Luteinising hormone-releasing hormone nasal spray as therapy for undescended testicle


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SUMMARY Twenty-two prepubertal children with unilateral cryptorchidism were treated. None had undergone previous medical or surgical treatment to modify the abnormal position of the testes, all of which were located in the inguinal canal. Treatment was with luteinising hormone-releasing hormone (LH-RH) nasal spray given for 7 days. 9 boys insufflated 100 µg LH-RH in each nostril 6 times per 24 hours (1200 µg/24 h); the remaining 13 boys insufflated 500 µg 12-hourly (1000 µg/24 h). An LH-RH test (50 µg IV) was carried out before and after therapy. Full descent of the testis into the scrotum was obtained in 7 out of the 22 cases; in a further 6 cases the testis moved down the inguinal canal.

Basal values of luteinising hormone and follicle-stimulating hormone and those for pituitary reserve remained unchanged before and after therapy, and were similar to the values of a control group. No correlation was found between response to therapy and bone age, testosterone level in serum, basal values or pituitary reserve of luteinising hormone or follicle-stimulating hormone.

Luteinising hormone-releasing hormone (LH-RH) therapy in the adult male affected by secondary hypogonadism is known to be effective (Isidori et al., 1974; Mortimer et al., 1974a, b). This releasing hormone, given by nasal spray, was also successfully used in the treatment of adult hypogonadotrophic hypogonadism (Isidori et al., 1974) and cryptorchidism in prepubertal boys (Happ et al., 1975). Since cryptorchidism is sometimes associated with gonadotrophin deficiency (Job et al., 1974; Koch and Rahlff, 1975; Hadziselimovic et al., 1976), we have studied the therapeutic effectiveness of LH-RH in relation to the pituitary reserve of gonadotrophins.

Materials and methods

Twenty-two boys with unilateral undescended testicle, aged from 5 to 11½ years, were treated. Bone age ranged from 4 years 10 months to 11 years 4 months and the difference between chronological and bone age never exceeded 6 months. All fell into the prepubertal stage of sexual development, the first stage of Tanner's (1962) classification. None had received previous medical or surgical treatment for testicular maldescent. In all cases the undescended testes were located in the inguinal canal, apparently along the normal descent way; none had retractile testes.

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With permission from the parents, an LH-RH test (50 µg IV) was performed (Cacciari et al., 1976) and treatment with LH-RH nasal spray (Hoechst AG) begun on the next day according to the following schedule. Therapy was given to 9 boys (group A) (mean bone age 7 years 4 months) who insufflated, according to the method of Happ et al., 100 µg to each nostril at 7, 8, 12 am, and 1, 7, 8 pm, a daily intake of 1200 µg LH-RH. 13 boys (group B) (mean bone age 7 years 8 months) received 500 µg of the releasing hormone at 8 am (200 µg into the right nostril and 300 µg into the left nostril) and at 8 pm (300 µg into the right nostril and 200 µg into the left nostril, a daily intake of 1000µg). LH-RH was given for 7 days, and the day after completing therapy an LH-RH test was repeated.

The pituitary reserve of gonadotrophins was studied by evaluating the peak, the maximum increase, and the area of the curve (Cacciari et al., 1975). Plasma testosterone was recorded before the start of treatment. After the course of LH-RH, those boys whose testes had failed to descend (partially or completely) were given treatment with human chorionic gonadotrophin (HCG) consisting of a weekly injection of 1000 U HCG for 6 weeks.

Bone age was evaluated by the Greulich and Pyle tables (1959). Plasma testosterone was measured by the radioimmunoassay method of Collins et al.
Table  Peak, maximum increase, and area of the LH and FSH curves (mean ± SEM) in the LH-RH test in 22 unilateral cryptorchid oys before and after LH-RH nasal spray therapy given in two dosage schemes (see text)

