

# Optimisation of thyroxine dose in congenital hypothyroidism

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## Optimum initial dosage remains unclear

The introduction of the screening programme for congenital hypothyroidism in the late 1970s and early 1980s has been rightly hailed as a major success in the prevention of neurological handicap. With a prevalence of between 1/3000 and 1/5000 live births, congenital hypothyroidism is by far the commonest metabolic disorder leading to neurological handicap; given the inexpensive nature of assays for thyroid stimulating hormone (TSH) and thyroxine treatment, its cost effectiveness must be beyond doubt. The improvement in outcome from intervention with thyroxine at an earlier stage than was hitherto possible, meant that for the majority of children treated with severe congenital hypothyroidism a near normal intelligence quotient (IQ) might be expected. Early reports tended to confirm this view, although a long term perspective suggests that there remain significant areas of cognitive deficit, particularly in visuospatial tasks, attention, and to a certain extent memory.<sup>1-3</sup>

In addressing some of these issues several groups have suggested that early diagnosis combined with high thyroxine dosing can reverse this deficit and normalise IQ.

### OUTCOMES OF CURRENT INTERVENTION

Neonatal screening and early replacement therapy with thyroxine has transformed the outlook for moderately affected (presenting total serum thyroxine concentrations greater than 40 nmol/l or presenting free thyroxine concentration greater than 5.5 pmol/l) individuals, normalising IQ at 5 and 10 years of age. Severely affected infants (presenting thyroxine less than 40 nmol/l), approximately 50% of the total, still develop a significant IQ deficit of approximately 10 points and may need special education.<sup>4,5</sup> This may be related to hypothyroidism in utero, but several studies using higher doses of thyroxine in infancy in an uncontrolled manner have suggested that the effects of severe congenital hypothyroidism could be mitigated.<sup>6,7</sup>

There are a number of problems associated with this approach. These largely

relate to developmental outcomes reported with different starting doses of thyroxine and inclusion of a wide range of disease severity. Furthermore, there are no reports of randomised controlled trials addressing these issues, which makes it difficult to dissect the balance between benefit and potential problems. Our group has recently conducted a systematic review of the literature, which highlights the problems associated with the interpretation of the dosing studies.<sup>8</sup> Of the 1271 papers identified, 14 met the search criteria based on statement of starting dose and assessment of development. In four comparative studies,<sup>5,9-12</sup> (560 patients) there was no consistent effect of starting dose of thyroxine; one study suggested higher doses led to more behavioural problems at a later age.<sup>12</sup> The variability in the classification of the disease severity, lack of adjustment for socioeconomic group and parental IQ, and doses actually used made meta-analysis difficult. This is in addition to more general problems, such as confounding secular trends in IQ score,<sup>13</sup> differential loss to follow up, the type of children refusing to participate, and how the assessment instruments were administered. The overall conclusion from this systematic review was suggestive and supportive of the concept that timing and dose may have a role in cognitive development, but the results of studies conducted to date are inconsistent and could not be considered conclusive.

Furthermore, none of the studies have addressed higher order skills; normalisation of IQ may not be the only goal and may distract attention from identifying more specific learning difficulties. In addition, consideration needs to be given not only to the potential benefits of higher dosing schedule but also to potential long term adverse effects. From the North American series there is a suggestion in the assessment at 7 years of age that the improvement in IQ was bought at the expense of poor attention, poor memory, and deterioration in social behaviour. If this were to be the case then the savings made in the educational sector from normalisation of IQ may not be realised if expenditure is required to address these needs. Other issues in thy-

roxine dosing need to be addressed, such as the longer term effect of using high doses of thyroxine on bone mineral density.

The optimal initial thyroxine dose for children with severe congenital hypothyroidism remains, therefore, unclear. In the UK the dosing schedule has ranged from about 6 µg/kg/day up to the currently used schedule of about 8–9 µg/kg/day, which is not too different from that used in Canada. The high dosing schedules take the dose up to 12–15 µg/kg/day. There has been a suggestion that by using these higher doses the serum thyroxine concentration is normalised quicker (eight days),<sup>14</sup> although the evidence that this has any effect on intellectual outcome is poor. An alternative approach suggested is to combine thyroxine replacement with the more biologically active form triiodothyronine. Such an approach has been advocated for the management of adults with acquired hypothyroidism.<sup>15</sup> This approach has support from the point of view of effects of triiodothyronine on peripheral tissues, but it has to be remembered that as far as the brain is concerned it is the deiodination of thyroxine within the neurones to triiodothyronine that is required. Simply giving triiodothyronine would not assist this process, as access to the target tissue—in this case the brain—would not be improved.

### MONITORING OF THERAPY

Monitoring the replacement of thyroxine requires careful assessment of anthropometric measures (height and weight), and regular measurements of serum free thyroxine, free triiodothyronine, and TSH concentrations. These measures need to be made fairly frequently during the first six months of life, not only because growth and change in body size is at its most rapid, but also because this is a critical time period for ongoing dendritic formation and neurological development. A suggested regimen is for samples to be taken at fortnightly intervals for the first month of life, monthly for the next three months, six weekly until 6 months, and three monthly thereafter to 1 year of age. At that point the follow up regimen can be relaxed to perhaps six monthly visits.

