รายงานผู้ป่วย

Adverse effects of ACE inhibitor (Enalapril) in infants with severe congestive heart failure

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ACE inhibitors are well established for the management of patients with congestive heart failure; and may render some adverse effects during the course of treatment. We report two infants with severe congestive heart failure, who did not respond to conventional management (digitalis, diuretics and prazosin). They developed hypotension, bradycardia, hypoglycaemia and acute renal failure while on high doses of enalapril (0.35 and 0.40 mg/Kg/day) for 10 and 15 days respectively. These serious adverse effects developed during the time the patients were sodium depleted. Dopamine, dobutamine, sodium and glucose supplement were administered to correct the adverse reaction. The renal function recovered in one patient but the other infant remained azotaemia and expired after developing nosocomial septicemia. The restoration of sodium balance and reduction of diuretics usage were essential for these patients during treatment with ACE inhibitors.

Key words. *ACE inhibitors, Adverse effects.*

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ยาในกลุ่ม angiotensin converting enzyme inhibitor (ACE inhibitors) มีประโยชน์อย่างมากในการรักษาภาวะหัวใจล้มเหลวเรื้อรัง แต่อาจก่อให้เกิดอาการไม่พึงประสงค์ต่างๆ ได้ บทความนี้ได้รายงานผู้ป่วยเด็ก 2 รายอายุ 4 และ 5 เดือนที่มีภาวะหัวใจล้มเหลวเรื้อรังและไม่ตอบสนองต่อการรักษาด้วยยา ดิจิตาลิส ยาขับปัสสาวะและ prazosin ผู้ป่วยเกิดภาวะความดันโลหิตต่ำ หัวใจเต้นช้าผิดปกติ ไตวายเฉียบพลันและภาวะน้ำตาลในเลือดต่ำ ภายหลังการรักษาด้วย enalapril ในขนาดสูง(0.35 และ 0.40 มก/กก/วัน) เป็นเวลา 10 และ 15 วันตามลำดับ โดยผู้ป่วยได้รับยาขับปัสสาวะร่วมด้วยเป็นครั้งคราว ภาวะแทรกซ้อนเหล่านี้เกิดขึ้นในขณะที่ผู้ป่วยมีภาวะโซเดียมในเลือดต่ำและได้รักษาภาวะแทรกซ้อนเหล่านี้โดยการหยุดยาให้น้ำเกลือและน้ำตาลทดแทนพร้อมกับให้ยา dopamine และ dobutamine ทำให้ความดันโลหิต อัตราการเต้นของหัวใจและการทำงานของไตกลับมาเป็นปกติในผู้ป่วย 1 รายภายหลังที่หยุดยา 6 วัน ส่วนผู้ป่วยอีก 1 รายยังคงมีอาการไตล้มเหลวและเสียชีวิตจากการติดเชื้อในกระแสโลหิตแทรกซ้อน ดังนั้นการใช้ยาในกลุ่ม ACE inhibitors ในผู้ป่วยที่มีหัวใจล้มเหลวเรื้อรังจึงควรระวังภาวะขาดเกลือโซเดียมและระมัดระวังการใช้ยาขับปัสสาวะ โดยภาวะแทรกซ้อนเหล่านี้เป็นสิ่งที่สามารถป้องกันได้

ACE inhibitor (Enalapril) has gained widespread acceptance for the treatment of intractable congestive heart failure in children and adults. It increases cardiac output, decrease left ventricular filling pressure and induces peripheral vasodilatation. [1-9] However nearly 50% of the patients developed some adverse effects during the course of therapy. Hypotension and renal insufficiency are the principal serious adverse effects of therapy being recorded. [2,10-12]

We report two cases of infants with severe congestive heart failure who developed hypotension, bradycardia, renal insufficiency and hypoglycaemia while on enalapril, which is a long acting ACE inhibitor. These untoward side effects occured during the time the patients were sodium depleted. The clinical course emphasize the relative importance of the sodium depletion state in the deterioration or recovery of this adverse reaction.

Case report

Case 1. A 4 month old infant with a large ventricular septal defect was admitted for severe congestive heart failure. On admission, his body weight was 2700 gm, blood pressure 98/58 mmHg and heart rate 141 beats per minute. He was initially treated with digoxin (0.012 mg/Kg/day), dichlorothiazide and prazosin (0.1 mg/Kg/day), but his condition did not improve. Dichlorothiazide and prazosin were then replaced by enalapril at a dose of 0.35 mg/Kg/day. The blood chemistry (Na 141 mEq/L, K 3.7 mEq/L, Cl 88 mEq/L, HCO_3 27.6 mEq/L), blood urea nitrogen (7 mg/dl) and creatinine (0.3 mg/dl) were normal. Furosemide was added intermittenly for the control of congestive symptoms. Ten days after treatment with enalapril, he developed hypotension (BP 55/36), bradycardia (HR 78/min.) and oliguria. Hyponatraemia (Na 132 mEq/L), hypoglycaemia (blood glucose 35 mg/dl) and increased blood urea nitrogen (34 mg/dl) were detected. An electrocardiography showed sinus bradycardia with normal PR interval. Dopamine, dobutamine, glucose and sodium supplement were administered to correct this imbalance afterwhich enalapril was discontinued. Three days later his blood pressure, heart rate, blood sodium and glucose returned to normal and the blood urea nitrogen was reduced to normal in 6 days.

