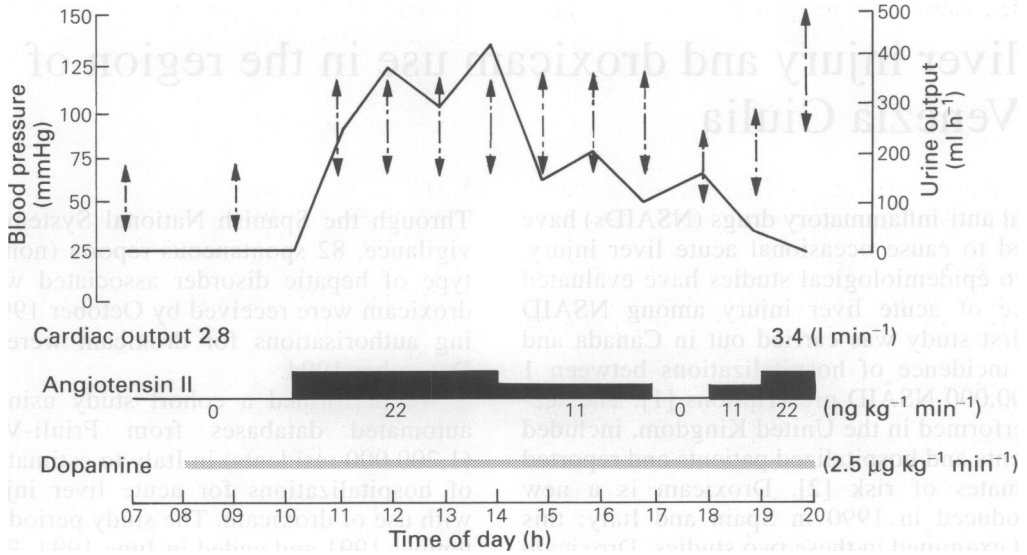
Enalapril overdose and the corrective effect of intravenous angiotensin II

We report a case of enalapril overdose complicated by profound hypotension and anuria. A 46 year old woman was found collapsed at home having drunk 5 pints of strong lager and taken 14 to 20, 10 mg tablets of enalapril over an 18 h period for 'chest pain'. Three months previously she sustained a subendocardial myocardial infarction with pulmonary oedema, but good left ventricular function (ejection fraction of 54%) and was commenced on an angiotensin converting enzyme (ACE) inhibitor (maintenance medication included diltiazem, bumetanide and isosorbide mononitrate). On arrival, blood pressure was unrecordable with a weak pulse at 50–60 beats min^{-1} and 1.5 l of 0.9% saline was administered intravenously. Blood profile showed a metabolic acidosis (hydrogen ion, 54 nmol l^{-1} and lactate, 4.3 $mmol^{-1}$) and renal impairment (urea 7.1 mmol l^{-1} and creatinine 248 μmol l^{-1}). Cardiac enzymes were within normal limits throughout. Her chest radiograph showed pulmonary congestion and oedema. Electrocardiogram showed no acute ischaemia, but a nodal bradycardia with retrograde P waves reverting to sinus rhythm following atropine. Echocardiography confirmed good left ventricular function without pericardial effusion. She was commenced on low dose Dopamine (2.5 μg kg^{-1} min^{-1}), but inspite of very high filling pressures and a bolus of noradrenaline (1 mg over 2 min), she remained anuric and hypotensive (80/50 mm Hg). Swan-Ganz thermodilution catheter was inserted and showed the following: right atrium 20/16 mm Hg (mean 18); right ventricle 37/17 mm Hg (mean 28); pulmonary artery 45/26 mm Hg (mean 34); pulmonary artery wedge 28 mm Hg; cardiac output 2.83 l min^{-1} (cardiac index 1.52 l min^{-1} m^{-2}) and peripheral vascular resistance of 1724 dyn s^{-1} cm^5. An intravenous infusion of angiotensin II (Hypertensin, Ciba Angiotensin II Val-5-amide) was commenced at 0.1 mg h^{-1} (22 ng kg^{-1} min^{-1}) with a dramatic increase both in blood pressure (110/70) and urine output (1500 ml in 4 h) (Figure 1). Reduction in the dose of angiotensin II was accompanied by a corresponding drop in blood pressure and urine output. Overnight her urine output and blood pressure were maintained and by the following morning, her cardiac output had improved to 4.29 l min^{-1} (with an index of 2.3 l min^{-1} m^{-2}). She required angiotensin II infusion for a period of 30 h before being discontinued. She made an unremarkable recovery with resolution of her pulmonary oedema and renal impairment. She later took her own discharge.

