



Congenital Adrenal Hyperplasia Clinic  
<http://www.cahisus.co.uk>



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NHS Foundation Trust

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### ***Questions answered by Professor Peter Hindmarsh***

*It is true that many centres work differently regarding the monitoring of their patients with CAH and it would not be prudent to comment on what or how other centres monitor their patients. However, what we can do in answering your questions is explain why we at Great Ormond Street offer full '24 Hour Profiles' to our patients who have CAH and other adrenal disorders that require glucocorticoid replacement therapy and what their value is in helping us treat the condition.*

The following questions have come through our website

**We have been told that as long as our child is well and is growing well that blood profiles are not necessary.**

Measuring growth is of course an important factor in monitoring congenital adrenal hyperplasia, however problems that relate to either poor growth or accelerated growth, happen **before** the problem **alerts** that the dose is not correct. This is also true of bone age which is another important measure, but again this tells us that the dose has not been correct for some time. For example, it may take up to 6-12 months to see a significant change in bone age.

Neither of these measures will show you that the distribution of cortisol that is being given is correct and although accelerated growth or advanced bone age will alert that an increase is needed, it does not show which dose needs altering.

We also worry about long term accrued side effects which can be caused by the wrong distribution of cortisol, so even if the bone age and growth do not cause concern, we like to look not only at these measures but also at how the cortisol is distributed over a 24 hour period.

The aim in congenital adrenal hyperplasia is to replace cortisol as closely as possible to the way in which the body normally produces it and by carefully looking at the cortisol levels in the blood over a 24 hour period we are able to fine tune doses. We do this by looking at how high the cortisol peaks in the blood and we check to see if there are periods where there is no cortisol in the blood. We also study how the cortisol is influencing the 17 OHP level which is a very important marker.

**I have been told that as the body produces different amounts of cortisol every day, how can looking at one day help?**

What profiles enable us to achieve is to make sure that the replacement cortisol value and the times that the dose of hydrocortisone is given, is as best as it can be. Although daily values of cortisol might vary slightly, we try to emulate the circadian rhythm which does not alter. We also use the 17 OHP levels over the 24 hour period to help us determine the actual dose needed. In fact the day to day variation of cortisol is not very much and only amounts to about 10-15%. We also know that if we do a profile one day and repeat it another then the difference between the days is quite small and in keeping with the 10-15% variation seen in blood profiles from people without CAH.

Using a blanket formula based on body surface area divided into two or three doses per day does not take into account the way the individual person metabolises hydrocortisone or that the distribution of cortisol that the doses give, is correct.

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Department of Endocrinology – Adrenal Clinic



**We do 17 OHP blood spots for three consecutive mornings before the morning dose and we have been told that if this 17 OHP level is within normal range then our child's CAH is in good control.**

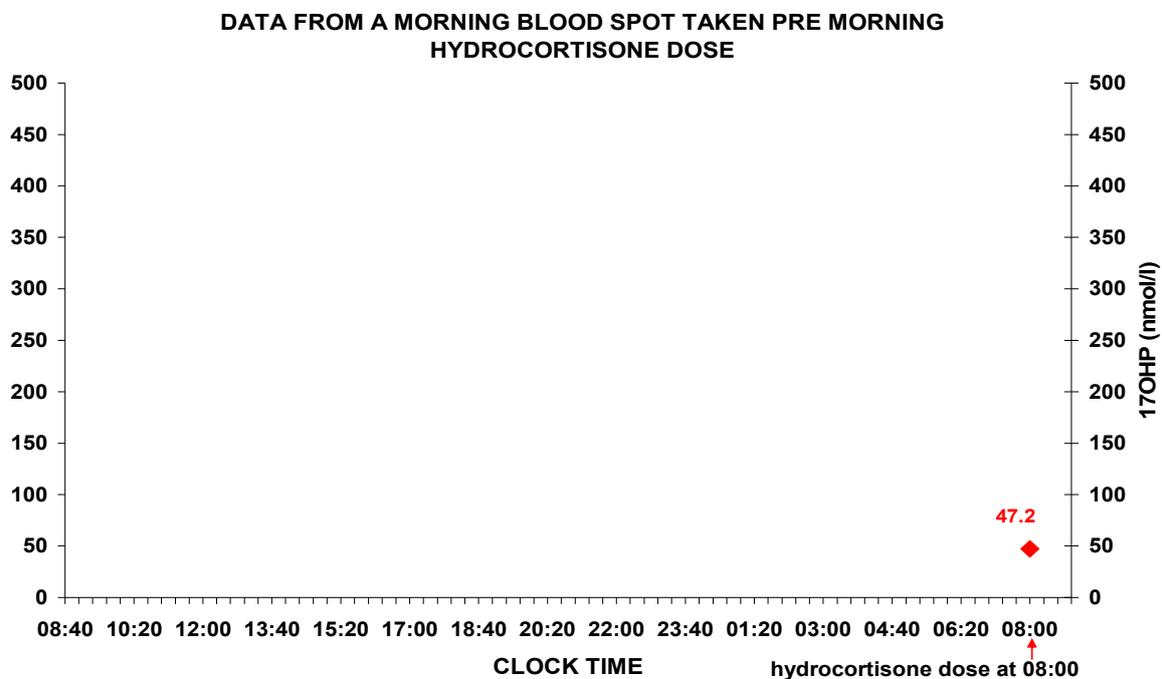
A blood spot shows you a snap shot of the 17 OHP level only at that moment of time (Figure: 1). It does not show the cortisol level, or in fact what happens for the rest of the day. This method does not allow for fine-tuning, because if this level is high, then which dose do you increase, the previous evening or the morning dose? What about the rest of the day? Is the cortisol level sufficient at the times where there should be cortisol? Is the cortisol peaking too high?

