

The Prevention of Pain from Sickle Cell Disease by Trandolapril

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A 48-year-old African-American woman with both sickle cell anemia and chronic pain was treated with a hydrophobic angiotensin I-converting enzyme (ACE) inhibitor. This resulted in the complete resolution of her pain. When the ACE inhibitor was deliberately stopped, her pain recurred, only to cease again after the ACE inhibitor was deliberately resumed. The activation of ACE may be an early step in the arterial vaso-occlusion typical of sickle cell disease.

Key words: vaso-occlusion ■ sickle cell disease ■ angiotensin II

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We present a 48-year-old African-American woman with sickle cell anemia who is the only surviving child of parents who had had six male stillbirths. Since her teens, she has had 3–4 painful crises yearly, each treated with fluids, analgesics and, occasionally, transfusions. Thirty-two months after moving to the area, she came to the hematology/oncology clinic in Modesto, CA. We documented approximately one emergency room visit for pain control, as well as IV fluids every two months for the previous year. During her 20s, she had an upper extremity arterial thrombosis requiring anticoagulation and skin grafting. She had been placed on low-molecular-weight heparin twice daily but had gone off this regimen. We began hydroxyurea, but before her hemoglobin F increased significantly, she had an arterial lower extremity thrombosis with loss of the terminal middle toe. Angiography demonstrated thrombosis in the iliac artery and superficial femoral artery. Retaplastase lysis was effective for the iliac artery, and a stent was angiographically inserted into the superficial femoral artery. The patient was placed on coumadin and clopidogrel. The hydroxyurea and low-molecular-weight heparin were also continued.

Coumadin was soon discontinued due to intolerance for the required dose monitoring without any further thrombosis. There was a sustained increase in hemoglobin F, and no further transfusions were required. Nevertheless, she continued to have persistent joint pain involving the elbows, hips and knees. Although she described having daily episodes of pain “for as long as she could remember,” the frequency and severity seemed to worsen during the winter months. She took 2–6 hydrocodone/acetaminophen tablets daily and used frequent hot baths to deal with almost daily episodes of arthralgia. There was never any joint swelling or tenderness. During one particularly severe painful crisis in late December 2005, she was hospitalized and received intravenous hydromorphone.

Outpatient blood pressure measurements had ranged between 98–128 systolic and 47–86 diastolic over the preceding two years. In the hospital, despite painful crises, pressures were never >145/84. After obtaining full informed consent to an investigation review board-approved protocol, trandolapril 1 mg orally daily was given, and blood pressure and heart rate were monitored frequently. Blood pressure ranged between 92/48 and 130/87 with heart rates of 62–86 over 12 hours after each dose of trandolapril.

She was pain free at discharge and remained on trandolapril 1 mg daily at bedtime. Except for a three-day period when she visited a colder climate and developed joint and chest pain, she used no pain medication for six months while she was on the trandolapril. As a test, and during a period of sustained warm weather, the trandolapril was discontinued. After two weeks, however, she again developed joint pain. Trandolapril was resumed and 15 tablets hydrocodone/acetaminophen were provided. She has had no pain and has taken no pain medications for >12 months now (as of February 2007). She continues on trandolapril 1 mg nightly.

DISCUSSION

Pain from sickle cell disease is a consequence of tissue hypoxia due to vaso-occlusion. Valine-6 in hemoglobin S causes the molecule to self-aggregate in the

deoxygenated state. A vicious cycle results, whereby hypoxia begets erythrocyte sickling and further hypoxia. Sickle cell patients respond to hypoxia with paradoxical vasoconstriction due to decreased NO production and increased resistance to NO.¹

Recently, it was proposed that angiotensin I-converting enzyme (ACE) may be a redox sensor, activated by hypoxia and reducing conditions.² Activation of ACE and overproduction of angiotensin II could help explain the prothrombotic tendency of patients with sickle cell disease as well as vasoconstriction.²

