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

HYDROCORTISONE

What is Hydrocortisone?

Hydrocortisone is a synthetic preparation of the steroid hormone cortisol.

- Steroids are names of specific hormones in the body and cortisol (hydrocortisone) belongs to the group of steroid hormones called Glucocorticoids and sometimes the term corticosteroids is used although technically this is not correct. This is because Corticosteroids refer to all the steroids from the adrenal cortex such as cortisol, mineralocorticoids and androgens.
- Glucocorticoids (glucose + cortex + steroid) play a very important part in regulating the metabolism of glucose and are synthesized in the adrenal cortex.
- Corticosteroids denote both the steroid groups, glucocorticoids and mineralocorticoids (both hormones produced by the adrenal cortex).
- Mineralocorticoids (mineral + cortex + steroid) regulate the body's minerals i.e. the body's salts and fluids. The major mineralocorticoid Aldosterone participates in regulating the sodium, potassium and water balance in the body.

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.

Why is hydrocortisone used and not longer acting steroids?

As hydrocortisone is synthetic cortisol, it is the most suitable drug for replacement purposes. Our 24 hour profile leaflet explains in detail how hydrocortisone works in the body. When taken orally it lasts in the body on average 6 hours. After the tablet is swallowed, it takes on average one to two hours to peak to the highest level, and then the cortisol level drops slowly over the next couple of hours, depending on the person's metabolism.

You might think the longer acting steroids would be better to use but this is not necessarily 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. Also, 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 figures in the table below (Fig: 1) 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.

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

Fig: 1

Side-effects

The side effects of overtreatment with hydrocortisone are as follows:-

Cautions: In children and adolescents growth retardation is the main concern. High blood pressure can result with the use of high doses and there is also a potential problem with the way that glucose is handled by the body. Osteoporosis may be problem although in CAH there is little evidence for this in the short term but in older patients problems have been reported in the older (40 years +) population. For more information on this please see our leaflet on "Assessing Bone Mineral Density."

Contra-indications: It is important to remember that hydrocortisone in CAH is replacement therapy. This means that it is safe to receive all vaccines

Side-effects:

Complications of High-Dose Glucocorticoid Therapy

Short-Term Therapy	Long-Term Therapy
Gastritis	Gastric ulcers
Growth arrest	Short stature
↑ Appetite	Weight gain
Hypercalciuria	Osteoporosis, fractures
Glycosuria	Slipped ephiphises
Immune suppression	Ischemic bone necrosis
Masked symptoms of infection, esp. fever and inflammation	Poor wound healing
	Catabolism
Toxic psychoses	Cataracts
Headaches	Bruising (capillary fragility)
Hypertension (high blood pressure)	Adrenal/pituitary suppression
	Toxic psychosis
	Striae - Stretch Marks

Fig:2

Complications of using too Low-Dose Glucocorticoid Therapy

Short-Term Therapy	Long-Term Therapy
Growth acceleration	Short stature as bone maturation advances
Reduced Appetite	Weight loss
Low blood sugar	
Tiredness	Muscle weakness
Collapse	Hypotension (low blood pressure)
Headaches	
Increased body hair	Impaired fertility
	Adrenal Rests
	Skin pigmentation from high ACTH levels

Fig: 3

Hydrocortisone Injections

As you can see in the graph below Fig: 4:-

- Hydrocortisone when given IV (into the vein through a cannula) it enters into the blood stream immediately peaks in the blood within minutes, and the cortisol levels then decreases over the next few hours.
- Hydrocortisone when given IM (injection into the muscle) it enters the blood stream quickly, peaks in the blood within 20 minutes and then decreases over the next few hours.
- Hydrocortisone when taken orally is absorbed in the gut quickly but takes longer to enter the blood stream and therefore takes a much longer to time to peak.

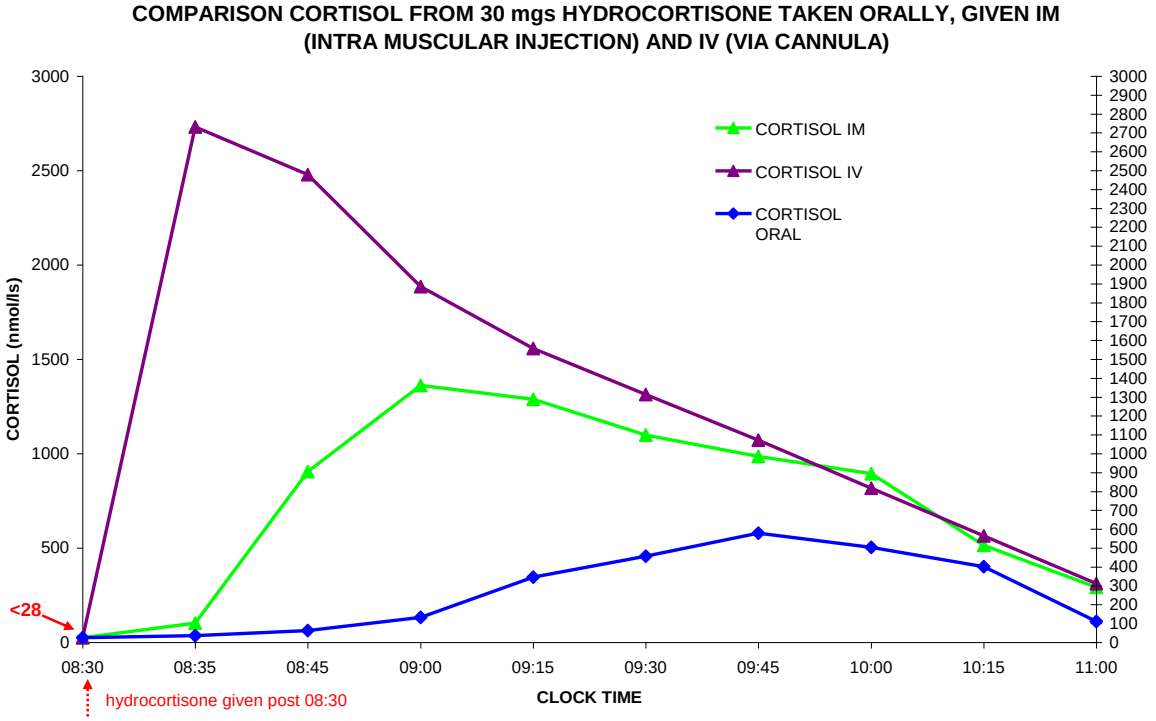

Fig: 4

As you can see from the graph, although IM and IV administration of hydrocortisone peaks in the blood much higher it does not last as cortisol in the blood for that much longer. This is especially important when a child is seriously unwell, and why if an injection has been given, should be admitted for observation.

Hydrocortisone has many effects. When used in an emergency we want the "stress" and glucose effects quickly but we must remember that these effects wear off quickly as you can see in the graph so they need to be backed up by admission for observation and further frequent hydrocortisone administration.

The effect on other areas such as 17OHP is different because as soon as the cortisol levels drop below <28 nmol/ls the patient is totally cortisol deficient and 17 OHP will start to rise.

This is why we like to give IM hydrocortisone if someone is unwell and unable to take tablets as IM means you get the cortisol in blood quickly

BUT it does mean that you need to be seen promptly as the graph also shows that the IM hydrocortisone does not last that long and is down to levels of 300 nmol/l 2.5 hours after administration.

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/l 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 IV study line in the graph (Fig: 4).

You can see in the graph that no matter how high you get the cortisol e.g. IV study line it does not prolong the cortisol in the blood very much longer. This means that when there are problems with hydrocortisone not lasting long enough you have to give it more often and not give more of it.

