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THE VALUE OF 24 HOUR PROFILES IN CONGENITAL ADRENAL HYPERPLASIA

Professor Peter Hindmarsh

In this article we think through the biology behind profiles and consider how they are undertaken. We look at how to analyse them and point out problems that can arise when samples are taken too far apart.

ASSESSING HYDROCORTISONE REPLACEMENT IN CONGENITAL ADRENAL HYPERPLASIA

Cortisol is the hormone that is not produced in people with CAH. In children it is replaced using hydrocortisone which is a synthetic form of cortisol. When we replace with hydrocortisone we try to mimic the way in which the body normally produces cortisol.

Cortisol is made by the adrenal gland and the levels in the blood vary during the day. This 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.

The graph below (Fig:1) shows the cortisol levels during a 24 hour period in a person without CAH.

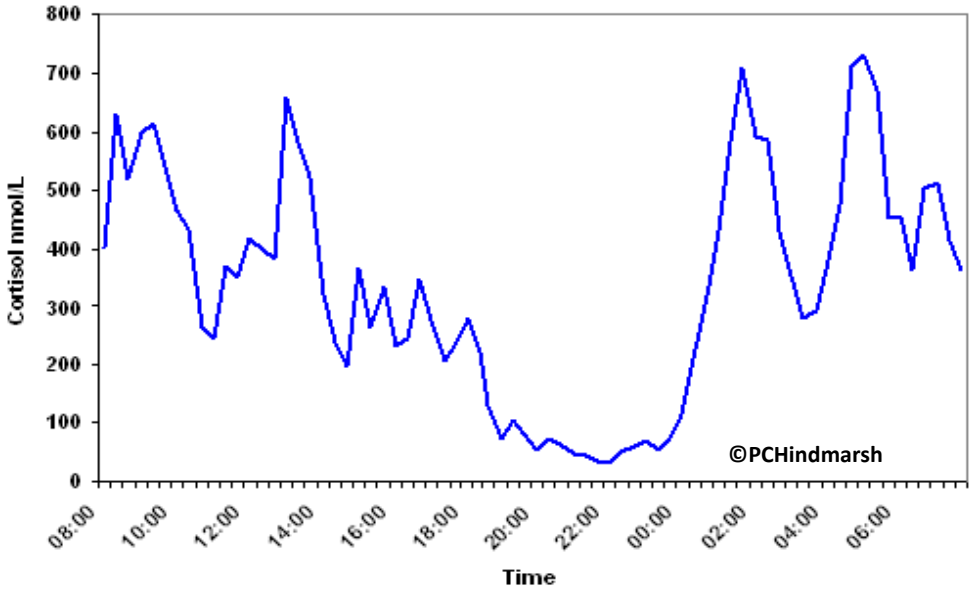


Fig:1

This graph illustrates the normal cortisol production of an individual who does not have CAH and it shows us that cortisol levels vary during the day and is a useful reference when we start to think about treating children and young people with hydrocortisone. The amount of cortisol production varies a little from person to person but the pattern the circadian rhythm is the same. This profile was done on 20 minute sampling.

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.

WHY GET CORTISOL RIGHT?

The main things to avoid are over and under treatment. Over treatment leads to weight gain, high blood pressure and potentially high blood glucose levels. In addition over time high cortisol leads to poor bone strength.

Under treatment not only means that the CAH goes out of control so that androgen levels increase but it leaves the person at risk of low blood glucose concentrations particularly during times of illness.

OUR CONCLUSIONS

After looking at lots of these types of profiles and checking out what our changes have done for people we have come up with the following thoughts:

1. In trying to achieve optimal control, it is important to consider the high peaks and low drops of cortisol. When studying all the data that a full 24 hour profile provides, the hydrocortisone dose and timing can be manipulated/adjusted to avoid excessive peaks and troughs of both 17OHP and cortisol levels, therefore causing less side effects.
2. Often these profiles will show that better control is gained by having smaller doses taken more frequently throughout the 24 hour period, which also ensures the patient is not cortisol deficient due to the relatively short half life of hydrocortisone. The data obtained from a 24 hour profile allows fine tuning of the dose in congenital adrenal hyperplasia.

