Hypopituitarism

THE VALUE OF 24 HOUR PROFILES IN ASSESSING CORTISOL REPLACEMENT IN HYPOPITUITARISM

Professor Peter Hindmarsh and Kathy Geertsma

Cortisol is produced in the body by the adrenal glands and the levels in the blood vary during the day. This production is called the Circadian Rhythm of cortisol. Values are high in the morning and early afternoon and low in the evening. You might like to think of cortisol therefore as a *get up and go* hormone. This pattern can be seen in Figure 1 which shows the cortisol levels of someone with a normal production over a 24 hour period. It is important to realise that not everyone has the same amount of cortisol in the blood but the production pattern known as the circadian rhythm is the same, except that the level of cortisol drops lower earlier in the evening in children.

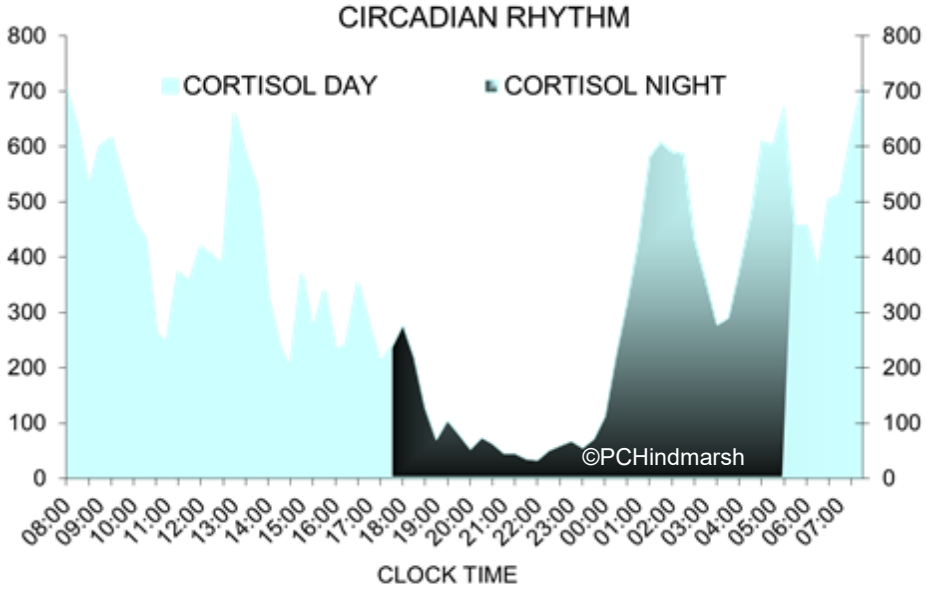

Figure: 1 The body's natural production pattern of cortisol over 24 hours known as the Circadian Rhythm

This diagram tells us that cortisol levels vary during the day and is a useful reference when we start to think about using glucocorticoids to replace cortisol.

WHAT DOES CORTISOL DO?

The quick answer is lots. It is important for many things the body does such as maintaining blood pressure and blood glucose levels. This is one of the reasons why we worry when people become ill and cannot take their hydrocortisone as blood glucose levels can go low. Cortisol is also important for helping fight infections and mobilising the body to deal with stress.

Also if you look at the cortisol values in Figure:1 particularly those in the early hours of the morning, there is a significant amount of cortisol in the blood stream and the reason for this is to keep blood glucose levels stable whilst we sleep.

Professor Peter Hindmarsh Professor of Paediatric Endocrinology http://www.cahisus.co.uk
Divisional Clinical Director for Paediatrics and Adolescents at UCLH "The ideas expressed are independent of the authors' affiliations.

ASSESSING CORTISOL REPLACEMENT IN HYPOPITUITARISM

In conditions such as hypopituitarism where cortisol production is compromised, it is necessary to replace the cortisol and bring the levels to as close as the body's normal production, as is possible. This is done by using a glucocorticoid steroid such as hydrocortisone. Hydrocortisone is the synthetic form of cortisol.

There are other similar drugs such as prednisolone and dexamethasone. Prednisolone and dexamethasone differ structurally from hydrocortisone and last longer in the blood as cortisol. The plasma half-life (how long the drug lasts in the blood) of prednisolone is around 6-8 hours, dexamethasone around 12 hours whilst hydrocortisone lasts between 4 - 6 hours. Although both prednisolone and dexamethasone last longer it is important to note that the biological half-life (how long effects of the drug last in the body) also last longer. The biological half-life of dexamethasone is between 36 and 72 hours, prednisolone is 12 to 36 hours and hydrocortisone is around 8 to 12 hours. The anti-inflammatory potential of dexamethasone is five to six times as potent as prednisolone. This means the prednisolone or dexamethasone may not be in the system but their other effects persist.