As a reminder:-

Intramuscular Hydrocortisone Doses For Emergency Use

Age range (years)	Dose (mg)
0 – 1	25
1 – 5	50
over 5	100

Fig: 5

Hydrocortisone when unwell

The natural response of the body when unwell or faced with trauma is to increase the amount of cortisol that is produced. The amount produced does vary with the stress but has not been well studied. As we know in CAH the body is unable to respond in this way, so extra hydrocortisone is needed. Currently we recommend doubling or tripling oral dosing if unwell for at least three to four days.

This may vary if there is gut upset as the hydrocortisone may not get absorbed as well as it would normally.

If you cannot take oral medication due to vomiting then you must have an IM injection (Fig: 5 for dose amounts) and seek medical help. The graph (Fig: 4) which is a profile illustrating what happens to the cortisol after an IM injection shows that you will be covered for a short period of time, so inject, then immediately seek medical help.
We cover these aspects in more detail in our leaflet on Emergencies

How to take hydrocortisone

As taking hydrocortisone on an empty stomach can cause problems such as gastritis, and in the long term stomach ulcers, it is best taken after food, or with milk.

Dosing

Maintenance Doses

In CAH the replacement value is usually worked out based on the following formula:-

15-18 mg/m^2 body surface area per day divided as b.d. (twice a day) or t.d.s.(three times a day)

Circadian Rhythm

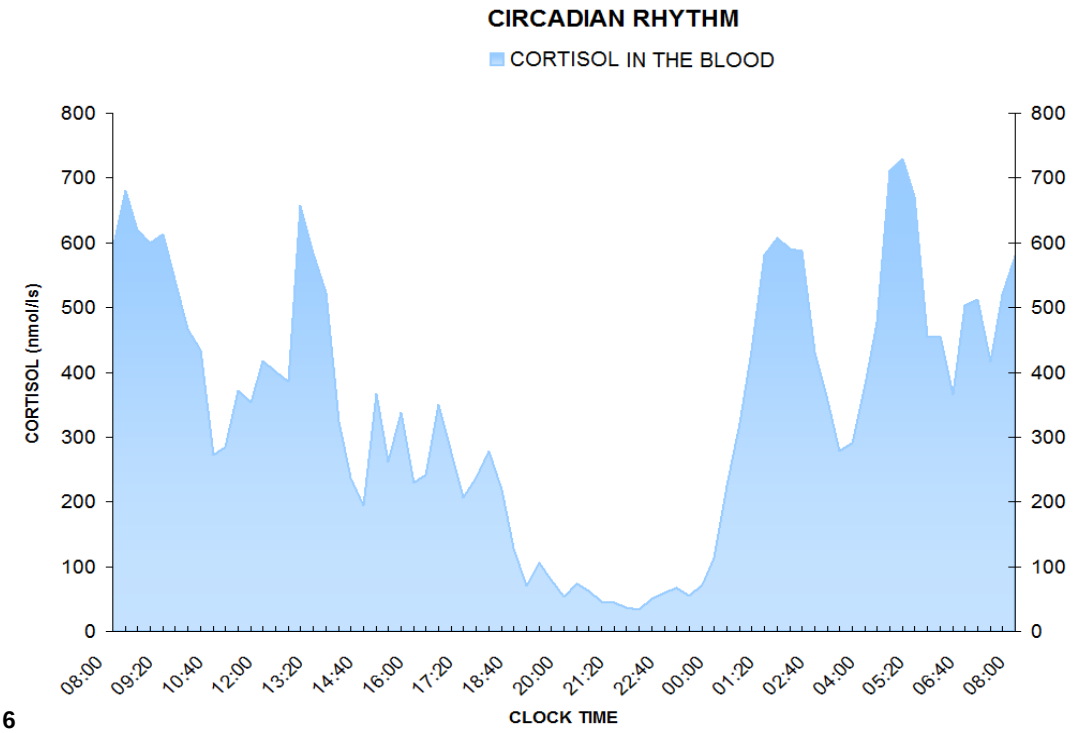

Fig: 6

The graph above (Fig: 6) shows the levels of cortisol a person without CAH would make during a 24 hour period. The highest amount is variable for the individual but the pattern which the production follows, is called the circadian rhythm. There are several important things to note:-

- The body is not without cortisol at any point
- The levels do drop low in the late evenings and then rise in the early morning.
- The body needs more cortisol when you wake up and less during the day

Hydrocortisone really needs to be given to try and mimic the normal pattern of cortisol in the blood and we explain more about this in our leaflet '24 Hour Profiles'. This means that you would need to take about half the TOTAL daily dose when you wake up, a quarter at lunchtime and the other quarter just before you go to bed (as late as possible).

However due to the half life of hydrocortisone it probably needs to be given 4 times per day but three times per day is often good enough. It is best to check times and doses by having a 24 hour profile, which enables the dose to be 'fine' tuned to suit the individual.

The following graph (Fig: 7) shows the results of profiles which clearly show the different patterns of cortisol you get when taking hydrocortisone twice a day against three times a day.

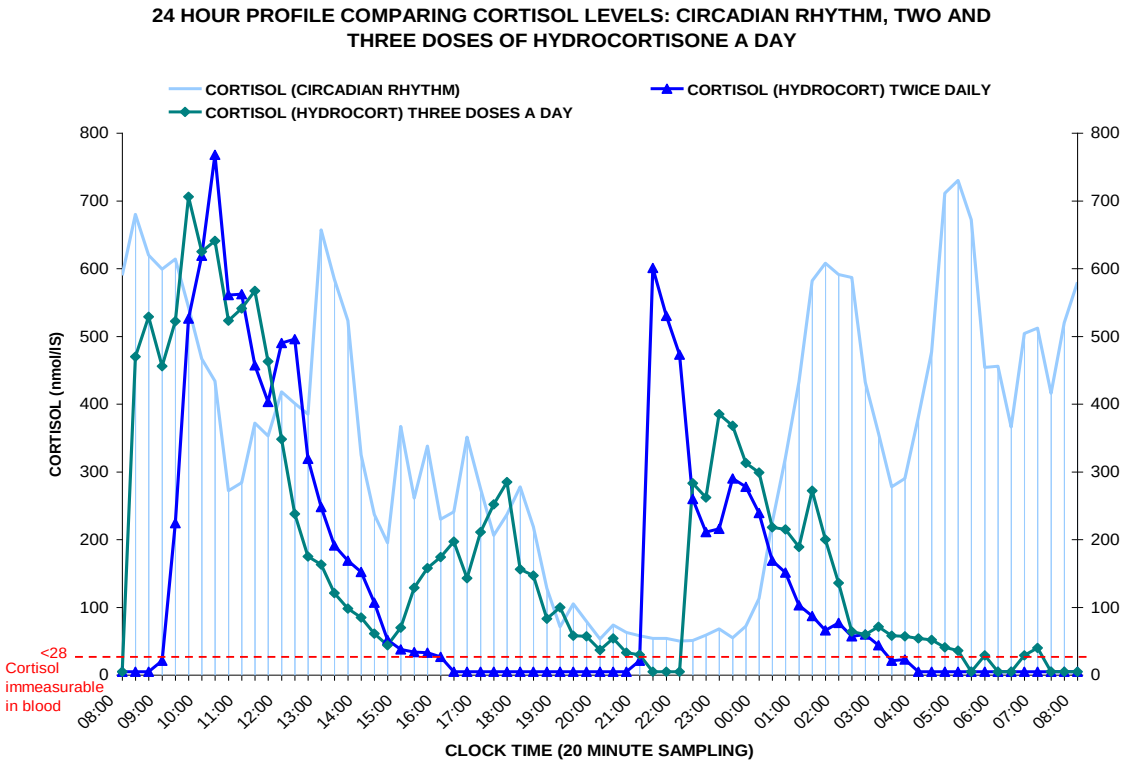

Fig: 7

As you can see in the graph above (Fig: 7) with twice dosing, there are vast periods where the cortisol levels are so low that it cannot measured in the blood. When taking three doses a day you can see that again there are periods where the cortisol is much lower than it should be but the peaks of cortisol are not as high.