What we need to remember is that we are trying to avoid the long term side effects and weight gain, as high cortisol levels will lead to increased glucose levels. There may also be periods where the individual's cortisol levels drop too low or in fact leave the individual without any traceable cortisol in the system which can lead to tiredness, lethargy, and headaches as well as leaving the person at risk of an adrenal crisis.

The aim of the cortisol replacement therapy is to have the right amount of cortisol at the right time of the day, not to 'treat' the 17 OHP level. Data has shown us that there is a time lag between the response of cortisol on the 17 OHP level and once the cortisol level is correct the 17 OHP level will follow.

We do not use morning 17 OHP blood spots or even pre dose blood spots because our data has shown us that this does not give us the information that we need to fine tune doses, i.e. avoid the high peaks of cortisol or periods where the cortisol levels fall too low and you cannot see this by looking only at the 17 OHP level.

To illustrate this we have plotted the data from a patient using blood spots to measure their 17 OHP level pre morning dose and this is the information that you would get from this measure.



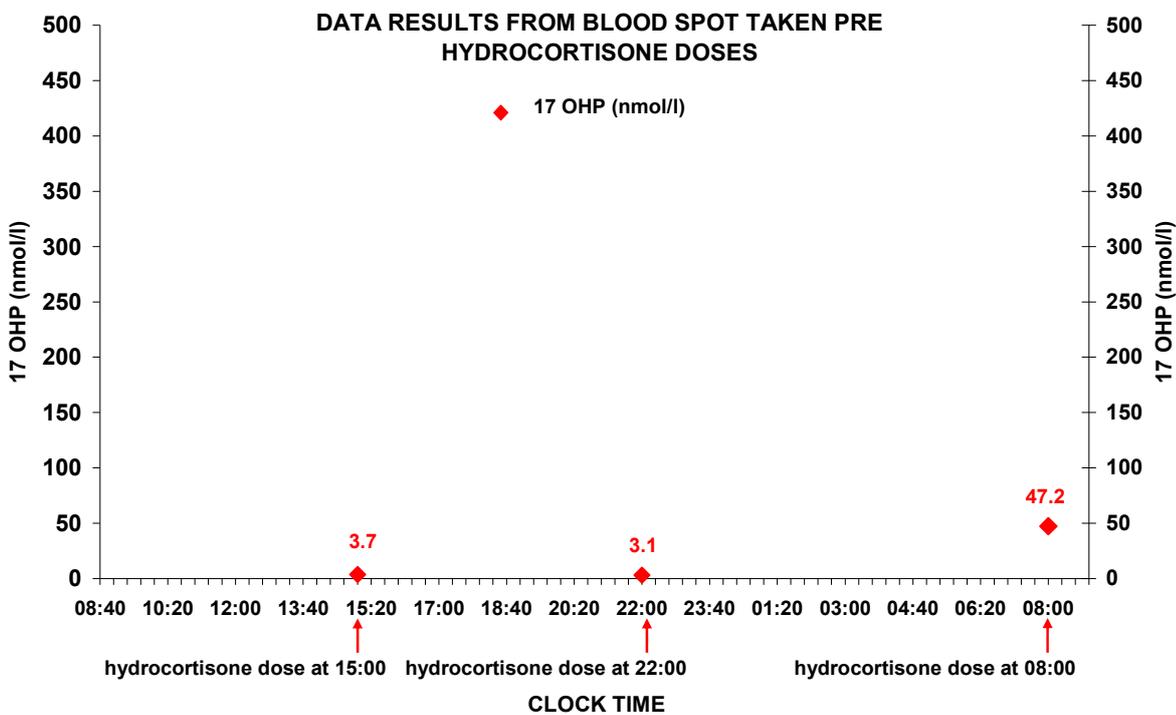
**Figure: 1 Blood spot sample taken pre morning dose at 08:00 hours**

If we consider the data in Figure: 1 by all accounts this result shows us that the level of 17 OHP is acceptable for this time of the day and we would think that no adjustments are needed.

