

family history of mental disorders in comprehensive care.

References

1. Jakimow-Venulet B: Hereditary factors in the pathogenesis of affective illness. *Br J Psychiatry* 138:450, 1981
2. Schulsinger H: A ten-year followup of children of schizophrenic mothers. Clinical assessment. *Acta Psychiatr Scand* 53:371, 1976
3. Wheeler EO, White PD, Reid EW, et al: Familial inci-

dence of neurocirculatory asthenia (anxiety neurosis, effort syndrome). *J Clin Invest* 27:562, 1948

4. Hoaken PCS, Schnurr R: Genetic factors in obsessive-compulsive neurosis? A case of discordant monozygotic twins. *Can J Psychiatry* 25:167, 1980

5. McKnew DH, Cytryn L, Efron AM, et al: Offspring of patients with affective disorders. *Br J Psychiatry* 134:148, 1978

6. Conners CK, Himmelhock J, Goyette CH, et al: Children of parents with affective illness. *J Am Acad Child Psychiatry* 14:600, 1979

7. Nielsen AC III, Williams TA: Depression in ambulatory medical patients. Prevalence by self-report questionnaire and recognition by nonpsychiatric physicians. *Arch Gen Psychiatry* 37:999, 1980

Gynecomastia Associated With Theophylline

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Gynecomastia is not rare; it is reported to occur in 60 to 70 percent of normal boys during puberty and 30 percent of asymptomatic adult men, with increasing frequency as men become older. Carlson's recent review¹ of the subject also lists many other pathological mechanisms that may cause gynecomastia (hypogonadism, neoplasms, refeeding after starvation, cirrhosis, hyperthyroidism, breast cancer). The condition may also be induced by various drugs.

When drug related, gynecomastia usually develops suddenly after the initiation of therapy and often abates when the drug is discontinued. This

report will describe a patient who developed gynecomastia while taking a drug not previously known to cause this problem—theophylline.

Case Report

A 61-year-old man with asthma of many years' duration was given theophylline (Theo-Dur) for the first time in 200-mg time-release tablets, which were taken every 8 to 12 hours. Pharmacy records indicate that the prescription for 100 tablets was refilled about once a month for six months.

The patient developed unilateral gynecomastia one to two months after starting therapy. He was continued on the drug for four months, as the theophylline was not considered to cause the gyn-

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ecomastia. Before and during this time the patient continued to take other medications, a combination of phenylpropanolamine and caramiphen edisylate (Tuss-Ornade) and hydrochlorothiazide, that he had used for many years. He also had been given an albuterol inhaler a few months before the theophylline. Other causes were sought (tests for human chorionic gonadotrophin and prolactin yielded normal results), but no abnormalities were detected.

As a trial only the theophylline was stopped. Within one month the gynecomastia lessened and finally disappeared. The theophylline was not restarted, and the patient continued to use all the other drugs without interruption.

The gynecomastia remained unilateral while it was present. There was no lymphadenopathy or any other abnormal finding on physical examination.

Discussion

Theophylline is a methylxanthine closely related to caffeine and theobromine.² These compounds are consumed by many cultures in such beverages as coffee (caffeine), tea (theophylline and caffeine), and cocoa (caffeine and theobromine). Prominent physiologic effects of these compounds include central nervous system stimulation, increase in heart rate, relaxation of bronchial smooth muscle, decrease in peripheral vascular resistance, diuresis, and increase in certain endocrine and exocrine secretions.

There is no clearly discernible mechanism whereby theophylline might induce gynecomastia. Van Dellen³ in 1979 described the studies of Peracchi, which demonstrated effects of theophylline on growth hormone. No studies have shown effects on gonadotrophins or primary sex hormones. It is of interest, however, that a recent publication⁴ has suggested a relationship between excessive coffee intake and painful fibrocystic breast disease in women. Perhaps a similar mechanism is the basis for the gynecomastia in this patient and the observations of these women.

The patient described above was questioned carefully to determine whether other exogenous sources might have caused the gynecomastia. A recent report⁵ describes gynecomastia in a young boy caused by estrogen-containing hair cream. No

such cause could be identified in this case.

The manufacturer of the theophylline product was contacted to find out whether the preparation might contain a contaminant or co-factor that could be the cause. The other ingredients of Theo-Dur (cellulose acetate phthalate, cetyl alcohol, diethyl phthalate, glyceryl monostearate, hydroxypropyl methylcellulose, lactose, magnesium stearate, myristyl alcohol, corn starch, sucrose, white beeswax) (according to D.E. Magnuson, Technical Affairs, Key Pharmaceuticals, letter, June 11, 1982) are not known to cause gynecomastia.

Although the patient was using other medication at the same time, these medications had been used for months or years previously without causing gynecomastia. Further, the patient has continued to use these medications even after the gynecomastia has disappeared. There may be some obscure interaction among some or all of these drugs to cause the gynecomastia, but the mechanism is not at all clear.

Summary

A 61-year-old male patient developed gynecomastia after starting theophylline. The gynecomastia regressed when the theophylline was discontinued. No other endogenous or exogenous cause for the gynecomastia could be found except for the theophylline.

References

1. Carlson HJ: Current concepts: Gynecomastia. *N Engl J Med* 303:795, 1979
2. Rall TW: Central nervous system stimulants (the xanthines). In Gilman AG, Goodman LS (eds): *The Pharmacological Basis of Therapeutics*, ed 6. New York, Macmillan, 1980, pp 592-607
3. Van Dellen RG: Theophylline, practical application of new knowledge. *Mayo Clin Proc* 54:733, 1979
4. Minton JP, Foecking MK, Webster DJT, Matthews RH: Response of fibrocystic disease to caffeine withdrawal and correlation of cyclic nucleotides with breast disease. *Am J Obstet Gynecol* 135:157, 1979
5. Edidin DV, Levitsky LL: Prepubertal gynecomastia associated with estrogen-containing hair cream. *Am J Dis Child* 136:587, 1982