PARENT COMMENTS:

As parents, we hate to see our children having blood tests. Yet, from the knowledge we have gained from our son having these, it really seems that the minor discomfort of having a profile, far outweigh the lifelong problems and upset that can be caused by both overtreatment and under treatment, particularly weight/growth issues. Although my son always had blood spot profiles, it was not until Professor Hindmarsh with his expert knowledge in cortisol replacement looked in detail at the cortisol derived from the hydrocortisone my son took, did we get any answers to his health issues.

The data showed that my son's body metabolises hydrocortisone very quickly and he was often without any cortisol which caused him tiredness and headaches. In previous years he had never had his cortisol levels checked, all his replacement therapy had been assessed only on his 17OHP levels. The 17OHP level was measured by doing the blood spots3 times (before each tablet was taken) over the 24 hours. Each time a level was out, his previous specialist simply increased his hydrocortisone dose, which caused so many side effects. What became very evident was that he was both very over treated and under treated and in fact he had periods where he had no cortisol in his bloodstream. What the full 24 hour profiles showed when studying the cortisol and the 17 OHP levels was that he really needed smaller, more regular doses throughout the day. Dosing four or five times a day can be considered a nuisance to some but having seen the difference, as many parents have, especially those who follow the circadian rhythm dosing, it is well worth the effort in achieving optimal replacement, resulting in good health, growth and fewer problems with weight gain.

My son's CAH was said to be very difficult to 'control' however it isn't really about controlling the 17OHP levels it is all about getting the cortisol replacement correct, after all that is what taking hydrocortisone is doing, replacing cortisol. The 17OHP follows the cortisol as there is a delay on the cortisol's effect on the 17OHP which is why it is called the feedback loop system.

In the graph below (Fig:10) when we add the full 17 OHP results from this profile we can see the following:

1. There are periods where the cortisol is dropping too low pre dose and is not lasting until the next dose is due to be taken, even though the 17 OHP level is within range. The symptoms a patient could suffer as previously described, are tiredness and headaches.
2. There are periods where the cortisol levels peak too high which causes the 17 OHP levels to drop too low. This could lead to weight gain and other side effects you get with over treatment.

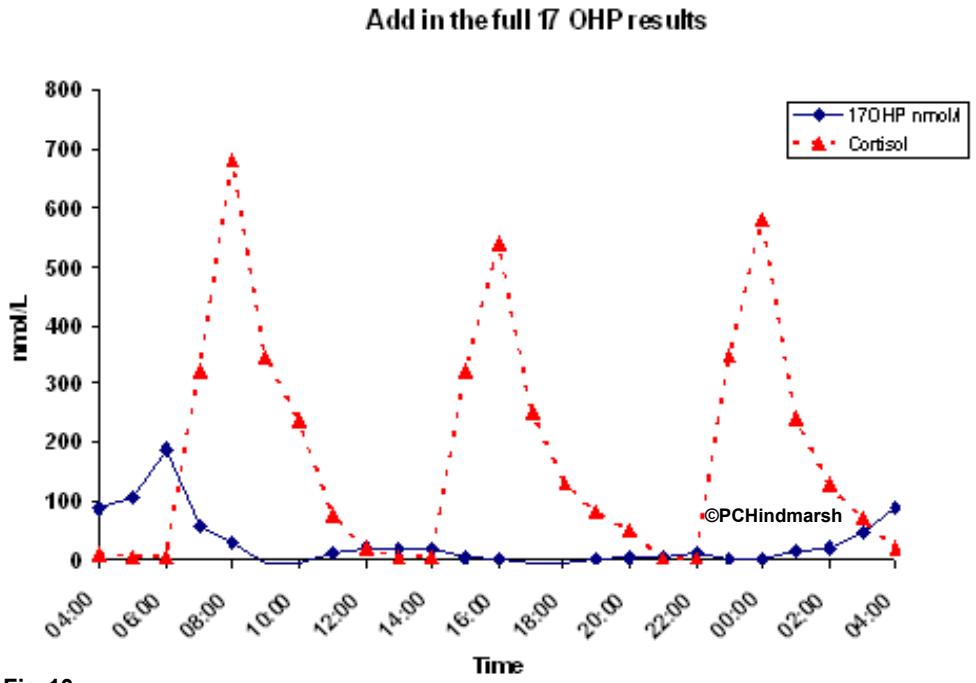


Fig:10

The results of both the 17 OHP blood sample taken in clinic, and the afternoon and evening pre-dose 17 OHP blood spots, show good control.

