

Switching AIs Often Effective for Joint Symptoms

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Denver Bureau

SAN ANTONIO — More than half of breast cancer patients who experience joint symptoms on one nonsteroidal aromatase inhibitor don't experience them on the other, results of a randomized, prospective trial suggest.

Moreover, at least three-quarters of patients who develop joint pain and/or stiffness on the nonsteroidal aromatase in-

hibitors (AIs) anastrozole (Arimidex) or letrozole (Femara) no longer experience joint symptoms if they are switched to tamoxifen, study investigator Dr. J. Michael Dixon reported at the San Antonio Breast Cancer Symposium.

"The message is, if you get joint symptoms on one drug, try switching to something else because there's probably something out there they can tolerate," Dr. Dixon, of the University of Edinburgh, explained in an interview.

The AIs are increasingly prescribed for up to a 5-year course in lieu of tamoxifen as adjuvant hormonal therapy in women with hormone receptor-positive early invasive breast cancer because of their superior efficacy in reducing the risk of recurrence.

New-onset musculoskeletal complaints are common in patients on the AIs. They are a leading cause of poor compliance and treatment discontinuation. To better understand these important side effects, Dr. Dixon and coworkers randomly as-

signed 182 women with early invasive breast cancer to 3 months of standard dosages of either anastrozole or letrozole, followed by 3 months on the other AI. After that 6-month period, all participants were placed on tamoxifen, because 5 years of tamoxifen was the standard practice in Scotland at the time.

Patients were evaluated in detail for side effects after 1, 2, and 3 months on each drug. Twelve subjects were forced to withdraw from the study because they couldn't complete at least 1 month on both AIs because of joint symptoms.

The investigators' hypothesis was that joint symptoms and bone turnover would be worse on letrozole, since it's the more potent of the two AIs in terms of reducing circulating estrogen levels. But their hypothesis wasn't borne out.

Of the 170 patients who completed the study, 131 reported new-onset joint pain while on an AI. But there was no significant difference between the rates associated with anastrozole and letrozole. Ten women reported joint stiffness.

A total of 56% of patients who reported joint problems on letrozole didn't experience them on anastrozole. And 55% of those who had joint symptoms on anastrozole didn't have them on letrozole.

Moreover, 85% of patients with joint problems on anastrozole had no joint problems when placed on tamoxifen. The same was true for 74% of women who had joint symptoms on letrozole.

On the other hand, 74% of patients who didn't experience joint problems while on anastrozole did have them on tamoxifen, as did 57% of those who didn't have joint symptoms on letrozole.

Dr. Dixon said that trying to wait out significant joint symptoms in the hope that they will abate over time is not a winning strategy. The large clinical trials of the AIs versus tamoxifen, such as the landmark 6,241-patient ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial, clearly demonstrate that the joint symptoms don't abate with time if patients remain on the offending drug. Indeed, in ATAC the prevalence of joint symptoms climbed steadily during the 5 years of treatment with either drug. He added that, in his own experience, NSAIDs "don't help all that much" for AI-associated joint symptoms. Other physicians at the conference estimated that about half of their affected patients benefit from NSAID therapy.

With regard to AI-induced bone turnover, Dr. Dixon and coworkers found that 2.5 mg/day of letrozole and 1 mg/day of anastrozole had virtually identical effects on bone metabolism, as measured by changes in parathyroid hormone, type 1 procollagen peptides, bone-specific alkaline phosphatase, and N- and C-terminal telopeptides. Bone turnover was greater at 6 months than at 3 months. Based on these results, he concluded that there is unlikely to be any difference between the two AIs in osteoporosis or fracture rates.

The study was funded by an unrestricted research grant from Novartis.

Dr. Dixon stated that he has no financial relationships relevant to this investigation to disclose. ■

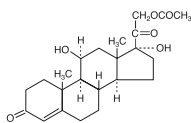
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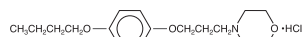
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Topical corticosteroids are anti-inflammatory and anti-pruritic agents. The structural formula, the chemical name, molecular formula and molecular weight for active ingredients are presented below.



hydrocortisone acetate
Pregn-4-ene-3,20-dione, 21-(acetoxy)-11,17-dihydroxy-, (11-beta)-
C₂₃H₃₂O₆; mol. wt. 404.50



pramoxine hydrochloride
4-(3-(p-butoxyphenoxy)propyl)morpholine
hydrochloride
C₁₇H₂₇NO₃·HCl; mol. wt. 329.87

CLINICAL PHARMACOLOGY: Topical corticosteroids share anti-inflammatory, anti-pruritic and vasoconstrictive actions.

The mechanism of anti-inflammatory activity of topical corticosteroids is unclear. Various laboratory methods, including vasoconstrictor assays, are used to compare and predict potencies and/or clinical efficacies of the topical corticosteroids. There is some evidence to suggest that a recognizable correlation exists between vasoconstrictor potency and therapeutic efficacy in man.

Pramoxine hydrochloride is a topical anesthetic agent which provides temporary relief from itching and pain. It acts by stabilizing the neuronal membrane of nerve endings with which it comes into contact.

Pharmacokinetics: The extent of percutaneous absorption of topical corticosteroids is determined by many factors including the vehicle, the integrity of the epidermal barrier, and the use of occlusive dressings.

