

Professor Peter Hindmarsh

Divisional Clinical Director for Paediatrics and Adolescents at
UCLH Developmental Endocrinology Research Group

Transcripts of the conference held on

Saturday 14th June 2014

Institute of Child Health

London

**WORKING TOWARDS A SINGLE
GOLD STANDARD CARE
PROTOCOL FOR EVERYONE OF ALL
AGES WITH CORTISOL DEFICIENCY**

Hosted by the

University College London Hospitals & Great Ormond Street Hospital

CAH Parent and Patient Group

Along with the Pituitary Foundation &

Addison's Support Group

Grateful thanks to

Dr Niki Karavitaki

Dr Quen Mok

Dr Rebecca Salter

Kathy Geertsma

Alice & Richard Jackman

Pat Mc Bride

Noel Hawks

SUMMARY REPORT OF MEETING HELD ON JUNE 14TH 2014

On the 14th June 2014 a joint meeting of the Congenital Adrenal Hyperplasia Parent and Patient Support Group of University College London Hospitals and Great Ormond Street Hospital for Children, along with the Addison's Support Group and The Pituitary Foundation, was held. The topic was cortisol replacement with particular emphasis on managing emergency situations. A range of speakers presented the basic problems in adrenal insufficiency, outlined normal cortisol production and considered methods of assessing and replacing cortisol. In addition, the role of paramedics in the ambulance service was described and the care that might be expected in Accident and Emergency presented.

INTRODUCTION

The meeting was introduced by Professor Peter Hindmarsh, Professor of Paediatric Endocrinology and Consultant in Paediatric Endocrinology at University College London Hospitals and Great Ormond Street Hospital for Children, who outlined what the meeting was about, namely working towards a single gold standard care protocol for everyone of all ages with cortisol deficiency. This was prompted by a number of news reports highlighting the problems individuals had faced with the emergency services and on a number of occasions these had tragically been associated with loss of life.

Professor Hindmarsh clarified what we meant when we say 'adrenal insufficiency.' This term is used frequently and loosely. Adrenal insufficiency simply refers to a reduction in, or loss of adrenal hormone production and in the case of this meeting, cortisol. It is important to realise that adrenal insufficiency is not a diagnosis. Adrenal insufficiency is caused by a number of conditions that affect the adrenal gland (primary causes), or the control system – the hypothalamus and pituitary (secondary).

These primary causes may be conditions such as Congenital Adrenal Hyperplasia (CAH), Addison's Disease, Adrenoleukodystrophy (ADL) or Adrenal Hypoplasia Congenita (AHC). In all of these conditions, the adrenal gland has either failed to form properly, or is incapable of producing the important hormone cortisol. In adrenal insufficiency due to hypothalamo-pituitary problems, the loss of cortisol production arises as a result of problems in the development of the pituitary gland, or because of damage to the pituitary gland relating to the presence of tumours or inflammation or following surgery to the gland in patients with Cushing's disease.

WHAT DO WE MEAN WHEN WE SAY ADRENAL INSUFFICIENCY

As stated previously 'Adrenal Insufficiency' simply refers to a reduction in or loss of adrenal hormone production. It is **NOT** a diagnosis. Adrenal insufficiency is caused by a number of conditions that affect the adrenal gland (Primary) or the control system (secondary) as illustrated in Figure: 1

Adrenal Insufficiency is not a Disease it is the result of a number of conditions

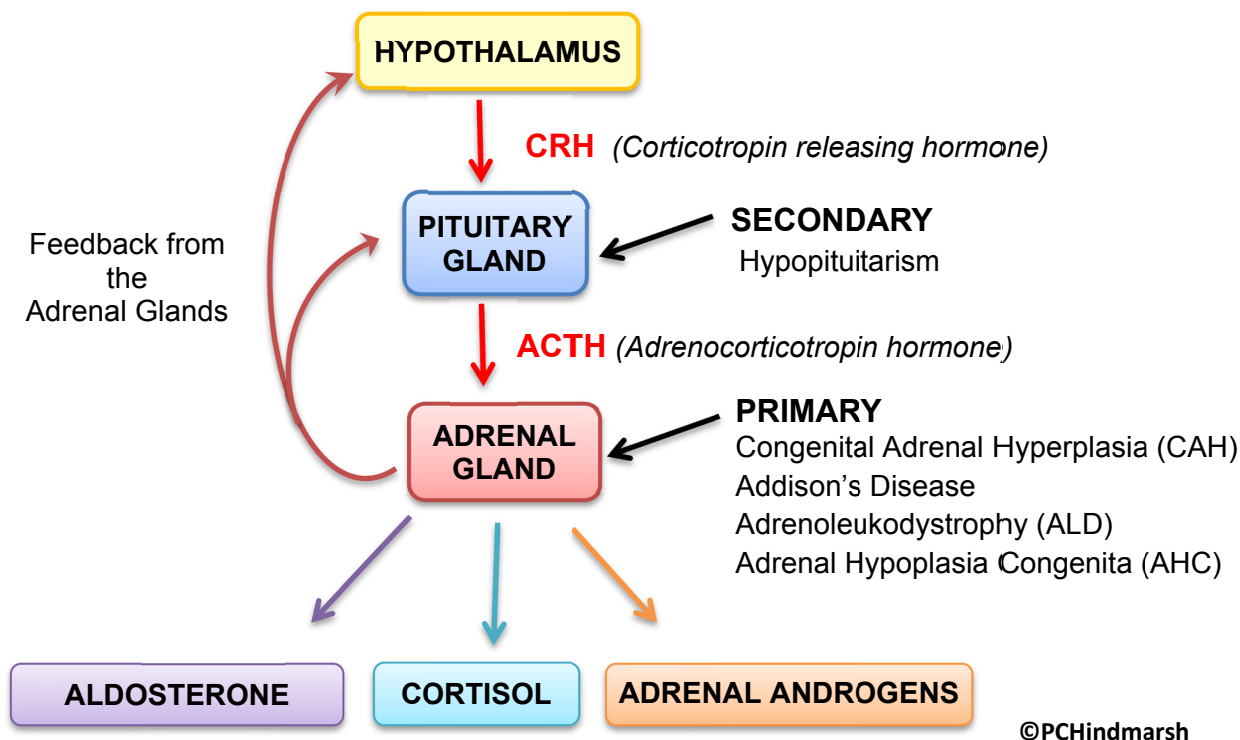


Figure: 1

Adrenal insufficiency is used as a descriptive term and, as Professor Hindmarsh reiterated, this is **not a diagnosis**. However, Adrenal Insufficiency is the most appropriate wording to be used on Medic Alerts, this being because it is the recognised terminology used by the ambulance services in their pathway system. The pathway alerts the emergency services that an injection of hydrocortisone is needed urgently.

We highly recommend that everyone who has any of the conditions above wears a Medic Alert at all times using the words Adrenal Insufficiency. Babies and toddlers will soon get used to wearing one and the chain can be shortened and links re added as the child grows. Although parents feel they are always with their child, it might be that something happens which may leave you unable to communicate with the emergency services. Paramedics who are usually on the scene first, as well as all other emergency staff involved in urgent care, are trained to look for medic alerts! If your child (or you) is not wearing one, they would not be aware your child (or you) needs that lifesaving IM hydrocortisone injection and a life could be lost due to this.

It was also important for us all to understand what is meant by an adrenal crisis and Figure: 2 shows the pathway of events that lead to severe problems and unfortunately in some instances, death.

ADRENAL CRISIS - PATHWAY OF EVENTS

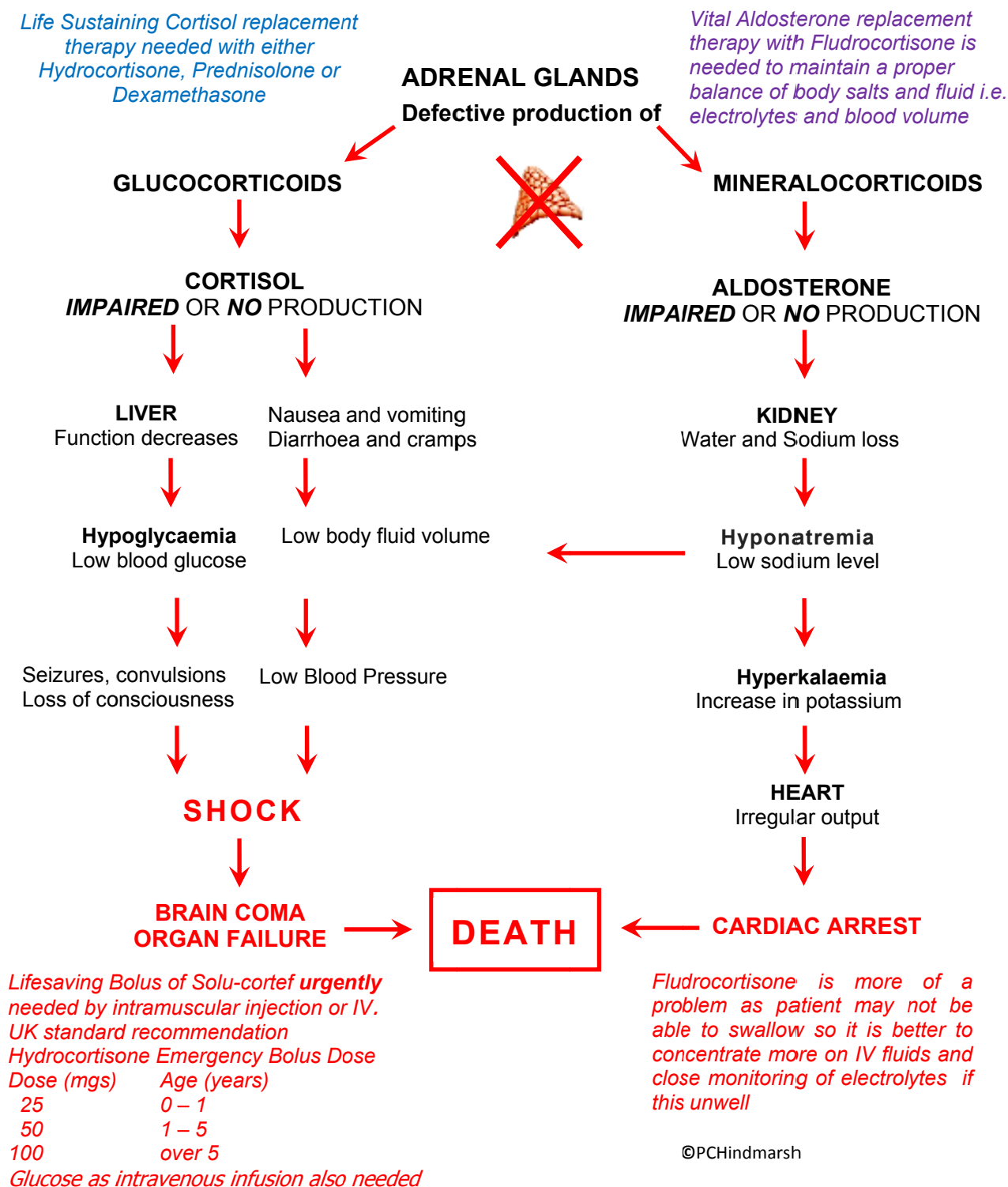


Figure: 2

PROBLEMS FACED BY PATIENTS WITH ADRENAL PROBLEMS – Dr Niki Karavitaki

Dr Niki Karavitaki, who is an Adult Endocrinologist from the Oxford Centre for Diabetes, Endocrinology and Metabolism, presented an overview of problems that people face with adrenal problems. Dr Karavitaki talked about the mortality rates that are associated with adrenal insufficiency. In congenital adrenal hyperplasia there is a 2.8 fold increase in mortality rates, compared to the general population, whereas in Addison's Disease this value is 2.2. Interestingly, in hypopituitarism, the mortality rate is 1.4 overall, but if the individual has normal cortisol production, then they have the same mortality rate as the general population, but if they are deficient in cortisol, then their mortality rate increases dramatically. These points suggest that it is the cortisol deficiency that is the major cause of problems in these conditions, and it was of interest to note that the major causes of death were infections and circulatory collapse.