While anthropometric aims are clear (normal height and weight gain), it is difficult to be sure what should be the main aim of biochemical monitoring. There are two possibilities. The first is to maintain a serum free thyroxine concentration in the upper half of the normal range and not to worry too much about what happens to the circulating serum TSH concentration. A number of studies show that serum TSH concentrations in patients with congenital hypothyroidism do not behave in

the same manner that we would expect with acquired hypothyroidism. A gradual decline of serum TSH concentrations, even in the face of normalisation of the circulating serum free thyroxine concentrations, can often be encountered in patients with congenital hypothyroidism. Serum TSH concentrations within the normal range can be observed by 6 months of age, but persistent elevations in about 10% of those treated can be noted up to 3 years of age.<sup>16</sup> The response to this could be to give more thyroxine; the danger is over treating the individual, which may in itself have deleterious effects on overall development. The second approach to the problem is to move to rapid normalisation of serum TSH concentrations on the basis that they reflect what the neurones are being exposed to with respect to ambient thyroxine concentration. This assumes that the dose-response curves of hypothalamopituitary and neuronal tissues are similar, which may not be the case.

This elevation of serum TSH concentrations, with serum free thyroxine concentrations within the normal range<sup>16-18</sup> has been attributed to suboptimal therapy or a reset thyroxine feedback mechanism.<sup>18, 19</sup> In patients with acquired hypothyroidism who are on thyroxine therapy and have normal serum concentrations of free thyroxine yet raised TSH concentrations, the question of compliance with therapy is always raised. The situation may not be the same, however, in congenital hypothyroidism because of the altered feedback. Evidence to support the latter is: augmented prolactin responses to exogenous thyrotrophin releasing hormone (TRH)<sup>20</sup>; the need for large doses of exogenous thyroxine to block the TSH response to TRH in adults with treated congenital hypothyroidism<sup>21</sup>; and the permanent resetting of thyroxine feedback in rodents who were transiently hypothyroid in the neonatal period.<sup>22</sup> However, the situation is likely to be even more complex as the mechanisms involved in setpoint maturation involve hypothalamic TRH secretion, pituitary TRH receptors, thyrotroph triiodothyronine nuclear receptors and cofactors, thyrotroph monodeiodinase activity, and TSH biosynthetic and secretory mechanisms

#### FACTORS INFLUENCING THYROXINE BIOAVAILABILITY

A number of factors have been identified which influence thyroxine bioavailability (see table 1). Given the serious nature of the condition and the fact that administration of medication is in the hands of a parent, the question of compliance with therapy is perhaps less of an issue than it might be in later years. The actual bioavailability of thyroxine following oral administration is approximately

**Table 1** Bioavailability of thyroxine

Thyroxine formulation
Severity of hypothyroidism
Maturity of hepatic glucuronidation
Metabolic clearance rate
Infant formulas
Iron supplements

81%. One of the simplest ways in which this can be altered is in terms of the type of thyroxine used. Thyroxine is not dispensed as a solution, but is often made up by crushing tablets and suspending them for administration. The danger of this approach is that unless adequate mixing of the suspension takes place, it is quite likely that the individual will be under dosed for part of the time and then overdosed. Given the limited range of thyroxine tablets currently available in the UK, this approach is understandable but not sustainable. Tablet sizes are 25, 50, and 100 µg, so intermediate doses of 12.5 µg increments are achievable and often sufficient from the clinical standpoint. Hepatic glucuronidation may well influence handling of thyroxine in the first few weeks of life, particularly in the congenital hypothyroid child who is born premature. Infant formulas, especially those that contain soya products, may influence thyroxine bioavailability. In the 1950s and 1960s, soya milk products were associated with alterations in thyroxine metabolism.<sup>23</sup> Major changes to the formulation took place during the 1960s, so that hypothyroidism associated with ingestion of these products effectively disappeared. However, it is possible that in patients that are heavily dependent on soya based feeds and who are receiving a fixed exogenous dose of thyroxine, problems may be encountered as a result of alterations in thyroxine bioavailability (less thyroxine via the enterohepatic circulation and altered thyroid binding globulin concentrations).<sup>24</sup> Hence careful attention needs to be paid to the diet in these individuals, and an increase in thyroxine dosing may be necessary to compensate for these changes.

#### CONCLUSIONS

The optimal initial thyroxine dose for infants with congenital hypothyroidism remains unclear. The question of whether high dose replacement therapy is more effective than standard dose in reversing the IQ deficit in patients with severe congenital hypothyroidism, without detrimental effects on behaviour, poor attention, poor memory, and deterioration in social behaviour remains unanswered. If IQ were to be improved by an increased dose at the expense of poor attention,

poor memory, and a deterioration in social behaviour, the need for special schooling might not be lessened. These issues cannot be resolved by retrospective analysis nor by some of the studies that are currently proposed, because none address the issue of higher order cognitive skills. The detailed evaluation and neuropsychological development programmes now available allow a thorough assessment of these skills; the executive functions of the prefrontal cortex can be assessed. More precise information on the effect of dose might be obtained from individual patient data meta-analysis of the available cohort data. Alternatively, it would seem more sensible, given the equipoise that exists within the paediatric community within the UK, to consider the possibility of conducting a prospective double blind randomised controlled study to assess the issues of benefits and safety which will allow definitive statements to be made.

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## STAMPS IN PAEDIATRICS.....

### Children's Day

The 14 November is celebrated in India as Children's Day, in memory of Pandit Jawaharlal Nehru's birthday. Nehru (1889–1964) was the first prime minister of Independent India and was called "chacha Nehru" by children because of his love and affection for them.

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