What this means from the dosing standpoint is that:-

- Hydrocortisone will need to be given at a minimum three times a day and something like four times a day would be more appropriate.
- Prednisolone is widely advised as a twice a day treatment but probably needs to be given three times a day.
- Dexamethasone is often given once day, overnight but probably needs something like twice a day in actual practice.

It also might result that if you take prednisolone twice a day, or dexamethasone once a day and consider the time it lasts as cortisol in the blood, you would be without cortisol in the blood stream for a significant period of the day.

A further advantage is that hydrocortisone can be measured as cortisol in the blood accurately but you cannot measure the cortisol from prednisolone or dexamethasone.

So although you might think the longer the better this is not simply the case as prednisolone and dexamethasone have a tendency to suppress growth which is why we use hydrocortisone in children. As prednisolone and dexamethasone are far more potent than hydrocortisone their use should be avoided in children because of the risk of growth suppression and weight gain.

Steroid	Duration of Action (as cortisol)(hours)	Peak Action (hours)	Growth Suppressing Effect	Dosing Effect on Growth	Mineralocorticoid Effect
Hydrocortisone	4 - 6	2	1	20mg	1
Prednisolone	6 - 8	4	5	4mg	0.8
Dexamethasone	12	Rather flat profile	80	0.4mg	0
Fludrocortisone	Used for salt losers				200

Figure: 2 This table shows the equivalent doses of dexamethasone and prednisolone compared with hydrocortisone.

The figures in the table show us that compared to hydrocortisone, prednisolone and dexamethasone are 5 and 80 times more likely on a dose for dose basis to suppress growth. Note also that the duration of action and peak of action for the steroids differ. Dexamethasone does not peak in its action like the other two steroids and so is likely to give a more constant exposure over time than the up and down profile of hydrocortisone and prednisolone.

Hydrocortisone is a glucocorticoid but it also has some salt retaining properties whereas other similar steroid drugs such as prednisolone and dexamethasone do not. It is also important to note that Fludrocortisone, which is the synthetic replacement for Aldosterone, has not only mineralocorticoid but also potent glucocorticoid activity. It is important to remember this when calculating the total daily glucocorticoid dosing: i.e. the contribution of 9α-fludrocortisone needs to be included in the total.

WHAT HAPPENS WHEN YOU TAKE A HYDROCORTISONE TABLET?

Hydrocortisone is absorbed very quickly from the gut. In fact the absorption is very efficient and nearly 100% is absorbed. If we measure cortisol in the blood after taking hydrocortisone then it looks like this: (Fig.3)

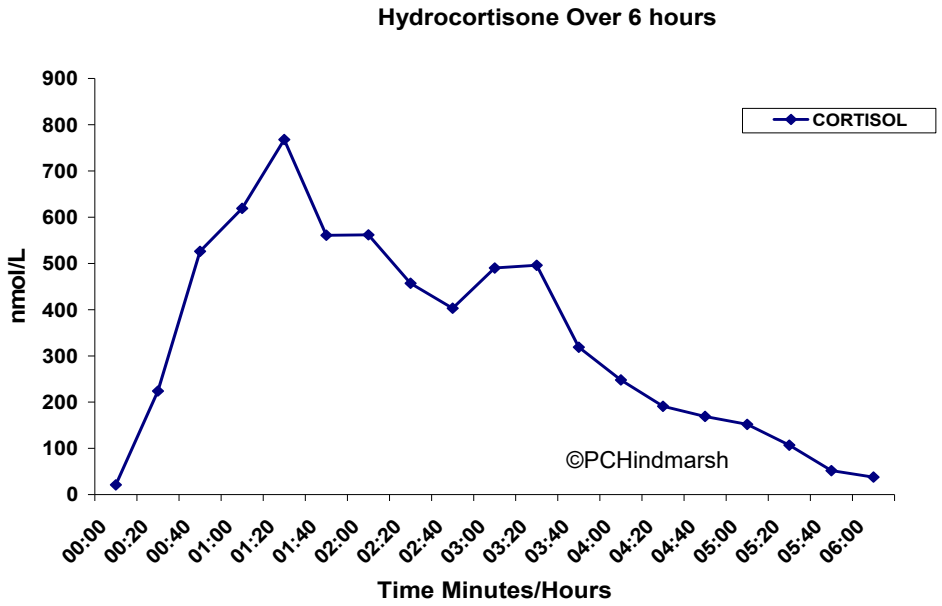

Figure: 3 Tracing the cortisol in the blood from a hydrocortisone tablet taken orally

This shows that in this person it takes about 1-2 hours for hydrocortisone to reach a peak and about 6 hours before the dose wears off. This graph also shows the importance of how long hydrocortisone lasts in the blood. This is known as the half-life of hydrocortisone which varies a little between people but on average is 80 minutes. This means that if you have a level of cortisol of 400 nmol/ls then 80 minutes later it will fall to 200 nmol/ls and after further 80 minutes it will be 100 nmol/ls. You can follow this principle perfectly by looking at the study line in the graph (Figure: 3).