As everyone's production of cortisol varies in the amount it peaks, in CAH we use both the actual cortisol level and the 17 OHP levels to determine whether we have the right dose of hydrocortisone to give the right amount of cortisol and the right level of control. Although tablets cannot mimic the exact circadian pattern we have found that many people achieve better control by taking their dose split into 4 times a day (Fig:11). This gives smaller peaks of cortisol and better coverage throughout the day, however this is really best to be confirmed by having a profile to ensure optimal control. The pump delivery method however can mimic the circadian rhythm (Fig: 12) as it can be programmed to deliver exactly the amount of cortisol at the precise times and rates suited to the person's metabolism.

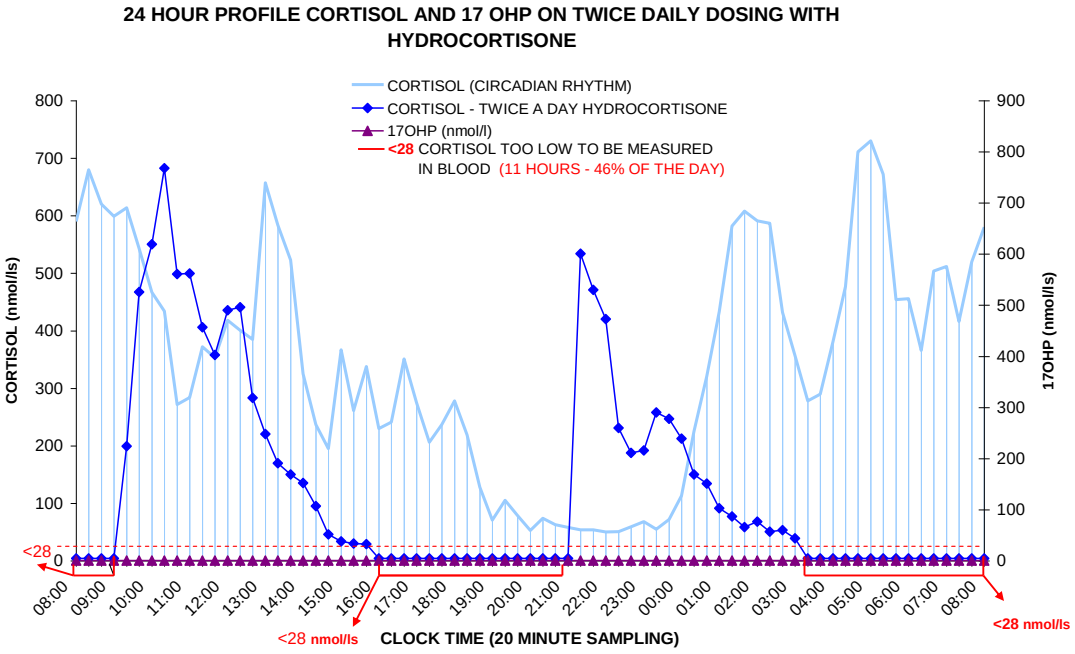

Fig:8

The above graph shows that you have two high peaks of cortisol, however for several hours of the 24 hour period you are totally without cortisol, so effectively you are undertreated with cortisol. During these periods the blood sugar could drop low, the person could suffer from headaches, tiredness, and feel generally not right.

However the 17 OHP in the chart is flat all measuring 0.3 nmol/ls which is too low and shows over treatment. This over treatment would cause weight gain as well as the long term side effects as stated in the long term side effects (Fig: 2) yet the individual could also suffer side effects of having no cortisol in the system at the times where this is evident.

Example 1

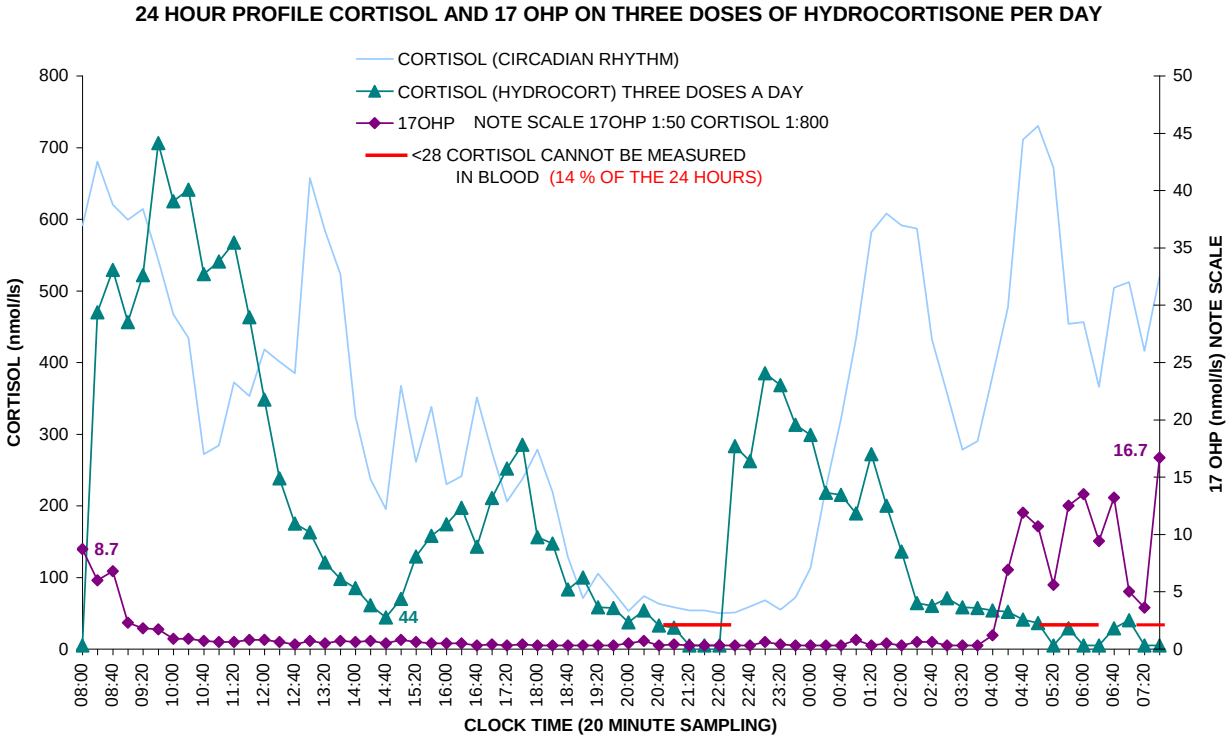

Fig: 9

The graph Example 1 (Fig: 9) traces the cortisol as it is taken three times a day by a person who has CAH. There are still periods where there is no traceable cortisol in the blood, however the 17 OHP is flattened (all under 1 nmol/l) and this level does not rise, until in the early hours of the morning (04:00hrs) when it reaches a level of 16.7 nmol/ls.

