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Accidental Ten Times Overdose Administration of Recombinant Human Erythropoietin (rh-EPO) up to 318,000 Units a Day in Acute Myocardial Infarction: Report of Two Cases

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Abstract: The cytokine erythropoietin protects the heart from ischaemic injury, in part by preventing apoptosis. But appropriate dose of erythropoietin for the protection of injured heart has not been studied. While we were researching the cardiac protective effects of erythropoietin in acute myocardial infarction, we experienced two cases of accidental nearly ten times overdose administration of erythropoietin up to 318,000 units instead of 33,000 units on the second day of three scheduled days of treatment. So a total of 384,000 units of erythropoietin were administered during three days. In case 1, the ALT level soared up to 386 U/l on the second day of administration and decreased slowly. It was back to normal state 3 months later. The AST level increased slowly up to 391 U/l and normalized 3 months later. Haemoglobin level was elevated up to 15.7 g/dl (14.7 g/dl at admission) and, 3 months later, normalized to 14.8 g/dl. In case 2, the ALT level was elevated up to 98 U/l on the second day of administration and decreased slowly. Three months later, the ALT level was normalized. The AST level also increased slowly up to 71 U/l and normalized 3 months later. Haemoglobin level was elevated up to 15.6 g/dl (13.8 g/dl at admission) and, 3 months later, normalized to 13.6 g/dl. In these two cases reported, these patients, even after massive overdose, tolerated it relatively well and the only side-effects we found were elevated liver enzyme and haemoglobin levels.

The cytokine erythropoietin protects the heart from ischaemic injury partly by preventing apoptosis (Fiordaliso *et al.* 2005). But appropriate dose of erythropoietin for the protection of injured heart has not been studied. While we were researching the cardiac protective effects of erythropoietin in acute myocardial infarction, we experienced two cases of accidental nearly ten times overdose administration of erythropoietin up to 318,000 units instead of 33,000 units on the second day of three scheduled days of treatment. So a total of 384,000 units of erythropoietin were administered during three days. We report here the course and side-effects of a massive overdose of erythropoietin.

Materials and Methods

Case 1. A 40 year old man with a history of substernal chest pain was presented to the emergency department. He had the medical history of type 2 diabetes and hypertension, and was a smoker with 40 packs/year. On clinical examination, he looked acutely ill and afebrile. His initial blood pressure was 110/70 mmHg, his pulse was regular, 80 beats/min. and his respiration rate was 20 breaths/min.

His ECG showed ST-elevation in leads V(1) to V(6). Cardiac enzymes were also elevated: creatine kinase(CK)-MB was 1.8 ng/ml, myoglobin was 475 ng/ml and cardiac specific troponin-I was 5.7 ng/ml. Two-dimensional thoracic echocardiography showed akinesia of the anterior and septal segments and ejection fraction of 51%. Acute coronary angiograms were obtained, which revealed total occlusion in the proximal left anterior descending artery. We successfully performed a percutaneous coronary intervention, and the final angiogram showed a good coronary flow without residual stenosis.

Erythropoietin was scheduled to be administered with 33,000 units a day for 3 days. First day erythropoietin was administered at 33,000 units before Percutaneous Coronary Intervention (PCI) as protocol, but on the second day were administered 318,000 units accidentally, then third day administered 33,000 units as protocol (fig. 1 & 3).

Case 2. The patient was a 46 year-old man without a significant medical history. He smoked 30 packs/year. He visited our emergency room complaining of substernal chest pain.

On clinical examination, he looked acutely ill and afebrile. His initial blood pressure was 110/60 mmHg and his pulse was regular at 80 beats/min. His respiration rate was 20 breaths/min.

His ECG showed ST-elevation in leads V(1) to V(6). Cardiac enzymes were also elevated: creatine kinase (CK)-MB was 18.2 ng/ml, myoglobin was 568 ng/ml and cardiac specific troponin-I was 2.51 ng/ml. Two-dimensional thoracic echocardiography showed hypokinesia of the anterior and septal segments and ejection fraction of 61.9%. Acute coronary angiograms were obtained and it revealed total occlusion in the proximal left anterior descending artery. We performed a percutaneous coronary intervention successfully. The final angiogram showed a good coronary flow without residual stenosis.

