

**SHARED CARE PROTOCOL
for the use of
GnRH AGONISTS
in
CENTRAL PRECOCIOUS PUBERTY
(CPP)**

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British Society for Paediatric Endocrinology & Diabetes
(BSPED)
May 2004**

**SHARED CARE PROTOCOL FOR GONADOTROPHIN RELEASING-HORMONE
(GnRH) ANALOGUE THERAPY**

Central precocious puberty (CPP) is a form of premature sexual maturation, with the early appearance of secondary sexual characteristics -

In girls - Breast development before 8 years of age.

Menarche before 9 years of age

In boys - Genital development (including testicular enlargement) before 9 years of age.

These are definitions based on established normal ranges.

- In girls the diagnostic age limit for breast development (Tanner Stage B2) corresponds to -2.5 to -3.0 SD from the mean, and for menarche -4 SD.
- In boys the limit of Tanner Stage G2 corresponds to approximately -2.5 SD.

There has, however, been a secular trend downwards in the age of puberty, and it has now been suggested that the cut-off age of precocious puberty for girls should be reduced to 7 years (and 6 years in those of Afro-Caribbean origin).

Other features of precocious puberty are:

- Development of pubic and axillary hair.
- Tall stature, especially in relation to parental heights.
- Rapid growth rate.
- Advanced skeletal maturation (assessed using bone age).

Important points

- CPP is due to premature activation of the hypothalamo-pituitary axis, and consequently not only the pattern, but also the consonance of puberty in CPP is the same as that seen in normal puberty.

- CPP almost certainly represents a spectrum of disease from a normal variant to rapidly progressive disease.

The estimated incidence is 1 in 5,000 to 10,000.

CAUSES OF CPP:

Idiopathic: Sporadic, familial

Organic

Hypothalamic hamartoma

CNS tumours: Astrocytoma, craniopharyngioma, ependymoma, glioma, pinealoma

CNS malformations: Arachnoid cyst, supracellar cyst, phakomatosis, hydrocephalus, septo optic dysplasia.

Acquired disease: CNS infections, CNS abscess, radiation, chemotherapy, trauma

Other: Adoption from abroad, abuse.

Overall, 90% of affected patients are female.

Idiopathic CPP occurs in only 30% of males, but in up to 80% of females.

There is overlap in the clinical and biochemical features of idiopathic and organic CPP. As a result it is currently recommended that all patients with CPP have MRI scanning of the brain (including pituitary and hypothalamus). Occult intra-cranial tumours are found in 4.8-13.3% of girls and 19.2% of boys with CPP.

HISTORY:

Age at presentation, growth, progression and development of pubertal & other features.

FAMILY HISTORY:

Heights, ages at puberty of parents

EXAMINATION:

Height, weight, pubertal staging, other features suggestive of underlying disease.

INVESTIGATIONS:

HORMONES:

LH/FSH (during iv. GnRH test),

Oestradiol, testosterone.

RADIOLOGY:

Bone Age

Pelvic Ultrasound (in girls)

MRI scan of head (including pituitary & hypothalamus).

Problems arising from CPP

- Social and psychological problems of tall stature, early development (and menarche).
- Loss of final height.

The aims of treatment are, therefore, to hold pubertal development in an emotionally immature child.

Indications for therapy

- a) True precocious puberty due to premature activation of the hypothalamic-pituitary-gonadal axis.
- b) Where puberty needs to be delayed in order to maximise growth potential eg. growth hormone deficient children following cranial irradiation, congenital adrenal hyperplasia.

Gonadotrophin releasing-hormone analogues

These are used in paediatric practice for the suppression of precocious puberty. There are four preparations currently available;

1. Buserelin.
2. Leuprorelin.
3. Triptorelin.
4. Buserelin.

The first is given by intranasal administration (in.), the remaining three by injection (im. or sc.)

Buserelin (Suprefact): Shire Pharmaceuticals

This is administered by nasal spray, and absorption is variable. The dosage depends on response, judged by repeated tests of LH and FSH suppression. The usual dose is 1 spray into each nostril 6 times daily. As compliance is often poor for 4 hourly therapy, and consequently breakthrough is much more common, many would reserve this therapy for patients who cannot tolerate the other preparations, but require treatment.

Cost of 100µg/metered spray; 4 x 10-g bottle with spray pump = £87.68.

Injectable GnRH agonists

Drug	<u>Leuprorelin</u>	<u>Goserelin</u>	<u>Triptorelin *</u>
Name	Prostap	Zoladex	Gonapeptyl
Manufacturer	Wyeth	AstraZeneca	Ferring
Preparation	Microsphere suspension	Depot pellet	Microsphere suspension
Licensed in CPP	No	No	Yes
Injection Site & Route	Abdomen – sc. Buttock, thigh – im.	Abdomen, buttock - Sc.	Abdomen – sc. Buttock, thigh – im.
3-4 weekly	Yes	Yes	Yes
10-12 weekly	Yes	Yes	No
Cost:	£125.40	£122.37	£105.95
Long-acting	£376.20	£366.81	n/a
Needle bore (gauge)	23g (sc.) 21g (im.)	16g. (3.6mg) 14g. (10.8mg)	22g (sc.) 21g (im.)