Topical corticosteroids can be absorbed from normal intact skin. Inflammation and/or other disease processes in the skin increase percutaneous absorption. Occlusive dressings substantially increase the percutaneous absorption of topical corticosteroids. Thus, occlusive dressings may be a valuable therapeutic adjunct for treatment of resistant dermatoses. (See DOSAGE AND ADMINISTRATION.)

Once absorbed through the skin, topical corticosteroids are handled through pharmacokinetic pathways similar to systemically administered corticosteroids. Corticosteroids are bound to plasma proteins in varying degrees. Corticosteroids are metabolized primarily in the liver and are then excreted by the kidneys. Some of the topical corticosteroids and their metabolites are also excreted into the bile.

INDICATIONS AND USAGE: Topical corticosteroids are indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses.

CONTRAINDICATIONS: Topical corticosteroids are contraindicated in those patients with a history of hypersensitivity to any of the components of the preparation.

PRECAUTIONS: General: Systemic absorption of topical corticosteroids has produced reversible hypothalamic-pituitary-adrenal (HPA) axis suppression, manifestations of Cushing's syndrome, hyperglycemia, and glucosuria in some patients. Conditions which augment systemic absorption include the application of the more potent steroids, use over large surface areas, prolonged use, and the addition of occlusive dressings.

Therefore, patients receiving a large dose of a potent topical steroid applied to a large surface area and under an occlusive dressing should be evaluated periodically for evidence of HPA axis suppression by using the urinary free cortisol and ACTH stimulation tests. If HPA axis suppression is noted, an attempt should be made to withdraw the drug, to reduce the frequency of application, or to substitute a less potent steroid.

Recovery of HPA axis function is generally prompt and complete upon discontinuation of the drug. Infrequently, signs and symptoms of steroid withdrawal may occur, requiring supplemental systemic corticosteroids. Children may absorb proportionally larger amounts of topical corticosteroids and thus be more susceptible to systemic toxicity. (See Precautions-Pediatric Use.)

If irritation develops, topical corticosteroids should be discontinued and appropriate therapy instituted.

In the presence of dermatological infections, the use of an appropriate antifungal or antibacterial agent should be instituted. If a favorable response does not occur promptly the corticosteroid should be discontinued until the infection has been adequately controlled.

Information for the Patient: Patients using topical corticosteroids should receive the following information and instructions:

1. This medication is to be used as directed by the physician. It is for external use only. Avoid contact with the eyes.
2. Patients should be advised not to use this medication for any disorder other than for which it was prescribed.
3. The treated skin area should not be bandaged or otherwise covered or wrapped as to be occlusive unless directed by the physician.
4. Patients should report any signs of local adverse reactions especially under occlusive dressings.
5. Parents of pediatric patients should be advised not to use tight-fitting diapers or plastic pants on a child being treated in the diaper area, as these garments may constitute occlusive dressings.

Laboratory Tests: The following tests may be helpful in evaluating the HPA axis suppression: Urinary free cortisol test
ACTH stimulation test

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Long-term animal studies have not been performed to evaluate the carcinogenic potential or the effect on fertility of topical corticosteroids. Studies to determine mutagenicity with prednisolone and hydrocortisone have revealed negative results.

Pregnancy: Teratogenic Effects: Pregnancy Category C: Corticosteroids are generally teratogenic in laboratory animals when administered systemically at relatively low dosage levels. The more potent corticosteroids have been shown to be teratogenic after dermal application in laboratory animals. There are no adequate and well-controlled studies in pregnant women on teratogenic effects from topically applied corticosteroids. Therefore, topical corticosteroids should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Drugs of this class should not be used extensively on pregnant patients, in large amounts, or for prolonged periods of time.

Nursing Mothers: It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable amounts in breast milk.

Systemically administered corticosteroids are secreted into breast milk in quantities NOT likely to have a deleterious effect on the infant. Nevertheless, caution should be exercised when topical corticosteroids are administered to a nursing woman.

Pediatric Use: Pediatric patients may demonstrate greater susceptibility to topical corticosteroid induced HPA axis suppression and Cushing's syndrome than mature patients because of a larger skin surface area to body weight ratio.

Hypothalamic-pituitary-adrenal (HPA) axis suppression, Cushing's syndrome, and intracranial hypertension have been reported in children receiving topical corticosteroids. Manifestations of adrenal suppression in children include linear growth retardation, delayed weight gain, low plasma cortisol levels, and absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilledema.

Administration of topical corticosteroids to children should be limited to the least amount compatible with an effective therapeutic regimen. Chronic corticosteroid therapy may interfere with the growth and development of children.

ADVERSE REACTIONS: The following local adverse reactions are reported infrequently with topical corticosteroids, but may occur more frequently with the use of occlusive dressings. These reactions are listed in an approximate decreasing order of occurrence:

Burning	Hypertrichosis	Maceration of the skin
Itching	Acneiform eruptions	Secondary infection
Irritation	Hypopigmentation	Skin atrophy
Dryness	Perioral dermatitis	Striae
Folliculitis	Allergic contact dermatitis	Miliaria

OVERDOSAGE: Topically applied corticosteroids can be absorbed in sufficient amounts to produce systemic effects. (See PRECAUTIONS.)

DOSAGE AND ADMINISTRATION: Topical corticosteroids are generally applied to the affected area as a thin film three to four times daily depending on the severity of the condition. Occlusive dressings may be used for the management of psoriasis or recalcitrant conditions. If an infection develops, the use of occlusive dressings should be discontinued and appropriate antimicrobial therapy instituted.

HOW SUPPLIED:

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