Dr Karavitaki concluded that, although treatment regimens have improved considerably, there is still a significant increase in loss of life, and that close attention was required to improving our management of acute illness particularly when due to infections.

Dr Karavitaki went on to describe other problems that are associated with cortisol replacement. The first that is encountered, certainly in adult practice, is difficulty in matching the replacement therapy with the normal circadian rhythm. Shown here (Figure: 3) is a picture of the normal circadian rhythm and superimposed on it is an example of 2 doses of cortisol given to an individual.

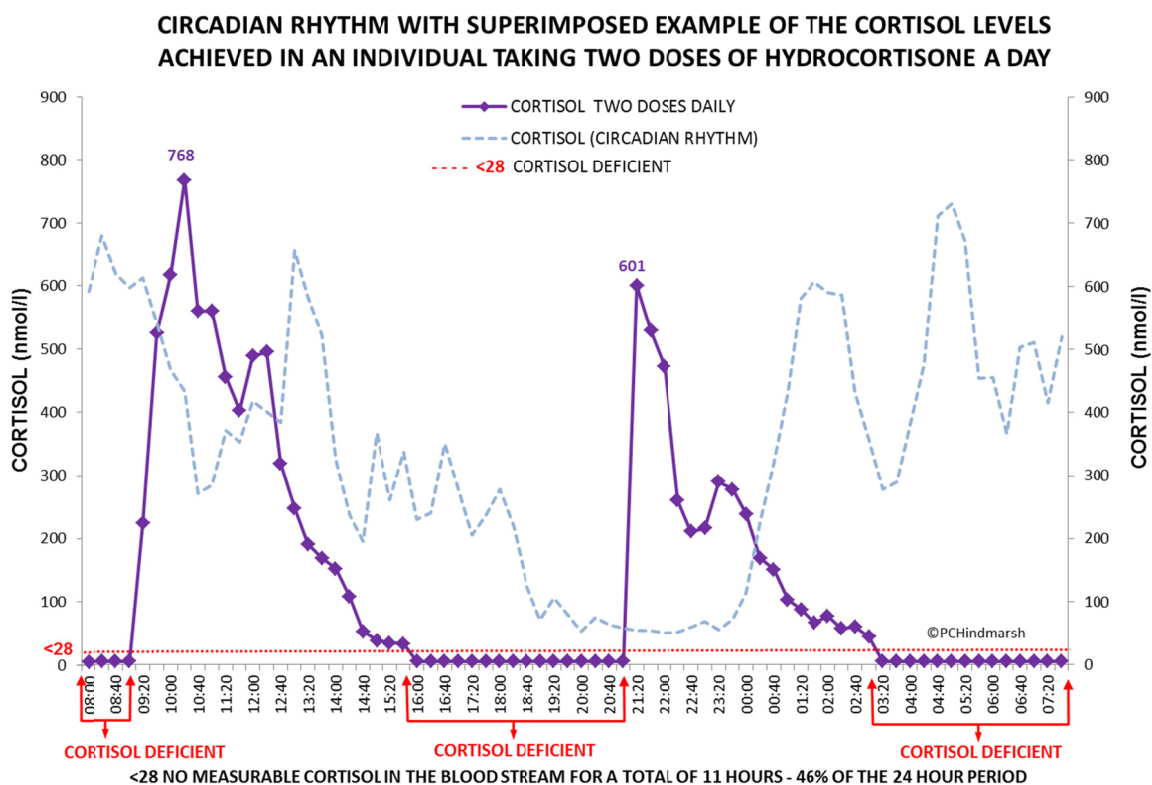


Figure: 3

This is quite a complicated graph, but it does illustrate the fact that for considerable periods of time the patient is either receiving large amounts of cortisol or there are periods of time when the individual is under-replaced or totally cortisol deficient.

It is under-replacement, Dr Karavitaki explained, which leads to impairment of wellbeing and the potential for life-threatening problems if an intercurrent illness should intervene.

With current medications there remains considerable problems with respect to osteoporosis, and it does seem that there is an increase in osteoporosis in patients on more than 25mg daily of Hydrocortisone. It is not clear whether doses between 20 and 25mg per day alter bone density, but this is the rationale for using 20mg as the top dose in adults.

Quality of life also appears to be reduced in both a German and Norwegian study. Of interest is that the Norwegian researchers went on and showed that quality of life improved when patients received hydrocortisone via a pump.

Dr Karavitaki also drew attention to the impact of high doses of hydrocortisone on measures of cardiovascular health. Waist hip ratio is a predictor of heart problems. The higher the ratio, then the more likely that there will be heart problems. In addition high doses of Hydrocortisone (more than 30mg per day) were associated with impaired handling of the sugar in the blood, an increase in the blood cholesterol, high blood pressure, obesity and, of course, the osteoporosis as noted above.

However, it should not be assumed that high doses will do this to everyone. This is because the adverse health effects are related to the amount of cortisol in the blood and this will vary between individuals because they will absorb and remove cortisol from the blood differently. This is explored further in the report of Professor Hindmarsh's work in this area.

All these problems stem from the difficulty in matching cortisol to the natural circadian rhythm.

In addition, adult patients tend to take their last dose at 6pm which means that during the day they would get a lot of hydrocortisone (nearly all their dose) whilst at night when the drive to the adrenal glands was maximal they had no cortisol in the blood at a time when naturally there should be some.

This would produce an over and under replacement situation and inability to mimic the natural circadian rhythm of cortisol.

NORMAL CORTISOL PRODUCTION – Professor Peter Hindmarsh

Professor Hindmarsh followed on from these observations and started by looking at normal cortisol production. He showed the meeting that the circadian rhythm of cortisol is present at all ages, and is the same in males and females as illustrated in Figure: 4 and Figure: 5.

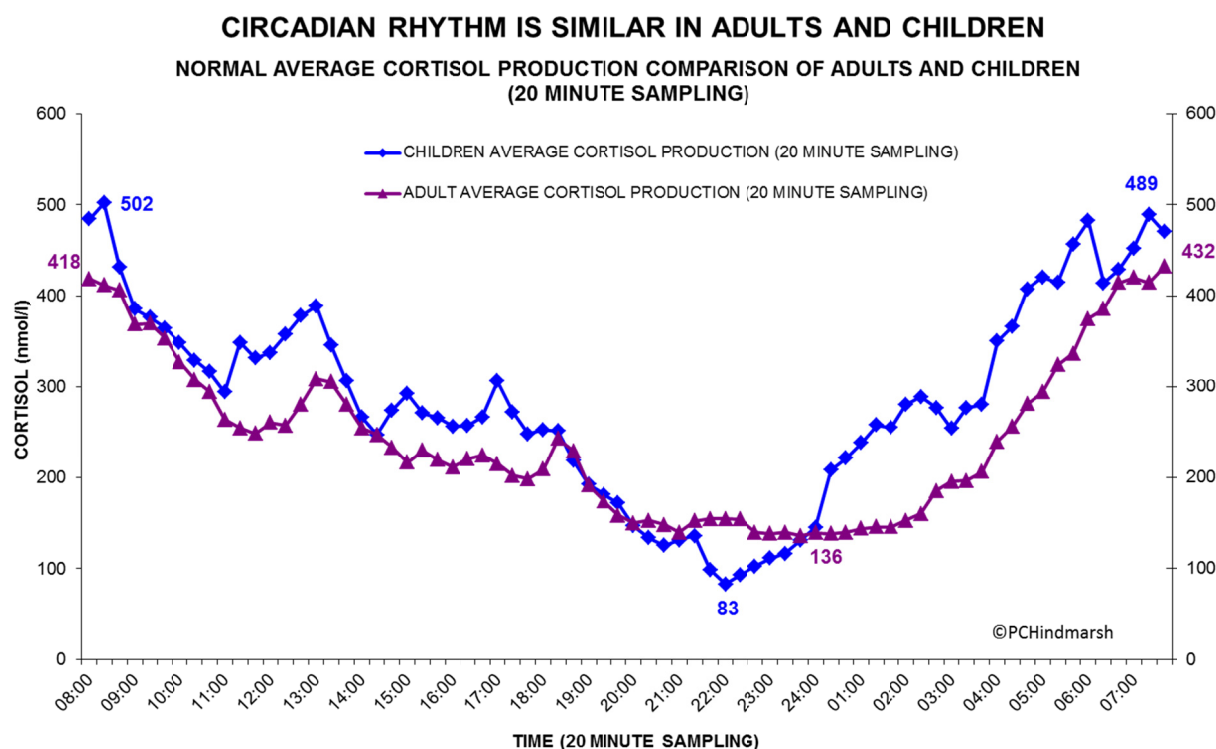


Figure: 4

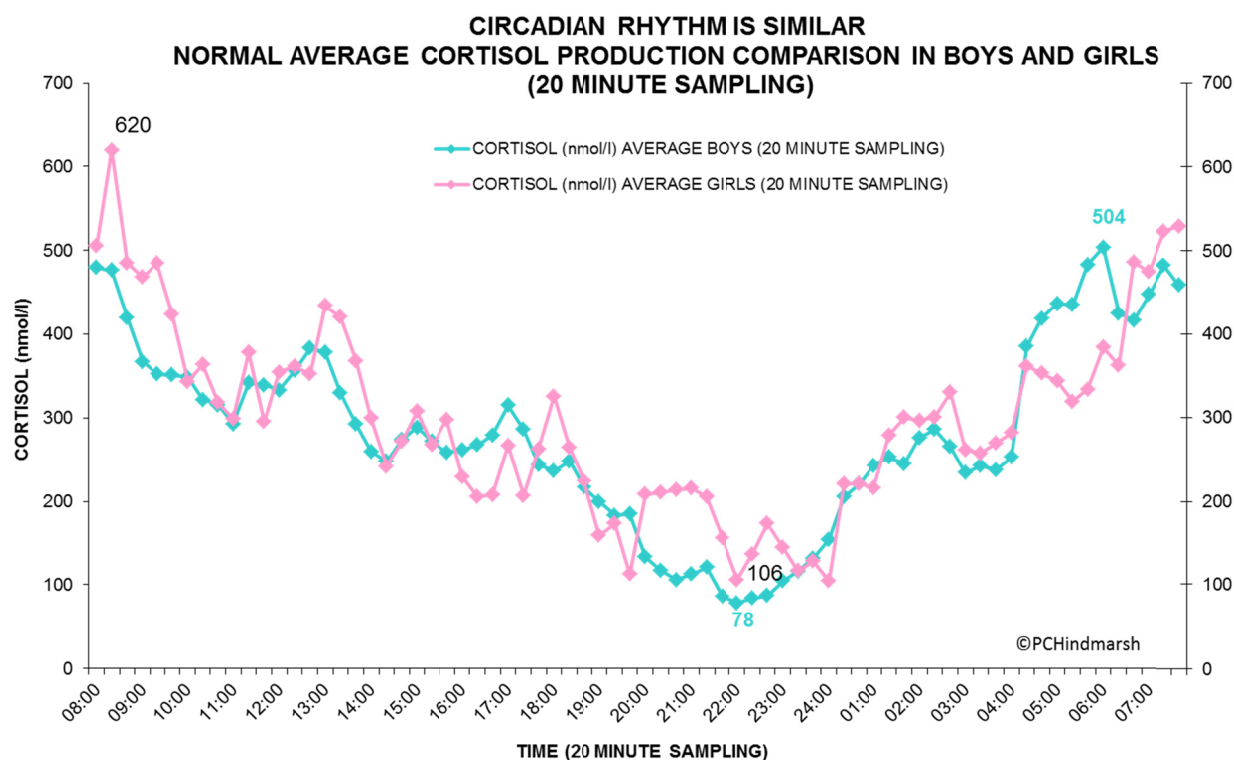


Figure: 5

Professor Hindmarsh drew to attention that at all times during the 24 hour period there is always some cortisol present in the circulation. In over 80 profiles from adults that he had studied, it was very unusual for cortisol levels to be undetectable. It is just as important at certain times of the day to have low values, as it was to have normal values.

