Sildenafil, an oral agent that has proven effective for the treatment of erectile dysfunction (ED), enables a natural erectile response to sexual stimulation by enhancing the relaxant effect of nitric oxide (NO) on the corpora cavernosa. NO activates guanylate cyclase, resulting in increased synthesis of cyclic guanosine monophosphate (cGMP), which induces corpus cavernosal smooth muscle relaxation, increased blood flow to the penis, increased intracavernosal pressure, and penile erection. Sildenafil is a potent inhibitor of cGMP-specific phosphodiesterase (PDE) type 5, which is the predominant PDE isozyme responsible for the degradation of cGMP in the corpora cavernosa. When the NO/cGMP pathway is activated, as occurs with sexual stimulation, inhibition of PDE type 5 by sildenafil causes increased concentrations of cGMP in the corpora cavernosa. Sexual stimulation is required for sildenafil to produce its beneficial pharmacological effects on erectile function.1

With the use of sildenafil, the most commonly reported adverse events were headache, flushing, dyspepsia, rhinitis, and color perception disturbances that were all mild to moderate in nature. No cases of priapism were reported with the use of sildenafil in clinically controlled trials.1,2 Patients who have conditions that may predispose them to priapism such as sickle cell anemia, multiple myeloma, or leukemia are, however, advised to use sildenafil with caution.3 We report here a case of priapism in a patient with sickle cell trait associated with the use of sildenafil.

The patient is a 39-year-old male with sickle cell trait (AS) and a past medical history that includes a subarachnoid cyst involving the optic chiasma diagnosed in 1994 and Bell’s Palsy/Ramsay Hunt syndrome in 1997. The patient suffered head trauma from a motor vehicle accident in 1998. The patient had sought urologic evaluation for erectile dysfunction (ED) and was prescribed sildenafil. After taking a dose of 50 mg, he had an erection within 15 minutes that was sustained even after ejaculation. His erection became sustained and painful for about 6 hours. The patient immediately noticed a loss of morning erection followed by gradual worsening of his ED, with complete loss of erection 3 months later.

Physical examination was not contributory. Laboratory evaluation showed: WBC 4.90; Hb 15.1 g/dL; Hct 44.4%; MCV 88.6 fl; Platelet 216/mL. Hormonal determinations revealed: FSH 3.0 mIU/mL (nl 1-8); LH 3.6 mIU/mL (nl 2-12); serum prolactin 14.3 µg/L (nl 3.00-19.0); testosterone 304 ng/dL (nl 262-1593). Hemo-globin (Hb) electrophoresis, isoelectric focusing, and globin separation by denaturing high performance liquid chromatography (HPLC) were consistent with sickle cell trait. Use of those three different methods should detect mutations with charge differences. Red cell separation by isopycnic density gradient that can detect alterations in mean corpuscular hemoglobin concentration (MCHC) that would predispose toward polymer formation was consistent with sickle cell trait. Mass spectroscopy can detect electrophoretically silent mutations of Hb. In this case, it revealed only the presence of globin chains with molecular weights corresponding to α, β², and β, as would be expected in sickle cell trait. We therefore conclude that the patient has sickle trait and has no detectable globin or red cell-based predisposition for polymer formation beyond that which is expected in sickle trait.

Priapism as a complication of sickle cell anemia is a well-known phenomenon, but has not been associated with sickle cell trait. The lifetime incidence of priapism in patients with sickle cell anemia was found to be about 45% in homozygous patients (HbSS) in a Jamaican study.4 Sickle cell disease is a condition with very varied phenotypic expression in patients with the same genetic defect.5

Patients with sickle cell trait are spared the major complications associated with sickle cell anemia, but a subset of AS individuals develop minor complications such as hyposthenuria (loss of ability of the kidneys to concentrate urine), splenic infarcts when exposed to hypoxic conditions or at high altitudes, and papillary necrosis.7 In addition, AS individuals are at risk for the rare occurrence of renal basal tubular carcinoma.8 The possibility thus exists that patients with sickle cell trait that suffer these complications might have gene modifiers (epistatic genes) that increase the risk for these pleiotropic phenotypic traits.

