Tests for growth hormone secretion

Str,—We were interested in the correspondence between Dr Addy and Professor Brook and Dr Hindmarsh on detecting organic illness through assessment of height velocity.1 2 The question, however, is academic and their arguments theoretical, since as we have recently shown, the assessment of height velocity in individuals is so imprecise as to be clinically meaningless. There is effectively no correlation between successive velocities, so that a single month velocity cannot possibly identify anyone.3 4

The Wessex Growth Study provides a practical demonstration of the problem. Thirty (17%) of the original cohort of 174 school entrants below the third height centile had identifiable organic disease. Eighteen of these were monitored over a period of three years alongside a cohort of 78 short 'normal' children in whom all pathology had been excluded. The height velocity of four of the short 'normal' children and two of those with organic disease was deemed to be on or below the third centile for velocity after the first year. Over the next 12 months, two of the short 'normal' subjects, and three of those with organic disease, were growing at a rate below the third centile, but the identity of the 'poor growers' changed from year one to year two.

We should abandon the notion that low 12 month velocities will effectively identify pathology. The children in the Wessex Growth Study with organic causes of short stature were identified at the beginning of year one on the basis of height screening alone.

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Mr Bailey and Ms Voss comment: Professor Healy is right to stress that velocity could, in some cases, be a useful discriminator in a screening context, but in our paper we were concerned mainly with the estimation of height velocities, and we showed that the imprecision attached to these estimations can be considerable. Unfortunately, disease-specific growth charts are rare and more are needed. In the case of Turner's syndrome such a chart is available and the mean velocity is shown to be lower than normal.1 2 If one were to screen for the disease by identifying all girls with a velocity less than the 3rd centile on the normal velocity chart, between the ages of 5–6 years, this would locate about 25% of girls with Turner's syndrome. On the other hand, screening for those below the 3rd centile for height, using the normal height chart at age 5 years, would pick out over 50% of these girls. (Actually, screening by height and then by velocity would be even better as girls with Turner's syndrome are on average shorter than normal and they also fall further behind with increasing age. As Professor Healy points out, however, the extra information gained may not be worth the delay involved.)

The problem of choosing an appropriate method of screening is further demonstrated by our letter in this issue regarding the comments of Dr Addy.5 In this, we describe how children in the Wessex Growth Study with pathology could not be distinguished from healthy children by their velocity over a single 12 month period. Certainly much work is yet to be done, and data collected on a variety of organic diseases, before it is possible to evaluate rival screening methodologies.

Terbutaline powder in asthma exacerbations

Str,—Inhaled β2 agonists are the most efficient means of relieving acute bronchoconstriction in asthmatic children. However, inhalation technique with a metered dose inhaler is often unsatisfactory particularly in young dyspnoeic children. Spacers have been shown to be useful in this setting.1 2 Asthmatic children may be reluctant to carry spacers during daily activities because they are cumbersome. The Turbuhaler (Astra, Turbuhaler in the UK) is a new multidose breath actuated pure powder inhaler available for the administration of terbutaline. It can be triggered by an airflow of 22 l/min, this is reached by almost all children over 5 years old in a stable condition and even by those with moderately acute asthma.3 Terbutaline given with a Turbuhaler is effective in the treatment of exercise induced asthma.4 It has not been reported yet if terbutaline with Turbuhaler is effective in children with acute asthma.

Twenty two children attending the hospital with acute wheeze were included in an open, randomized, parallel study comparing the efficacy of 0·5 mg of terbutaline given either with a Turbuhaler or with a metered dose inhaler attached to Nebulhaler (Astra). Administration of the drug was carefully supervised and consisted of one inhalation by the Turbuhaler or two consecutive puffs of terbutaline introduced separately by the Nebulhaler at one minute intervals as previously described.5 6 Before, 15 and 30 minutes after treatment we measured specific airway resistance (sRaw in cm H2O/l/s, body plethysmograph 2800, Physiosystem), forced expiratory