Erythropoietin was scheduled to be administered at 33,000 units a day for 3 days. First day erythropoietin was administered at 33,000 unit before PCI as protocol, but on the second day 318,000 units were administered accidentally, on the third day 33,000 unit as protocol were administered (fig. 2 & 4).

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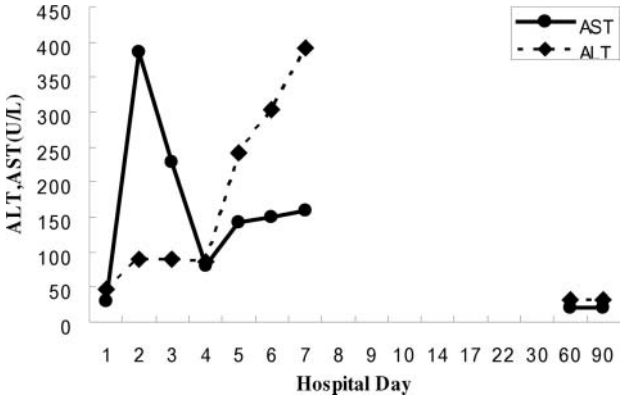

Fig. 1. ALT and AST level in case 1.

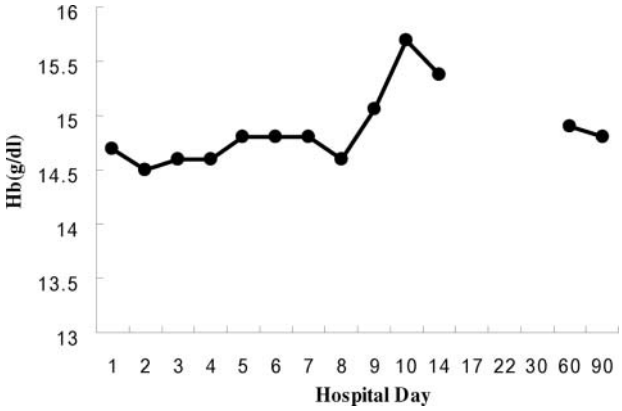

Fig. 3. Haemoglobin level in case 1.

Results

Clinical course and side effects.

Toxicities of erythropoietin are listed below

1. Headache, low fever and hypodynamia, muscle pains and joints pains
2. Allergic reaction such as rash, including allergic shock
3. Elevation of blood pressure
4. Nausea, vomiting, poor appetite and diarrhoea
5. Itching, skin eruption
6. Retinal haemorrhage, splenomagaly, epistaxis, oedema, arthralgia, myalsia, seizure
7. Increase of haemoglobin/haematocrit
8. Elevation of ALT and AST.
9. Leukocytosis, eosinophilia, thrombocytosis, serum K level elevation, BUN/Cr level elevation, uric acid level elevation

In the course of close observation, we found none of the specific symptoms we expected as side-effects of erythropoietin, and no abnormal objective findings on physical examination. Only two abnormal findings were reported on blood chemistry. Liver enzyme (ALT and AST) was elevated and haemoglobin level was elevated (table 1).

In case 1, the ALT level soared up to 386 U/l on the second day of administration and decreased slowly. It came back to normal 3 months later. The AST level increased slowly up to 391 U/l and normalized 3 months later. Haemoglobin level was elevated up to 15.7 g/dl (14.7 g/dl at admission) and 3 months later normalized to 14.8 g/dl (fig. 1 & 3).

In case 2, the ALT level was elevated up to 98 U/l on the second day of administration and decreased slowly. Three months later, the ALT level was normalized. The AST level also increased slowly up to 71 U/l and normalized 3 months later. Haemoglobin level was elevated up to 15.6 g/dl (13.8 g/dl at admission) and 3 months later normalized to 13.6 g/dl (fig. 2 & 4).

