

***DR PETER HINDMARSH
READER IN PAEDIATRIC
ENDOCRINOLOGY
(Great Ormond Street Hospital
for Sick Children &
The Middlesex Hospital ,UCLH,
London)***



***VIEWS ON CONGENITAL
ADRENAL HYPERPLASIA***

A PROCESS OF CARE

Document kindly written by Dr Hindmarsh and therefore entirely accurate – thank you!

A Process of Care

The management of patients with 21 hydroxylase deficiency congenital adrenal hyperplasia (CYP 21) should be viewed as a process of care rather than individual contacts with various Health Care professionals. In the management of a chronic illness this type of approach is quite helpful as there are points at which certain levels of expertise are appropriate to be involved in the health care process and at other times no input is required. The concept is also useful as it allows for a more holistic approach to the child and family to be undertaken. This is particularly important as families come to terms not only with the day-to-day rigours of steroid hormone replacement but also the implications of the diagnosis for themselves and their offspring's future.

The process of care in CYP 21 starts with the diagnosis of the individual. Usually this is precipitated by a salt losing crisis in males or the presentation with ambiguous genitalia in females. The components at this stage of the care process include the diagnostic tests, which include karyotype studies, biochemical definition, molecular confirmation and the management of steroid replacement and salt balance. At the same time two additional components introduce themselves in the care process. The first is the need to consider support and advice from a Paediatric Urologist/Surgeon/Gynaecologist who is well versed in the management of this condition regarding the ambiguous genital appearance in females. The aim is to define the underlying anatomy, which can probably be most easily achieved by examination under anaesthesia. There may be a need for further surgical work to be undertaken in the first 18 months of life to address the problems associated with the presence of a urogenital sinus. There is no indication at this stage for an urgent correction of the clitoral hypertrophy. There are wide variations in the appearance of the clitoris and there is something to be said to delay the actual correction until the child has grown a little and the overall appearance can be assessed in the context of the growing and developing child. However, one can appreciate the sensitivities of the family in this situation and a careful and mutually respectful dialogue is required at this stage to determine the approach best suited to this particular family.

Running parallel with the medical components of care is the need to involve at this early stage support systems for the family. These are probably best provided by psychological services as they are well trained in the management of the grieving process, which is an important component of adapting to the imposition of a chronic illness upon a family with a newly diagnosed child. Early contact also allows for establishing a long term support process. In addition the psychologist role is also to act as an advocate for the child and family in a process which at this stage is heavily medically focussed and brings with it potential problems or conflicts between the views of the family and the direction in which the medical teams may wish to go.

The care process extends itself with the developing and maturing child and issues surrounding the psychology of the process are dealt with in more detail by Polly Carmichael in her presentation. The remainder of this presentation relates to medical aspects of CYP21 management.

Steroid Therapy in Congenital Adrenal Hyperplasia

The conventional approach to steroid therapy in CYP21 is to use the glucocorticoid hydrocortisone to replace the missing cortisol and 9- α fluorocortisone to replace the missing mineralocorticoid – aldosterone.

Over the years the dosing schedule for hydrocortisone has gradually decreased and the current recommendations are to use doses between 12 – 18 mg/m² body surface area/day divided into either a twice or thrice daily regimen. This dose is higher than the daily cortisol production rate of normal individuals as the aim of therapy is to suppress the drive to the adrenal glands and also with oral medication the dose has to compensate for some recirculation in the gut.