The early morning, pre-dose 17 OHP blood spot would show an out of range 17 OHP result, however there is a great difference of opinion on what the optimal 17 OHP level at this time should be.

If the early morning dose was increased based on this, it would only give an even higher morning cortisol peak and cause the 17 OHP level to drop even lower, but the 17 OHP would rise again as soon the cortisol drops well before the next dose is due.

This would increase the side effects. If the evening dose was increased you would get the same scenario. Studying the graph above this patient's medication could be fine tuned by changing the timing of the doses and giving 4 smaller doses a day.

SO WHAT IS HYDROCORTISONE?

Hydrocortisone is a 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: – prednisolone for 6-8 hours, dexamethasone 12 hours.

You might think the longer the better but this is not simply the case as prednisolone and dexamethasone have a tendency to suppress growth which is why we use hydrocortisone in children. A further advantage is that we can measure hydrocortisone in the blood but not prednisolone or dexamethasone.

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.

The table below (Fig:2) shows the equivalent doses for these two glucocorticoids against hydrocortisone:

Steroid	Duration of Action (hours)	Peak Action (hours)	Growth Suppressing Effect	Dosing Effect on Growth	Mineralocorti-coid Effect
Hydrocortisone	6	2	1	20 mgs	1
Prednisolone	8	4	5	4 mgs	0.8
Dexamethasone	12	Rather flat profile	80	0.4 mgs	0
Fludrocortisone					200

Fig:2

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.

It is also important to consider the impact of fludrocortisone which is used as a replacement of aldosterone in salt-losers.

Fludrocortisone has not only mineralocorticoid but also potent glucocorticoid activity (a bit like dexamethasone) as shown in the table and it is important to remember this when calculating the total daily glucocorticoid dosing: i.e. the contribution of 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).

This shows that it takes about 1-2 hours for hydrocortisone to reach a peak and about 6 hours before the dose wears off.

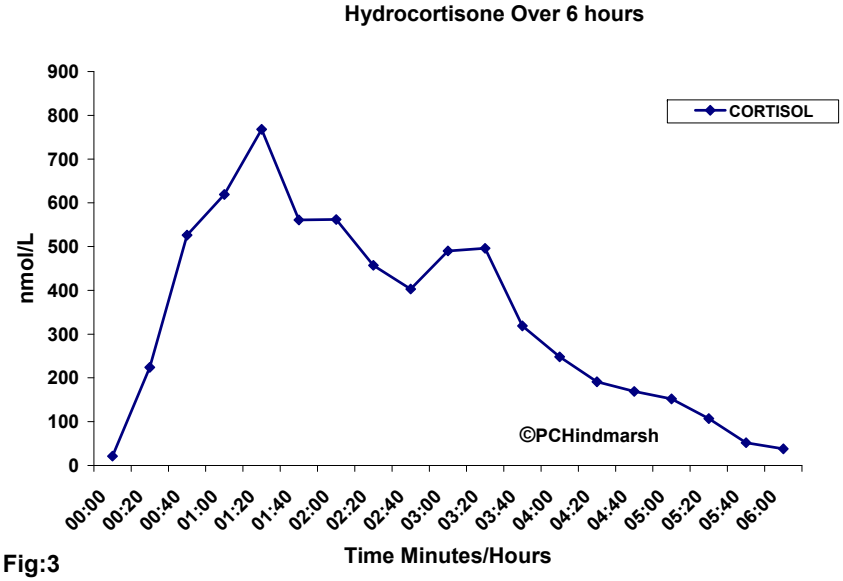
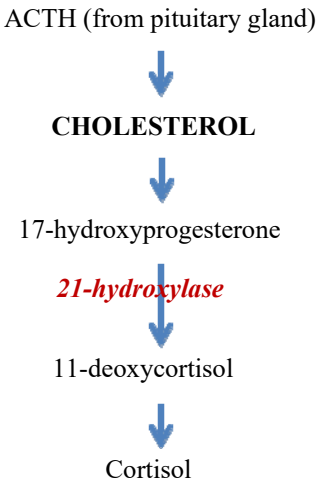


Fig:3

HOW DO HYDROCORTISONE AND 17OHP INTERACT?