So what we can see from this graph is again an example of over treatment and under treatment and if looking at a one off level of 17 OHP, say pre morning dose, how would you know which dose to lower? You might get a rise in the 17 OHP but you would not know what would happen the rest of the day if you look at the cortisol level of 44 nmol/ls at 14:40 hrs as opposed to the circadian rhythm there is still a considerable difference in level cortisol in the system at that time of the day (over 200 nmol/ls) however there is no rise in the 17 OHP. This continuous over treatment (verified by the 17 OHP) and under treatment (verified by periods of low or no cortisol) would lead to the long term side effects listed in the tables (Fig: 2 and Fig: 3)

Example 2

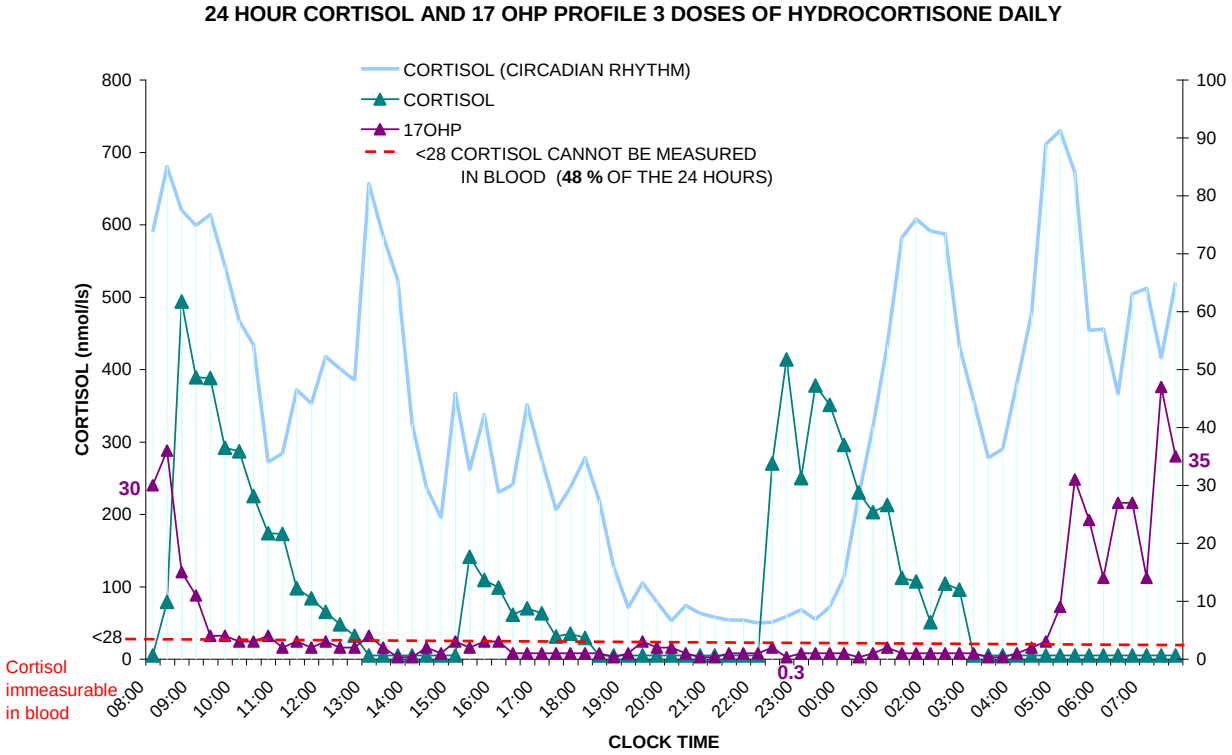

Fig:10

The graph Example 2 (Fig:10) is a profile from a different individual also taking 3 doses of hydrocortisone a day. Remember that each person may take a different dose of hydrocortisone based on the formula mentioned for maintenance dosing, i.e. 15-18 mg/m^2 body surface area per day, so the peaks of hydrocortisone will differ, even with that of the circadian rhythm.

If you were to judge overall control of this patient merely on a 'one off' blood sample taken at 08:00hrs before morning dose of hydrocortisone is taken and consider only the 17 OHP level, it would seem that this patient has optimal control. However a 24 hour profile shows that by looking at the daily distribution of cortisol you will see that in fact this patient is cortisol deficient for 48% of the 24 hours! The 17 OHP is also very flattened and shows evidence of overtreatment for most of the 24 hours!!

If you were to take a sample pre the lunchtime dose the result would show the 17 OHP to be 4 nmol/ls which again would show good control, and if you looked the 17 OHP pre the 10 pm dose, it would show a level of 1 nmol/l which would indicate the lunchtime dose would need reducing, which would reduce the cortisol and may well increase the period of having no cortisol present, as the cortisol levels post 17:00 hrs are already low. This profile once again shows how important it is to look at the cortisol.

24 HOUR PROFILE CORTISOL AND 17 OHP ON FOUR DOSES OF HYDROCORTISONE A DAY

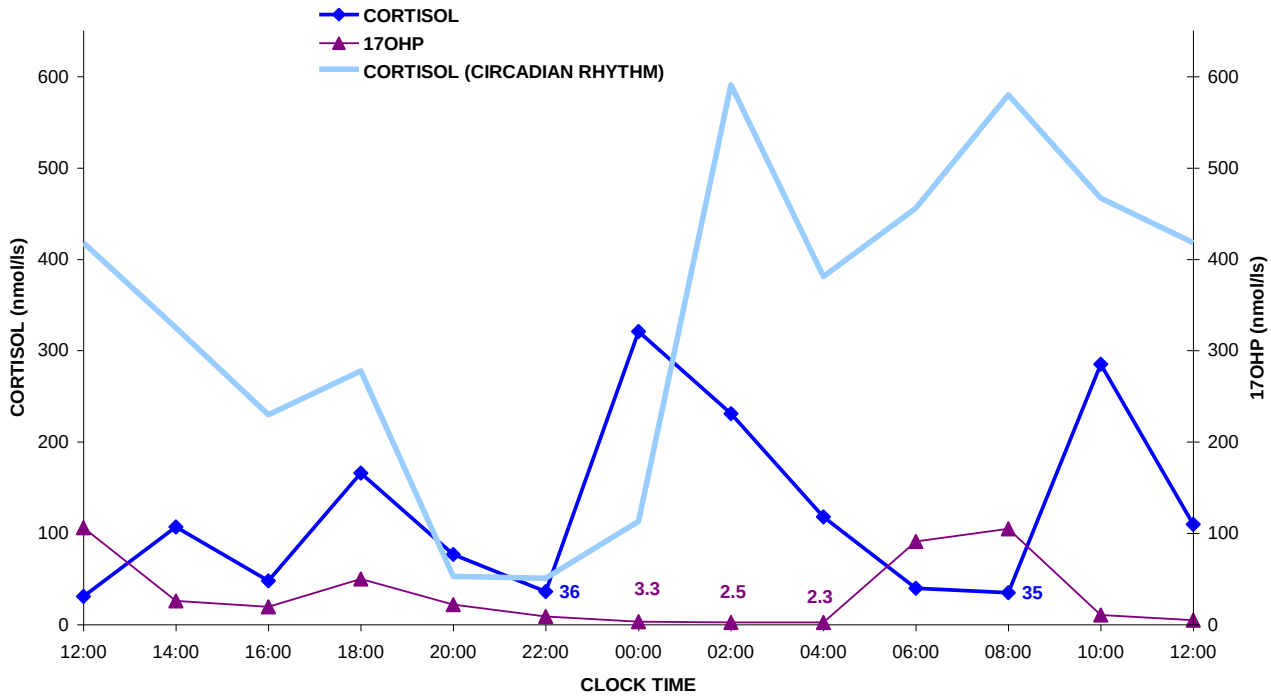

Fig:11

In the graph above (Fig:11) we can see that this patient is never without cortisol in the blood, however if following the circadian rhythm you would need to move the last dose to midnight which would give better cover in the early mornings which would bring the morning 17 OHP lower. It is important to remember that everyone needs differing amounts of cortisol to bring the 17 OHP levels into a normal range. The patient in this profile is a child so they would need less cortisol, this is also why it is important to have 24 hour profiles, so each patient with CAH can have their doses individually adjusted to the right amount and the correct time it needs to be taken to avoid as many of the side effects which are listed in Fig: 2 and Fig: 3, as possible.

CIRCADIAN DOSING

These examples along with the extensive data we have collected over the years with doing 24 hour profiles have produced strong evidence that you need to **CONSIDER THE CORTISOL & THEN 17 OHP WILL FOLLOW**. There is sound mathematical reasoning for doing this as it is cortisol that determines 17OHP. The two do not run exactly together however as there is a lag between a change in cortisol levels and what then happens to 17OHP. This is because of the feed back loop from cortisol through the pituitary gland and down to the adrenal. It takes about 60 minutes for a change in cortisol to reflect itself in 17OHP and emphasises the need for multiple samples to fine tune control rather than just one or two or even three samples.