In addition, Professor Hindmarsh also showed how cortisol is spread across the day and night as shown in Figure: 6 below. This, he said, should help guide replacement therapy in terms of the proportion of total daily dose used.

SPREAD OF CORTISOL THROUGH THE 24 HOUR PERIOD

Time Segment	Percentage of Total Cortisol Secretion during Time Segment	
	Children	Adults
06:00 – 12:00	38.4	26.4
12:00 – 18:00	21.2	21.2
18:00 – 24:00	10.7	7.2
24:00 – 06:00	29.7	45.2

©PCHindmarsh

Figure: 6

It is also important to consider how each different glucocorticoid, these being Hydrocortisone, Prednisolone and Dexamethasone, last in the body.

To help with this, Professor Hindmarsh introduced the idea of half-life. The half-life of a drug is the time taken for 50% of the total amount in the circulation to disappear. The half-life values for Hydrocortisone, Prednisolone and Dexamethasone are shown in Figure 7.

Glucocorticoid	Hydrocortisone	Prednisolone	Dexamethasone
Half-Life in Blood (hours)	1.5	2 - 3	3.5 – 4.5
Duration of Action (hours)	6	8-12	36
Peak Action (hours)	2	4	Rather flat profile
Growth Suppressing Effect	1	5	80
Dosing Effect on Growth (mgs)	20	4	0.25-0.4

©PCHindmarsh

Figure: 7

However it's not *just* the half-life that is important, it is also the duration of action. The duration of action of a drug is longer than half-life, because of the way that drugs work on different systems in the body. What is important to notice is that the duration of action, which will tell you a lot about side effects, varies with these 3 medications, so it is more likely that with Dexamethasone, which has a duration of action of around 36 hours, more problems might be encountered than with Hydrocortisone, which has a duration of action of 6 hours.

These numbers also tells us what the likely dosing schedule ought to be. So for Hydrocortisone, a 4 times per daily dosing regimen would be most likely. The table also shows us how potent these agents are. Professor Hindmarsh, being a paediatrician, used the example of growth and showed that Dexamethasone was 50 - 80 times more likely to suppress growth than Hydrocortisone as 0.25 - 0.4 mg of Dexamethasone will stop growth whereas 20mg of hydrocortisone would be needed to have the same effect.

There are other factors which influence how we are going to dose with glucocorticoids. Bioavailability, or how much comes into the body when it's taken in orally, is important. Interestingly, oral Hydrocortisone reaches a peak in the blood 67 minutes after ingestion. That is the average but there is quite a range in the population and the range goes from as low as 20 minutes right up to 200 minutes. There is considerable variation which needs to be considered when thinking about dosing with the drug.

What was even more dramatic was the variation in half-life. In a study of 51 patients that Professor Hindmarsh presented, the fastest half-life recorded was 40 minutes and the slowest was 225 minutes. More than a five times difference!

This huge variation in both absorption and half-life in the population means that dosing has to be specifically tailored to the individual.

It is not just that dosing needs to be tailored in this way it also means that care has to be given to the timing of the dose. This is because the half-life of the drug and probably the absorption changes over the 24 hour period.

For example, as illustrated in Figure: 8 the same dose given to an individual, say 5mg at lunchtime (shown by the first red arrow) has a completely different peak value, compared to 5mg given at night (shown by the second red arrow).

24 HOUR CORTISOL PROFILE

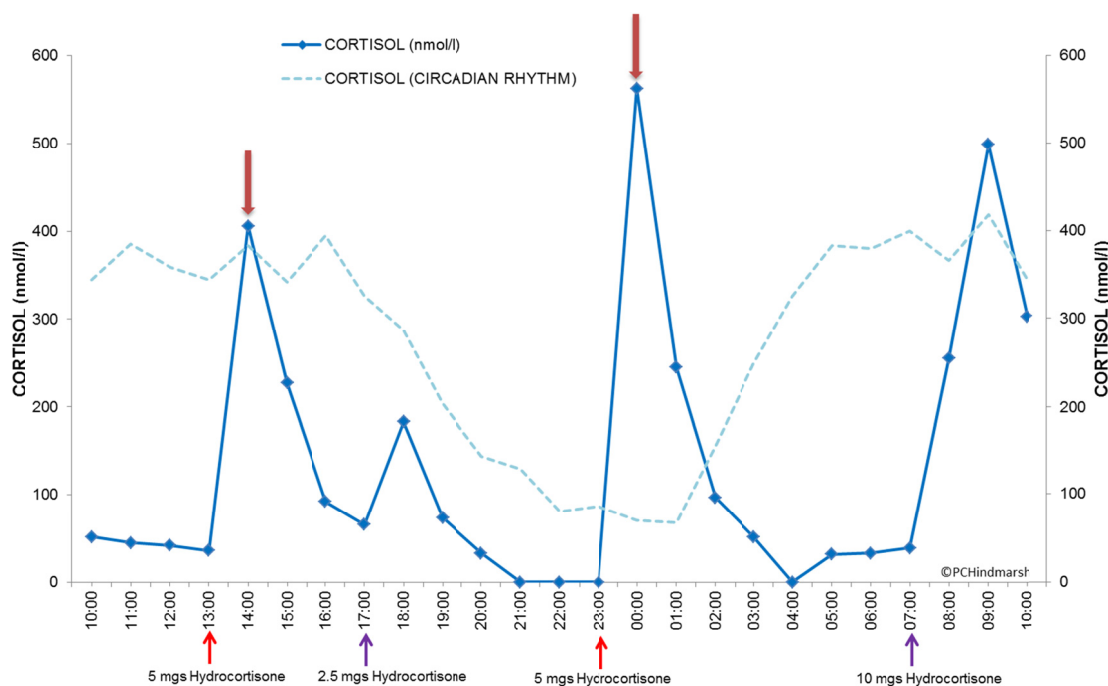


Figure: 8

Professor Hindmarsh showed an example of this and how, even on a 4 times per day regimen, the profile didn't quite match that of the circadian rhythm. Professor Hindmarsh put great emphasis on the fact that the timing of the administration of Hydrocortisone is extremely important for these reasons and for a further one. He introduced a new idea called "cortisol stacking" see Figure: 9

CORTISOL STACKING - WHY TIMING IS IMPORTANT

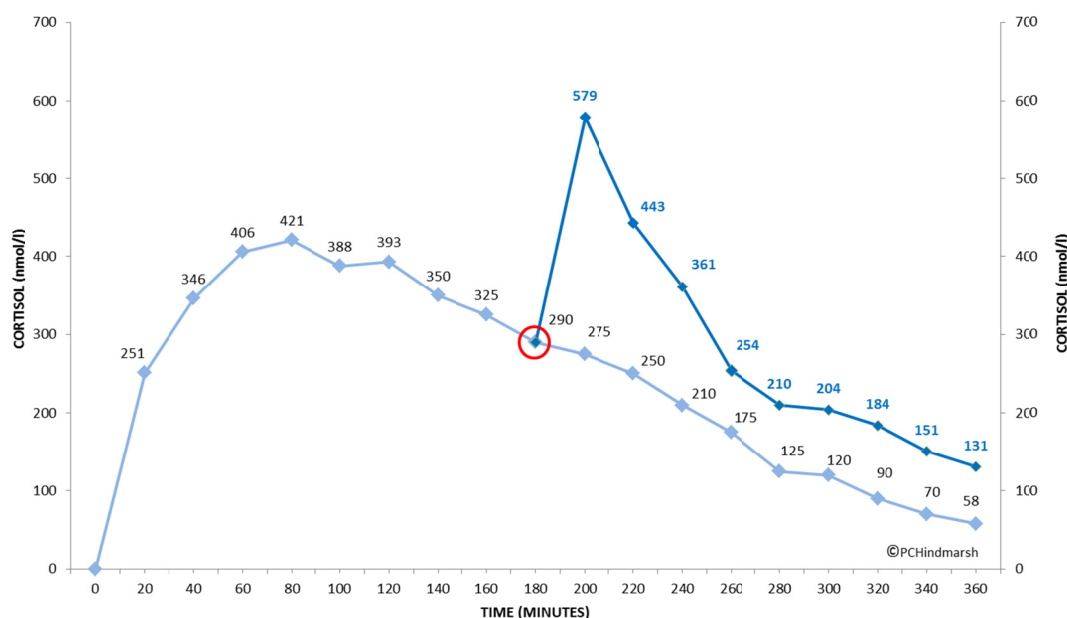


Figure: 9

In this situation what happens is that if a reasonable period of time is not allowed between doses, then one dose becomes superimposed on the other, and quite high levels can be attained without the individual realising. At the concentration point shown in the red circle if extra dose is taken then high values of 579 nmol/l ensue which might not be expected. This means that doses must be given at fixed times and that those times need to be worked out on the basis of time of day and how the individual absorbs the drug and how quickly they remove it from the circulation.

The presentation then looked at ways in which a better approximation to the circadian rhythm could be achieved. The use of Plenadren was considered but the drug seems to generate an extremely high peak and its duration of action does not seem to be much longer than that of Prednisolone.

What surprised the audience, however, was how well delivering Hydrocortisone using an insulin pump device was as can be seen in Figure: 10 and Figure: 11.