In people without CAH there is no real interaction between cortisol and 17OHP because 17OHP levels are low compared to cortisol. Remember the pathway of how cortisol is produced from cholesterol? It looks like this: (Fig:4).



Remember that the block is in making cortisol, so you get an increase in ACTH to compensate, which raises 17OHP as it is before the block.

Fig:4

Looking at the afternoon result in the graph (Fig:8) shows the control maybe alright. What is not clear is how this is achieved. Is the hydrocortisone dose just right or perhaps too high? Is the timing of the doses alright as they could easily have run out of hydrocortisone earlier and about to escape from control? Remember what we said about 17OHP not changing much until about 1 hour or so after a cortisol is high.

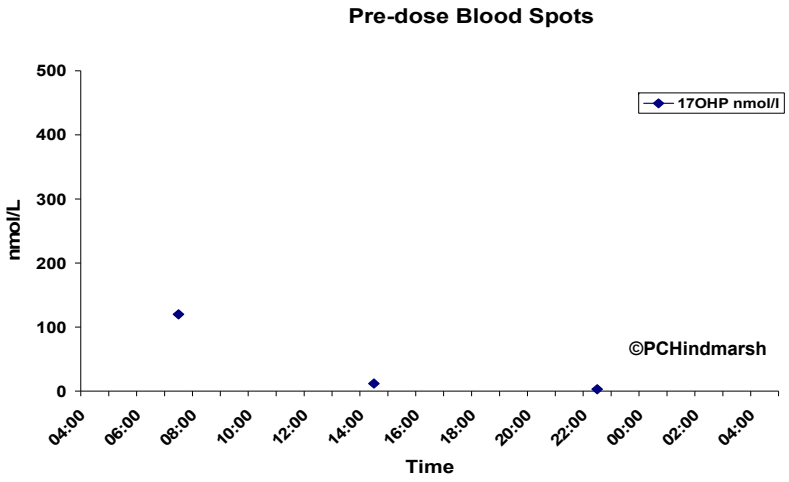


Fig:8

However if we add the cortisol results to this as in the chart below, (Fig:9) you will see that this patient is experiencing high peaks of cortisol, however the cortisol is not lasting until the next dose. This is often apparent when children feel tired or get headaches at lunchtime. The 17OHP looks fine but it is the cortisol that matters at this point from the symptoms standpoint. This is why a full profile would be informative, as the balance between control (17OHP) and over/under treatment (cortisol) can be determined.