<table>
<thead>
<tr>
<th></th>
<th>LH (mIU/ml)</th>
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<th>FSH (mIU/ml)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Basal value</td>
<td>Maximum increase</td>
<td>Area of curve</td>
<td>Basal value</td>
<td>Maximum increase</td>
<td>Area of curve</td>
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<tr>
<td></td>
<td>Before</td>
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<tr>
<td>Normal boys (n = 29)</td>
<td>1.81±0.15</td>
<td>4.37±0.52</td>
<td>2.56±0.51</td>
<td>20.64±2.28</td>
<td>2.13±0.22</td>
<td>6.33±0.56</td>
</tr>
<tr>
<td>Cryptorchid boys (n = 22)</td>
<td>1.98±0.39</td>
<td>4.97±0.71</td>
<td>3.03±2.15</td>
<td>20.86±1.95</td>
<td>2.78±0.58</td>
<td>7.37±5.84</td>
</tr>
<tr>
<td>LH-RH dosage A (n = 9)</td>
<td>1.43±0.49</td>
<td>5.20±0.65</td>
<td>3.67±4.11</td>
<td>19.30±2.03</td>
<td>2.74±0.33</td>
<td>7.00±5.83</td>
</tr>
<tr>
<td>LH-RH dosage B (n = 13)</td>
<td>2.32±0.32</td>
<td>4.82±4.64</td>
<td>2.58±1.39</td>
<td>21.82±1.97</td>
<td>2.80±0.68</td>
<td>6.55±5.85</td>
</tr>
</tbody>
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LH = luteinising hormone; FSH = follicle-stimulating hormone.
(1972) the antiserum being obtained from rabbits pretreated with an antitubercular vaccine, as previously described (Cacciari et al., 1974). Serum gonadotrophins were measured by the double antibody radioimmunoassay method of Reuter et al. (1973).

For statistical analysis Student’s t test was used. In order to study correlations between bone age, basal testosterone, pituitary reserve, and response to therapy, the patients were classified as follows: (1) no response (the position of the testis did not alter); (2) partial response (definite movement down the inguinal canal); and (3) full descent of the testis into the scrotum.

Results from LH-RH tests carried out on 29 short normal boys served as controls.

Results

Treatment of the 22 cases resulted in 7 (32%) achieving descent of the testis into the scrotum. Of these, 2 (22%) were on dosage scheme A, and 5 (39%) on scheme B. In 6 cases (27%), 3 from each dosage group, the effect on the testicular position was partial. In the remaining 9 cases (41%) there was no effect on the testicular position. No difference in the clinical response of the two dosage schemes was observed.

The basal values for luteinising hormone (LH) and follicle-stimulating hormone (FSH) and the pituitary LH and FSH reserve in the 22 cases did not alter after therapy (Table), and did not differ from those of the control group. No correlation was found between the response to treatment and bone age, basal plasma testosterone level, basal values of LH and FSH, or pituitary reserve of LH and FSH.

Of the 15 boys treated with HCG after LH-RH treatment, one (belonging to the group which had partially responded to LH-RH) achieved complete descent of the testis.

Discussion

The use of LH-RH nasal spray therapy in cryptorchidism seems capable of producing good results in a short time. The percentage of positive results (32%) that we obtained at the end of a week’s treatment was higher than that reported by Happ et al. (1975) with a treatment schedule similar to our group A. Those authors continued the therapy for several weeks and obtained a good result in 71% of cases. Conventional therapy with HCG has given positive results varying from 20 to 90% (Bader, 1971). So great a variability cannot be due only to the differences in treatment, but must imply that different criteria are used in evaluating cryptorchidism and in differentiating true cryptorchidism from retractile or ectopic testis. We think that we can exclude those cases where the testes were retractile, since the testis could not be brought down into the scrotum despite repeated examinations. On the other hand, we cannot be certain that there was no case of ectopic testis as it is well known how difficult it is to differentiate this.

Our results suggest that the hormone need be administered in only two injections per 24 hours, and that the effectiveness of therapy is independent of age. We found no correlation between response to therapy and bone age or basal testosterone level.

The rationale for treating cryptorchidism with LH-RH nasal spray was the efficacy of such treatment for secondary hypogonadism in the adult (Isidori et al., 1974), and the finding of an LH deficit in a certain number of cryptorchid patients (Koch and Rahlf, 1975; Hadziselimovic et al., 1976; Werder et al., 1976). We therefore expected to find that the response to this form of therapy would correlate with gonadotrophin basal levels and/or gonadotrophin pituitary reserve; and further that this therapy would result in an increase in pituitary reserve and tonic secretion of LH and FSH. However, the response to therapy in our cases did not correlate with the gonadotrophin status either before or after therapy, while the hormone studies carried out before and after the course of therapy failed to show any modification in gonadotrophin secretion as a result of the therapy. We conclude therefore that the efficacy of releasing hormone treatment does not depend on the correction of gross abnormalities of gonadotrophin secretion. It is sufficient to induce repeated small and diminishing stimuli to obtain good therapeutic results in cryptorchidism. The best results were obtained in cases where the undescended testicle was located near the external inguinal ring. No side effects were observed during or after LH-RH nasal spray treatment.

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References

during the insulin induced hypoglycemia test in the normal and obese child, *Journal of Clinical Endocrinology and Metabolism, 40*, 802–806.


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