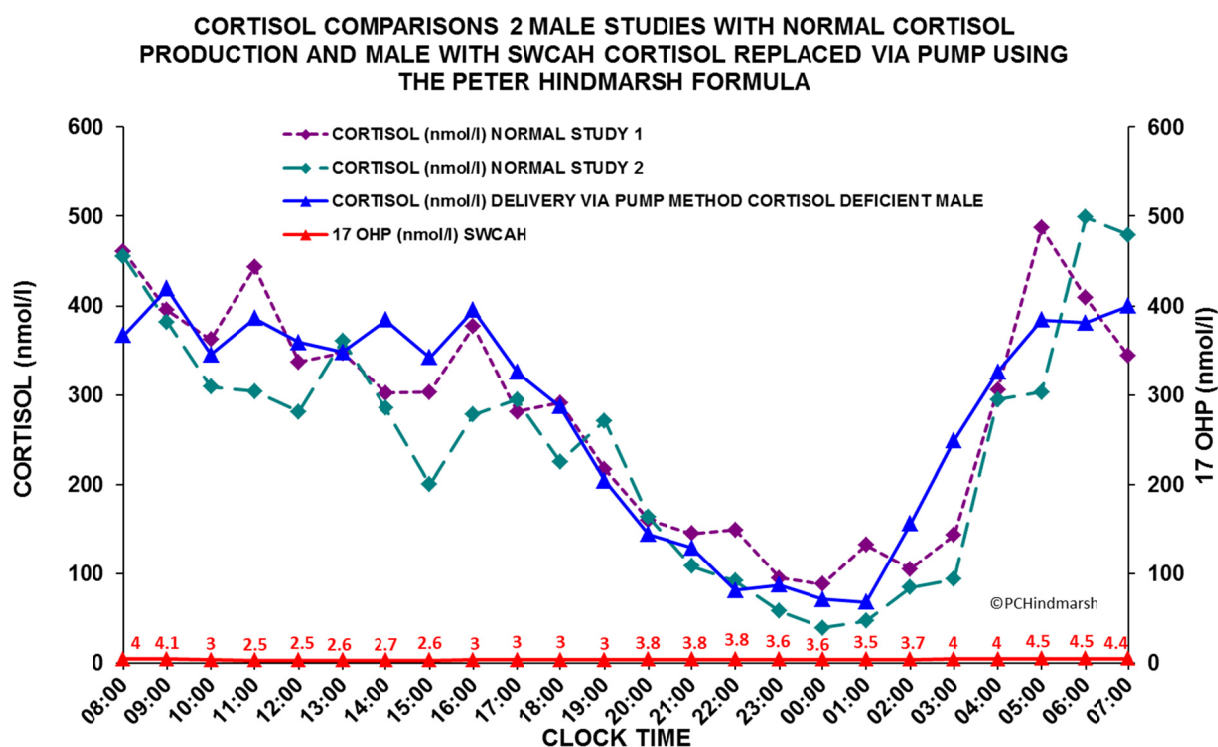


Figure: 10

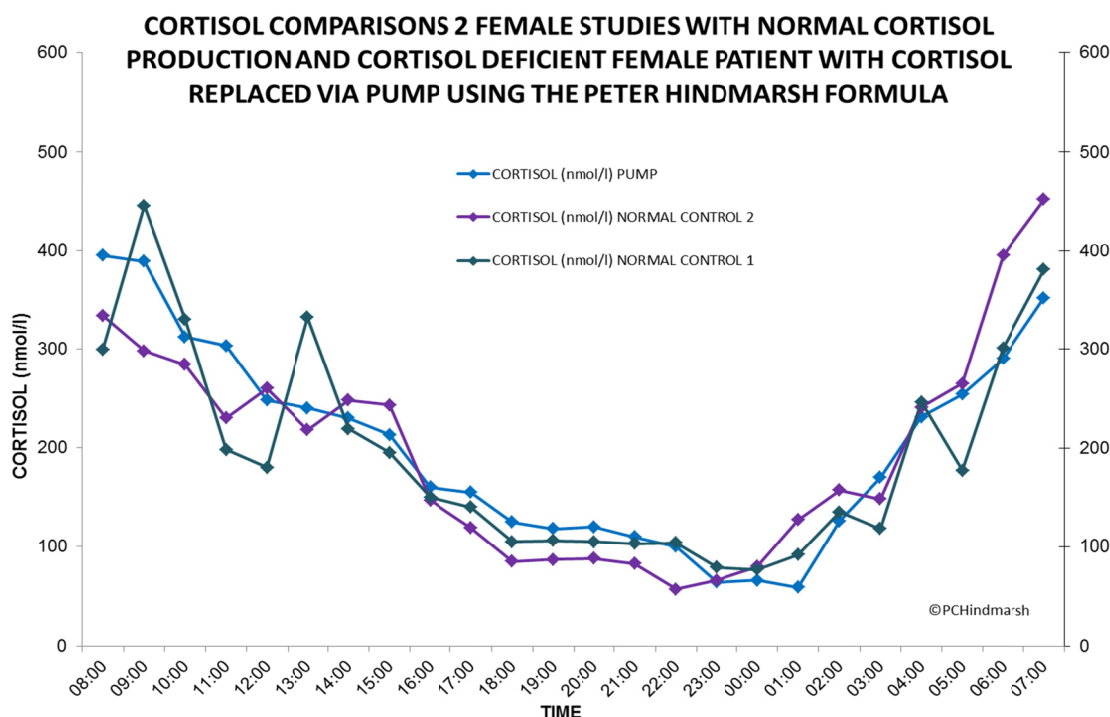


Figure: 11

The pump delivery of cortisol mimicked the circadian rhythm perfectly. It meant that a smaller dose of Hydrocortisone could be used over a 24 hour period compared with oral tablets and perfect control was demonstrated in terms of the condition congenital adrenal hyperplasia, where a normal circadian rhythm of cortisol was achieved with a normal measurement of the marker 17-Hydroxyprogesterone. There was considerable interest in this mode of delivery from the audience and, following the presentation, a practical session on pump therapy was enthusiastically received by the attendees. A formal clinical trial in using the pump method to replace cortisol is planned in the not too distant future.

MONITORING REPLACEMENT THERAPY AND MANAGING EMERGENCIES

MONITORING REPLACEMENT THERAPY – Professor Peter Hindmarsh

The afternoon session started with Professor Hindmarsh outlining methods for monitoring replacement therapy. He demonstrated what a one-off blood sample would look like (Figure: 12) and how little information could be gained from that or from 2 or 4 hourly day curves, when considering cortisol replacement.

He reminded people that hydrocortisone acts differently when taken at different times of the day, Figure:8 and that you need to consider the individual variance in the half-life, so the dose is taken at the optimal time to avoid cortisol stacking as illustrated in Figure: 9, or periods of cortisol deficiency as seen in Figure: 3.

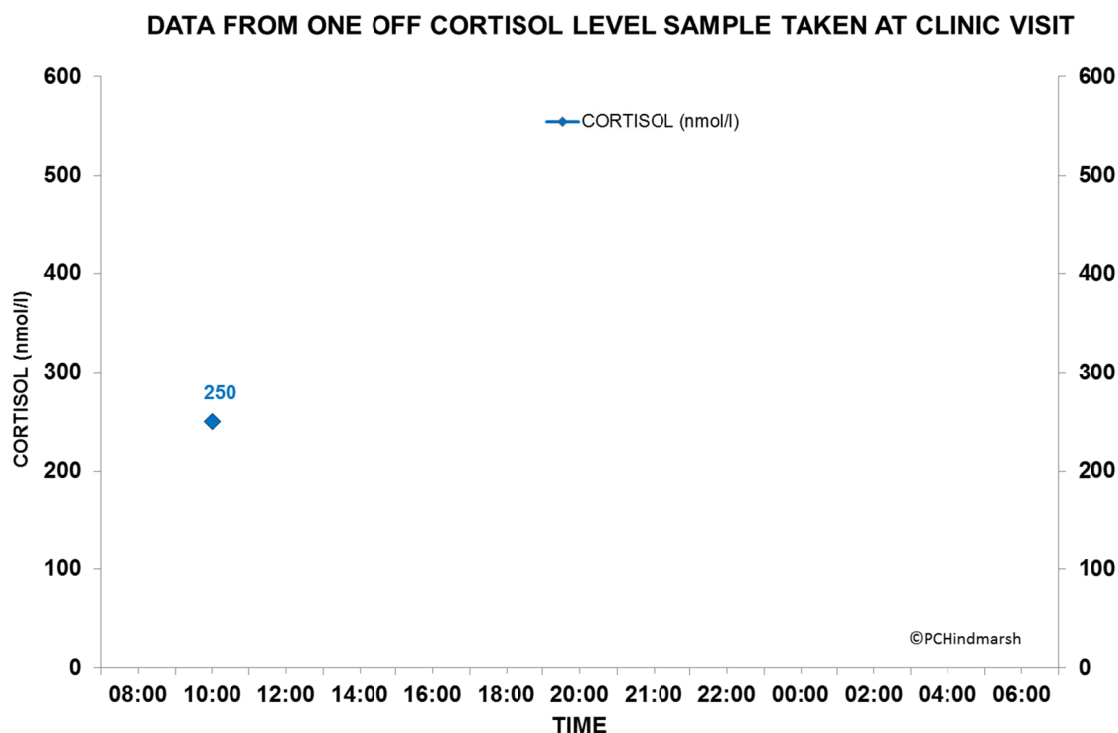


Figure: 12

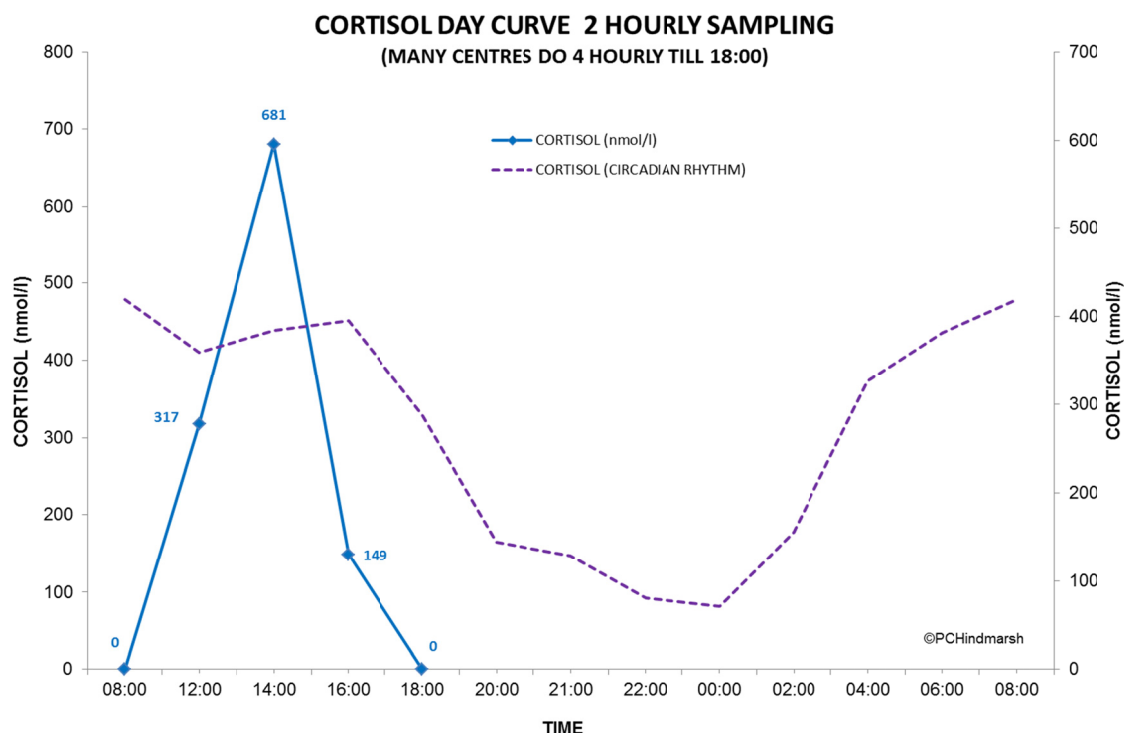


Figure: 13

The first observation on this graph (Figure: 13) is the very high cortisol peak of 681 nmol/l which would lead you to think that the morning dose is too high. We can see that at 18:00 there is no cortisol left in the blood to measure, and we actually have no idea when the next dose is to be taken and how long it will last in the system. However when we add in the data from a full 24 hour profile as shown in Figure: 14, we get a totally different view of the distribution of cortisol.

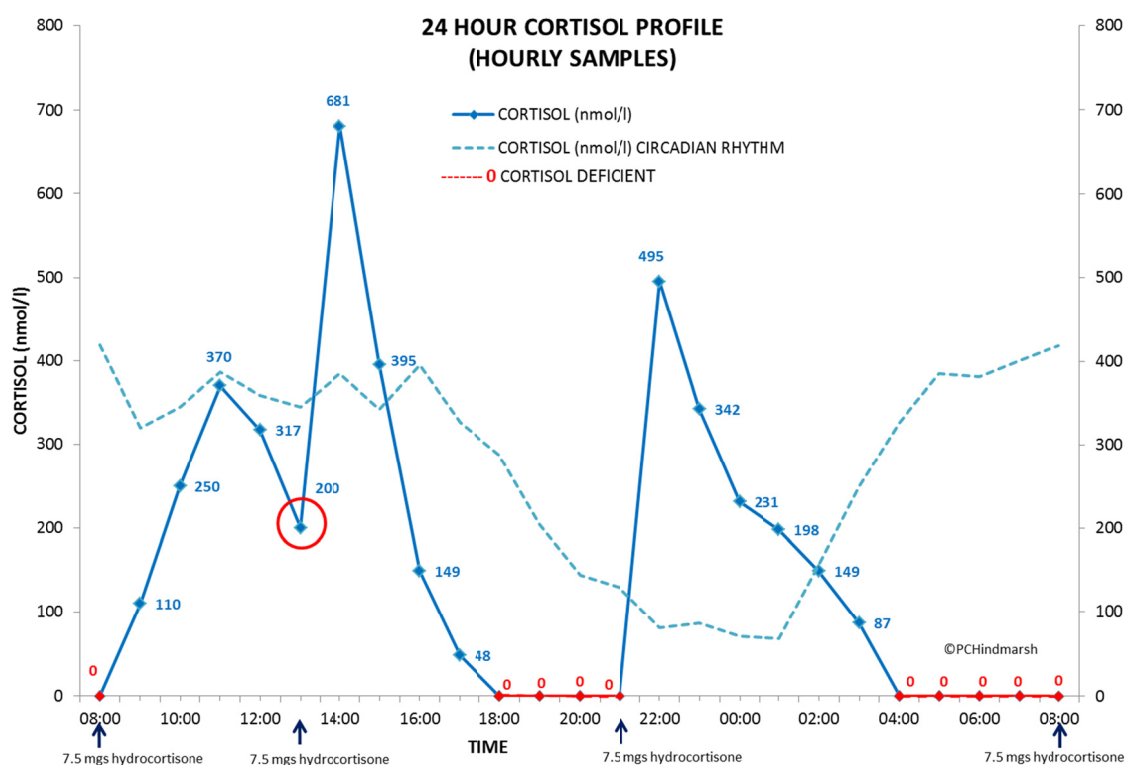
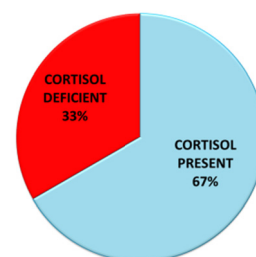


Figure: 14

The data in Figure 14 give the following information:-

- 13:00 dose shows another example of cortisol stacking leading to the very high peak at 14:00 hours.
- The patient is cortisol deficient from 18:00 until the next dose at 21:00 and we can see from the circadian rhythm that there should be cortisol in the system at this time.
- The 21:00 dose is taken too early to give early morning cover.
- The patient is without cover from 04:00 until the next dose is taken at 08:00, this being a time when the cortisol should be at the highest level in the system.
- The morning peak is happening too late in the morning at 11:00.
- The absorption and peak of the 08:00 and the 21:00 from the same dose of hydrocortisone is different.
- The patient is without any cortisol for a total period of 8 hours which is 33% of the 24 hour period; this on a daily basis every day will lead to long-term side effects as well as making the patient vulnerable to hypoglycaemia and adrenal crisis in illness.