Results in efficacy of the two systems after inhaling 500 μg of terbutaline. Results are mean (SD)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Nebulhaler</th>
<th>Turbuhaler</th>
</tr>
</thead>
<tbody>
<tr>
<td>sRaw (cm H2O/l/s):</td>
<td>Initial</td>
<td>14±1 (3–5)</td>
</tr>
<tr>
<td></td>
<td>15 Minutes</td>
<td>7±4 (2–0)</td>
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<tr>
<td></td>
<td>30 Minutes</td>
<td>6±5 (1–7)</td>
</tr>
<tr>
<td>FEV1 (ml):</td>
<td>Initial</td>
<td>1200 (290)</td>
</tr>
<tr>
<td></td>
<td>15 Minutes</td>
<td>1530 (840)</td>
</tr>
<tr>
<td></td>
<td>30 Minutes</td>
<td>1560 (600)</td>
</tr>
<tr>
<td>PEF (l/min):</td>
<td>Initial</td>
<td>184 (47)</td>
</tr>
<tr>
<td></td>
<td>15 Minutes</td>
<td>214 (56)</td>
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<tr>
<td></td>
<td>30 Minutes</td>
<td>233 (54)</td>
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</tbody>
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volume in one second (FEVbrid, in ml, Pulmotron, Physiosystem), peak expiratory flow rate (PEFR in f/min, mini Wright), heart rate (pulses/min). Results as mean (SD) were compared by analysis of variance. The Neubhalar group (11 in each) did not significantly differ in age (Neubhalar: 8.5 years, range 4.5–13 and Turbuhaler: 10 years, range 6–14). There was no difference between the baselines for these variables. Results in efficacy are presented in the table. Both treatments were effective at 15 minutes to improve lung function compared with baseline (p<0.01 for all variables) with little further improvement at 30 minutes. No difference between treatments could be demonstrated at any time for these variables.

No cardiovascular effect was observed in the Neubhalar group. In the Turbuhaler group, a slight increase in heart rate (median: 80 to 86 pulses/min) was observed.

In conclusion, inhalation of terbutaline via Turbuhaler gave similar increase in lung function as a metered dose inhaler plus Nebulizer in children above the age of 5 years with moderately acute exacerbation of asthma. The Turbuhaler is easy to use and to carry and can be recommended for paediatric use.

References

Evaluation of a pen injector system for growth hormone treatment

Str.—We agree with many of the comments of Gluckman and Cutfield about convenience and compliance using a pen injector system (0.5 unit increments up to a maximum of 4.0 units per injection) and the important role of a nurse educator. The authors have demonstrated that if convenient doses of growth hormone using a pen injection system are administered, such as 2 or 4 units (which by serendipity fit the 0.5 unit increments and divide into 16 with no residual) then indeed this pen system is accurate and efficient. However, the authors have convincingly argued that traditional fixed dose regimens of 4 units three times a week are abused and that the dose of growth hormone should be related to the patient’s size. If the dose schedule of growth hormone is related to either weight or surface area, then usually the resulting dose will not be convenient using this pen injection system, which may lead to wastage of growth hormone at the end of the cartridge or to the inappropriate injections of 3.5 units, what happens to the 2 units remaining in the cartridge vial? Dosage for small children may prove difficult, because of 0.5 units per increment dose selection. For example, a child of 0.6 m² treated with a physiological replacement regimen of 15 units/m²/week as a daily injection, will necessitate large steps in dose schedule. The difference between 1.0 and 1.5 units per injection is the equivalent of dosages of 11.5 and 17.5 units/m²/week respectively, which makes an accurate dose impossible for the administrator. Of course, there remains the possibility of having varying doses on different days of the week, but this would probably be counterproductive for both convenience and compliance. Although the optimum dose regimen for children in the patient group is not yet determined, it is important to use such a pen system for growth hormone administered during the pubertal growth spurt is unknown, many authors have recommended an increase in dose. The limitation of this pen system to a maximum of 4 units per injection makes a daily regimen of 20 or 30 units/m²/week difficult to achieve in pubertal children. In a similar fashion, pharmacological doses of growth hormone using such a pen system for girls with Turner’s syndrome will have severe limitations: because of the restriction of maximum dose, a schedule of 30 units/m²/week will restrict the use of the pen system to a child of less than 0.93 m² surface area.

