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FUNCTIONAL UROLOGY

Antifungal azoles – new antidote for chronic pelvic pain?

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Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is a poorly–defined condition or a group of conditions in which chronic pain in the genital area and pain during prostate palpation are the two most common features. Causative treatment is rarely available since in most cases the etiology in unknown. Paradoxically, long–term antibiotic therapy is recommended and often relieves symptoms despite negative cultures of urine, semen or prostate biopsy samples. Compared to placebo drugs that are used as first–line therapy, it shows the following advantages: anti–inflammatories (risk ratio 1.7, 95% CI 1.4–2.1; P <0.001), α–blockers (risk ratio 1.4, 95% CI 1.1–1.8; = 0.013), antibiotics (risk ratio 1.2, 95% CI 0.7–1.9; P = 0.527) [1]. New forms of therapy are desperately needed for men after the failure of first–line therapy. In this issue of CEJU, Dr. Ahmed F. Kotb and colleagues present their experience with fluconazole used for treating persistent CP/CPPS symptoms. Using fluconazole 2x400 mg PO, daily authors observed response rates at about 70%. This is a surprisingly good result bearing in mind that these patients failed primary treatment. To my knowledge, this is the first report in medical literature on such a form of CP/CPPS therapy. Although mepartricin, which has been found to improve symptoms for six or more points in the NIH–CPSI scale, has an antifungal effect as well, this drug does not absorb from intestines and its mechanism of action relies on the hormonal effect. Fungal etiology of CP/CPPS in otherwise healthy, immunologically non–compromised men has not been reported yet, thus these observations have to be considered with caution.

Furthermore, one may find other explanations of the positive effects of fluconazole therapy in comparison to antifungals. The placebo effect is strong in chronic conditions that can spontaneously wane or aggravate. Systematic review and meta–analysis of trials on CP/CPPS have found that placebo improves the total NIH–CPSI score on average of 2.4 points (95% CI: 1.7–3.2). A positive effect on all specific domains of the score was also reported–pain: 1.34 (95% CI: 0.88–1.79); voiding: 0.59 (95% CI: 0.33–0.84); quality of life: 0.95 (95% CI: 0.62–1.27). There was no evidence of a changing placebo effect over time [2]. For this reason, only placebo–controlled trials may prove efficacy of a specific treatment in CP/CPPS.

Chronic pain conditions coexist with increased anxiety, perceived stress, and a higher profile of global distress when compared to asymptomatic controls. Both these disturbances and chronic central sensitization by nociceptive stimuli affect hypothalamic–pituitary–adrenal (HPA) axis, causing a decrease of plasma adrenocorticotropin hormone and blunting its stress response curve. In patients with CP/CPPS, cortisol levels remain intact under stress conditions but the slope of the awakening cortisol is steeper [3]. Both ketoconazole and, to the lesser extent, fluconazole also influence this hormonal axis by inhibiting synthesis of cortisol and other steroids [4]. Hormonal effects of azoles may modulate HPA axis reversing the vicious circle of pain, stress, and hormonal dysregulation. Two drugs affecting hormonal milieu of the prostate, finasteride and mepartricin, have been proven to improve symptoms in CP/CPPS patients. Azoles may be a new hormonally–active group of agents used in this indication.

The most recent possible explanation of fluconazole efficacy in CP/CPPS comes from the Texas Health Science Center whose researchers have reported on potential analgesic effects of ketoconazole [5].This drug has been used in their experiment as a broad–spectrum cytochrome P450 (CYP) inhibitor. CYP is involved in oxidation of linoleic acid into its metabolites (OLAMs) and OLAMs are agonists of the TRPV1 ion channel involved in transmitting pain signals from inflammation or injury involving tissue. In this study it has also been found that ketoconazole possesses an unexpected antihyperalgesic effect. Treatment with ketoconazole inhibited a release of endogenous TRPV1 agonists from the inflamed tissue. However, since ketoconazole inhibits multiple oxidative enzymes including CYPs, the biochemical mechanism of action requires further evaluation. Fluconazole

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does not have the same profile of CYP inhibition, but both substances share many pharmacologic and biochemical effects. These results are complimentary to clinical effects found by urologists from Egypt. All above hypotheses of antifungal, antisteroid, and antihyperalgesic effects of azoles deserve scientific attention before this group of agents can be involved in the treatment of patients with CP/CPPS.

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