In summary there is over and under treatment which on a day to day basis will cause long term side effects. The distribution of cortisol is poor and better coverage would be to adjust dosing times and for hydrocortisone to be taken 4 times a day.

Professor Hindmarsh explained that as more frequent blood samples were taken then the amount of information that was generated increased. The ultimate profile would be one with samples taken every 20 minutes because the half-life of cortisol is 80 minutes so frequent sampling like this would always identify the true peaks and troughs. 24 hour profiles created with 1-2 hourly samples were a good compromise. These profiles allow for a more detailed account of the dose and for the timing of medications to be taken into account which means the clinician can determine more easily whether under or over exposure to cortisol is taking place, whether the cortisol is being absorbed at a reasonable rate and cleared in a normal fashion. This type of profile, although it is time consuming to create, has been the mainstay of assessment at University College London Hospitals (UCLH) and Great Ormond Street Hospital (GOSH).

When monitoring CAH most centres do not measure cortisol levels and rely solely on 17 OHP blood spots which are done pre dose. The results of the blood spots can give a very false picture when they are considered on their own as there is a lag in the effect of the cortisol on the 17 OHP.

The best way to explain this is to illustrate the testing as we have done with the cortisol levels.

Figure: 15 shows the 17 OHP results from blood spots taken pre dose.

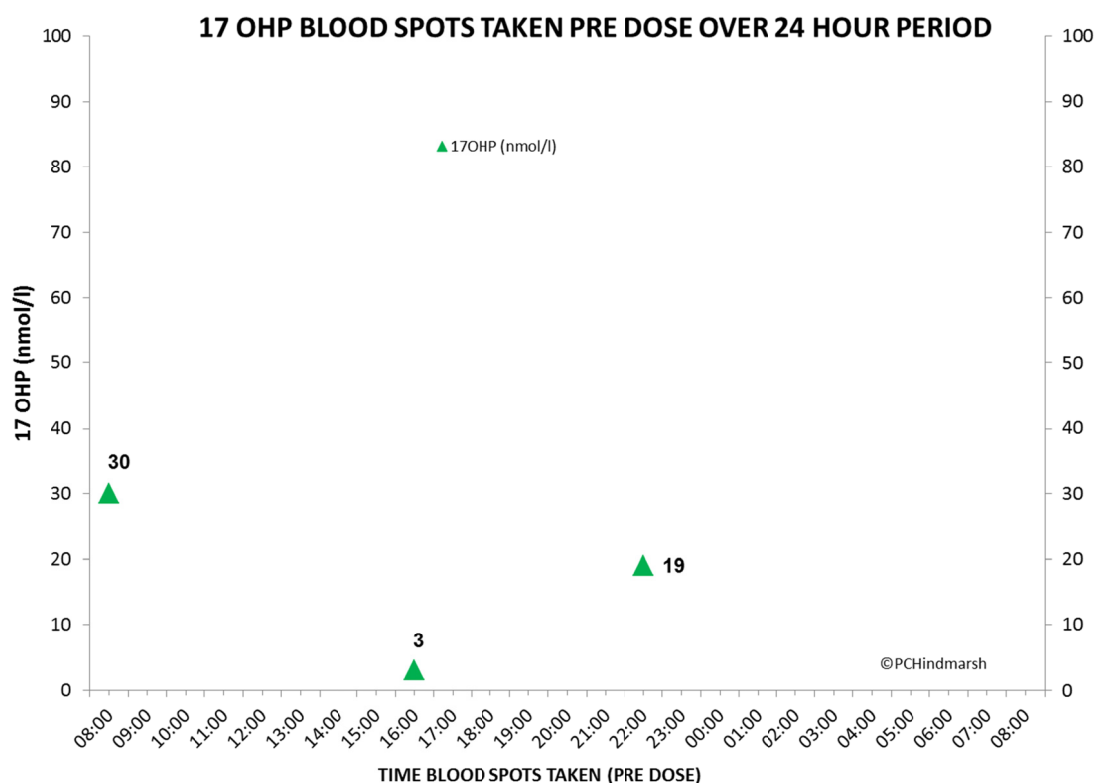


Figure: 15

The 17 OHP results from the blood spots (green triangles in Figure: 15) show that the morning 17 OHP level is 30 nmol/l which is an 'acceptable level' because this is a pre-dose measurement and the follow on result from the effect of the hydrocortisone taken at 22:00 the previous night. Many centres differ in their opinion of what the acceptable pre the morning dose 17 OHP level should be, this variation ranges between 5 nmol/l to 100 nmol/l. Therefore, depending on the centre, there could be an increase in the dose of hydrocortisone to bring the 17 OHP level lower or even a decrease in the dose to allow the 17 OHP level to rise higher.

The optimal 17 OHP level for the rest of the day usually ranges from under 5 nmol/l to 10 nmol/l, again this depends on the centre. When we look at the 17 OHP level at 16:00 in this patient (Figure: 15) which is 3 nmol/l this level looks acceptable and the control appears good at this time of the day.

However, when we note that the 17 OHP level has risen to 19 nmol/l at 22:00, this level is above the normal range and would therefore indicate that an increase needs to be made to the 15:00 dose of hydrocortisone in order to bring down the 17 OHP level at this time.

Blood spot measurements of 17 OHP levels taken pre dose, is the method that is used the most to monitor CAH by the majority of centres in the UK. This means that **only** the 17 OHP levels are considered and that the level of cortisol in the blood stream is never measured.

Over all the blood spot profile results in Figure: 15 show that the control of the CAH in this patient appears good.

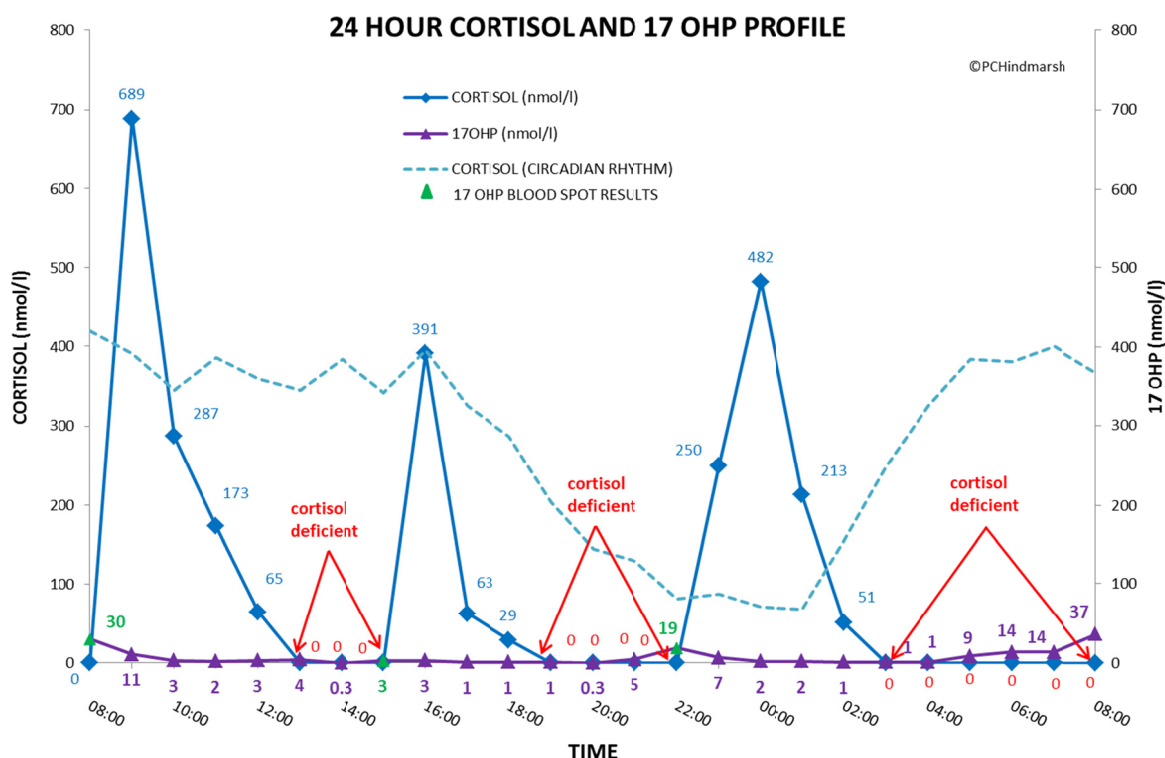
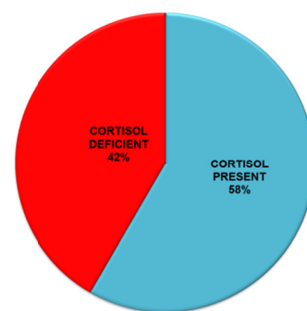


Figure: 16

However when we add in the data from this patient's full 24 hour profile as illustrated in Figure: 16 and look at the cortisol replacement in detail, which we do both at GOSH and UCLH, we get a very different view on which to base any adjustments in medication. We study the cortisol distribution and the affect this has in relationship with the 17 OHP. In Figure: 16 although the 17 OHP levels are not excessive we can see immediately that the cortisol replacement in this patient is not optimal.

This profile data shows that the patient has no measurable cortisol in the blood for at least 10 hours (42%) of the 24 hour period. Patients can suffer symptoms such as headaches, fatigue, lack of stamina, brain fog, as well as low blood glucose levels. In fact when looking only at the 17 OHP results from the blood spots (green triangles) there would be no evidence to relate any of these symptoms to their CAH as this will be deemed as being in good control, yet the list of symptoms are **ALL** symptoms of cortisol deficiency which the patient has for 10 hours of the 24 hour period! Increasing the dose which is the common practice will not alleviate the symptoms but add to the side effects, especially weight gain.



On further study of the data in Figure: 16 we can also see that the peaks of cortisol are very high and this again is evident when we consider the 17 OHP levels because they are very low at various times of the day. The high cortisol levels suppress the 17 OHP and the 17 OHP takes some time to recover even when we consider the lag of action between the two hormones. 17 OHP is a good marker for telling us how

much cortisol the body requires but because of the time lag of the effect the cortisol has on the 17 OHP it is important to get the replacement cortisol correct first and then the 17 OHP level will follow. We have seen evidence on how the optimal replacement and distribution of cortisol brings the 17 OHP level down to the normal levels and the normal rhythm in our work using the pump method and our experience in the vast number of 24 hour profiles we have performed. This is evident in the pump graph, Figure: 10 and here you can see that when getting the cortisol distribution correct first and foremost, the 17 OHP follows.

As previously mentioned when looking at the rise in the 17 OHP level at 22:00, the patient may have been told to increase the 15:00 hydrocortisone dose and although this might have suppressed the 17 OHP level the peak of cortisol at this time would have been much higher and the patient would still have been cortisol deficient because the dose would not have lasted longer in the system but increased the peak of cortisol which is already too high.