Some parents have noticed better growth and less weight issues in their children by changing the timing of the doses to follow the circadian rhythm by waking them up to give a dose of hydrocortisone in the early hours of the morning.

This is a very difficult regime to follow, but it is better to give the last dose as late as possible at night, so the cortisol can suppress the ACTH surge which in turn causes the 17 OHP to rise. The way the dose needs to be split is as follows:

TIME	% of daily dose
Midnight	30%
07:00	35%
12:00	20%
18:00	15%

Pump Therapy

Using a diabetic pump for the delivery of hydrocortisone, you can work out the rates of delivery to continually infuse the hydrocortisone subcutaneously at a rate to suit the individual's metabolism to follow the circadian rhythm.

The pump site only has to be changed every 3 to 4 days and the pump cartridge filled with hydrocortisone which does not take very long. The modern inserters make it relatively painless to insert the plastic cannula and are simple to use. Pumps also have the function to double or triple rates which are programmed into the pump, so it is easy to switch to either rate as and when needed.

The bolus function infuses a good amount of cortisol, which can be used when unwell to give a boost to the cortisol levels at any time at the simple press of a button.

There are sport pumps, which are waterproof which means you can swim or surf with the pump on. The development and design of these pumps are improving all the time and there is soon to be a patch pump (rather like a smokers nicotine patch), which 'self' inserts, it is wireless and the pump itself is small and slim. The pump has an alarm to warn you when the reservoir is running low and if delivery is stopped for any reason. It is also possible to link the pump to a computer programme and trace the delivery times and amounts.

The graph below (Fig:12) shows how the pump achieves perfect control, resulting in normal levels.

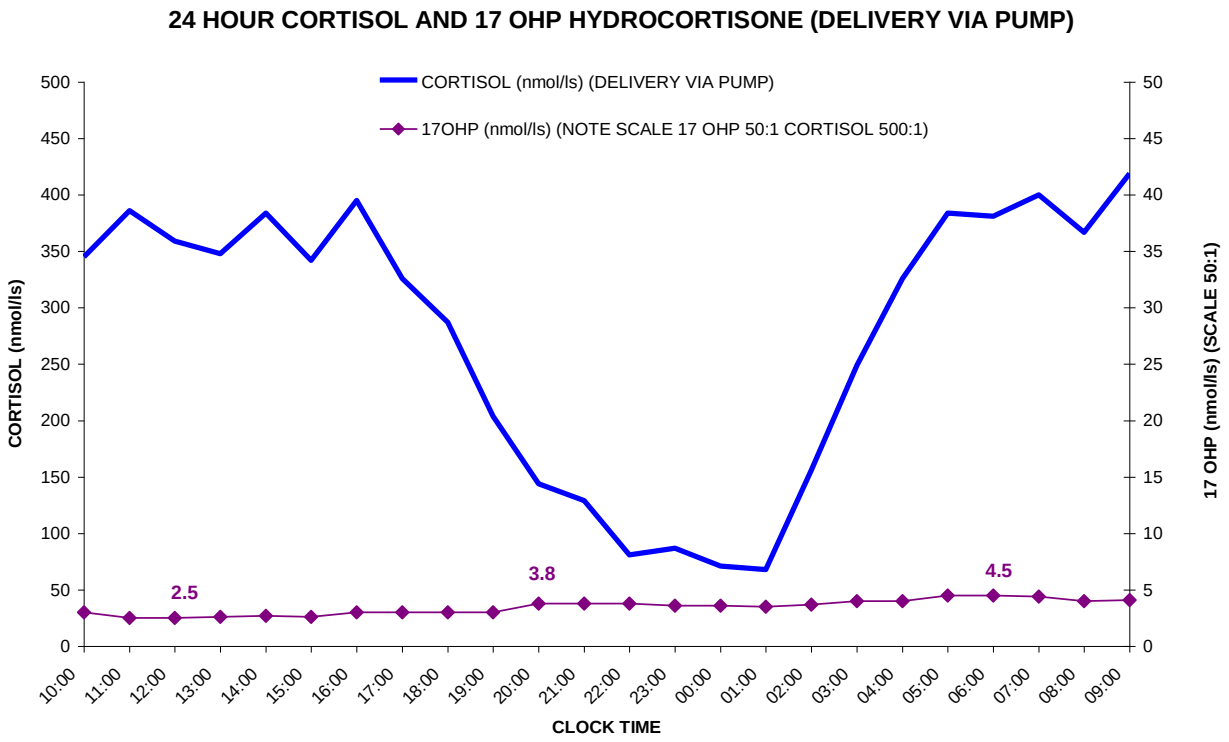

Fig:12

What we can see from this type of delivery is that fine tuning the dose of cortisol, (which can be done with increases/decreases as small as .025 mgs per hour) gives optimal 17 OHP levels and as the graph shows, 17 OHP follows the diurnal rhythm (day and night rhythm) perfectly – in the same way as a person without CAH would. Also note that the highest peak of cortisol is just over 400 nmol/ls which is a lot lower than this patient needed cortisol wise to gain control of the 17 OHP before using the pump, this is because of the way the cortisol is distributed during the 24 hours by the pump. Not only did this result in the patient experiencing fewer side effects, unexpected growth occurred, it achieved excellent weight control, greatly improved stamina, fitness and general health.

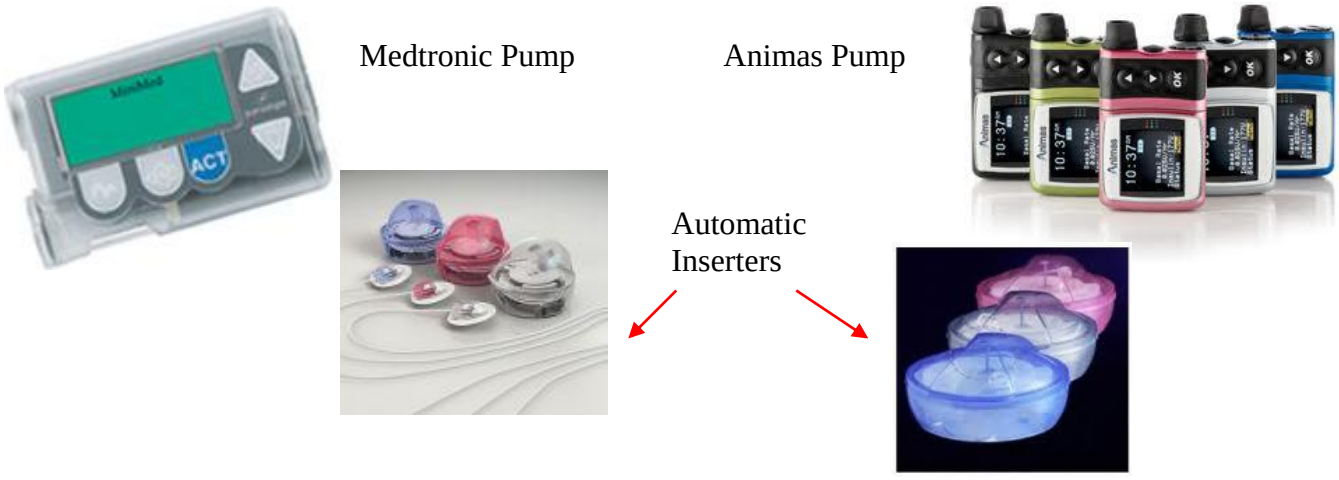

Fig:13 Examples of Pump

MISSING DOSES

It is very difficult to always remember every single dose so occasionally you may miss one and generally this does not matter as far as control is concerned because when taking your dose again regularly, the cortisol should bring the 17 OHP back to what it was before. However as the following series of graphs illustrate, you are left for long periods where there is no cortisol in the blood stream. This can lead to a drop in blood sugar, blood pressure, cause headaches, tiredness, lethargy and generally not feeling right.