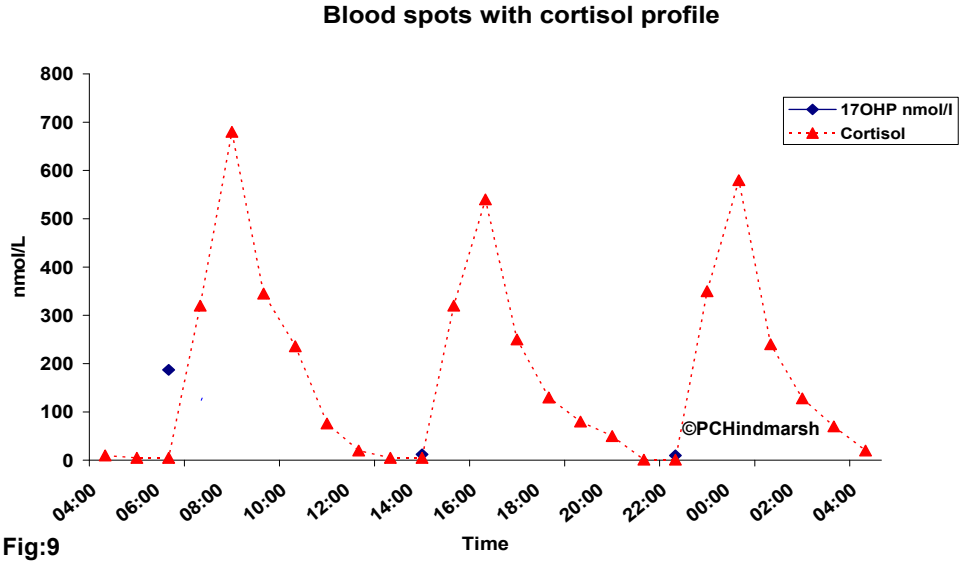


Fig:9

Blood Tests and Blood Spots

Let's just think again on those single blood tests or tests taken at infrequent time intervals. We are using a different set of data now from another patient.

If a one off blood test was taken just after 12.00h in clinic and we plot the result on a graph, (Fig:7) this is the information we would get.

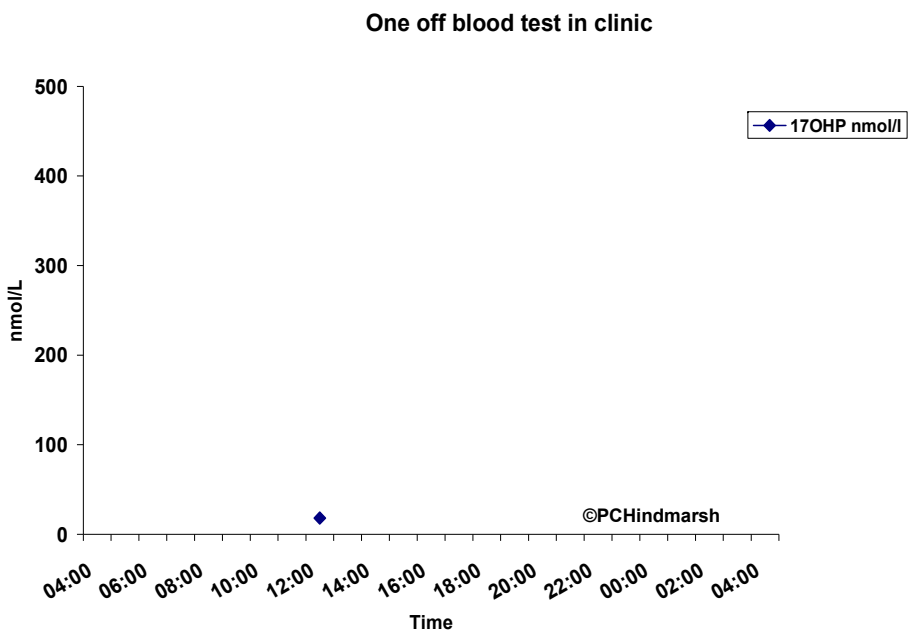


Fig:7

You would say based on this 17 OHP result that we are doing well and no changes are required. However we have no idea of the exact time the tablet was taken in relation to the dose, it might have been taken earlier or later than usual, we have no idea of the cortisol level, and no idea what is happening the rest of the day to the 17 OHP or cortisol.

BLOOD SPOTS

These certainly let us do more tests. If we plot the results of pre-dose blood spots in the next chart on page 9 (Fig:8) this is the information we would get from the data which does not show the peaks and troughs of 17OHP or the cortisol.

If we were to join these dots we do not see a true picture of what is happening to the 17 OHP.

The problem with this is that it is not possible to be sure what needs to be changed. Increasing the evening dose will not help the 22.00h 17OHP as it is low anyway and is unlikely to make much difference to the early morning sample as the time course of hydrocortisone is such that the system will not be suppressed much after 03.00h.

It is possible to have below normal 17OHP levels and even normal 17OHP levels and for there to have been no measurable cortisol in the blood for several hours.

SO HOW DO CORTISOL AND 17OHP RELATE TO EACH OTHER?

This gets a bit technical but bear with us.

As you can see in the hydrocortisone profile the cortisol peaks around 1–2 hours after taking a dose, but because the cortisol has to tell ACTH to dampen down, this takes a bit of time before we see a change in ACTH and a bit more time as the adrenal gland switches off the production of 17OHP.