In the neonatal period and infancy a three times a day regimen is required and overall in the longer term better control is generally achieved by a thrice daily regimen. However, there are clearly a number of individual who can cope quite well with a twice daily regimen and in whom control is excellent. Whatever regimen is chosen the pattern of hydrocortisone delivery is not the same as the normal body rhythm of cortisol as Figure 1 shows:

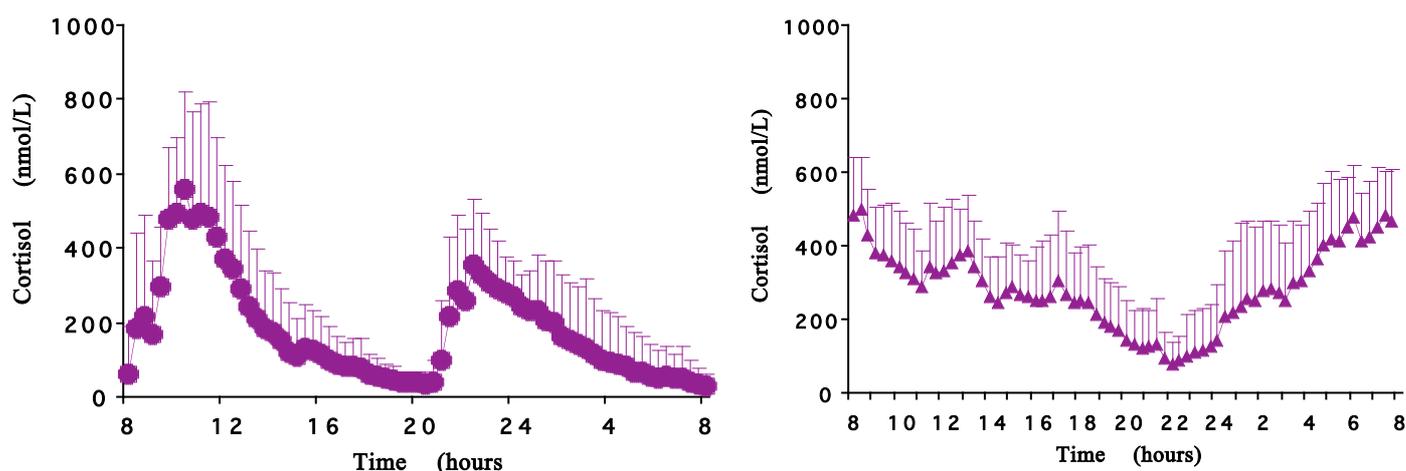


Figure 1

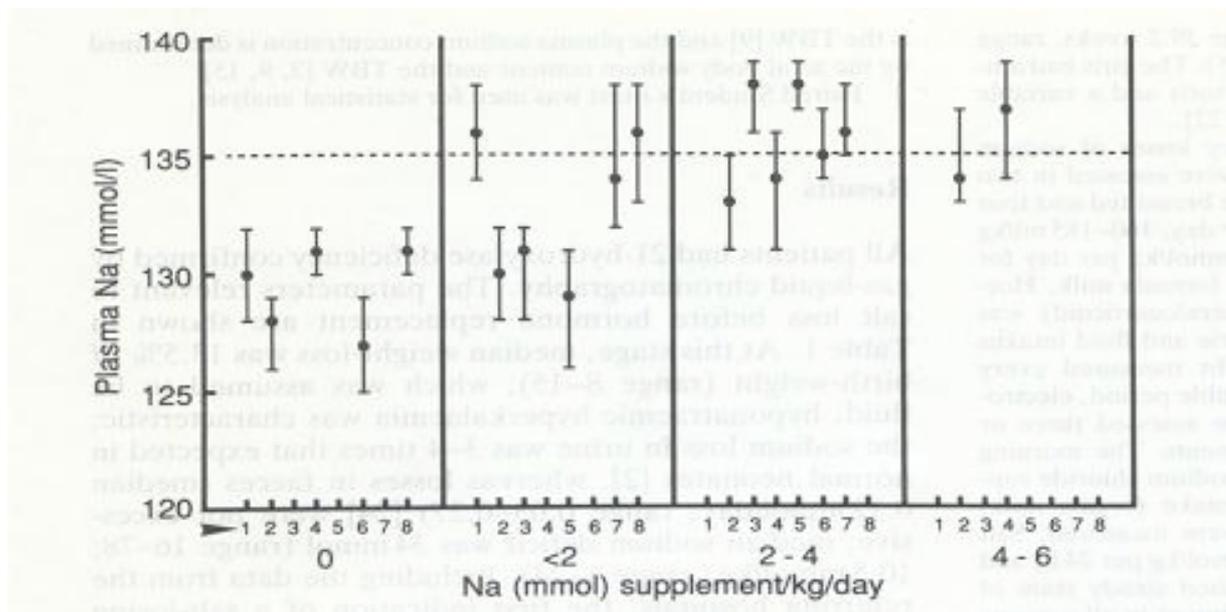
Whilst during the day adequate peak cortisol concentrations can be achieved following the morning dose of hydrocortisone, a gradual decline occurs just as in the normal situation, but by midnight there is very little hydrocortisone in the circulation on a twice daily regimen. Because of bed times and the oral nature of the medication, hydrocortisone is usually given as the child retires to bed. The net result of this is to provide a further boost to the cortisol concentrations in the blood, but this is at a time when the body usually does not see any cortisol and questions must be asked as to what significance of this inappropriate exposure is. The aim of the night time dose is to suppress the rise in ACTH and cortisol, which starts from about midnight and reaches its peak in the early hours of the morning. The early night time dose of hydrocortisone does not achieve this as by the time the early morning surge is taking