Missing doses regularly will lead to under treatment and result in all the problems that are in the table (Fig: 14) for example, growth can be seriously affected, in younger children this can lead to precocious puberty (early puberty). The 17 OHP will increase and spiral out of control, the adrenals will enlarge and you will end up needing huge doses of steroid to bring everything back into control. It is also dangerous to miss tablets regularly as it means there are large periods of the day when there is no cortisol. Most days might be fine but should you become unwell then there is a serious chance of collapse and loss of consciousness as there is no cortisol around to help fight the infection or for the body to cope with injuries should they occur.

In teenage years compliance can become a problem and it is important to explain the consequences that will occur in later life, from missing doses regularly. With boys this can lead to adrenal rests in the testes which can ultimately lead to infertility or low sperm count. In girls the high androgens can upset the function of the ovaries leading to irregular periods and poor egg production. An androgen is a steroid hormone and is the precursor of testosterone (male hormone - which increases the male physical characteristics) for example androstenedione and DHEA..

Fig:14 illustrates what happens to the cortisol levels if you miss a dose, remembering that as soon as cortisol is too low, the 17 OHP will rise, so without cortisol, it will soon spiral into the hundreds. 17 OHP is a steroid hormone and not an androgen; it is the precursor to cortisol. The 17 OHP level is used as a marker for the most common type of CAH 21- Hydroxylase (the rarer forms of CAH which are 11-beta hydroxylase and 3-beta hydroxysteroid dehydrogenase deficiency they also look at other hormone markers).

Even if you miss a dose it is always good to take it as soon as you can after you realise that you have missed it as it allows the system to be brought back under control more quickly

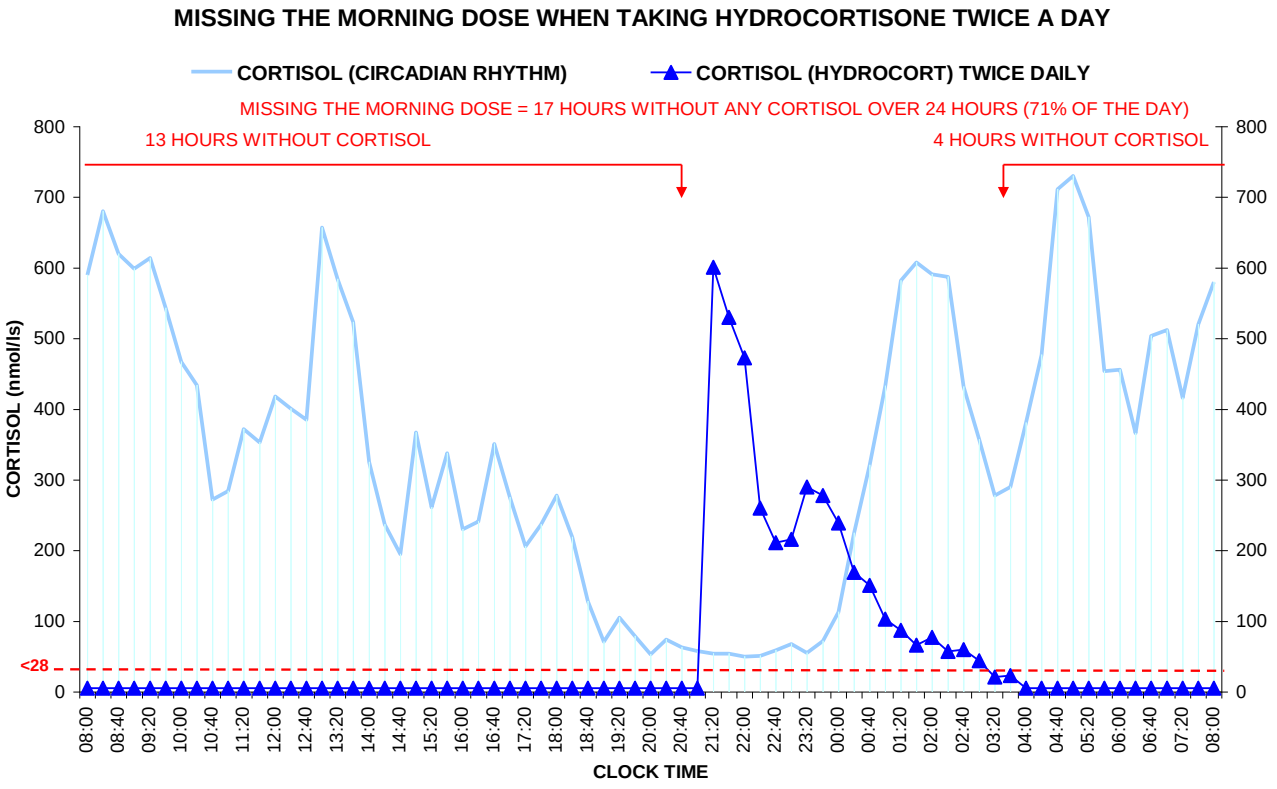

Fig:14

The graph above shows what happens to the cortisol levels if you miss the morning dose when taking hydrocortisone twice a day. Due to the low levels from 4.00 am in the morning, there is no cortisol around for 17 hours missing the times when the body would naturally make the highest amounts.

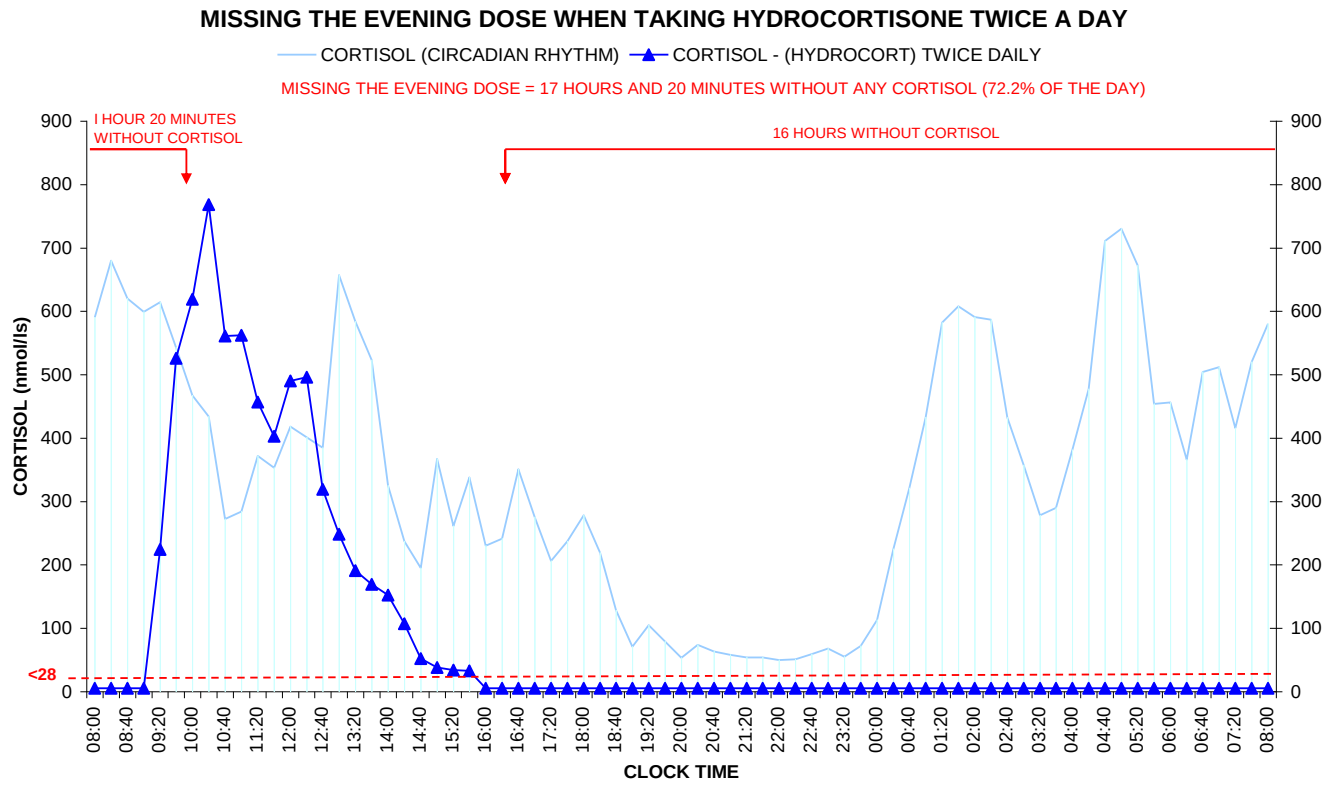

Fig: 15
This graph show what happens if the evening dose is missed. From 4 pm in the afternoon, (due to the cortisol not lasting long enough from the morning dose) there is again a period of over 17hours where there is no trace of cortisol in the blood.

