Committee on Drugs

Treatment of Congenital Hypothyroidism

State and regional programs have been instituted in the United States and Canada for the screening of newborn infants for congenital hypothyroidism, and this topic was the subject of a recent report by the Committee on Genetics.1 The incidence of this disorder—averaged in several large series—is approximately 1 per 5,000 live births; therefore, these screening procedures represent a major advance in preventive medicine. Based on 3,160,000 live births in the United States in 1974, approximately 600 new cases of congenital hypothyroidism will be diagnosed each year through these screening programs and by recognition of affected infants by individual practitioners. These screening procedures result in earlier recognition of the disorder and thus a younger age at diagnosis; there also is increased knowledge about thyroid hormone homeostasis in the fetus and newborn infant. Therefore, it is appropriate to review dosage recommendations for treatment of infants with congenital hypothyroidism. In general, these recommendations are applicable to infants and young children with hypothyroidism regardless of the cause.

Neonatal Physiology

Production of thyroid hormones by the fetus begins by midgestation. Because of limited transplacental transfer, fetal development is almost entirely dependent on endogenous production. The thyroid gland secretes thyroxine (T₄) and triiodothyronine (T₃). Most of the circulating T₃ is formed by peripheral monodeiodination of T₄, although marked thyroid-stimulating hormone (TSH) stimulation also increases the levels of circulating T₃. A recent major advance is the recognition that the fetus preferentially forms the metabolically inactive reverse T₃ (rT₃) from T₄. At present, T₃ appears to be the biologically active thyroid hormone at the cellular level, and T₄ may be a circulating prohormone. For example, athyrotic adults treated with T₃ have T₃ levels similar to those in normal adults.²

There is a dramatic surge of TSH immediately after birth, and the blood levels of both T₃ and T₄ are elevated well above those in normal adults. Later during the first week of life, serum rT₃ begins to fall toward the lower levels characteristic of healthy children and adults.³ Because of these dynamic changes within a few days after birth, values for serum levels of thyroid hormones obtained in newborn infants must be compared to the normal range for the postnatal age at which they were obtained.³⁵

Conversion of T₄ to T₃ in peripheral tissues is decreased when the patient has malnutrition postoperatively and in a variety of disease states. Serum levels of T₃, fall and rT₃, may rise. Thus, small-for-gestational-age or ill neonates may have changes in thyroid hormone levels which may be confusing. Such alterations may provide an important metabolic regulatory mechanism for the neonate, and there may be situations in which it is not clear whether a deviation from average is pathologic or physiologic.

Diagnosis

Screening tests use filter paper impregnated with a drop of blood obtained by heel stick, frequently obtained when phenylketonuria screening is performed. A radioimmunoassay procedure is used to determine total T₄ level; a TSH determination is made on low or borderline samples. Although initial studies appeared promising, screening of cord blood specimens for rT₃ is not practical because about 12% of the normal population would require retesting.⁴ Venous or capillary specimens for confirming tests are requested when the values fall below a defined limit, and confirmation usually consists of determinations of TSH level and a repeated T₃ measurement. Physicians caring for newborn infants should become familiar with the procedures recommended in their locale. Where no general screening program is in effect, physicians may elect to use commercial laboratories, some of which perform daily assays of T₃ on filter paper specimens (with TSH on borderline-low specimens) for a nominal cost (as little as $3). The laboratory selected should be able to perform
reliable assays with rapid reporting of deviant values.

Mailing of specimens and processing by central laboratories require several days to a week or two, and treatment need not be delayed pending the results of confirmative tests. Normal adult standards for T, must not be used to evaluate neonatal thyroid function. To do so may lead to failure to diagnose the condition with disastrous effects on prognosis.

Clinical examination remains an important aspect of diagnosis and follow-up. This is particularly true because it has yet to be demonstrated from prolonged experience with large-scale screening programs that false-negatives will not occur. Complaints suggestive of hypothyroidism in neonates include such common, though usually innocent, symptoms as persistence of mild jaundice, skin mottling, constipation, slow feeding, and hoarse cry. Paradoxically, some infants have had diarrhea. These findings should prompt a complete physical examination without delay. Telephone management alone is not adequate.