* Also available in unlicensed preparation (Decapeptyl, Ipsen) cost £105.05 for 4.2mg.

- Leuprorelin and goserelin are both available in 3-4 weekly preparations and also 10-12 weekly long-acting preparations.
- Only one preparation (triptorelin, Gonapeptyl, Ferring) is currently licensed in CPP.
- As Prostap and Gonapeptyl are microsphere suspensions, smaller doses can be administered in very young children (eg. <20kg). The sc. rather than im. route is preferable in all children with these preparations, as this is less painful.
- Local anaesthetic cream &/or local anaesthetic is usually required with goserelin.

Mode of action of GnRH agonists

All of these drugs are synthetic analogues of naturally occurring gonadotrophin releasing hormone (GnRH) which possess greater potency than the natural hormone, binding to the GnRH receptor. As a result there is an initial period of stimulation, which is usually blocked using the anti-androgen cyproterone acetate, given (usually) for the first six weeks of therapy at a dose of 70mg/m²/day.

Chronic administration results in an inhibition of gonadotrophin production and subsequent suppression of ovarian and testicular steroid production. These effects are reversible on discontinuation of therapy.

Assessment of response to therapy

Development of 2^o sexual characteristics, uterine/ovarian size, growth rate & bone maturation should be monitored clinically, sonographically & radiologically.

- The best single test is probably GnRH stimulation.
- Basal serum testosterone levels may be useful in boys, but conversely oestradiol appears not to be as useful in girls.

GnRH analogue side-effects

- Local irritation: at the injection site with sc. or im. analogues (the injection site should be varied periodically), or nasal irritation with buserelin.
- As a result of suppression of the gonadal axis eg. hot flushes, and mood swings.
- Hypersensitivity: rashes, pruritus, asthma & rarely anaphylaxis.
- Others: headache, visual disturbance, dizziness, arthralgia/myalgia, hair loss, peripheral oedema, GI disturbances, weight gain, sleep disorders.

Referral criteria

- a) Children with precocious puberty should be referred to a hospital specialist with expertise in their assessment.
- b) Children should not be placed on GnRH analogue therapy before specialist evaluation has been completed.
- c) Once the diagnostic criteria for CPP amenable to GnRH analogue therapy have been satisfied, consultant and GP should agree a strategy for shared care appropriate for each child.
- d) The consultant will recommend commencing a GnRH analogue at an appropriate dose, and will provide the GP with a full report justifying GnRH analogue therapy.

Guidelines for shared care strategy

- a) When initially commenced on a GnRH analogue, a child with precocious puberty will require more frequent hospital supervision to ensure an adequate response.
- b) Once stabilised, a child with precocious puberty with no other medical problems does not require frequent hospital supervision and may remain the primary responsibility of the GP.

Shared care protocol for GnRH analogues in central precocious puberty

- c) A minority of candidates for GnRH analogue therapy have, or continue to have complex health disorders requiring specialist management, eg. following cranial irradiation. GP and specialist must discuss each case in order to agree a treatment and shared care strategy.

GP responsibilities

- a) Providing family with advice on the need for investigation of the child's precocious puberty.
- b) Prescribing the GnRH analogue when this is part of a shared care agreement.
- c) Arranging that someone from the practice will be available to administer the second and subsequent injections.
- d) Reporting adverse effects of therapy to specialist or deputy.
- e) Liaising with endocrine specialist to agree long-term therapy based on predicted benefit.

Endocrine specialist responsibilities

- a) Arranging for the first injection to be given by the endocrine clinic specialist nurse.
- b) Reviewing patient's pubertal development, growth and response to treatment at 3 to 6 monthly intervals. Monitoring will include height and weight measurements, pubertal staging, bone age assessment at approximately 12 monthly intervals, and hormone measurements as indicated.
- c) Advising GP as to continued justification for GnRH analogue therapy.
- d) Reviewing associated drug therapy.
- e) Auditing patient's response to GnRH analogue therapy compared to nationally agreed criteria.

Duration of therapy

Once started, treatment is generally continued until an age when puberty can be allowed to recommence. This will vary with each child, but will tend to be at around 10 -11 years of age.

Shared care protocol for GnRH analogues in central precocious puberty

In terms of height, with GnRH agonist therapy:

- Final height is increased in treated patients compared to pre-treatment, and also untreated patients.
- GnRH agonist treatment does not improve FH in girls beyond 8 years of age.
- Results are not as good in boys as girls.

However

- 75% of patients reach their genetic target height range.
- 40% reach their individual target height range.
- More than 90% of females have a final height > 150cm.

Complete reversibility of hypothalamo-pituitary-gonadal axis has been demonstrated after discontinuation of therapy. Fertility & pregnancy outcome are unaffected in women (although an increase in polycystic ovarian syndrome (PCOS) has been described in some).

Spermatogenesis is unaffected in men

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