Case 2. A 5 month old girl with a large ventricular septal defect and patent ductus arteriosus developed intractable heart failure. She did not respond to conventional treatment with digoxin (0.015 mg/Kg/day), furosemide and prazosin (0.1 mg/Kg/day). On admission, her body weight was 3250 gm, the blood pressure and heart rate were 92/60 mmHg and 132 beats/minute respectively. Blood electrolytes (Na 140 mEq/L, K 3.9 mEq/L, Cl 99 mEq/L and HCO_3 30 mEq/L), blood urea nitrogen (12 mg/dl) and creatinine (0.4 mg/dl) were within normal limits. Prazosin was discontinued and enalapril was introduced initially using 0.2 mg/Kg/day. The congestive symptoms did not improve, the dosage of enalapril was then increased to 0.40 mg/Kg/day and furosemide was added intermittenly. Subsequently hyponatraemia (Na 130 mEq/L) was noted after continuing the treatment for 15 days. Two days later, she developed hypotension (BP 62/30 mmHg), sinus bradycardia with normal PR interval (HR 65/min.), oliguria and hypoglycaemia (blood glucose 40 mg/dl). Her blood sodium level decreased further to 125 mEq/L. The blood urea nitrogen and creatinine rose to 51 mg/dl and 1.1 mg/dl respectively. All medications were discontinued. She was then treated with dopamine, dobutamine, sodium and glucose. Four days later, her blood pressure, heart rate, blood glucose and sodium returned to normal but the blood urea nitrogen and creatinine continued to rise to 69 mg/dl and 1.6 mg/dl respectively. She developed respiratory failure, nosocomial septicemia and expired 3 days later.

Discussion

ACE inhibitors have multiple sites of action on the circulatory system. The main mechanism is inhibition of renin angiotensin system by decreasing plasma angiotensin II and aldosterone concentration. They also increase the formation of bradykinins, vasodilatory prostaglandins and decrease the secretion of norepinephrine. Of these sites of action, the peripheral vasodilatation and decreased afterload is the proposed mechanisms on which the management of congestive heart failure is based. [4-7,9]

Systemic hypotension and renal insufficiency are the principle adverse effects of ACE inhibitors in patients with congestive heart failure. [13,14] These events take place most commonly at the beginning of the treatment or in the presence of sodium depleted state (Na < 130 mEq/L) or following a recent occurrence of significant diuresis. [13,15] The hypotensive symptom and azotaemia can be reversed if adequate sodium replesion is achieved. [13,15] Our two patients developed symptomatic hypotension and acute renal insufficiency while on enalapril and intermittent furosemide. Hyponatremia is also noted during the development of these adverse reactions. The sodium depleted state may be caused by restricted salt intake or increased dose of diuretics. The blood pressure and renal function responded to sodium replacement therapy in one patient; but renal function of the second patient did not improve. This may be due to the more severe sodium depletion in the second patient.

Systemic hypotension leading to renal hypoperfusion may be the main cause of renal insufficiency in our patients. Nevertheless, renal failure on a combination of diuretics and ACE inhibitors manifests itself independently with the drop in blood pressure. [16,17] In patients with severe congestive heart failure, the renin angiotensin system is intimately linked to the maintenance of renal function. Angiotensin II help adjust the intraglomerular pressure in order to maintain glomerular

filtration. Blockade of the renin angiotensin system interferes with the haemostatic mechanism for renal excretion and induce renal insufficiency. The magnitude and rapidity of onset of renal insufficiency is also determined by the degree of sodium depletion. [2,15] Moreever patients with severe congestive heart failure often have hyponatraemia. Therefore in preventing these adverse reactions, special care should be taken to avoid significant or excess concurrent diuretic therapy and at the same time to encourage the repletion of sodium storage.

Our two patients had sinus bradycardia while they, were hypotensive. The slow heart rate could not be explained just by the effect of digitalis, and the effect of ACE inhibitor could have contributed to this event. Unlike other vasodilators, the reduction of peripheral vascular resistance with ACE inhibitors is not associated with a reflex increase in the heart rate. The mechanism of this effect can be explained by the antiadrenergic effect of ACE inhibitor, due to its inhibition of the formation of angiotensin II which promotes the release of norepinephrine from adrenergic terminal neurones, increases the parasympathetic tone and down regulation of baroreflex. [18] The lack of normal compensatory mechanism caused by the action of ACE inhibitors may be harmful to patients with heart failure who develop hypotension. Therefore the benefit of combining ACE inhibitor with digitalis must be evaluated.

The patients also developed hypoglycaemia during the episode of hypotension and renal insufficiency. ACE inhibitors decrease the circulating epinephrine and enhance insulin sensitivity which could explain the lowering of blood glucose level.[19,20] However, this event may be precipitated by malnutrition, inadequate intake and severe congestive heart failure. [21,22] During treatment with ACE inhibitors in patients with severe congestive heart failure, blood glucose should be determined periodically especially in patients with malnutrition.

Conclusion

We report two infants with severe congestive heart failure who developed hypotension, bradycardia, renal insufficiency and hypoglycaemia while on treatment with enalapril. These adverse effects were noted while the patients were hyponatraemic. This suggests that the level of sodium depletion is one of the major factors in determining the ability of ACE inhibitors to induce untoward effects in patients with congestive heart failure. In cases where heart failure is being treated with a combination of ACE inhibitor and diuretic, the restoration of positive sodium balance is mandatory to maintain the haemodynamic equilibrium.

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