We agree that pen injection systems are a considerable advance in convenience to patients. However, if optimum treatment regimens are prescribed, these should not be introduced in a system with inflexible dose selection which may be detrimental to accurate dose schedules and potentially wasteful of expensive resources.

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Dr Cutfield and Professor Gluckman comment: Sister Hamill and Dr Stanhope hope to have misinterpreted the major theme of our paper. We addressed patient perception and satisfaction of growth hormone delivery systems, not growth hormone treatment. Publications to date have largely ignored patients’ perception of growth hormone delivery. As the primary goal of growth hormone treatment is to promote greater psychosocial wellbeing, achieved in part by attempting to increase adult height, it is essential to consider patient acceptance of the method of treatment. In our study most children and their families prefer a pen to a syringe delivery system. Children self-administered at an earlier age with the pen than with the syringe, we presume these are real differences perceived by the patients. If the prime motive of treatment was large steps in dose psychosocial wellbeing, then use of the injector pen, despite a minor compromise in dose regimen, must be considered by the physician in the choice of treatment modality.

If there is a real advantage to the extreme accuracy of the regimens proposed by Hamill and Stanhope, hopefully pharmaceutical companies will take part in funding vials giving varying growth hormone concentrations to allow more precise titration of dose using pens or other easy use administration devices.

Day case ligation of patent ductus arteriosus in preterm infants

Str.—I read with interest about the brave new world of day case ligation of patent ductus arteriosus (PDA) in preterm infants and was relieved to learn that infants were not discharged home on the day of surgery. The authors are to be commended on developing a safe and efficient service but are not justified in concluding in their abstract that ‘if it is carried out early [ligation of PDA] will reduce the time before extubation and discharge from the intensive care unit’. They present no control data to support this conclusion. Indeed they refer in their discussion to a multicentre comparative study which showed no significant difference in mortality, duration of respiratory support, and number of days in hospital between infants receiving medical or surgical treatment.

My own experience (also uncontrolled) over the last 10 years in a neonatal intensive care unit serving approximately 5 500 births a year is that surgical ligation of PDA in preterm infants is very rarely necessary, only one infant having been operated on in the neonatal period. During this time we carried out 92 infants of birth weight ≤1500 g of which 173 had birth weight ≤1000 g. Our survival rates compare favourably with the other four large perinatal region centres and long-term follow-up (beyond 14 days) is now rarely needed.

Fluid restriction, early use of indomethacin, effective treatment of underlying lung disease including dexamethasone, and above all patience will allow the preterm infant’s duct to close in all but exceptional cases. I am very worried at the apparent early resort to surgery which many appear to adopt.

It is essential to show an operation is safe and readily available, it must also be shown to be necessary.

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Dr Satur and Dickinson comment: As cardiologists and cardiac surgeons at a supraregional centre for paediatric cardiac surgery we see a highly selected group of patients with a patent arterial duct, namely those referred by paediatricians specifically for ligation of the duct because the measures suggested by Dr Dodd had either failed or were considered inappropriate. Our conclusions at the end of the paper relate only to this group of patients. We have shown that if a paediatrician feels that active surgical management of the duct is necessary he or she should not delay in referring the case, because of the hazards of transportation and operation. However we would agree entirely with the statement that the operation must be shown to be necessary. Because of the small size of our patients we cannot address the wider issues relating to the management of the patent arterial duct in the neonatal unit. We
Terbutaline powder in asthma exacerbations.

P Rufin, M R Benoist, J De Blic, G Braunstein and P Scheinmann

Arch Dis Child 1991 66: 1465-1466
doi: 10.1136/adc.66.12.1465-c

Updated information and services can be found at:
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