Physical signs—present in approximately one-half the infants with hypothyroidism—include lethargy, hypothermia, feeding problems, failure to gain weight, respiratory problems, a large anterior and posterior fontanel, dry skin, thick tongue, hoarse cry, and umbilical hernia. If a goiter is present, it is diagnostic of thyroid disease, unless the mother has been treated with an antithyroid drug or iodides.

Definitive diagnostic studies are indicated in infants with suggestive historical and/or physical findings, and in whom early diagnostic efforts do not rule out hypothyroidism, whether or not the infant has been part of a screening program.

Infants with an ectopic thyroid gland, such as a lingual thyroid, may have adequate or borderline thyroid function for months or even years; therefore, a normal T, level in the neonatal period should not be considered absolute evidence against congenital abnormalities of the thyroid.

Laboratory Examinations

Infants with absent or inadequate thyroid function characteristically have a low T, level and an extremely elevated TSH level. Because there may be some overlap in T, values between normal and mildly hypothyroid infants, the finding of an elevated TSH level is more sensitive and reliable. Knee and ankle films for bone age may be helpful. The distal femoral epiphysis is not ossified in full-term infants with hypothyroidism. A technetium Tc 99m scan may reveal the absence of thyroid tissue, and it is preferable to the use of iodine 131 for this purpose because the radiation dose is lower.

A diagnostic error can be made in the infant with hypothyroidism caused by pituitary insufficiency or hypothalamic dysfunction. The TSH level, which is elevated in primary hypothyroidism, will be reported as normal in these infants. Deficiencies of other pituitary hormones, if they are documented, will aid in the diagnosis.

Further diagnostic dilemmas include infants who may have a low T, level because of prematurity, hypoproteinemia, deficiencies in thyroid binding globulin, or illness from nonendocrine causes. The results of thyroid function tests frequently are confusing. When interpretation is difficult, the disease should be managed in consultation with a physician experienced in the diagnosis and treatment of thyroid disease in infants.

Initiation of Treatment

If the initial history and physical examination are suggestive, blood should be drawn for definitive thyroid studies (to include at least a determination of T, and TSH levels) and treatment begun promptly. When congenital hypothyroidism is suspected on clinical grounds, diagnostic efforts and treatment generally should not be withheld until the results of screening tests are received. Prompt treatment improves the prognosis for later mental development. There is no known risk in initiating appropriate replacement therapy; therefore, it seems safer to err on the side of beginning treatment, which can be discontinued if necessary when the results of thyroid function tests are available. If screening tests are abnormal, the physician should obtain blood for definitive tests and begin therapy while waiting for confirmation.

If a firm diagnosis cannot be made on the basis of the laboratory findings but there is a strong clinical suspicion of congenital hypothyroidism, a conservative approach would be to ensure euthyroidism with replacement therapy until 1 or 2 years of age. At this age, medication can be stopped and definitive diagnostic studies can be carried out; this treatment plan avoids the potential risk of the infant incurring serious, permanent brain damage.

Choice of Replacement Agent

A number of thyroid hormone preparations are commercially available. These include desiccated thyroid U.S.P., desiccated thyroid standardized by bioassay, thyroglobulin (Proloid), synthetic levothyroxine sodium (Synthroid, Letter), syn-
dose may be 0.025 mg/day. The dose for starting and in infants at risk for cardiac failure, the patient is unable to take oral medication, 1, may premature infants weighing less than 2,000 gm infants, 0.0375 mg is an appropriate dose. In full-term, newborn infants. For most of these growth or during brief periods of noncompliance. Further examinations should be performed at least at 6 and 12 months of age and yearly thereafter. Length should be plotted at each visit, and total T level (and/or TSH level) should be measured when necessary to monitor compliance and assist in making dosage adjustments. Bone age may also be helpful in assessment.

**Dose Adjustment**

The doses of T recommended for infants and children by some standard sources are excessive. Before learning that T is formed outside the thyroid gland by monodeiodination of T, it was thought that, when T, alone was given, higher levels were needed to provide an adequate hormone effect. This is now known to be fallacious, and the use of older dose tables for synthet-
ic T$_{3}$ may result in iatrogenic hyperthyroidism. Recent work$^{10,11}$ has established appropriate doses for children more than 1 year old.