place, cortisol concentrations resulting from the hydrocortisone administered are on the decline - just at the moment when you need more hydrocortisone. There are only really two solutions to this particular problem. Either to develop some slow release depot preparation or to give the hydrocortisone much later. This would necessitate waking the child around about midnight and as such is probably not a practical option in the majority of circumstances. It has been suggested that higher doses given at night would achieve better suppression but the handling of hydrocortisone by the body argues against this unless extremely high doses were to be used and side effects would ensue.

For many years we thought that the management of the salt side of things was relatively straight forward, in that, 9-alpha fludrocortisone was administered in a dose of 100 micrograms/m²/day. Salt supplementation in infancy as Figure 2 shows:

Figure2

SODIUM REQUIREMENTS IN CYP21



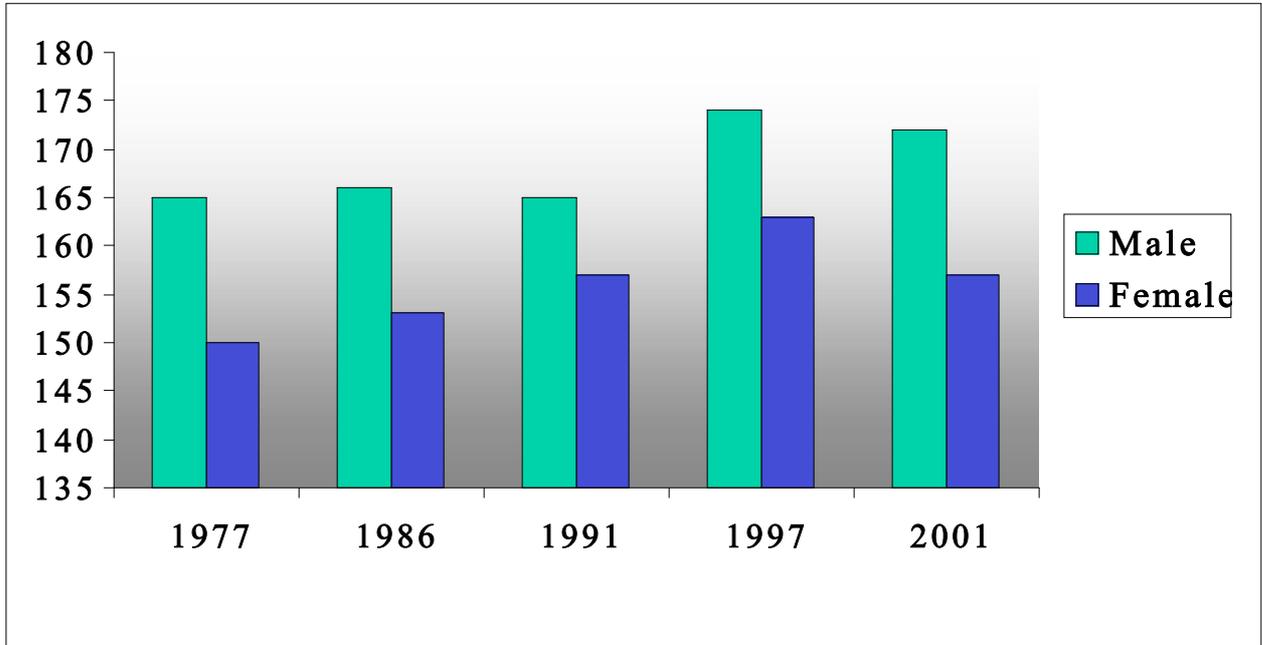
This activity will not return to normal values and the plasma sodium concentrations will remain stubbornly low.