WHAT ARE WE TRYING TO DO WITH 24 HOUR PROFILES?

With a 24 hour profile we test the cortisol levels in the blood at either hourly or two hourly intervals over a 24 hour period. This allows us to answer four questions:

1. Am I having too much hydrocortisone – the cortisol peak measures too high
2. Am I having too little hydrocortisone – the cortisol peak measures too low
3. How long does the hydrocortisone last – the cortisol level falls too low before the next dose is taken.
4. Am I having the right amount of cortisol at the right times of the day - this will be a guide to see how many doses a day are required, and the best times to take doses.

The 24 hour profile would not normally be achievable in out-patients and therefore an admission would be required.

BUT CAN WE GET THIS INFORMATION FROM A BLOOD TEST?

A single blood test shows a 'snap shot picture' of the cortisol at that moment. They can be valuable to do because if the sample is taken just before the next dose is due, the result will show how much cortisol is left in the blood stream from the previous dose of hydrocortisone. However, if a single sample is taken at any other time you would need to relate the result to dose and the exact time the dose was taken and factor in the person's clearance rate. In fact, unless the samples are taken with respect to dosing then it is very hard to interpret and results can be misleading.

One off blood test do not show the peak of cortisol after the hydrocortisone doses are taken or the low troughs between doses and therefore the sample does not give a full picture of what is happening throughout the 24 hours.

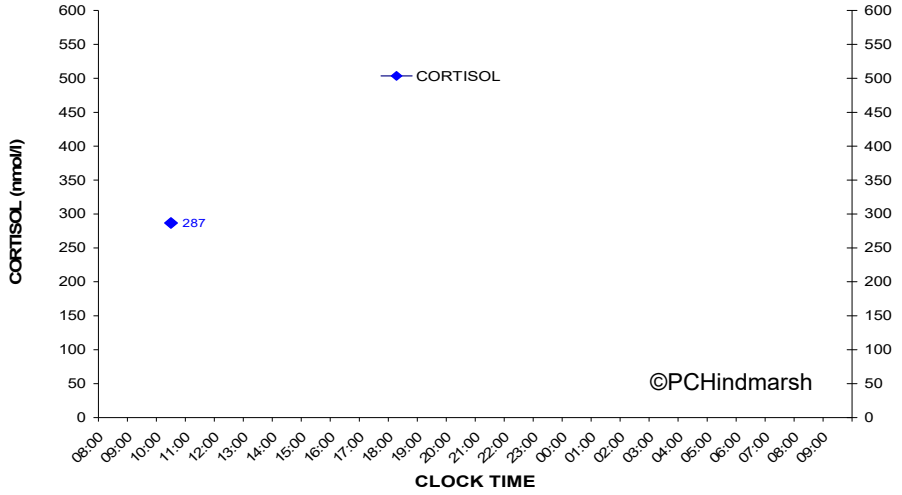

Figure: 4 The graph above shows us the data from a one off blood test taken at 10:00 am

The result is difficult to interpret and if an increase was felt necessary, what about the rest of the day?
We cannot see how long the dose is lasting. If however, we add in the data we would get from a 24 hour profile with hourly samples, we would get the data as shown in Figure: 5.

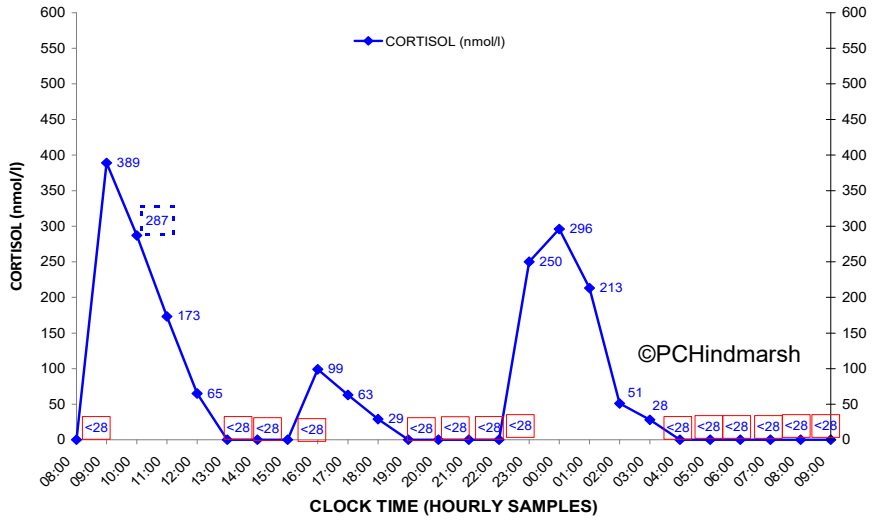

Figure: 5 The results of a 24 hour cortisol profile showing the values in this patient who is taking 3 doses of hydrocortisone a day.