Discussion

Since the first cloning and clinical testing of erythropoietin fifteen years ago, the use of erythropoietin has become widespread in the treatment of anaemia (van der Meer *et al.* 2004). Recent studies show that erythropoietin plays a protective role in brain ischaemia. Erythropoietin is now considered to be applicable to a variety of disorders including cerebral ischaemia, myocardial infarction, and chronic congestive heart failure (Maiese *et al.* 2005). Erythropoietin modulates a broad array of cellular processes that include

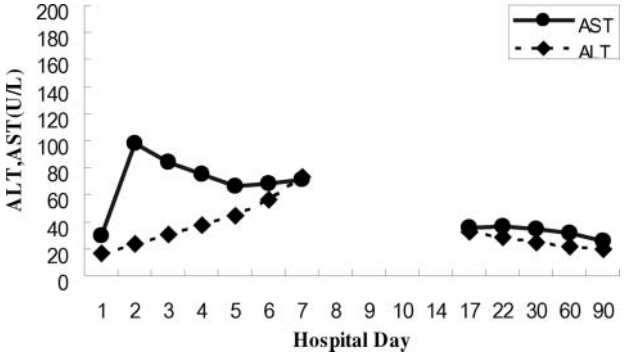

Fig. 2. ALT and AST level in case 2.

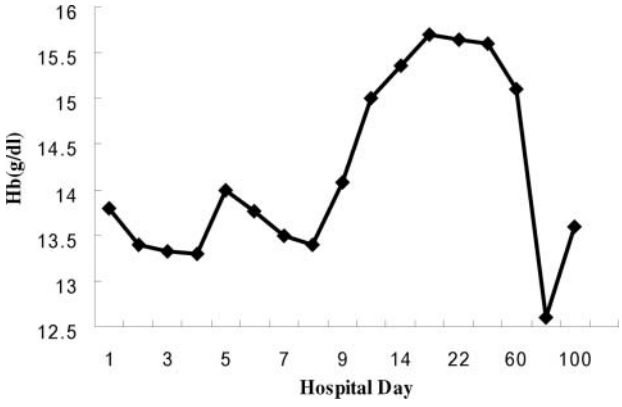

Fig. 4. Haemoglobin level in case 2.

Table 1.

Serial laboratory parameters of patients with erythropoietin overdose.

	Case 1				Case 2			
Hospital day	Day 1	Day 2	Day 10	Day 90	Day 1	Day 2	Day 10	Day 90
Hb (g/dl)	14.7	14.5	15.7	14.8	13.8	13.4	15.0	13.6
Hct (%)	42.7	41.5	47.8	41.4	40.3	40.8	47.1	40.4
WBC (/mm^3)	9500	8400	6500	6200	12600	7200	6300	5600
Platet (/mm^3)	329000	268000	282000	261000	195000	181000	161000	244000
ALT (U/l)	30	386	159	20	30	98	72	26
AST (U/l)	47	90	391	31	17	24	73	20

(Hb=haemoglobin, Hct=haematocrit, WBC=white blood cell, RBC=red blood cell, ALT=alanine aminotransferase, AST=aspartate aminotransferase).

progenitor stem cell development, cellular integrity, and angiogenesis. As a result, cellular protection by erythropoietin is robust and it inhibits the apoptotic mechanisms of injury, including the preservation of cellular membrane asymmetry to prevent inflammation (Maiese *et al.* 2005).

The most frequent side-effect of erythropoietin is hypertension (0.75%). Headache, palpitation, nausea, vomiting, dyspnoea, hyperkalaemia and diarrhoea are also reported.

We have researched the protective effects of erythropoietin in high doses, and did not experience any serious side-effects of erythropoietin. In these two cases here reported, two patients even after massive overdose, tolerated it relatively well and the only side-effects we found were elevated liver enzyme and haemoglobin levels. These patients were followed up as out-patients and the elevated levels soon normalized.

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