Thoughts on Potential Long term problems in CAH

With the introduction of hydrocortisone in the 1950s survival with the most severe form of CYP21 became possible. However, the dosing schedules of hydrocortisone was not well established and it was not until the 1970s and 1980s that it was evident that growth problems resulted with the attempts to suppress the adrenal axis. As the dosing schedule has become refined the height outcome for both males and females has improved to the point where data suggest a near normal outcome (Figure 3):

Figure 3

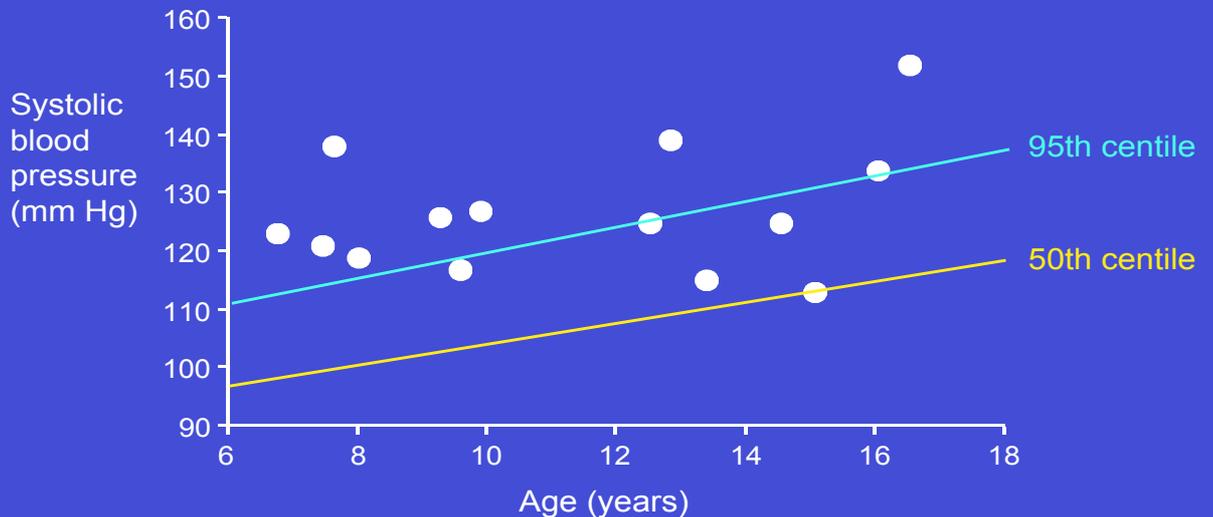
FINAL HEIGHT IN CAH - SALT LOSING FORM 1977 - 2001