Normal growth is the best indicator of adequate treatment. A T$_{4}$ dose of 0.05 mg is generally adequate throughout the first year of life. After this, the dose should be increased to 0.003 to 0.005 mg/kg/day$^{10,11}$ until the adult dose of about 0.15 mg is reached in early or midadolescence. Most adolescents and adults are euthyroid while receiving 0.15 mg in a single daily dose.$^{12}$ The definitive criterion of dose appropriateness is clinical euthyroidism; an occasional patient will require an unusual dose ranging from 0.1 to 0.3 mg/day. Although the laboratory values are helpful, they cannot be substituted for clinical judgment. Occasionally a patient will be seen who is clinically hyperthyroid or hypothyroid even though the serum total T$_{4}$ level is normal, as statistically defined. The dose for these patients should be adjusted on clinical grounds, or additional testing may be indicated.

Overtreatment is to be avoided. In the past, excessive doses have been recommended with the rationale that a slight underdose is harmful but a slightly excessive dose is not. The occurrence of minimal brain damage in children with thyrotoxicosis during infancy$^{13}$ suggests that this assumption is probably fallacious. Further complications of excessive treatment are acceleration of bone age and premature craniosynostosis.

**Drug Interactions**

In both children$^{14}$ and adults,$^{15}$ hyperthyroidism accelerates and hypothyroidism slows drug metabolism. The magnitude of this effect usually is unknown, but it may be substantial. The possibility of drug toxicity at standard doses in hypothyroid patients and diminished drug effect in hyperthyroid patients must be kept in mind. Phenobarbital increases the clearance of thyroid hormones, and other enzyme inducers may have a similar effect. The dose of thyroid hormone may require adjustment when anticonvulsant therapy is initiated, adjusted, or discontinued. A number of drugs (e.g., heparin, phenytoin, and sex steroids) alter binding of T$_{4}$ to thyroid-binding globulin and other serum proteins. If the patient is under treatment with these drugs or has an abnormality of plasma protein levels, the total T$_{4}$ measurement may be misleading. Some, but not all, clinicians find the free T$_{4}$ measurement to be helpful in these patients. Final reliance may have to be placed on clinical judgment, which is aided by measurements of growth and bone age.

**Conclusions**

Screening for neonatal hypothyroidism represents an important advance in preventive medicine. The treatment of congenital hypothyroidism is effective, inexpensive, and not difficult for physician, parent, or patient. The likelihood of disability is always reduced and may be prevented.

**Recommendations**

The Committee on Drugs recommends the following:

1. Physicians caring for children should participate in state, regional, or provincial screening programs for hypothyroidism and should maintain a high level of clinical suspicion to assure the earliest possible diagnosis of congenital hypothyroidism.

2. Levothyroxine in a usual starting dose of 0.025 to 0.05 mg/day should be used for treatment.

3. Dose adjustments should be made on the basis of patient response, particularly growth and development, and by measurements of serum T$_{4}$ level, bone age, and/or other appropriate laboratory determinations.

4. Consideration should be given to interactions with other drugs and disease states so appropriate dose adjustments will be made.

**Committee on Drugs**

Sydney Segal, M.D., Chairman; Sanford N. Cohen, M.D.; John Freeman, M.D.; Reba M. Hill, M.D.; Benjamin M. Kagan, M.D.; Ralph E. Kauffman, M.D.; Albert W. Pruitt, M.D.; Lester F. Soyka, M.D.; Stanley M. Vickers, M.D.

**Consultants:**

John D. Crawford, M.D.; Jean H. Dussault, M.D., M.Sc.; A. B. Hayles, M.D.; Geoffrey P. Redmond, M.D.

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There are increasing reports of serious side effects in children with clinical use of imipramine in high doses. Our analysis of the EKG effects of imipramine in 25 hyperactive and 8 school phobic children suggests that children on a dose of imipramine of 3.5 mg/kg or more are likely to show an increase in PR interval of .02 seconds or more and that such increases are more likely to occur in patients with a small pretreatment PR interval. In 7 children the PR interval prolongation was above the rate-corrected norm. EKG monitoring seems desirable in children maintained on imipramine dose of 3.5 mg/kg or more. J Am Acad Child Psychiatry 17:60, 1978.
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Pediatrics 1978;62;413

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