Previous patients with angiotensin converting enzyme (ACE) inhibitor overdoses have been treated in differing ways including haemodialysis [1] and naloxone [2] with variable success. Simple fluid infusion, either alone [3–6] or in combination with a low dose of dopamine [7], has been shown to be an effective treatment. However, in this case these measures proved ineffective. More recently, there has been a report by Jackson and colleagues [8] of the successful treatment of an enalapril overdose by angiotensin infusion. The patient had been managed with intravenous fluids, dopamine and adrenaline without success. However, the addition of an angiotensin infusion



brought about a major improvement in blood pressure and urine output. The dosages used were somewhat in excess of those used in our case (180–1080 μg h^{-1} *vs* 100 μg h^{-1}) possibly reflecting the relative doses of enalapril ingested. Interestingly, they also report a junctional bradycardia, but this is in the context of simultaneous verapamil overdosage (7.2 g). The bradycardia was sustained and only resolved after angiotensin infusion. Angiotensin II is known to have effects on the parasympathetic nervous system by attenuating the vagally mediated cardiac reflexes [9]. Thus it seems likely that the junctional bradycardia reflects the parasympathetic agonist activity of ACE inhibitors [10]. Certainly in our experience, the nodal bradycardia responded promptly to atropine.

There are some notable inconsistencies with our case. Firstly, the angiotensin infusion was given for 30 h (36 to 48 h post ingestion) and since the plasma half-life of enalaprilat is 36 to 40 h, it may be necessary to continue the infusion for several days. Secondly, the peripheral vascular resistance is not particularly low, but the measurement was made following initial therapy with vasoconstrictors. Finally, the presence of pulmonary oedema in the face of normal left ventricular function is anomalous. This may reflect the degree of bradycardia, and fluid ingestion and administration over a protracted period of anuria.

In conclusion, we recognise that angiotensin is a useful adjunct in the treatment of an ACE inhibitor overdose. The use of an angiotensin infusion is indicated when conventional treatment with vigorous fluid replacement and low dose dopamine has been unsuccessful. We would recommend that a suitable regime would start at 20 ng kg^{-1} min^{-1} of angiotensin II. The dose should then be adjusted according to the response in blood pressure and urine output.

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Acute liver injury and droxicam use in the region of Friuli-Venezia Giulia

Non-steroidal anti-inflammatory drugs (NSAIDs) have been reported to cause occasional acute liver injury. Recently, two epidemiological studies have evaluated the incidence of acute liver injury among NSAID users. The first study was carried out in Canada and reported an incidence of hospitalizations between 1 and 2 per 100,000 NSAID prescriptions [1]. The second study performed in the United Kingdom, included both outpatients and hospitalized patients and reported similar estimates of risk [2]. Droxicam is a new NSAID introduced in 1990 in Spain and Italy; this drug was not examined in these two studies. Droxicam is a pro-drug of piroxicam and is transformed completely into piroxicam prior to intestinal absorption. Through the Spanish National System of Pharmacovigilance, 82 spontaneous reports (none fatal) of any type of hepatic disorder associated with the use of droxicam were received by October 1993 [3]. Marketing authorisations for droxicam were suspended in December 1994.

We performed a cohort study using the regional automated databases from Friuli-Venezia Giulia (1,200,000 residents) in Italy to estimate the incidence of hospitalizations for acute liver injury associated with use of droxicam. The study period started in September 1991 and ended in June 1994. Persons aged 10 to 79 years entered the study cohort after their first prescription for droxicam and were followed until the