Some centres may like to see the morning 17 OHP at a level lower, so may suggest an increase to the evening dose in the hopes of achieving this however they have no real data to see what the evening 17 OHP level is or in fact how much cortisol is in the blood stream. To reduce this 17OHP level you would need a very high evening dose of hydrocortisone because the duration of action of hydrocortisone is only 6-8 hours, and this would not make the cortisol in the blood last longer, so it is unlikely that it would have much impact on the morning 17OHP level but it would result in a much higher cortisol exposure in the evening.

Unless the dose is given at 01:00 – 02:00 hours then it is unlikely that any dose will impact to a significant degree on the morning pre-dose 17OHP level.

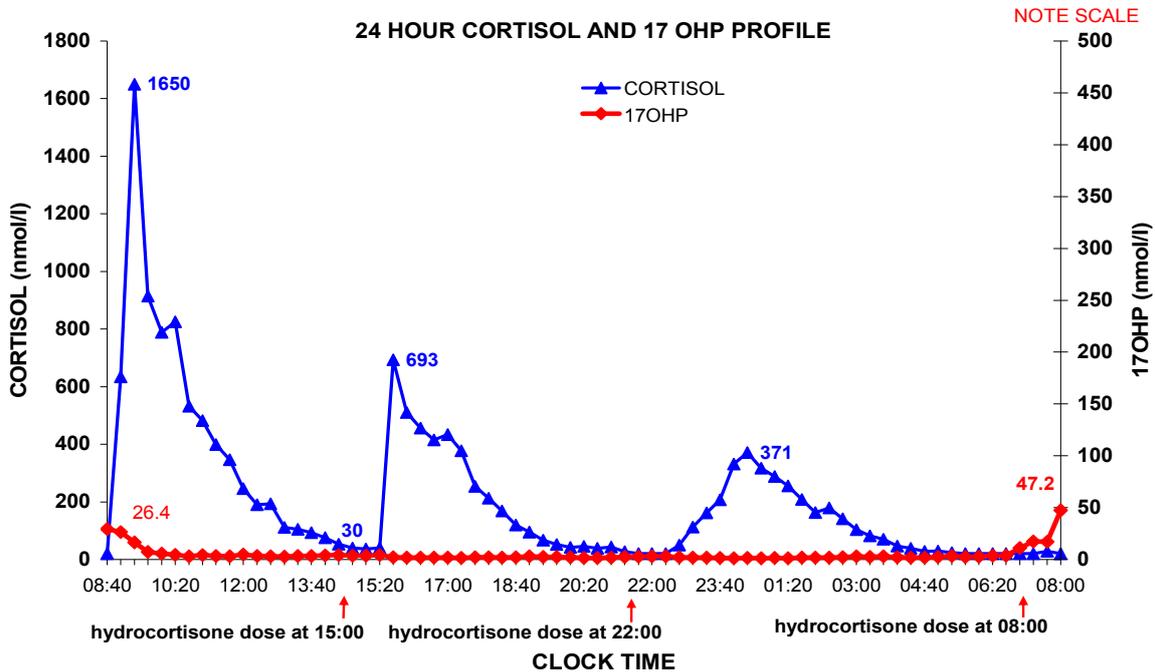
If we now add in the data that we would get if we took blood spots pre each dose taken during the day on the same individual, Figure: 2 shows us the data we have to consider when adjusting doses.



**Figure: 2 Blood spot 17 OHP results from samples taken pre dose throughout the day**

Looking at the 17 OHP results in Figure: 2 we would say control is very good and no adjustments need to be made and in fact we would be really pleased.

