

Checking what you have done

Once the dosing has been adjusted to match the circadian rhythm, the next step is to undertake a 24 hour profile. For information on this, please see our leaflet on 24 hour profiles <http://www.cahisus.co.uk/leaflets.htm>

From the 24 hour profile we can get all the information that we need on how high the cortisol value goes after the administration of the dose, how long it is around in the blood for and whether it is removed from the circulation quicker than normal. It also tells us times of the day when there is no hydrocortisone (cortisol) around so we might consider readjusting the 6 hourly dosing schedule to ensure adequate coverage throughout the 24 hour period. This is important as when there is no cortisol around, blood glucose levels can drop resulting in hypoglycaemia.

The circadian rhythm can be mimicked precisely by using the pump method. The hydrocortisone (Solu-Cortef) is continuously infused via the diabetic pump, through a cannula which is inserted subcutaneously. The rates are worked out to suit the individual's metabolism and these are programmed into the pump to kick in automatically over the 24 hour period.

The great thing about this method is that the dose can be accurately titrated by very small amounts, such as 0.025 mg per hour. The graph below (Figure: 3) traces, by hourly blood sampling, the cortisol levels of two healthy males (purple and green lines) and the cortisol levels delivered by the pump (blue line) using the Peter Hindmarsh formula, in an adult male who is cortisol deficient. This comparison shows how the right amount replacement cortisol is achieved.

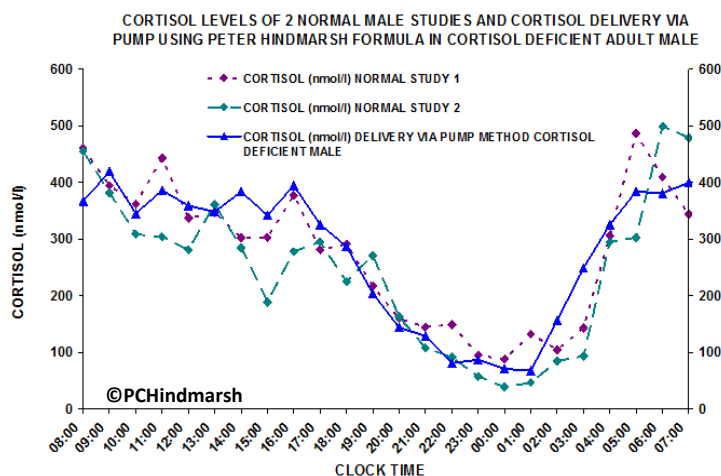


Figure: 3



Adrenal Hypoplasia Congenita

CIRCADIAN RHYTHM DOSING

Professor Peter Hindmarsh

To allow children and young people with Adrenal Hypoplasia Congenita to work with their parents and us to discover and develop their own capacity to be responsible for their own life

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"The ideas expressed are independent of the editors' affiliations. Data provided is from current literature and should always be discussed with your endocrinologist"

Circadian Rhythm Dosing

General

Cortisol is produced from the adrenal glands into the blood in varying concentrations over a 24 hour period.

There is a higher level of cortisol in the blood between approximately 06.00h (6 am) and 12 noon than at any other time of the day.

By 20.00h (8 pm) the values of cortisol that can be measured are very low and it is these changing levels/concentrations that occur throughout the 24 hour period, that is known as the circadian rhythm.

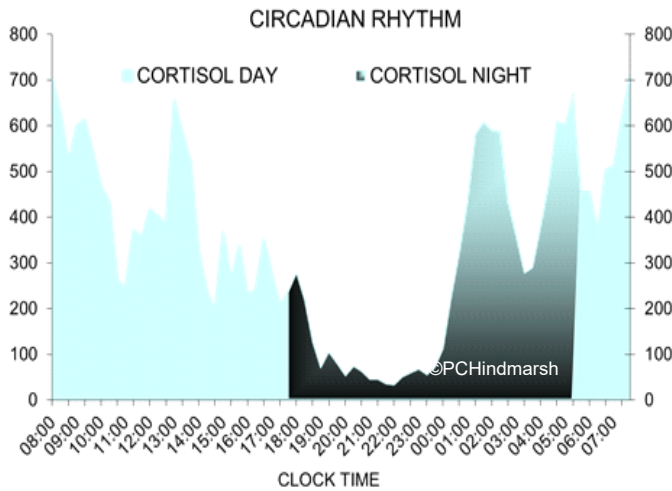


Figure 1

Figure 1 above shows an example of the circadian rhythm production of cortisol in an individual without Adrenal Hypoplasia Congenita.