The effects of sildenafil lead to prolonged relaxation of smooth muscles in the corpora cavernosa and hence restoration of the natural erectile response to sexual stimulation. Nevertheless, the associated stagnation of blood within the corpora cavernosa results in local hypoxia, and in SS individuals the degree of deoxygenation may be sufficient to lead to erythrocytic rigidity and sickling, which can lead to priapism.9 To our knowledge, this complication has not been reported in AS individuals. The susceptibility of a patient with sickle trait to this condition might also depend on the effects of inherited modifier genes, which are yet to be identified.

Physicians should be aware of the possibility of sildenafil causing priapism in patients with sickle cell trait, although we do not know the incidence rate of this event. In the meantime, the
manufacturers should advise against the use of this drug in sickle trait individuals until more data are obtained.

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References

To the editor:

A single tube multiplex PCR method to detect the common α⁺ thalassemia alleles

Alpha thalassemias are the commonest single gene disorders in humans. Two different deletions (−α³.7 and −α⁴.2) in the α globin genes (−α) on the short arm of chromosome 16 are the most common cause of this disorder. Natural selection, by providing protection against a severe form of malaria, is believed to be responsible for elevating and maintaining high frequencies of these heritable genetic defects in various regions of the world where malaria is or has been endemic. This was recently emphasized in an incisive study that suggested that α⁺ thalassemia may have a major impact on childhood survival in coastal Papua New Guinea by providing continued protection against several infections. This very attractive hypothesis needs to be evaluated in different geographical/environmental contexts.

Accurate estimation of the frequency of α⁺ thalassemia in the population requires DNA analysis. The conventional approach has been to characterize these deletional forms of α⁺ thalassemia by Southern blot hybridization using radioactively labeled probes, a time-consuming, labor-intensive, and expensive procedure. For these reasons, its application to any large-scale screening program was extremely difficult, even though it was very useful for diagnosis of individual patients. With the advent of polymerase chain reaction (PCR)-based methods, detection of α⁺ thalassemia deletions have become relatively simple and cost-effective. PCR-based approaches, however, require multiple tube amplifications for precise characterization of the two major, −α³.7 and −α⁴.2, alleles. Although wieldy for diagnostic purposes, multi-tube testing is cumbersome for large epidemiological screening. In an effort to develop a technique suitable for population screening for α⁺ thalassemia, we have established a multiplex PCR amplification procedure carried out in a single tube for detecting −α³.7 and −α⁴.2 alleles.

In a previously described PCR-based method, selective amplification of the mutant −α³.7 and normal alleles were carried out in separate tubes with distinct primer pairs and experimental conditions. For detecting the deleted allele, oligonucleotide primers flanking the deletion were chosen, and experimental conditions were such that the normal allele did not amplify, as the priming sites are >5 kb apart. Presence of the normal allele in the same sample was confirmed in a separate PCR experiment using one of the primers selected within the sequence of the deletion. For testing the presence of the −α⁴.2 allele, a single-tube multiplex PCR with three primers was carried out in which the normal and the −α⁴.2 alleles were recognized by fragment sizes of 2.1 kb and 550 bp, respectively. Overall, three separate PCR reactions had to be carried out to diagnose the presence of two major α⁺ thalassemic determinants.

We have developed a single-tube multiplex long PCR method to detect the normal, −α³.7 and −α⁴.2, alleles using primers described earlier. This PCR was performed in 25 µL with 0.6 µmol/L primers A, B, D, and E, 350 µmol/L of each dNTP, 2.25 mmol/L MgCl₂, 7.5% DMSO, 1.75 units of Expand Long Template DNA polymerase in supplied buffer-3 (Roche GmbH, Mannheim, Germany) and 25 ng of genomic DNA in the PTC-200 thermal cycler (MJ Research, Watertown, MA). After 2 minutes of initial denaturation at 92°C, 10 cycles were performed with denaturation at 92°C for 40 seconds, annealing at 58°C for 1 minute and extension at 68°C for 6 minutes followed by 20 cycles where extension time was increased by 20 seconds after each cycle. PCR products were analyzed in 1% agarose gel in TAE buffer. The expected diagnostic fragment sizes were 1.8 kb, 2.1 kb, and 3.2 kb for −α³.7, −α⁴.2, and normal alleles.

Figure 1. Schematic representation of α₁ and α₂ genes showing position and orientation of primers. Primers A and B amplify a 1.8 kb fragment and D and E amplify a 2.1 kb fragment for −α³.7 and −α⁴.2 deletions, respectively. An amplification product of 3.2 kb for A and E primer pair indicates the presence of normal allele.