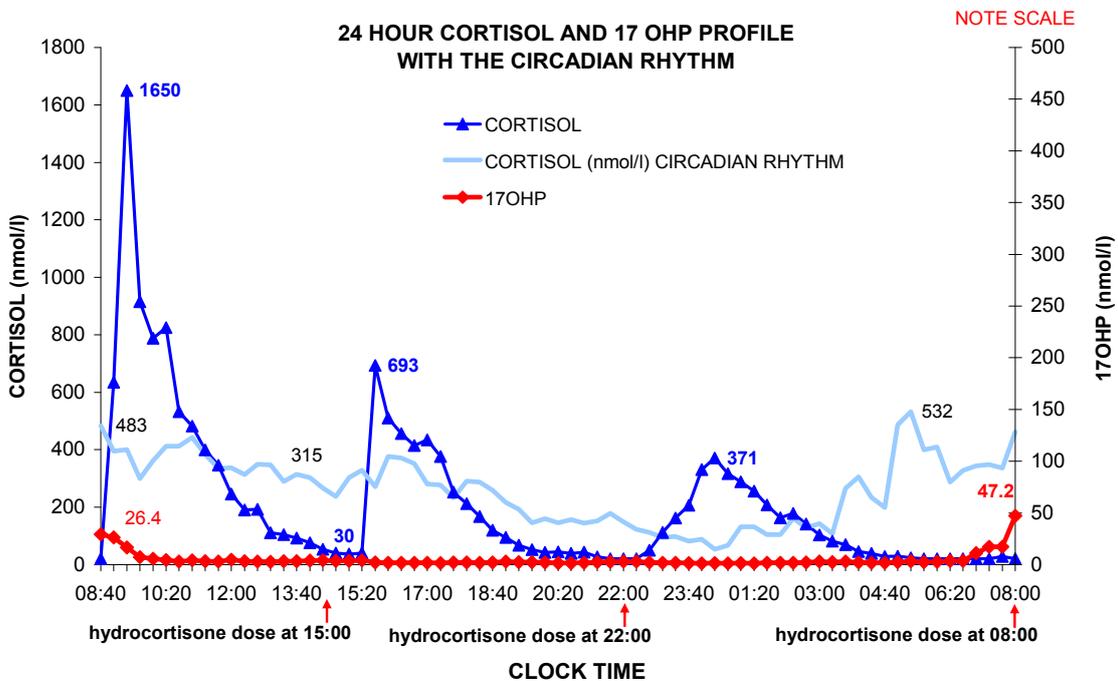
However if we now put in all the data we have from the results of a 24 hour profile as shown in Figure: 3, then carefully consider the replacement cortisol and the 17 OHP levels we see a very different picture!



**Figure: 3 Data obtained from a 24 Cortisol and 17 OHP profile.**

What Figure: 3 shows us, is that the morning dose gives a cortisol peak value of 1650 nmol/l which is extremely high, so although the 17 OHP level might show the control is good, the actual cortisol level shows us the replacement values are far too high.

So to give us even further information we now plot in the circadian rhythm in Figure: 4



**Figure: 4 Data from a 24 hour profile and the circadian rhythm of cortisol**



Now that we have all this information we look at the light blue line which shows us when the body should have good levels of cortisol and when we compare the values the patient has, we can see that there are periods where the cortisol is dropping too low, especially around midday and this remains low until after the next dose kicks in which was taken at 15:00 hours. We can also see that cortisol from the 15:00 hour dose peaks at 693 nmol/l which again is too high for the time of the day, this high cortisol level will cause side effects.

The data also tells us that the very high peaks of cortisol have also flattened the 17 OHP production even though the cortisol levels drop for periods during the day. This is particularly obvious around 03:00 hours where the cortisol from the hydrocortisone dose taken at 22:00 hours drops very low. The 17 OHP then remains low despite the data showing us that there is no cortisol in the blood from 04:00 hours until after the next dose is taken at 08:00 hrs.

Looking at all the 24 hour profile data we can see that this patient is both under and over treated and several adjustments need to be made to their dosing to avoid side effects. We would work on moving to 4 smaller doses a day, adjusting the times the doses should be taken to give a better distribution of cortisol at the times the body needs it.

Remember what we are trying to do in congenital adrenal hyperplasia is to replace the cortisol with hydrocortisone as closely as possible to the body's normal cortisol production and not 'treat' the 17 OHP level. The 17 OHP level is however, a very important marker and is used as a check to see if we have the cortisol distribution correct.

There is a time lag between the effect the cortisol has on the 17 OHP, so even if we were to measure the cortisol at the same time as we took a blood spot this would not give us a true picture, in fact if we measured cortisol pre the 08:00 dose there would be no traceable cortisol in the blood. Increasing the night time dose would not raise this cortisol level, as we know that an increase in cortisol does not last longer in the blood, it would however substantially increase the peak we see at midnight, leading to excess cortisol at that time.