Professor Peter Hindmarsh Professor of Paediatric Endocrinology *http://www.cahisus.co.uk*
Divisional Clinical Director for Paediatrics and Adolescents at UCLH "The ideas expressed are independent of the authors' affiliations.
Data provided is from current literature and should always be discussed with your endocrinologist first"

If we compare the body's normal cortisol production, the circadian rhythm (light blue dashed line) in Figure: 6 with the cortisol levels of the replacement hydrocortisone (solid blue line), we can see that there are periods over the 24 hours where the replacement cortisol falls too low, as well as periods where there is no measurable cortisol (<28) in the blood. Remember that what we are trying to do when replacing cortisol is to try to replace it as closely as possible to how the body would make it.

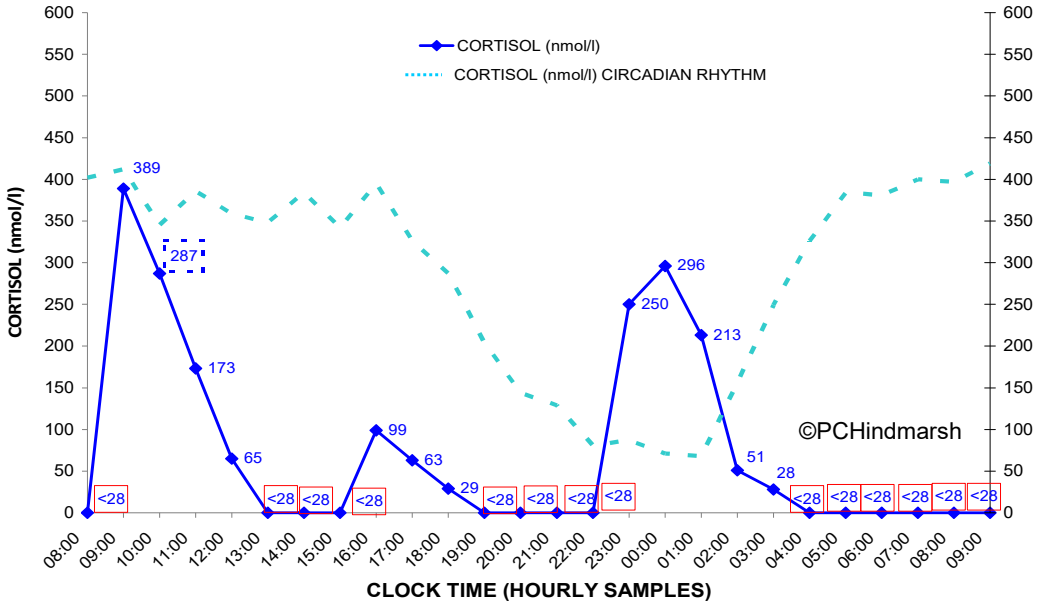

Figure: 6 Cortisol profile showing the cortisol distribution from the oral hydrocortisone compared to the circadian rhythm.

So what Figure: 6 shows us is that this patient runs low on cortisol around noon and then is without any traceable cortisol in the blood stream from around 13:00 hours and remains this way until their next tablet which is taken after the 15:00 hour sample. We can see that the cortisol levels in the early evening are low and that there is no traceable cortisol in the system at 19:00 hours until the next dose is taken at 22:00 hours. Although the natural rhythm of cortisol is low at this time of the evening, there is still cortisol in the blood stream. We can see that the normal production starts to rise in the early hours of the morning and remains high however the replacement cortisol from the hydrocortisone is out of the system around 03:00 in the morning, leaving this individual without any cortisol for around 5 to 6 hours.

Incidentally, we can also see that this patient did not take their morning tablet at 08:00 hrs. This particular individual on their current dosing schedule is without cortisol for 10 hours of the 24 hour period!

SO HOW DO YOU DO A PROFILE?

You need an intravenous (in the vein) cannula that is put in under local anaesthetic cream, so that lots of small samples can be taken. It may seem that a lot of samples are taken but in reality the amount of blood is not excessive – about an egg-cup full. 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.

If the cannula is working well, there is no pain when the blood is taken.

As well as measuring cortisol other hormones such as ACTH can be measured at times that you would be unable to achieve in out-patients.

Can you use saliva samples to do a 24 hour profile?

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 the 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.

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 using this method we are not directly measuring the cortisol that we are getting from the hydrocortisone which is taken to the organs, so 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.

24 hour profiles have allowed us to fine-tune our patients' replacement doses of hydrocortisone, which we believe will prevent many long term side-effects that arise from over and under treatment. We believe in getting the replacement values and distribution of cortisol as close as possible to the body's normal production. We have already seen many benefits in the medium and short term side-effects.