Although we have done extremely well in getting the growth outcomes to be near normal, there are additional issues that have evolved as time has gone on. In the attempts to improve the height outcome, rather higher doses of hydrocortisone have been used and the net effect has been to generate in our patients a higher prevalence of obesity. This obesity appears to have its origins quite early on in the whole growth process, as by the age of five years many of the children show increase in body fatness, which is most manifest by the age of ten. The cause of this is not clear but we strongly suspect, that high doses of hydrocortisone used to suppress the axis in the first one or two years of life are important in this regard. The overall effect of this increase in obesity is to raise potential problems with respect to the production of insulin and the maintenance of normal glucose concentrations in the blood. At present we know that the plasma insulin concentrations are high in children with adrenal hyperplasia, but we do not know whether this means that they are destined to develop problems such as diabetes.

Figure 4

Blood Pressure in Males with CYP21



What we do know from our studies is that blood pressure in children with adrenal hyperplasia can be a problem and Figure 4 shows problems with respect to blood pressure in some of our male children with adrenal hyperplasia. What we see in this particular picture is high blood pressure values above the average (50th centile) for age. We are unclear at this stage as to what we should be doing about this. It is clear that if you reduce the 9-alpha fludrocortisone dose during adolescence from the conventional 100 micro grams/m²/day then most of the obesity and blood pressure effects can be ameliorated. We do not know how the increase of blood pressure comes about and it may relate to either our ongoing use of quite high doses of fludrocortisone during adolescence or due to the exposure early on in life to fludrocortisone and salt supplementation. This problem needs to be resolved, but as we are learning that older children and adolescents require less 9-alpha fludrocortisone we should have a more flexible approach and reduce the dose of 9-alpha fludrocortisone based on regular annual measurements of plasma renin activity.

Changes in Glucocorticoid Dose with Age

Adolescence is a particularly taxing time for both medical practitioners and parents! During this time the individual is adapting to an independent life style and there is a marked increase in risk taking behaviour in the adolescent population as they test out their role. During adolescence it has been noted that control of adrenal hyperplasia can often worsen and in many circumstances this may reflect this risk taking behaviour of the adolescent in terms of non-concordance with hydrocortisone and fludrocortisone therapy.

This is probably an explanation only in part to the problems in adolescence with adrenal hyperplasia control. There are real physiological changes that take place, which also make the situation more difficult. During adolescence there is an increase in the removal of cortisol and therefore, hydrocortisone from the circulation such that the normal disappearance time of cortisol decreases from approximately 80 minutes for 50% removal to 50 or 60 minutes during adolescence. The effect is more pronounced in females, which means that during puberty and in females in particular the effectiveness of hydrocortisone is going to be lessened because there will be less around in the circulation for an increased period of time. The way in which to tackle this particular problem is not to increase the amount of hydrocortisone that is administered, but rather to give the dose more frequently, which is where the three times per day regimen really triumphs. On occasions it may be necessary to go to a four times per day regimen but this is extremely unusual.

The reason for this increase in clearance of cortisol relates to the pubertal growth spurt because growth hormone, which is involved in the spurt of growth, alters the way in which cortisol is handled in the body. In addition, in females there is an increase in the special protein, which holds on to cortisol in the circulation. This protein increases in the presence of female sex hormone so that more is available to take up any cortisol in the circulation so that less is available to work in the body. It is a combination of all these factors in puberty, which makes the management of children at this age a particular challenge.

Conclusions

We have come a long way since the 1950s when hydrocortisone had such a dramatic effect on the survival of children with CYP21. We now expect these children to grow into adults and that their growth pattern will be normal for their age. As we refine the dosing schedule we have become more aware of additional problems that these children may have as a result of survival. This is probably because our therapeutic interventions are not as subtle and sophisticated as we would like them and that these interventions although dramatically effective in terms of survival of the individual may have some longer term problems eg. obesity, which we now need to address. The challenge for the management of CYP21 in the next five years is to refine our treatment therapies to allow better modes of delivery of some of our agents such as hydrocortisone and to keep careful monitoring of potential problems associated either with the disease or our therapies.