If you consider these high levels of cortisol from tablets taken every day for many years, there are bound to be many long term side effects, as well as short term side effects. 24 hour profiles also allow us to measure other hormones such as ACTH, fasting lipids, insulin and glucose levels, LH, FSH, Testosterone, Estradiol, Androstenedione, resting and active Plasma Renin Activity, DHEAS as well as monitor blood pressure at different times of the day and night. These measures allow us to 'fine tune' our patient's doses thus preventing both short term and long term side effects and ensure good health and wellbeing.

### **How much blood is taken, this seems an awful lot?**

The 24 hour profile in Figure: 3 and Figure: 4 have been done using 20 minute sampling. We use different protocols for different ages which are either samples taken every hour, or two hourly samples with an extra sample taken pre dose if the dose times falls between the two hours. For very young children we use a different protocol where we do less sampling. Although it may seem a lot of blood, only a small amount is taken each time and amounts in total to about an egg cup full.

### **How do you take the blood?**

We use a venous cannula which is inserted into a suitable vein in the back of the hand or in the arm; the area is first numbed with an anaesthetic type cream. We then draw the blood through the cannula and if this is working well, there is no pain involved.

### **I have a blood test in clinic can control be shown on this?**

One off blood tests result in the same scenario as having blood spots as you do not know what is happening the rest of the day. Often centres do not measure cortisol when doing a single sample so you have no idea of the amount in the blood at that time. The sample must also be related back to when the last dose was taken and what that dose was. The 17 OHP level can also rise in some people in reaction to the draw, and again, you would be basing the total daily dosing schedule on one sample, as in the blood spot. When doing a profile we fit the cannula well before we start looking at the samples where we know there has been no reaction to the insertion.



### **Can you use saliva samples to measure cortisol?**

We do not use the cortisol measurements in saliva for several reasons; the main being that the cortisol measured in saliva is not the cortisol level that is going to the organs, which is the measurement we are interested in. It is rather like a 'by product' and it can also be influenced by other factors, such as caffeine from coffee, tea or certain sodas and fruit juices. What we want to measure is the level of cortisol in the blood that the hydrocortisone tablet provides, so we know that there is sufficient or an excess level of cortisol to be carried in the blood to all the organs in the body.

### **We do 24 hour urine collections, is this as accurate?**

24 hour urine collection has been suggested as an option. This would measure the amount of the breakdown products of 17OHP and cortisol in the urine. The problem is that if you use 24 hours then it is simply an average value so you would not be able to determine which dose needed changing, or in fact how the cortisol is distributed throughout the day, i.e. how high each dose is peaking and lasting, or if there are periods where there is no cortisol in the blood stream.

In addition this test is only useful if levels are out of control because if the levels are in control it is not so easy to separate good control from over treatment.

To use urine only would really mean collecting urine every two hours at a precise time which is quite a task. Anything longer would mean losing detail. However we are not directly measuring the cortisol that we are getting from the hydrocortisone which is taken to the organs. Again this is also rather looking at 'by product' of cortisol.

Finally, even if you use very frequent measures in the urine it may not match with blood as there is a time lag between what happens in blood and urine because the blood steroids have to be altered in the liver then passed out in the urine which adds to the time gap.

### **Is it possible to completely switch off the production of 17 OHP?**

Yes we have seen several cases where the production of 17 OHP has been switched off by years of high dosing with hydrocortisone or other steroids. In several cases, this has even led to questioning the correct diagnosis.

This can be looked at by testing with ACTH to stimulate the adrenal glands. This may be possible with a short stimulation test but often longer stimulation (over a week) may be needed. This is because it is necessary to wake up the adrenal gland to get it moving after suppression.

### **I am an adult, would you recommend 24 hour profiles to adults?**

24 hour profiles help at all ages as the principles in treatment are the same in that we want to mimic the normal circadian rhythm. In children we do them frequently because the child is growing so doses change frequently. This is less so in adults however weight and therefore body surface area can alter and because we want to minimise exposure to high cortisol levels yet maintain good control profiles are helpful.

It has been suggested that simply measuring the adrenal androgens can be helpful. Unfortunately this is not the case. First, this can only be done in females as males produce androgens from the testes. Second, it assumes that androgens are a good marker which is not the case as the dose of hydrocortisone needed to replace cortisol is different from the dose needed to switch off androgens from the adrenal. Finally, it does not tell us if the person is over treated or which dose of hydrocortisone is to be altered. Our data has shown us that it is possible to have a seemingly normal androgen level and a seemingly normal 17 OHP level however there may be periods throughout the day where there is no measurable cortisol in the blood.

***For further reading please read our leaflets titled 'The Value of 24 Hour Profiles' and 'Hydrocortisone' on our website***