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Gynecomastia with Ketoconazole

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Three of forty men developed bilateral gynecomastia upon ketoconazole treatment. Symptoms abated despite continued therapy. This appears to be a direct drug effect on breast tissue.

Ketoconazole (Janssen Pharmaceuticals, Inc.) is an orally absorbed antifungal agent currently under investigation in humans for a variety of superficial and systemic mycoses, including coccidioidomycosis (1). Little toxicity from this agent has been detected (4). We have noted gynecomastia and breast tenderness in three of our male patients who, with their informed consent, were being treated with ketoconazole for disseminated coccidioidomycosis. One of them was receiving no medication other than ketoconazole. Endocrinological evaluation was normal in two patients.

Patient 1. A 35-year-old (95-kg) black male was treated with ketoconazole (200 mg/day) for the recent onset of facial cutaneous coccidioidomycosis. Within 2 weeks, the patient began to notice left chest wall tenderness; after 1 month, bilateral gynecomastia was detectable. The patient was taking no other medications.

Patient 2. A 51-year-old (56-kg) black male had been treated with ketoconazole in doses up to 600 mg/day for meningeal and cutaneous coccidioidomycosis since April 1979. A relapse of his meningitis occurred in February 1980. Ketoconazole was discontinued, and intrathecal miconazole was instituted. After 3.5 months, oral ketoconazole was reinstituted at a dose of 1,200 mg/day. Within 3 weeks of institution of the higher dose, the patient noticed painful swelling of both breasts. Phenytoin (Dilantin), acetaminophen, codeine, and docusate sodium (Colace) were the only other medications the patient was taking.

Patient 3. An 87-year-old (80-kg) white male developed coccidioidal lesions on the upper lip and preauricular skin. He was treated with 200 mg of ketoconazole per day for this condition. Six weeks later, he noted bilateral pain and tenderness in his pectoral area, and examination disclosed gynecomastia. The patient had been taking spironolactone, digitalis, and furosemide (Lasix) for many years because of congestive heart failure. He had had one self-limited episode of breast tenderness 6 years previously.

In our first two patients, no causal factors other than ketoconazole could be identified. Testicular exam, routine liver function studies, and radioimmunoassay hormone levels in serum (prolactin, luteinizing hormone, estradiol, chorionic gonadotropin, and testosterone) were normal. The third patient was an elderly male with chronic congestive heart failure treated for several years with spironolactone and digitalis. His bilirubin was slightly increased. Furthermore, luteinizing hormone was markedly increased, and testosterone was depressed, consistent with age-related testicular dysfunction. Any of these conditions or medications might have contributed to his breast enlargement (2, 3, 5, 6, 8-10). However, the temporal association with the start of ketoconazole treatment suggests that this drug also may have played a role. Two of the three patients developed gynecomastia within weeks of institution of low doses of ketoconazole (200 mg/day). Our second patient developed symptoms 3 weeks after ketoconazole was restarted at a higher dose. If higher doses are used more commonly in the future, gynecomastia may become a more frequent side effect. Gynecomastia has not been reported with other imidazoles such as miconazole, which has been used more extensively in the treatment of fungal infections.

In at least two of our patients, ketoconazole neither suppressed androgenic nor stimulated estrogenic hormone production, two potential mechanisms of drug-induced gynecomastia (5-7, 10). These findings raise the possibility that ketoconazole may have a direct effect on tissue receptors. However, we were unable to demonstrate either interference or potentiation of estrogen binding. Ketoconazole over a range of 10^{-9} M to 5×10^{-5} M did not displace [^{3}H]-estradiol from cytosolic receptors in either rabbit or human endometrial tissue (studies performed

by David Grasso).

Ketoconazole at doses up to 400 mg/day has appeared relatively free of untoward side effects (4). Of 40 male patients whom we have treated with ketoconazole, 3 have developed gynecomastia. These 40 patients had received anywhere from 11 days to 28 months of treatment at doses ranging from 200 to 1,200 mg/day (only two patients received doses higher than 400 mg/day). The finding of gynecomastia associated with ketoconazole in two additional patients in various trials involving several hundred male patients has been reported by other investigators to the drug manufacturer. Although the overall incidence of gynecomastia is uncertain, our experience suggests it may be more common than previously recognized. Even so, this side effect may not seriously limit the use of this oral antifungal agent in the treatment of systemic mycoses. In our three patients, medication was continued despite toxicity because of the seriousness of the underlying disease. In all three patients, the breast pain abated after several weeks, although gynecomastia has persisted.

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LITERATURE CITED

1. **Brass, C., J. N. Galgiani, S. C. Campbell, and D. A. Stevens.** 1980. Therapy of coccidioidomycosis with ketaconazole. Rev. Infect. Dis. **2**:656–660.
2. **Clark, E.** 1965. Spironolactone therapy and gynecomastia. J. Am. Med. Assoc. **193**:157–158.
3. **Gordon, G. G., J. Olivo, F. Rafei, and A. L. Southren.** 1975. Conversion of androgens to estrogens in cirrhosis of the liver. J. Clin. Endocrinol. Metab. **40**:1018–1026.
4. **Graybill, J. R., and D. J. Drutz.** 1980. Ketoconazole: a major innovation for treatment of fungal disease. Ann. Intern. Med. **93**:921–923.
5. **Lewinn, E. B.** 1953. Gynecomastia during digitalis therapy. N. Engl. J. Med. **248**:316–320.
6. **Loviaut, D. L., R. Menard, A. Taylor, J. C. Peta, and R. Sankin.** 1976. Spironolactone and endocrine dysfunction. Ann. Intern. Med. **85**:630–636.
7. **Novab, A., C. F. Kass, and J. S. LaDue.** 1965. Estrogen like activity of digitalis. J. Am. Med. Assoc. **194**:30–32.
8. **Olivo, J., G. G. Gorden, F. Rofei, and A. L. Southren.** 1975. Estrogen metabolism in hyperthyroidism and in cirrhosis of the liver. Steroids **26**:47–56.
9. **Williams, M. J.** 1963. Gynecomastia: its incidence, recognition and host characterization in 447 autopsy cases. Am. J. Med. **34**:103–112.
10. **Wolfe, C. J.** 1975. Gynecomastia following digitalis administration. J. Fla. Med. Assoc. **62**:54–55.