Missing a dose when taking three doses of hydrocortisone a day.

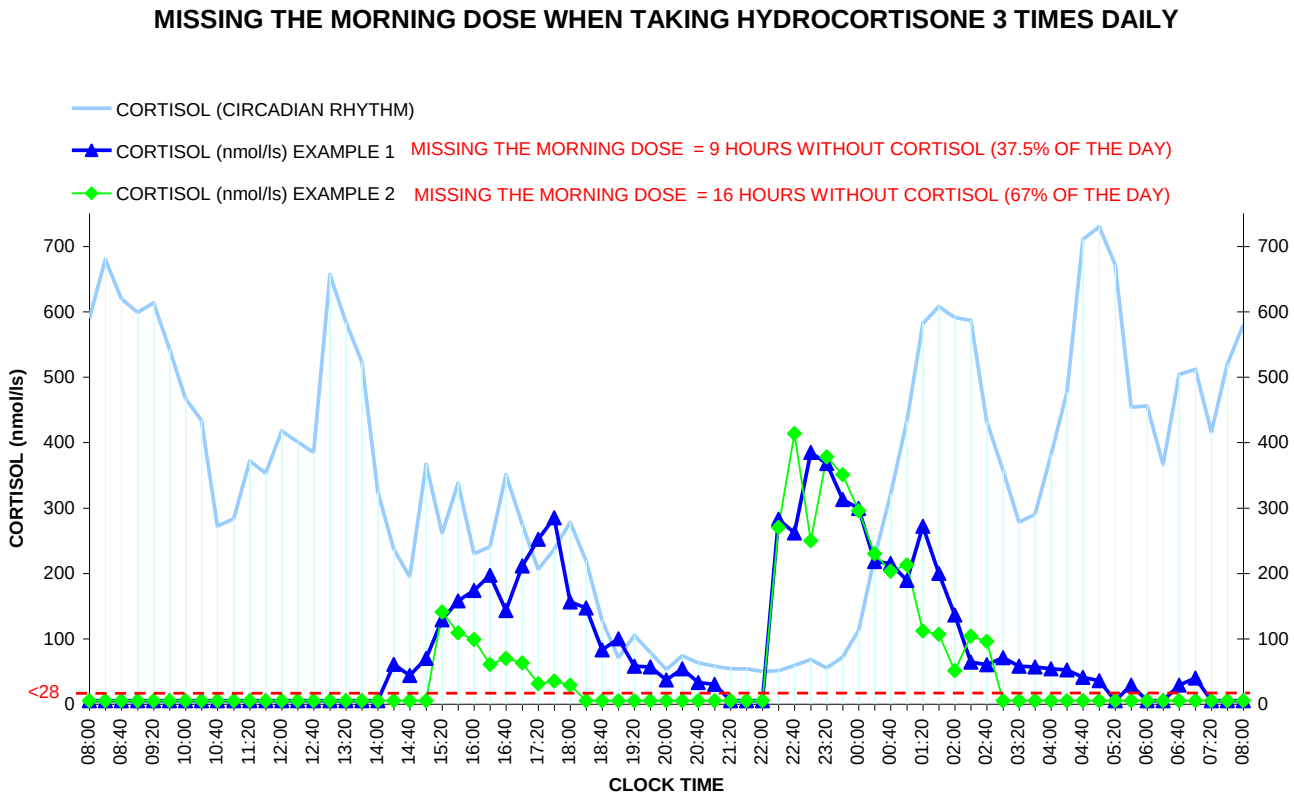

Fig:16

This graph illustrates gives two examples of what would happen to the cortisol if the morning dose was missed. Both examples show that the cortisol is already depleted or very low in the early hours of the morning, at a time when normal cortisol levels would be peaking, so in fact there is no cortisol in the blood stream until the lunchtime tablet is taken. Both examples also show that the cortisol from the lunchtime dose does not last until the evening dose is taken and although there is usually a low level of cortisol at this time of the day, there is still some in the blood stream as can be seen in the circadian rhythm – a person without CAH.

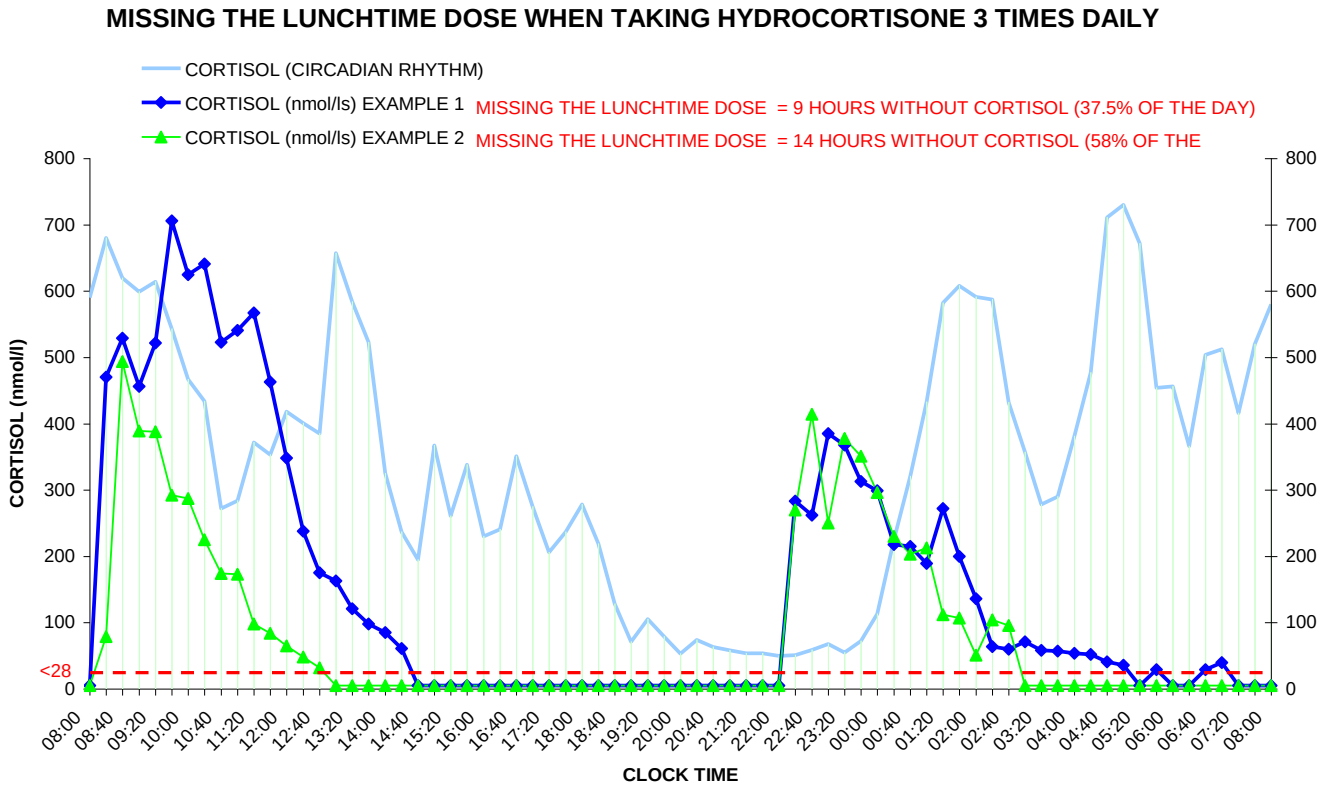

Fig:17

This graph shows the importance of taking the lunchtime tablet. It is also interesting to note the difference in both examples in how long each dose lasts, this being clearly evident when the evening doses are traced as both peak with similar amounts of cortisol, yet Example 2 metabolises cortisol more quickly than Example 1.