This switch off takes about 1 hour after the peak of cortisol.

WHAT ARE WE TRYING TO DO WITH PROFILES?

With a 24 hour profile you test not only the 17OHP but the cortisol at either hourly or two hourly intervals during the night and early morning.

This allows us to answer three questions:

1. Is the cortisol replacement optimally distributed – the cortisol & 17OHP measure.
2. Am I having too much hydrocortisone – the cortisol peak measure.
3. Am I having too little hydrocortisone – how long does the hydrocortisone last.

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

CAN WE GET THIS INFORMATION FROM BLOOD SPOT TESTS?

The blood spots show a 'snap shot picture' of only the 17OHP at that moment. They are very valuable to do because at that time, just before the dose, if the 17OHP is too high, you know that you either need more hydrocortisone or take it more frequently and if the 17OHP were too low the dose may need reducing but by how much?

This method does not show the peaks after the cortisol is taken and the troughs as the cortisol is metabolised and therefore does not give a full picture of what is happening between doses.

What you would need to do here is to carefully time samples pre and about 3 hours post dose to get a feel for the effect of hydrocortisone.

Unless the samples are taken with respect to dosing then it is very hard to interpret and results can be misleading.

SO HOW DO YOU MAKE A PROFILE?

You need an intravenous cannula that is put in under local anaesthetic cream so that lots of small samples can be taken every 1 to 2 hours.

If the cannula is working well, there is no pain and even if the patient is upset it doesn't really affect the 17OHP, so you get more accurate readings.

You measure cortisol and 17OHP but you can also measure lots of other things (hormones) on the same sample such as ACTH, androstenedione and measures of how well the testes or ovaries are working and at times that you would not normally be able to achieve in out-patients, i.e. early morning when the ACTH starts to rise.

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.

THE 24 HOUR PROFILE

It is important to realise that if you take too few samples and/or do not relate them to the dose then you may get falsely reassuring information.

This is particularly relevant in 'one off' blood tests; it is ***essential*** to know the cortisol value, 17OHP and the time the tablet was taken as without considering all this vital information you could get false information suggesting poor control because you hit an odd occasion when 17OHP is high or too low.

A common example of this is a sample taken, or blood spot done pre breakfast when the hydrocortisone given at 22.00 hours the previous evening is out of the system by the next morning causing the 17OHP value to be high, however after the morning dose, the 17OHP comes down within range again as the cortisol rises.

An example of this can be seen in the graph below (Fig:5)

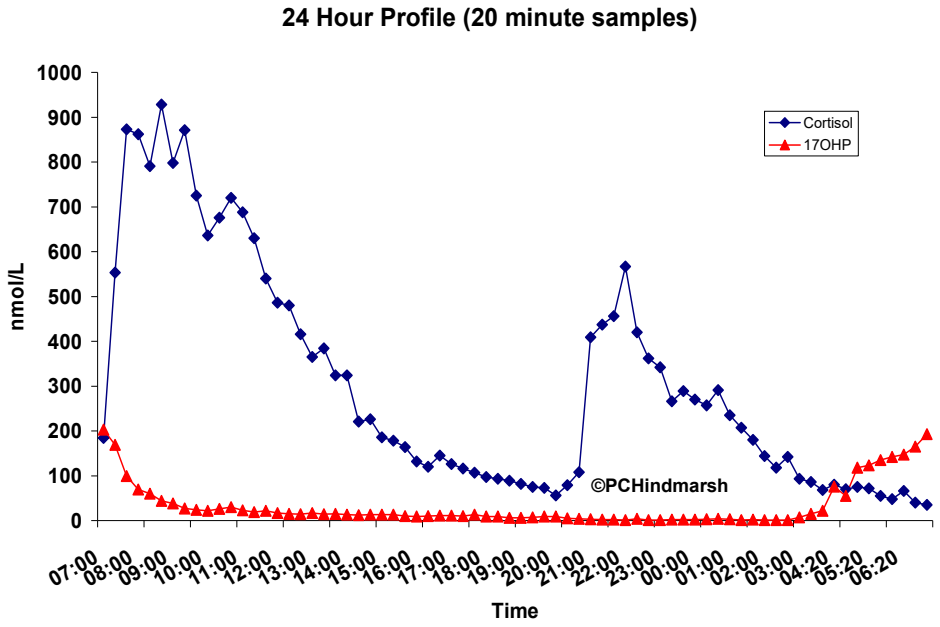


Fig:5

Here you can see the high 17OHP in the morning which settles once the hydrocortisone tablet is taken first thing after waking.

