Management of congenital adrenal hyperplasia

Urinary steroid estimations—review of their value

C. C. BAILEY, G. M. KOMROWER, AND M. PALMER

From the Royal Manchester Children's Hospital, Pendlebury, and Christie Hospital and Holt Radium Institute, Manchester

SUMMARY A retrospective study was made of 16 children with 21-hydroxylase-deficient congenital adrenal hyperplasia of the salt-losing variety, who were treated with fludrocortisone and prednisone and were in good health during the period under review. The height velocity of the children was subnormal, height achievement was poor, and their bone ages retarded. Urinary 17-oxosteroid and pregnanetriol excretion were used to monitor the therapy of the children and these data have been related to growth velocities. In spite of urinary steroid figures in excess of those published as desirable for monitoring therapy, the children failed to grow properly, probably as a result of glucocorticoid overdosage. Published urinary steroid criteria are considered too strict and in order to achieve them one would need to give unnecessarily high doses of steroid. Regular measurement of height velocity and skeletal maturation rate are better indicators of therapeutic control and should lead to more satisfactory growth and ultimate height.

Children with congenital adrenal hyperplasia have been studied by various authors and in general have been shown to be of short stature (Bergstrand, 1966; Laron and Pertzelan, 1968; Rappaport *et al.*, 1968; Stempfel *et al.*, 1968; Sperling *et al.*, 1971; Bailey and Komrower, 1974; Brook *et al.*, 1974). This may be caused either by premature closure of the epiphyses with advanced skeletal maturation in those coming to diagnosis late, or by the growth-retarding effects of steroid therapy (Raiti and Newns, 1970; Bailey and Komrower, 1974).

It has been stated that the optimal dosage of steroid for pituitary suppression and steroid replacement should be between 15 and 40 mg hydrocortisone/m² per day up to the age of 8 years, thereafter increasing to 75 mg/m² per day at puberty (Migeon, 1968; Sperling *et al.*, 1971; Raiti and Newns, 1970; Brook *et al.*, 1974). Progress usually has been monitored by clinical observation and by measurement of the urinary excretion of 17-oxosteroids and/or of the specific metabolite pregnanetriol.

Patients and methods

Sixteen patients (15 girls, 1 boy) were studied retrospectively; all were cases of 21-hydroxylase deficiency of the salt-losing type who had been treated in this unit since the first 3 months of life. The children were

measured on a stadiometer at 3-monthly intervals and although the measurements were taken by four different observers the results when plotted on height centile charts gave smooth curves. In addition, the height velocities when calculated and plotted on to height velocity centile charts also gave smooth curves, suggesting that observer error was small. The height velocities were calculated on whole year increments and were then expressed as standard deviation scores using the data for velocity standards of Tanner *et al.* (1966). The first year of life was excluded as were measurements after the age of 7 years because of the great variations in velocity possible during these periods.

Urinary 17-oxosteroid and pregnanetriol estimations were carried out at 3-monthly intervals on 24-hour urine specimens. As soon as the child became fully continent these collections were carried out at home. A single high value was checked by repeating the test after an interval of one month. Levels for 17-oxosteroid <1.5 mg/24 h under the age of 4 years and <2.5 mg/24 h thereafter were taken as indicating satisfactory control. A pregnanetriol level <0.5 mg/24 h at any age was thought to be satisfactory.

The children were all treated during the period of this study with prednisone and fludrocortisone. The fludrocortisone dosage was adjusted to try to maintain urinary Na excretion <200 mEq/24 h. In most cases this was achieved by a dose of 0.1 mg daily.

Received 1 July 1977

Results

Fig 1. shows the height velocities for the children plotted as standard deviation scores (SDS). The height velocity for each child is plotted at the midpoint for age between the two points at which the measurements were made. It illustrates that the standard deviation scores are mainly negative and that the growth rate for these children was subnormal.

Table 1 shows the 17-oxosteroid excretion of the children expressed as a mean for the whole group for each year of age. It illustrates that the values were

Table 1 Urinary 17-oxosteroid excretion (mg/24 h) of 16 children

Age (years)	Mean	Standard deviation
1-2	1.58	± 1.27
2-3	1.12	± 0.79
3-4	1.51	± 0.84
4-5	2.38	± 1.24
5-6	1.7	± 0.73
6-7	2.32	± 1.5

mainly within our prescribed limits, 74% of the estimations falling within this range. However, the range of values obtained was wide, 0.1-6.5 mg/24 h. Table 2 shows the pregnanetriol excretion of the

Table 2 Urinary pregnanetriol excretion (mg/24 h) of 16 children

Age (years)	Mean	Standard deviation
1-2	1.57	± 2.19
2-3	1.59	± 2.3
3-4	0.99	± 1.26
4-5	2.61	± 3.15
5-6	1.62	± 1.9
6-7	2.03	± 2.58

Fig. 1 Height velocity standard deviation scores (SDS) for 16 children plotted at the midpoint between which height measurements were made.

children expressed in the same manner, but illustrating that the levels were higher than our prescribed limits, only 41% of the estimations being <0.5 mg/24 h. Again this range was wide, from undetectable to 12.0 mg/24 h.

Fig. 2 shows the 17-oxosteroid excretions calculated as a mean of the measurements taken within each year of height velocity measurement for each child and plotted against height velocity (SDS). The correlation coefficient is not significant ($r = 0.23$, $P > 0.05$). Fig. 3 shows the same data for pregnanetriol. The correlation coefficients are not significant ($r = 0.12$, $P > 0.05$).

Fig. 2 17-oxosteroid excretion plotted against height velocity.

Fig. 3 Pregnanetriol excretion plotted against height velocity.

