

Ketoconazole in the Management of Precocious Puberty Not Responsive to GnRH-Analogue Therapy

Precocious puberty is characterized by the intermittent pulsatile secretion of luteinizing hormone (LH) that reflects the episodic release of gonadotropin-releasing factor (GnRH or LHRH) from the hypothalamus. The pharmacologic principle employed therapeutically is that continuous infusion of GnRH (or the daily administration of a long-acting analogue) leads to subsensitivity (down regulation) of GnRH receptors on the gonadotrophs, thus annulling the release of the gonadotropins. Although most children with precocious sexual development will have the normal pubertal process turned on early (idiopathic precocious puberty), some boys have what appears to be autonomous Leydig cell function with low basal and GnRH-stimulated gonadotropin output (so-called testotoxicosis, or a form of gonadotropin-independent precocious

sexual development). These youngsters would not be expected to respond to long-acting GnRH-analogue therapy.

The authors treated three such boys with the antifungal preparation ketoconazole. All had failed to respond to GnRH-analogue therapy. Ketoconazole treatment (200 mg every 12 hours) was started at least one month after discontinuation of the GnRH-analogue therapy. Within 24 hours, the testosterone concentrations fell significantly (less than 20 ng/dl in two of the three subjects). Measurement of 17-hydroxyprogesterone concentrations revealed an inverse relationship to testosterone concentration. There were no significant changes in the low urinary levels of gonadotropins. Basal cortisol concentrations were unchanged, but the peak response to adrenocorticotrophic hormone (ACTH) was blunted. The testicular response to

human chorionic gonadotropin (hCG) was also unchanged following ketoconazole treatment. Striking improvements in behavior were noted within the first 48 hours of therapy, with disappearance of erections and masturbatory activity.

With increasing dosages of ketoconazole, the behavioral gains were sustained and the testosterone concentrations remained low. The height velocity was significantly diminished from 15 cm/yr to 6 cm/yr.

Holland FJ, et al: *N Eng J Med* 1985; 312:1023-1028.

Editor's comment—Most commonly, isosexual precocious development is due to central precocious puberty—that is, the normal pubertal mechanisms are activated too early. The efficacy of GnRH stimulatory analogue (agonist) therapy has been well documented. However, it is ineffective in patients with gonadotropin-independent sexual precocity. Ketoconazole was chosen because data suggest that this agent may interfere with testosterone biosynthesis through relatively selective effects on the C17-20 lyase step in steroid hydroxylation.

These preliminary data, which show reductions in height velocity and in the rate of bone maturation, are promising for boys with gonadotropin-independent sexual precocity. Although ketoconazole therapy ought to be effective in idiopathic precocious puberty, it would appear that GnRH-analogue therapy is preferable—there is low toxicity and, by now, a good deal of experience. Although none of the boys exhibited hepatic toxicity to ketoconazole, treatment of adults with this hepatically metabolized agent has been associated with abnormalities in liver enzyme levels. Thus, for the rare disorder of testotoxicosis, and possibly for other forms of gonadotropin-independent sexual precocity, ketoconazole is logical and effective therapy. Because of the drug's potential hepatotoxicity and possible adrenal toxicity, patients being treated with it require intensive follow-up.

Infants With Birth Weights Less Than 1,001 g: Survival, Growth, and Development

At the University of North Carolina, 56 infants who weighed 1 kg or less and who were born in 1980 were cared for in the Newborn Intensive Care Unit. A surprising 52% survived the first year. Most of those who did not survive died during the first seven days.

Twenty-five infants were measured between birth and 16 months of age. Catch-up growth was apparent in many, but even when the growth plots were adjusted for age, 11 of 25 were below the fifth percentile for weight (four of the 11 were believed to be small-for-gestational-age infants). The heights appeared to be comparable to weights. Small head circumference at 12 to 16 months was closely related to low weight. Six of the 11 infants had chronic respiratory failure and five did not.

Development remains guarded, but optimism is reflected in the data. Twelve of 15 infants tested for hearing and language were found to be normal. Nineteen, including three of four survivors with birth weights less than 801 g, were free of neuro-

developmental difficulties, as defined in the study. They had physical and mental development indices of 86 or greater for their adjusted ages, and only two had permanent visual impairment. Four infants were mildly handicapped, and four were moderately to severely handicapped. A correlation between head circumference and a developmental handicap was apparent when the infants were tested at 12 to 16 months. The authors readily admit that the follow-up was short and that some children now classified as normal will probably be handicapped in the future, since learning disabilities cannot be predicted at this early age. Moreover, hearing deficits, now unrecognized, may subsequently become apparent.

Kraybill EN, Kennedy CA, Teplin SW, et al: *AJDC* 1984;138:837.

Editor's comment—There is indeed reason for optimism. This group of patients and similar groups must be studied for an extended time. The editorial board will review this topic in further detail in future issues of this publication.