Notice the effect of the evening dose which has high peak at 22.00h but notice the 17OHP was low anyway. However, when you want the hydrocortisone to suppress the 17OHP, early hours of the morning (04.00h onwards) the hydrocortisone is wearing off.

This tells you that the best way to deal with the problem is to have the hydrocortisone as late as possible the previous evening and preferably about 01.00 - 02.00h!!

WHAT INFORMATION DO YOU GET?

We have an actual patient plot here of cortisol and 17OHP in the graph below (Fig:6) This person has hydrocortisone at 08.00 h, 15.00 h and 22.00h.

1. You can see the height of the cortisol peaks and judge if too high or too low.
2. This is important as hydrocortisone peaks two hours after taking it, so a sample taken at this time, will show how high the cortisol peaks:-
   a). If the peak is too high, this will over suppress the 17OHP which will then drop too low. This would show the dose is too high and could be lowered (evening plot in yellow).
   b). If the cortisol is too low, the 17OHP will be higher than it should be so the dose needs to be increased (morning at 06.00h)

Then by studying the graph as a whole, you would see how long the cortisol is lasting in the system, which can be used to establish the best time to take doses.

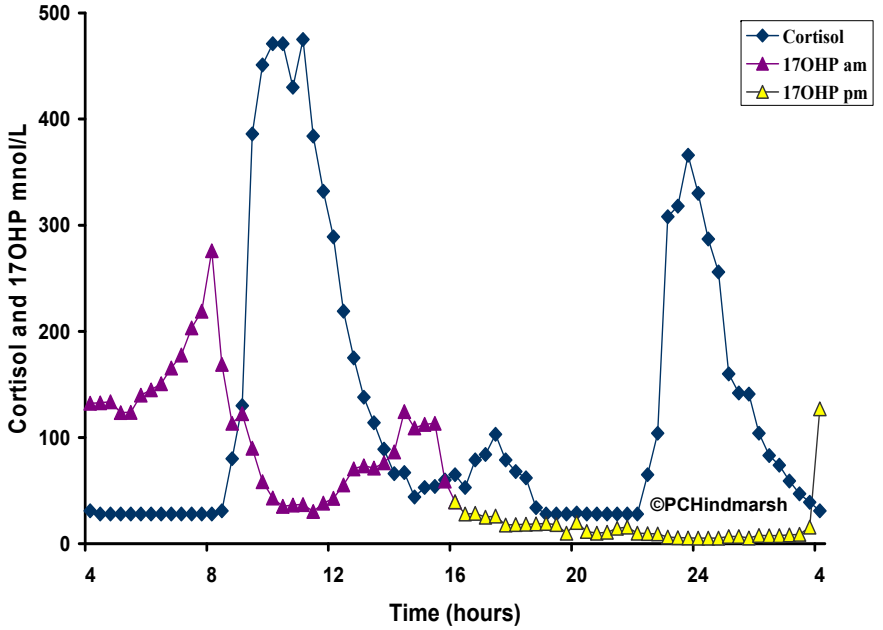


Fig:6

1. Fast metabolism: in this scenario the cortisol would clear the system very quickly and although you would achieve a high peak of cortisol, it would rapidly fall and therefore not suppress the 17OHP sufficiently. What would then occur is a peak of 17OHP and a dip of cortisol way before the next dose of hydrocortisone is due to be taken. Almost like the situation at 15.00h in the graph.

This could mean that in order to gain better control, smaller doses taken more frequently would be better suited.

2. Slow metabolism: in this scenario, the cortisol remains in the system for a longer period of time and therefore doses can be taken less frequently.