Discussion

In a previous communication on this group of patients (Bailey and Komrower, 1974) we reported delayed skeletal maturation and significant short stature. All of the children were below the 25th centile for height, 6 were on or below the 10th centile, and 10 were on or below the 3rd centile. Skeletal age was delayed by 6 months or more in 10 of the children, was equivalent to chronological age in 3 children and was advanced in 3 children. We explained these findings on the basis of the specific effect of the drugs used or, and more likely, drug overdosage. The established criteria for good control in the group of children were: (i) absence of salt-losing crises, (ii) minimal steroid side effects including steady growth along the centile line, (iii) skeletal age comparable with the chronological age, and (iv) no sign of virilisation. The biochemical criteria have been described in the Methods section.

The children were in good health during the period of study. Although the retarded skeletal age is interpretable as a steroid effect, no children showed any other sign of steroid toxicity. There were no signs of excess virilisation in any of the patients and salt-losing crises were rare. One girl had three such episodes and one boy several episodes, which were almost certainly due to the inconsistent administration of the drugs by his parents.

The dose of prednisone was, when expressed as its equivalent of hydrocortisone, between 10 and 30 mg hydrocortisone/m² per day. This is well within the limits prescribed by Migeon (1968), Sperling *et al.* (1971), Rappaport *et al.* (1968), and Brook *et al.* (1974) for effective pituitary suppression of ACTH with minimal growth inhibition. Various authors (Van Metre *et al.*, 1960; Raiti and Newns, 1971) have reported that prednisone has a greater growth suppressing effect than cortisone acetate or hydrocortisone and this may have contributed in part of the growth inhibition in our children.

The 24-hour urinary steroid metabolite figures were used to adjust therapy in our patients; we did not make any changes in treatment after a single abnormal result, but only when the check investigation gave a similar answer. When the figures are expressed as means for the whole group it can be seen that we were successful in maintaining 17-oxosteroid levels within our prescribed limits, while we failed to do so in respect of pregnanetriol. This suggests that had we attempted to suppress pregnanetriol excretion any further by increasing the dose of steroid we would probably have seen even more growth retardation and might have seen other side effects of the drug. Hamilton (1972) states that it might be most

appropriate to use the specific metabolite pregnanetriol excretion to control therapy in children with 21-hydroxylase defect and adds that the optimal daily excretion figure is not known. From our data, levels of 1.0 mg/24 h have been associated with undue short stature, and it is obvious that our criteria for therapeutic control in this disorder have been too strict; one could readily allow for a greater daily output of the metabolites to the child's advantage. Urinary steroid measurements are, however, invaluable in the establishment of the diagnosis, in the stabilisation of the condition in the early months of life and in the handling of the salt-losing crises.

We suggest that after the first birthday, a good clinical assessment at 3- and then 6-monthly intervals, including measurements of length and bone age to determine the rate of growth, is a better way of regulating maintenance therapy, reserving the estimation of urinary steroid output for the occasional situation where the child is sick and not thriving. In this we are in full agreement with Hamilton when he states that 'the adequacy of the administered glucocorticoid is best indicated by continued linear growth and ossification maturation at the normal rate'.

References

- Bailey, C. C., and Komrower, G. M. (1974). Growth and skeletal maturation in congenital adrenal hyperplasia. A review of 20 cases. *Archives of Disease in Childhood*, **49**, 4-7.
- Bergstrand, C. G. (1966). Growth in congenital adrenal hyperplasia. *Acta Paediatrica Scandinavica*, **55**, 463-472.
- Brook, C. G. D., Zachmann, M., Prader, A., and Mürset, G. (1974). Experience with long term therapy in congenital adrenal hyperplasia. *Journal of Pediatrics*, **85**, 12-19.
- Hamilton, W. (1972). *Clinical Paediatric Endocrinology*, pp. 130-131. Butterworth, London.
- Laron, Z., and Pertzalan, A. (1968). The comparative effect of 6 α -fluoroprednisolone, 6 α -methylprednisolone and hydrocortisone on linear growth of children with congenital adrenal virilism and Addison's disease. *Journal of Pediatrics*, **73**, 774-782.
- Migeon, C. J. (1968). Updating the treatment of congenital adrenal hyperplasia. *Journal of Pediatrics*, **73**, 805-806.
- Raiti, S., and Newns, G. H. (1970). The management of congenital adrenal hyperplasia. *British Journal of Hospital Medicine*, **4**, 509-512.
- Rappaport, R., Cornu, G., and Royer, P. (1968). Statural growth in congenital adrenal hyperplasia treated with hydrocortisone. *Journal of Pediatrics*, **73**, 760-766.
- Sperling, M. S., Kenny, F. M., Schutt-Aine, J. C., and Drash, A. L. (1971). Linear growth and growth hormonal responsiveness in treated congenital adrenal hyperplasia. *American Journal of Diseases of Children*, **122**, 408-413.
- Stempfel, R. S., Sheikholeslam, B. M., Lebovitz, H. E., Allen, E., and Franks, R. C. (1968). Pituitary growth hormone suppression with low-dosage long-acting corticoid administration. *Journal of Pediatrics*, **73**, 767-773.

Tanner, J. M., Whitehouse, R. H., and Takaishi, M. (1966). Standards from birth to maturity for height, weight, height velocity and weight velocity: British children (1965). *Archives of Disease in Childhood*, **41**, 454–471; 613–635.

Van Metre, T. E., Jr., Niermann, W. A., and Rosen, L. J. (1960). A comparison of the growth suppressive effect of

cortisone, prednisone and other adrenal cortical hormones. *Journal of Allergy*, **31**, 531–542.

Correspondence to Dr C. C. Bailey, Seacroft Hospital, Leeds LS14 6UH.