These daily high peaks of cortisol will lead to short term side effects, especially weight gain which is a common problem in CAH as well as the long term side effects associated with over treatment and this happens because **ONLY** the 17 OHP levels are considered and the cortisol is not measured.

In summary, Figure: 15 shows that the testing of the 17 OHP only indicates that this patient has good control of their CAH however when looking at the cortisol and 17 OHP levels in Figure: 16, we can see that this person has poor cortisol replacement with times where there is over treatment and under treatment. The profile shows that that this patient requires smaller, more frequent doses, which will give lower peaks and better overall distribution of cortisol.

What we must consider is that in CAH the treatment is to replace the missing hormone cortisol. Therefore the replacement should be considered carefully in getting the distribution of cortisol correct, as then 17 OHP and androgens such as androstenedione will then also normalise.

Correct cortisol replacement will prevent many of the very common short term side-effects and the long term side effects which are reported in the adult studies recently undertaken in the UK and USA.

Professor Hindmarsh also considered salivary cortisol measurements along with urine measurements. The problem with both these measurements is that they are excellent for detecting high concentrations of cortisol, but very poor at delineating whether under exposure is taking place. When measuring cortisol in the blood we are measuring the cortisol from the hydrocortisone which is being carried to the organs whereas the saliva and cortisol measurements are by-products and therefore not necessarily an accurate measurement of cortisol in the body. Saliva cortisol measurements can also be influenced by many other factors such as food, drink, acidity etc. There are a series of biological reasons for this but generally speaking, the conclusion was that 24 hour blood profiles are the best way to progress this kind of dose evaluation.

The talk also looked at the optimum time to give doses in the evening. Professor Hindmarsh pointed out, using a graph, that giving the dose at 6pm was likely to lead to a considerable period of time, almost 50% of the day and night, when the individual had no cortisol in their system. This was particularly critical and likely to impact on an individual overnight, because the normal cortisol rise from about midnight was absent and this would leave the individual at potential risk for collapse and hypoglycaemia, as shown in Figure: 17.

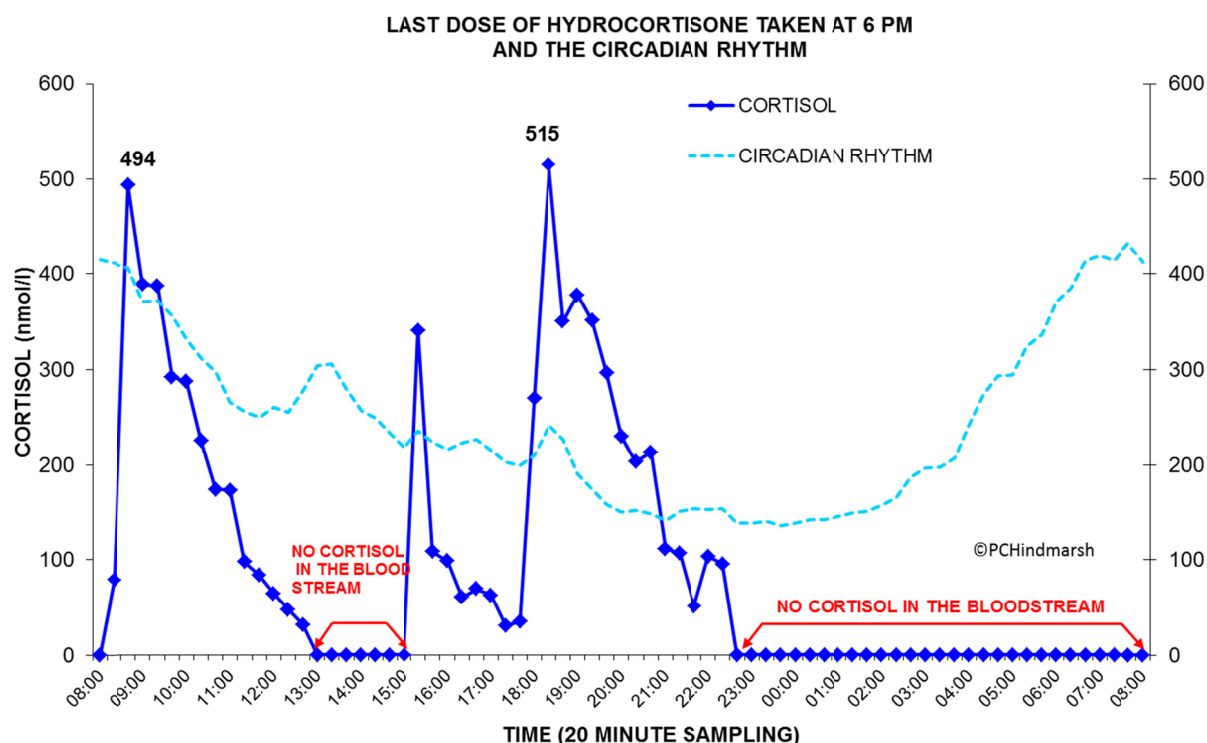
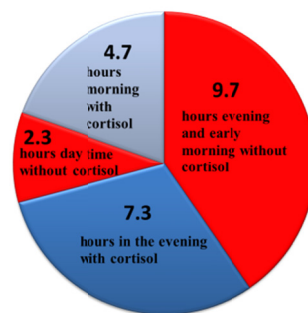


Figure: 17

Although many people say that giving hydrocortisone doses late at night prevents the person getting off to sleep, the data from a recent survey that we have undertaken did not support this theory.

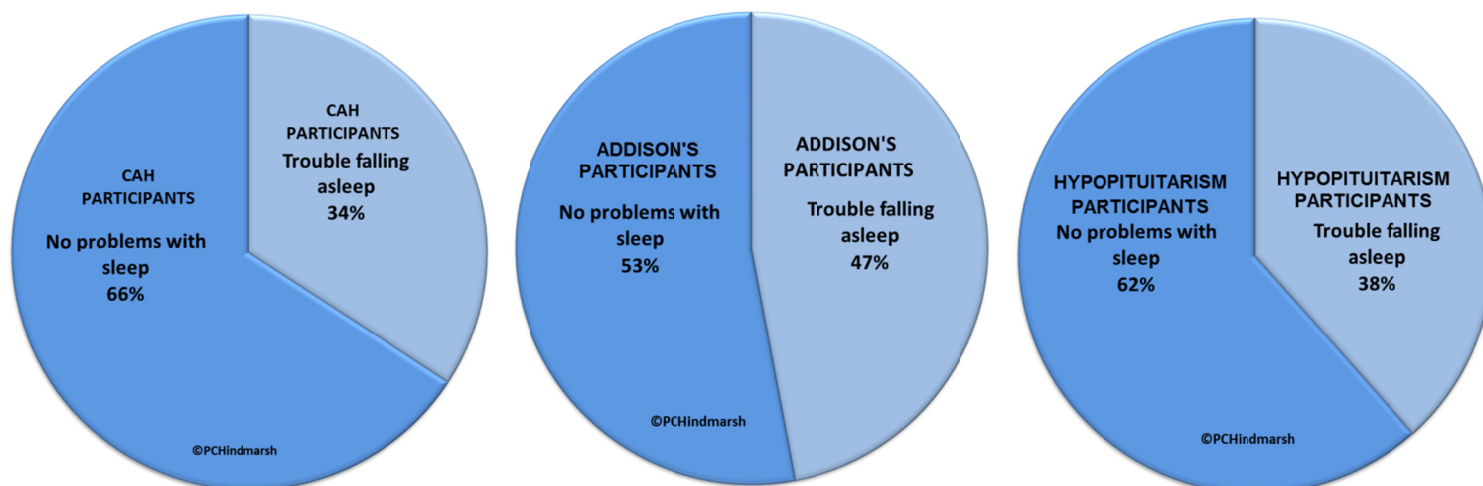


Figure: 18

As we can see from the data in Figure: 18 the participants with the least problems in falling asleep were those who have CAH. All these patients take the medication as late as possible at night in order to prevent the natural surge of ACTH which occurs in the early hours of the morning. This surge causes the adrenal glands to increase cortisol production. When no cortisol can be made control is easily lost at this time of the night.

The hypothalamus is the part of the brain that controls the drive of hormone production in the body. The human body does not function differently in someone who has one of these conditions however it depends on which part of the hypothalamic-pituitary-adrenal axis is damaged or malfunctioning, as to the way the normal cortisol production is compromised.

This is why when replacing cortisol we need to consider replacing the missing cortisol as close as is possible to the body's normal production in order to keep the body functioning well as the body relies heavily on this very important hormone for normal function.

In CAH an enzyme deficiency causes the cortisol deficiency and the lack of cortisol signals the hypothalamus to drive the pituitary to make high levels of ACTH which in turn causes the adrenal glands to grow large in their efforts to produce cortisol. This growth or enlargement of the adrenals gives the condition its name – adrenal 'hyperplasia', 'hyper – too much', 'plasia – growth'. The adrenal glands still produce other hormones known as androgens. DHEA (Dehydroepiandrosterone) and Androstenedione (A4) and a percentage of these hormones are then converted into adrenal derived testosterone. To stop the adrenals from growing and producing excess amounts of these androgens, the ACTH drive from the pituitary gland in the brain, needs to be controlled by ensuring there is the right amount of cortisol in the system in the early hours of the morning to dampen down the ACTH surge.

In Addison's, the adrenal glands have become smaller than normal through various causes and they have an impaired function in producing cortisol, there is no extra growth to cause problems with extra androgens, in fact they are small. In congenital adrenal hypoplasia (hypo - small, under developed, plasia – growth) the adrenals at birth are under developed and do not produce enough cortisol. As the adrenal glands do not produce cortisol, the hypothalamus as in CAH, drives the pituitary to produce ACTH and the ACTH levels become higher which causes hyperpigmentation.

This drive of ACTH occurs each time the cortisol level drops too low. The hyperpigmentation often gives doctors a clue that the patient may have Addison's. This is also why many patients who are taking all their cortisol replacement during the day with their last dose at 6 pm, still suffer hyperpigmentation because there is still the natural surge of ACTH in the early hours of the morning and no cortisol around to dampen it down. In fact this is over and under treatment and will result in long term side effects.

In Hypopituitarism it is the pituitary gland that is the cause of the cortisol deficiency. The production of ACTH is diminished through damage to the pituitary gland or removal due to tumours so there is no ACTH to drive the adrenal glands to produce cortisol, so the adrenal glands without the ACTH drive do not get the signal to produce cortisol. In this situation they lose the stimulation and the adrenal glands become small as well. Cortisol is easier to replace than ACTH so hydrocortisone tablets are the mainstay of therapy.

In Hypopituitarism it is also just as important to replace the cortisol as close as possible to the body's normal production to ensure that the rest of the system works properly, especially in the early hours of the morning, when there should be good levels of cortisol to keep up the blood glucose levels whilst we sleep.

