Indomethacin-Associated Sexual Dysfunction

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Indomethacin, one of the most potent inhibitors of prostaglandin synthetase, is used not only for the various arthritides but also for patent ductus arteriosus and premature labor.[1,2] Its greater potency enhances efficacy but also contributes to its side-effect profile. Gastropathy, renal insufficiency, and headaches are encountered with greater frequency in patients taking indomethacin than in those taking other nonsteroidal anti-inflammatory drugs (NSAIDs).[3–6] Impotence has not yet been reported as a side effect of this potent prostaglandin inhibitor or any of the other NSAIDs. Described herein is the first report of indomethacin-associated sexual dysfunction.

CASE REPORT

S.H. is a 60-year-old man with a long history of thoracic and lumbosacral back pain. He had no pain radiation to legs, paresthesias, weakness, or night or weather-related pain. Examination revealed decreased range of motion throughout the thoracic and lumbar spine and chest expansion of only 1 in. X-ray films of the lumbosacral spine showed evidence consistent with bilateral sacroilitis. Rheumatoid factor and histocompatibility antigens (HLA-B27) were negative, but the erythrocyte sedimentation rate (ESR) was elevated at 68% (normal 40% to 54%). The patient was given indomethacin, 75 mg sustained release once daily to be taken with food or milk. He noted decreased libido and impotence following 2 to 3 weeks of sustained-release indomethacin therapy. He discontinued the indomethacin himself and noted resolution of sexual dysfunction within 1 week. Six months later naproxen, 500 mg twice daily, was prescribed. The patient reported improvement in his back pain taking this NSAID and continued it for 1 to 2 days on occasion when symptoms flared. In follow-up the patient did not report any sexual problems despite therapy with this NSAID. He had no history of sexual dysfunction prior to indomethacin therapy. He and his wife refused subsequent challenge with indomethacin.

During the ensuing treatment of the back problem, the patient also experienced mild symptoms of benign prostatic hypertrophy and also passed a calcium oxalate-phosphate renal stone. An x-ray film of the abdomen demonstrated possible early changes of the pelvis suggestive of Paget's disease. The patient had no signs or symptoms of coronary artery disease or peptic ulcer disease. The patient's work and marital relationship remained unchanged and satisfactory throughout the period surrounding the initial diagnosis and treatment of the patient's ankylosing spondylitis. The patient fully accepted the diagnosis only after confirmation by a rheumatologist and orthopedist. He appeared to accurately report his inconsistent compliance with prescribed medications. Throughout his care, the patient was concerned about many somatic symptoms and requested thorough explanations after detailed descriptions. He has been seen in follow-up for 3½ years with no further complaints of sexual dysfunction.

DISCUSSION

Impotence, which affects 25% of the male population by the age of 65 years, may result from a variety of neurogenic, hormonal, vascular, and psychogenic causes.[7] Erection as the initial event of the excitement phase of the normal sexual response cycle is thought to be primarily under control of the parasympathomimetic system. Emission and ejaculation are mediated adrenergically by the sympathetic nervous system. Hormonal influences on the sexual response focus on testosterone and prolactin. Testosterone is necessary to maintain libido. Hyperprolactinemia reduces the responsiveness of the testes to lutenizing hormone, which is a major stimulus for testosterone secretion. Additionally, excess prolactin reduces the conversion of testosterone to dihydrotestosterone, the active metabolite. Intact vascular and central nervous system function is a prerequisite for a normal sexual response at any phase.

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Prostaglandins $F_2\alpha$, E_1, and E_2 have been found to be involved in the control of human penile tumescence and erection, thereby having an impact on the sexual response as well.[8] Administration of prostaglandin E_2 has been shown to lead to a significant rise in intracavernosal pressure (from 24.9 ± 7.9 mmHg to 68.4 ± 21.1 mmHg).[9]

Impaired sexual function as a consequence of drug therapy has been previously recognized and reviewed.[10,11] The association of reserpine, clonidine, and methyldopa with sedation and depression contribute to the ability of these drugs to induce impotence.[10] Clonidine, metoclopramide, phenothiazines, butyrophenones, and cimetidine elevate plasma prolactin levels; sexual dysfunction has been reported following their use.[10] The antiandrogen effect of estrogens, spironolactone, and cyprotenone and the anticholinergic effects of tricyclic antidepressants, disopyramide, and benztropine account for their association with impotence.[10] The sympatholytic effects of guanethidine and possibly lithium are associated with failure of ejaculation.[10] Phenoxybenzamine, thioridazine, and prazosin have α-adrenergic antagonistic properties, which are thought to be the underlying mechanism of sexual dysfunction encountered with these agents.[10] To date, prostaglandin inhibition has not been implicated as an underlying mechanism of drug-induced sexual dysfunction.

Inhibition of prostaglandin production by indomethacin appears to affect adversely the erection phase of the sexual response, as it requires prostanoid involvement. In fact, long-term diabetes has been shown to lead to diminished prostaglandin release and is felt to contribute to the development of diabetic impotence.[12] It is unknown to what extent the sustained-release formulation contributed to this patient's presentation, but prolonged exposure to prostaglandin inhibition without the benefit of windows of prostaglandin recovery between peak levels, as would be expected with a non-sustained-release product, may have been a factor. That sexual dysfunction has now first been described following indomethacin therapy is in keeping with its relative potency. Indomethacin is second only to diclofenac in its ability to inhibit prostaglandin synthetase, acting at a concentration of 1.6 μmol/L compared with 5.6 μmol/L for indomethacin and 3300 μmol/L for aspirin.[13]

While the temporal relationship between onset and resolution of sexual dysfunction symptoms seems to implicate sustained-release indomethacin, other possibilities merit consideration. Chief among these would be a temporary psychologic dysfunction in a patient with a history of somatic anxiety who was resisting the diagnosis of ankylosing spondylitis. Additionally, ankylosing spondylitis itself may have been a contributing factor. In a study enrolling 33 men with ankylosing spondylitis, four (13%) admitted to periods of impotence, while 12 (39%) had experienced decreased libido.[14] Although the number of patients enrolled is too small to ascribe statistical significance, the adverse effect on neurovascular components of the sexual response bears mentioning. A literature search failed to reveal any association between renal calculi, benign prostatic hypertrophy, or Paget's disease with impotence. Because of the strong temporal relationship in this patient, indomethacin sustained-release is the more probable cause of this patient's transient sexual dysfunction.

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