Of course in Adrenal Hypoplasia Congenita there is a problem with the cortisol production, so the circadian rhythm is absent.

In endocrinology, what we like to try and do is to mimic as close as possible, the normal hormone production. We do this because we believe that the natural production of the hormone must be advantageous to the individual.

In the case of cortisol, what we aim for is to mimic as close as possible, the circadian rhythm. As a result, we have to think of how we deliver the dose of glucocorticoid throughout the 24 hour period to achieve this.

Types of Glucocorticoid

There are three types of glucocorticoids that can be taken orally to replace cortisol in Adrenal Hypoplasia Congenita.

Hydrocortisone: is a synthetic form of cortisol and can be measured accurately in the blood.

Prednisolone: is similar to cortisol but has been modified slightly to prolong the duration of action.

Dexamethasone: is structurally different and a fluorine atom has been introduced which significantly alters how the molecule is handled. The fluorine atom prolongs the duration and action of dexamethasone.

Dexamethasone cannot be measured accurately in the blood.

The table below (Figure: 2) shows the different peaks and duration of action of these three glucocorticoids.

Steroid	Duration of Action (hours)	Peak Value in Blood (hours)	Growth Suppressing Effect (potency)	Dosing Effect on Growth
Hydrocortisone	6	1-2	1	20mg
Prednisolone	8	3-4	5	4mg
Dexamethasone	12	Rather flat profile	80	0.4mg

Figure: 2

Hydrocortisone has a quick onset and the cortisol peaks to the highest level usually around 1-2 hours after being taken.

The cortisol obtained from the tablet lasts in the blood circulation between 4– 6 hours.

Hydrocortisone also has an anti-inflammatory action which usually lasts between 6 – 8 hours.

For more details on how hydrocortisone works see our hydrocortisone leaflet <http://www.cahisus.co.uk/leaflets.htm>

Prednisolone

Prednisolone being slightly modified usually peaks around 3-4 hours after being taken.

Its action as cortisol usually lasts about 6 - 8 hours.

Prednisolone is more potent than hydrocortisone and the anti-inflammatory action can last more than 12 hours.

Dexamethasone

Dexamethasone doesn't have such a peaky nature and tends to last for anything up to 12 hours in the circulation as cortisol but its duration of action as an anti-inflammatory can be anything up to 24 hours.

What this means from the dosing standpoint is that:

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

How to do circadian dosing

We are going to think how hydrocortisone should be given throughout a 24 hour period. We know through research that the secretion of cortisol from the adrenal gland varies throughout a 24 hour period.

What we find is:

- * Between 06.00h (6am) and 12 noon, 35% of the total cortisol over a 24 hr period is produced
- * Between 12 noon and 18.00h (6pm), 20% of the total cortisol over a 24 hr period is produced
- * Between 18.00h (6pm) and midnight, 15% of the total cortisol over a 24 hr period is produced
- * Between midnight and 06.00h (6am), 30% of the total cortisol over a 24 hr period is produced.

So for example, if the total amount needed per day was 20 mgs of hydrocortisone, we would give 7 mg at 06.00h (6 am), 4 mg at lunchtime, 3mg at 16.00h (4pm) and 6 mg at midnight. We give the dose at 16.00h rather than 18.00h because of a natural burst of cortisol at that time.

Due to the different nature of prednisolone, we would give it three times a day in slightly different proportions which would be

- * 45% at 06.00h (6am)
- * 20% at 14.00h (2pm)
- * 35% at midnight.

As dexamethasone does not have peaks of concentration like hydrocortisone and prednisolone, it would not be possible to administer circadian dosing.