As sleep interruption is the main cause for people with Addison's and hypopituitarism to take their last dose at 6 pm, we looked at the time of the last dose of hydrocortisone and whether the participant had sleep issues. See Figures: 19 – 21

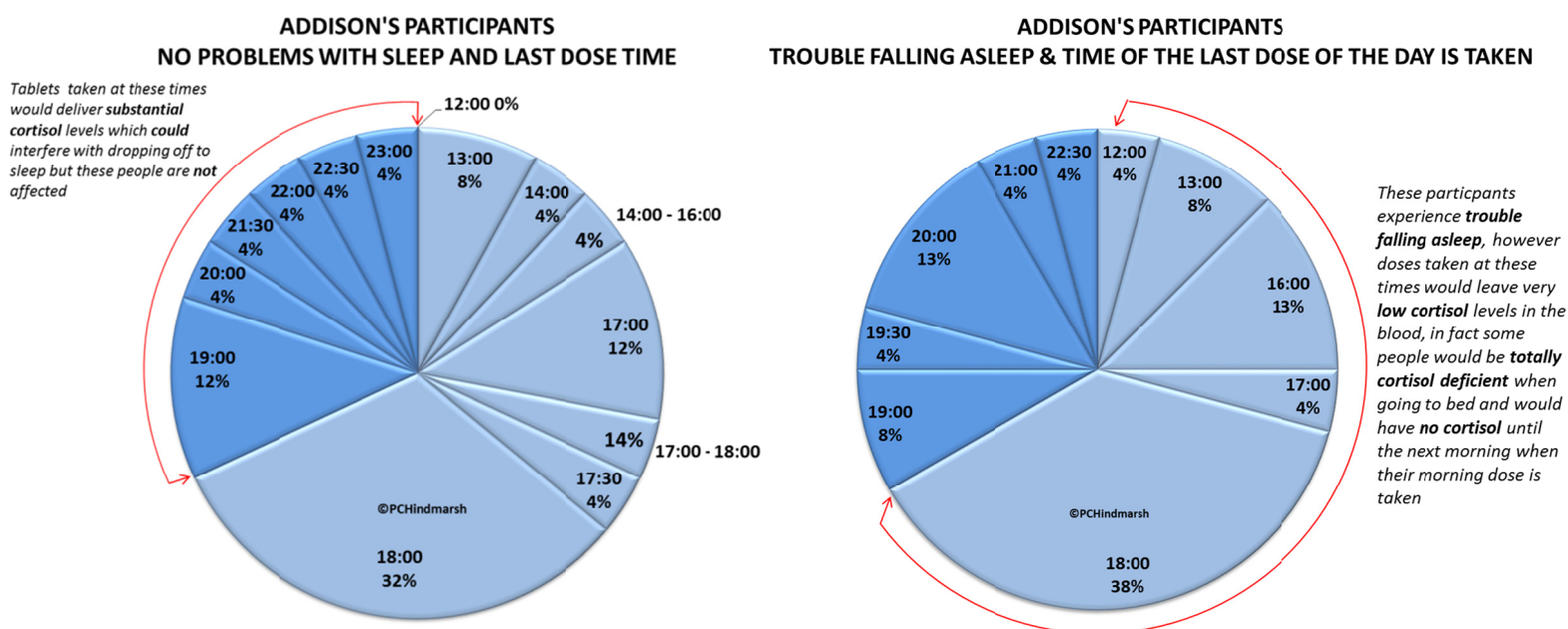


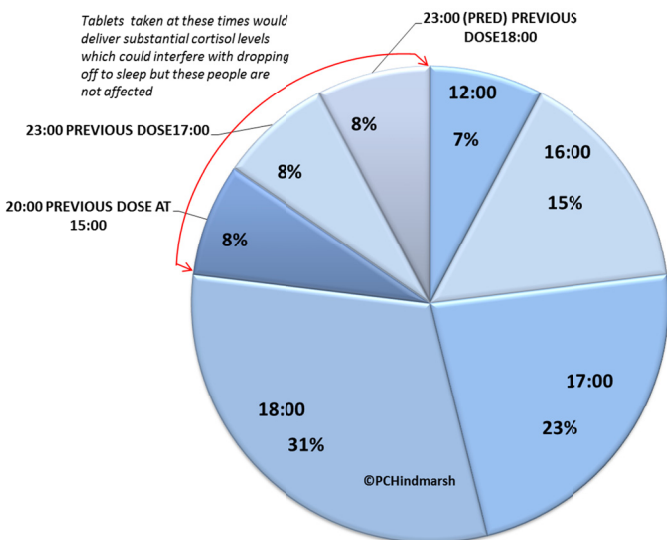
Figure: 19

The data in Figure: 19 illustrate the time that the last dose of the 24 period was taken and whether the participant has problems in falling asleep.

The most popular time for the Addison's group to take their last dose was at 18:00 hrs. The data showed that 38% of those who take their last dose at 18:00 experience trouble falling asleep, this is despite taking their tablets specifically at 18:00 to avoid this issue. This result was slightly higher than the 32% who take their tablets at 18:00 and do not experience problems falling asleep.

Participants who took their last dose of the day as early as noon or 13:00 still experienced problems in falling asleep!

HYPOPITUITARISM - NO TROUBLE FALLING ASLEEP & TIME OF LAST DOSE TAKEN AT NIGHT



HYPOPITUITARISM - TROUBLE FALLING ASLEEP & TIME OF LAST DOSE TAKEN AT NIGHT

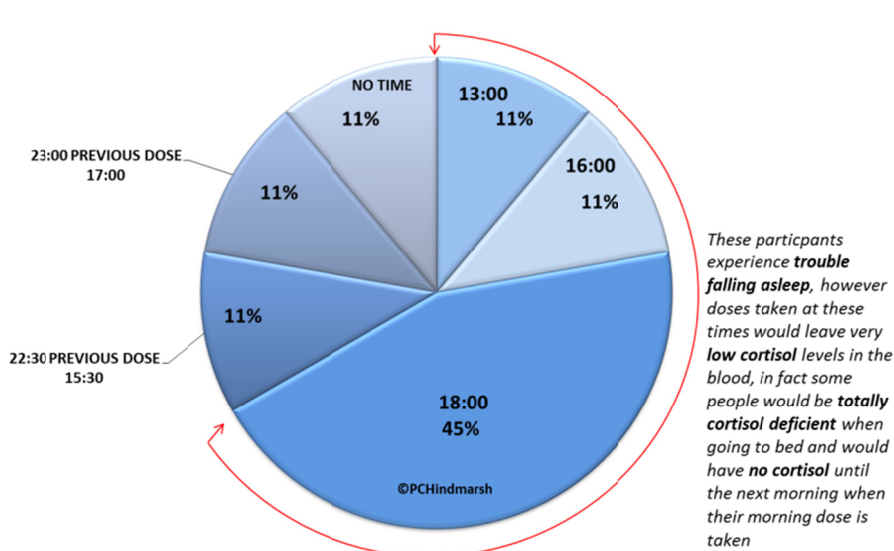
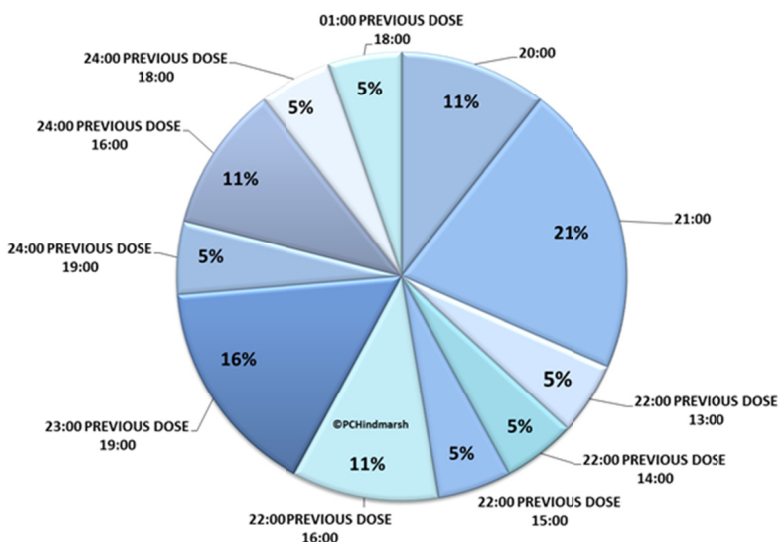


Figure: 20

The data in Figure: 20 illustrates that the participants with Hypopituitarism had a higher percentage (45%) of those who had trouble falling asleep and who took their tablet at 18:00 compared to that of 31% who had no problems in falling asleep. The data shows that 45% of the participants who took their last dose at 18:00 still experience problems in falling asleep despite taking the dose at this time to avoid this problem! Again it is interesting to note that participants who took their last dose at 13:00 and 16:00 still experienced problems in falling asleep.

CAH - NO TROUBLE FALLING ASLEEP & TIME OF LAST DOSE TAKEN AT NIGHT



CAH - EXPERIENCE TROUBLE FALLING ASLEEP & TIME OF LAST DOSE TAKEN AT NIGHT

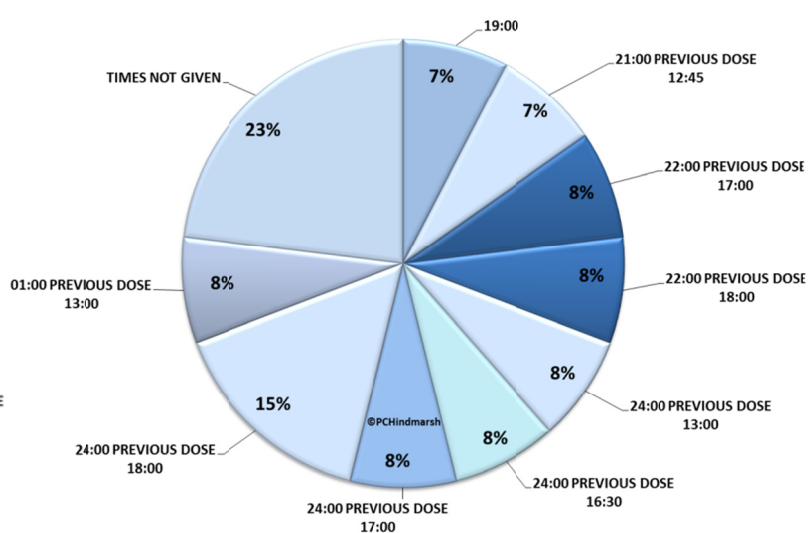


Figure: 21

As explained in CAH, the last dose of hydrocortisone is taken as late as possible at night. What the data in Figure: 21 tells us is that those who take their medication later in the evening have less problems in falling asleep, for example those who took their last dose at 21:00 21% had no problems in falling asleep compared to 7% who experienced problems falling asleep. Although there were 23% who did not give exact times in what time they had their last dose, it was stated as late as possible.

Overall when you look at the data in Figure: 18, 66% of CAH participants have no problems in falling asleep. They all take their last dose much later than those participants with Addison's or Hypopituitarism, where the majority take their last dose at 18:00 or earlier in the day.

So overall based on the data collected there was no difference in sleep onset between those who took their tablets late or early.

Professor Hindmarsh also pointed out that there is a limit as to how high you can raise the cortisol level in the blood by increasing the dose. This idea was new to many members of the audience and a good discussion followed on how to dose for emergency situations.

Increasing a dose, for example, from 10 to 30mg does not lead to a tripling in the blood values as illustrated in Figure: 22. In fact, they barely double. The reason for this is because of the various proteins that are in the blood that cortisol binds to, so that they rapidly become saturated, and the additional cortisol that is being given is essentially cleared through the kidneys.

There was a good and long discussion on the importance of increasing dosing during illness, but it was pointed out that going to extremes such as tripling or quadrupling therapy was unlikely to make significant increments to the level of cortisol in the blood.

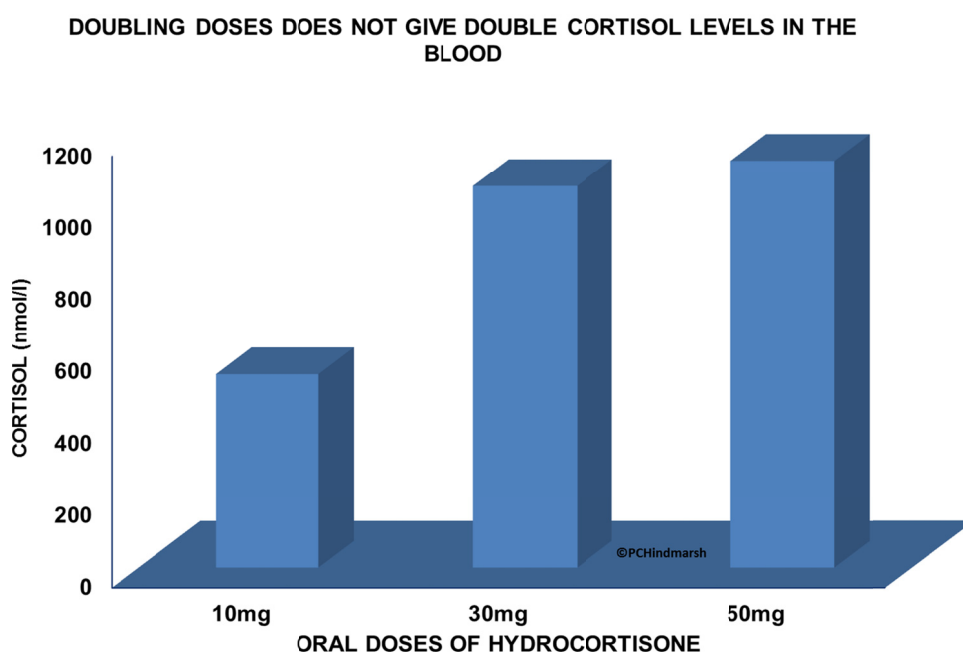


Figure: 22

The presentation then went on to look at the handling of illness, particularly from a children's perspective. Professor Hindmarsh did emphasise, however, that although he was discussing issues regarding childhood illness, the principles also applied to adults.