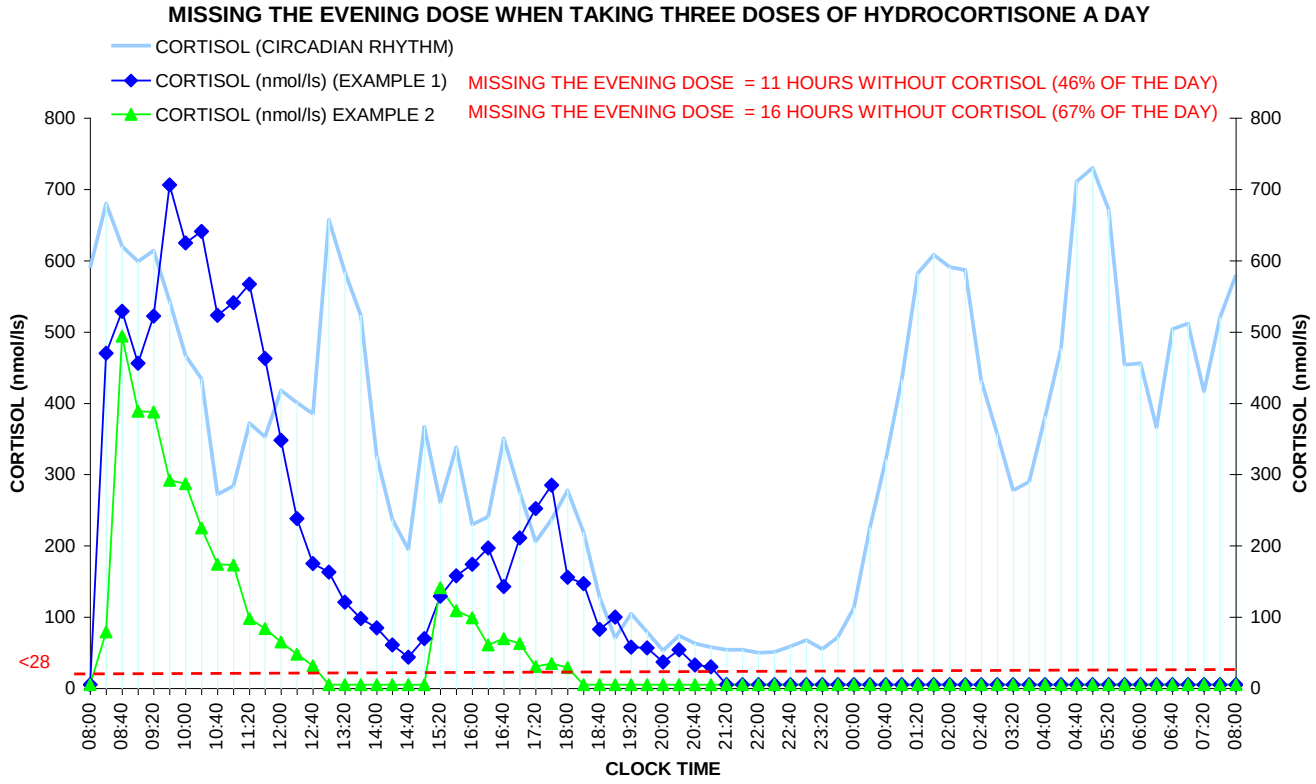

Fig:18

Missing the evening dose would leave the individual without cortisol for almost half of the 24 our period in as can be seen in Example 1 and Example 2 would be without cortisol for 16 hours.

DRUG INTERACTIONS:

Some drugs alter the way hydrocortisone is metabolised in the blood and it is important to check with your endocrinologist if you are prescribed any of the following drugs listed in Fig:19

Please note; it is important to inform and discuss with your endocrinologist if you are thinking of taking the contraceptive pill.

Hydrocortisone belongs to Glucocorticoids and will have the following interactions:

The table shows on the left the particular drug and on the right what effect hydrocortisone will have on the effect of the drug. Some drugs like the barbiturates or the oral contraceptive pill upset hydrocortisone metabolism and how much cortisol appears in the blood as a result.

ACE Inhibitors	Antagonism of hypotensive effect
Acetazolamide	Increased risk of hypokalaemia
Adrenergic Neurone Blockers	Antagonism of hypotensive effect
Alpha-blockers	Antagonism of hypotensive effect
Aminoglutethimide	Metabolism of corticosteroids accelerated (reduced effect)
Amphotericin	**Increased risk of hypokalaemia (avoid concomitant use unless corticosteroids needed to control reactions)**
Angiotensin-II Receptor Antagonists	Antagonism of hypotensive effect
Antidiabetics	Antagonism of hypoglycaemic effect
Aspirin (also Benorilate)	Increased risk of gastro-intestinal bleeding and ulceration Corticosteroids reduce plasma-salicylate concentration
Barbiturates and Primidone	**Metabolism of corticosteroids accelerated (reduced effect)**
Beta-blockers	Antagonism of hypotensive effect
Calcium-channel Blockers	Antagonism of hypotensive effect
Carbamazepine	**Accelerated metabolism of corticosteroids (reduced effect)**
Carbenoxolone	Increased risk of hypokalaemia
Cardiac Glycosides	Increased risk of hypokalaemia
Clonidine	Antagonism of hypotensive effect
Coumarins	**Anticoagulant effect possibly altered**
Diazoxide	Antagonism of hypotensive effect
Diuretics	Antagonism of diuretic effect
Diuretics, Loop	Increased risk of hypokalaemia
Diuretics, Thiazide and related	Increased risk of hypokalaemia
Erythromycin	Erythromycin possibly inhibits metabolism of corticosteroids
Hydralazine	Antagonism of hypotensive effect
Ketoconazole	Ketoconazole possibly inhibits metabolism of corticosteroids
Methotrexate	Increased risk of haematological toxicity
Methyldopa	Antagonism of hypotensive effect
Mifepristone	Effect of corticosteroids (including inhaled corticosteroids) may be reduced for 3-4 days after mifepristone
Minoxidil	Antagonism of hypotensive effect
Moxonidine	Antagonism of hypotensive effect
NSAIDs	Increased risk of gastro-intestinal bleeding and ulceration
Nitrates	Antagonism of hypotensive effect
Nitroprusside	Antagonism of hypotensive effect
Oestrogens	Oral contraceptives increase plasma concentration of corticosteroids
Phenytoin	**Metabolism of corticosteroids accelerated (reduced effect)**
Progestogens	Oral contraceptives increase plasma concentration of corticosteroids
Rifamycins	**Accelerated metabolism of corticosteroids (reduced effect)**
Ritonavir	Plasma concentration possibly increased by ritonavir
Somatropin	Growth promoting effect may be inhibited
Sympathomimetics, $Beta_2$	Increased risk of hypokalaemia with concomitant use of high doses
Theophylline	Increased risk of hypokalaemia
Vaccines	High doses of corticosteroids impair immune response; avoid use of live vaccines

Fig: 19