The ACE D/D genotype has been associated with deep vein thrombosis and pulmonary embolism in African-American male patients.^{3,6} The contribution of the ACE D/D genotype to venous thromboembolism may be more pronounced for African Americans than Caucasians.^{3,7} Indeed, the ACE D/D genotype is an excellent candidate for the so-called "African gene" responsible for the approximate five-fold increased incidence of end-stage renal disease among Americans of African ancestry.³⁻⁵

Because there is no report on the frequency of the ACE D/D genotype in sickle cell disease, we offer the following preliminary data. A small group of African-American patients with sickle cell trait or sickle cell anemia from St. Louis Regional Hospital, an inner-city hospital, and the St. Louis VA Medical Center, were genotyped at the ACE I/D locus using methods previously described.³ (The subject of this case report was not included.) The results are presented in Tables 1 and 2.

Table 1 shows the ACE I/D genotypes of a "control" population.³ The frequency of the D allele reported for African Americans varies somewhat in the literature, perhaps because of differing degrees of Caucasian admixture.³ The value we found (0.58, Table 2) is similar to other reports (e.g., 0.60⁷).

For the control group, genotype frequencies were the same in both black men and women, and both groups satisfied the Hardy-Weinberg equilibrium. Of 33 total patients with sickle cell trait, genotyping was successful in 31, consistent with the rate of failure seen previously.³ Of 29 total patients with sickle cell disease, genotyping succeeded in 28 patients. No gender difference in genotype or allele frequency was observed (Tables 1 and 2).

Neither the sickle cell trait nor sickle cell anemia samples satisfied the Hardy-Weinberg equilibrium. This may be due to the admittedly small sample sizes. But it may also reflect natural selection. The ACE D/D frequency tended to be depressed in patients with sickle cell trait and even lower in patients with sickle cell disease, although these differences were not statistically significant. Both groups had a lower frequency of the D allele (0.50) relative to the control group (0.58, Table 2), although these results were again not statistically significant due to the small sample sizes involved.

Since sickle cell disease is characterized by complications already associated with the D allele and the D/D genotype, such as deep vein thrombosis,^{3,7} we expected the frequency of the D allele to be elevated in sickle cell trait and sickle cell anemia. However, we observed the opposite trend.

The explanation may lie in the degree of circulatory pathology seen with hemoglobin S. For example, the thrombosis seen in sickle cell disease is much more intense than that seen in the general population, as our patient illustrated. Thrombosis in the arterial, as opposed to the venous, circulation is rare in the general population.⁸

The D/D genotype and overproduction of angiotensin II may be lethal in fetuses with sickle cell anemia, resulting in fetal wastage, as suggested by our patient's family history.

This case raises some additional questions. Why has nobody else seen such a dramatic effect on sickle cell pain with an ACE inhibitor, although they are indicated in sickle cell patients with proteinuria⁹? Could the clinical effectiveness depend on the dose and hydrophobicity of the ACE inhibitor,^{2,10} as we have seen in diabetic and hypertensive nephropathy⁵? How long will trandolapril eliminate pain in this patient? Will trandolapril eliminate further episodes of arterial occlusion in this patient?

It is hoped that additional clinical experience with this patient and others with sickle cell anemia will soon answer these questions.

Table 2. Allele frequencies

Controls (Pooled BM, BW)	HgbAS	HgbSS
D 0.58	0.50	0.50
I 0.42	0.50	0.50

Table 1. Genotype frequencies

	Controls (BM) (n=1,020)	Controls (BW) (n=148)	HgbAS (n=31)	HgbSS (n=28)
ACE				
D/D	338 (33.1%)	49 (33.1%)	9 (29.0%)	6 (21.4%) ^a
I/D	510 (50.0%)	75 (50.7%)	13 (41.9%)	16 (57.1%) ^b
I/I	172 (16.9%)	24 (16.2%)	9 (29.0%)	6 (21.4%) ^c

Genotype frequencies did not differ significantly between controls and patients with HgbAS ($\chi^2=3.2$; $p>0.05$), nor between controls and patients with HgbSS ($\chi^2=1.76$; $p>0.05$); a: 3 black men, 3 black women; b: 7 black men, 9 black women; c: 3 black men, 3 black women

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