Professor Hindmarsh introduced the idea of 2 levels at which intervention needed to be escalated.

1. In level 1 there is sickness without vomiting in which case double dosing is needed.
2. In level 2 there is also vomiting.

If vomiting occurs 1 hour after a hydrocortisone dose then the medication is likely to have been absorbed and no repeat dose is needed. However, if vomiting occurs within an hour then the dose should be repeated. If vomiting occurs again then an intramuscular injection of hydrocortisone is needed and the person should go straight to Casualty. In addition, he demonstrated a number of features of the service at UCLH and GOSH, which include literature on emergency management. These are all available on the website <http://www.cahisus.co.uk/>

He also emphasised that double dose did not last longer in the blood and in illness it is important to realise this. This is important to remember and is illustrated in Figure: 23 which compare cortisol levels attained from 30 mgs of hydrocortisone given orally, intramuscularly by injection and intravenously via a cannula, in the same patient, showing that duration of exposure is similar. This means that in addition to giving higher amounts more frequent doses are also needed roughly every 4-6 hours.

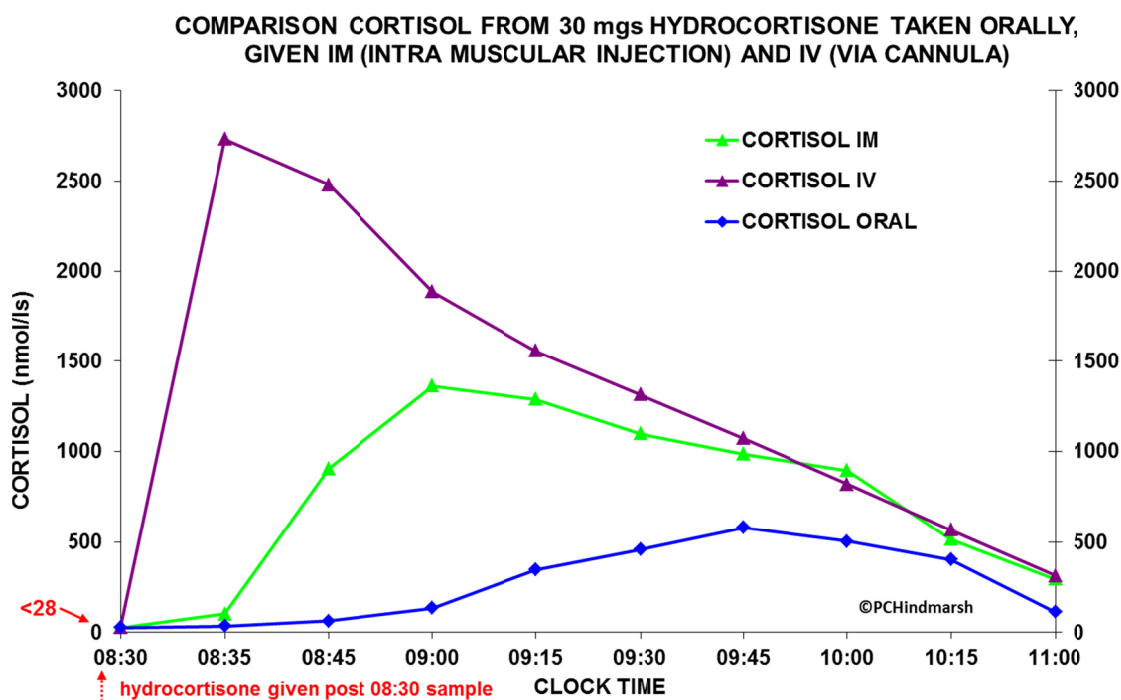


Figure: 23

Studies have shown that in serious illness, the natural production of cortisol remains at a high constant rate throughout the 24 hours and if you have no cortisol in the blood stream, you are then at very serious risk of a drop in blood glucose levels and adrenal crisis.

Professor Hindmarsh then explained that he started a 'More at 4' campaign which is introducing an extra dose at 04:00 hours. The reason for this is that we know that there is a natural surge of ACTH at that time and that absorption is good at that time of the day and this is the time where the cortisol from that last tablet taken even when taken as late as possible at night will drop to a low value leaving patients at risk of an adrenal crisis. The 04:00 dose must be double and based on the morning dose, i.e. equivalent to double the morning dose. This is an extra dose **in addition to** the morning dose. **The morning dose should also be double dose and needs to be taken at the usual time.** More can be read on this in our leaflets which we have written for all the conditions on our website www.cahisus.co.uk

Professor Hindmarsh also emphasised the importance of having a bolus dose **BEFORE** and **AFTER** a general anaesthetic. Many centres only prescribe a bolus dose before the anaesthetic is given however patients also need a bolus when they wake up from an anaesthetic. Patients with any form of cortisol deficiency should not be starved for longer than 6 hours and blood glucose levels should be monitored before and after surgery. Full details of dealing with dosing and general anaesthetics can be found on our website, <http://www.cahisus.co.uk/> We advise our patients to keep a copy of the protocol with their emergency kits.

WHAT WE HAVE DONE FOR OUR PATIENTS AT UNIVERSITY COLLEGE LONDON HOSPITALS AND GREAT ORMOND STREET HOSPITAL FOR CHILDREN

Professor Hindmarsh spoke about a new service he is setting up at UCLH, which is a unique service for young adults. UCLH do already have an adolescent service for up to the age of 19 years old with a dedicated ward, however this innovative service is the first in the UK for young adults and will be for patients aged 19 years to 25 years old. The service will offer outpatient appointments, as well as in-patient care. There will be a dedicated ward and full 24 hour profiles as well as other endocrine investigations will be offered. The service also hopes to introduce a drop in clinic for those who feel they need help.

We have also worked hard to produce the following

- Adrenal insufficiency card – hospital contacts and instructions for medical staff.
- Emergency letter – tailored to each condition (important for those with hypopituitarism).
- How to call an ambulance - in line with the ambulance pathway system.
- Protocols set up for our patients with the ambulance service.
- Open access – ward protocols.
- General anaesthetic protocol – bolus dose before and after.
- Letter to GP's – summary of care, patient flagged always to be seen, guidelines on condition as well as prescription needs – extra tablets for illness.
- Letters to paediatricians re summary of care.

- Guidelines for illness and emergencies.
- Nursery and school leaflets with emergency contact details, guidelines on illness and tablet dose and time.
- Provide emergency injection training.
- Ampsnaps, provided **free** for emergency kits.
- Emergency advice contact service 24 hours every day of the year.
- Advice on dosing when travelling

All available at no cost to download or access from anywhere in the world on our group website www.cahisus.co.uk

AMBULANCE PERSONNEL – Dr Quen Mok

Dr Quen Mok, who is a Consultant Paediatric Intensivist at Great Ormond Street, and a paediatric member of the Joint Royal College Ambulance Liaison Committee, presented the information on how ambulance services currently operate.

She pointed out that currently in England there are 10 ambulance service trusts and that there is likely to be further rationalisation taking place in the number of trusts. Concern had been expressed by the Department of Health regarding the delivery of ambulance services and the need for proper evaluation of the role of paramedics.

This was particularly important in rare conditions that are part of the subject matter of the study day. The 2006 Ambulance Guidelines contained a series of drugs that could be administered by ambulance personnel.

The audience learnt that all ambulances are equipped with Hydrocortisone and Glucagon for administration, so this is extremely important news that needs to be conveyed to all members so that they are also aware that emergency support with Hydrocortisone is available when paramedics arrive on an emergency situation. Within the ambulance protocols, the dosing schedules are outlined for different ages, along with the indications for Hydrocortisone use.

The presentation reviewed these indications and they appeared to be in accordance with the recommendations that are available by the support groups.

The important message that Dr Mok communicated was that **Adrenal Insufficiency was a key phrase** to communicate to the emergency services in an acute situation.

Not all ambulance trusts allowed paramedic staff to administer Hydrocortisone. However, given the ease of administration of this preparation, which they use as Solu-Cortef, and the harmless nature of giving an injection as opposed to leaving an individual in an adrenal crisis, it was felt that we should check out with the ten ambulance trusts in England what their current position was and to work with them to ensure that Hydrocortisone could be given by paramedic staff.

This means that in all emergency kits Solu-Cortef should be prescribed as that will then be consistent with what the ambulance paramedics are used to dealing with.

WHAT TO EXPECT IN ACCIDENT AND EMERGENCY DEPARTMENTS – Dr Rebecca Salter

Dr Rebecca Salter, a Consultant in Paediatric Accident and Emergency Medicine from Imperial Healthcare, presented an overview of what to expect on arrival at an accident and emergency department. She pointed out that it depends in part on how an individual gets to casualty.

If this is a walk-in, then registration and triage is mandatory, whereas if the individual comes in through the ambulance service, that aspect is undertaken by the ambulance personnel. Dr Salter pointed out that there were standards that individuals with conditions such as **adrenal insufficiency should be reviewed within 15 minutes of arrival.**

The process can be expedited by the notification on an accident and emergency record systems that the individual is a special case and has adrenal insufficiency. This would then prompt the accident and emergency staff to equip the receiving area with the necessary resuscitation equipment, such as intravenous fluids, glucose and Hydrocortisone for injection. This preparation can take place, if the individual is brought in through the ambulance service, by notification from the paramedics at the scene of pick up.

A key point that came across was the accident and emergency staff often not knowing current medication doses. Dr Salter pointed out that a simple notification from the endocrine consultant to the senior accident and emergency consultant was all that was required and that this information could then easily be entered into the accident and emergency case records.

It was also noted that cross referencing to associated protocols could also be undertaken. It was felt that this would be immensely helpful for the standardisation of care and resuscitation in the accident and emergency environment. A key point of this is that the onus for setting up this process of improving care in accident and emergency lies with the endocrinologist in charge of the case

OUTCOME OF THE MEETING

The meeting was viewed by all as a success and many participants had achieved a better understanding of their condition and what to do in emergency situations. There is clearly some work to be done with various NHS Bodies such as the Ambulance service and also Medical Bodies to ensure a consistent approach to the treatment of people with adrenal problems.

This we plan to do in the coming 6 months.

We also undertook a questionnaire on the conditions and steroid replacement. One of the most striking issues that emerged was the points made about side effects. So prominent were these issues that we plan to hold another joint meeting on Saturday 14th March 2015 to address these questions and other findings that the questionnaire highlighted.

Keep an eye out on our Facebook page for when bookings open

<https://www.facebook.com/pages/CAH-Great-Ormond-Street-Parent-and-Patient-Support-Group/320900711287880>

CONCLUSIONS

1. Dosing at 6pm is not a good idea as this leads to approximately 8-12 hours without cortisol and means that the body will be unable to keep blood glucose levels up when asleep. This is particularly dangerous when unwell.
2. Dosing and timing of dosing is very important and needs to be individualised.
3. In CAH blood spot profiles do not show whether the cortisol replacement and distribution is optimal, it is simply treating the 17 OHP levels. 17 OHP levels can be within the normal range, however the patient can be cortisol deficient. It is very important to aim to get the cortisol correct which should be the real objective as the hydrocortisone is replacing the missing cortisol. Once this is achieved the 17 OHP levels and androgen levels will fall into the normal range. Optimising cortisol replacement will avoid short and long term side effects.