



## USING THE PUMP METHOD TO DELIVER CORTISOL ADRENAL HYPOPLASIA CONGENITA

*By Professor Peter Hindmarsh and Kathy Geertsma*

### Introduction

Mimicking the circadian rhythm of cortisol secretion is the ideal way of treating people with Adrenal Hypoplasia Congenita (AHC) also known as congenital adrenal hypoplasia. We try to do this in a number of ways by giving hydrocortisone orally 3 or 4 times a day but although we try our best to get this as correct as possible, it is not exactly the same as the normal circadian rhythm. However it is possible to mimic the circadian rhythm by using pump therapy. To see how hydrocortisone works when using it to replace cortisol, have a look at our hydrocortisone leaflet, where you will find examples of how the hydrocortisone (cortisol) works and how long it lasts when taken twice, three, and four times a day.

People with AHC can be both *under* and *over* treated even if 'one off blood' tests show the level to be within normal range which is why having a full 24 hour profile to look at the cortisol levels either hourly or two hourly is so valuable. Often patients complain of headaches, weight issues, tiredness, lethargy and describe many of the symptoms that indicate low or high cortisol values. Side effects, like the ones described can be a result of having periods of the day where the cortisol peaks too high and periods where the levels drop too low or in fact where no cortisol can be measured in the blood. To learn more about this please read our leaflet "The Value of 24 Hour Profiles in Assessing Cortisol Replacement in Adrenal Hypoplasia Congenita."

### How the Pump delivers

The pump method not only delivers the cortisol in a way which mimics the circadian rhythm, but also the way cortisol is naturally processed in the body, i.e. in the same way as a person who does not have AHC. In someone without AHC, cortisol is released directly from the adrenal glands into the blood stream and is then processed in the liver. When replacing cortisol in tablet form, the cortisol is first ingested into the stomach, processed through the liver and only then released into the blood stream. The pump method bypasses the stomach and you get 100% absorption straight into the blood stream.

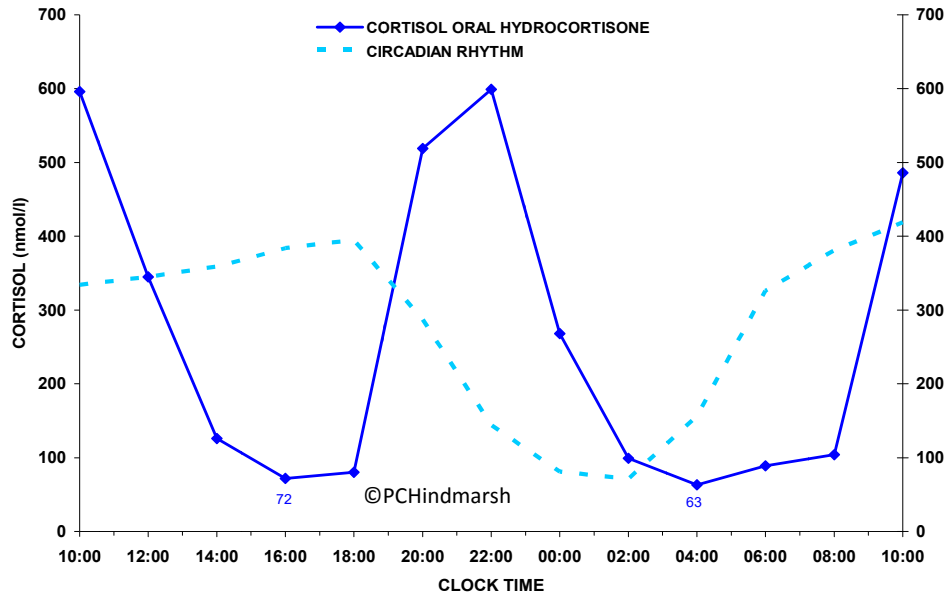
The pump also allows us to adjust the dose accurately by very small amounts, at any time in the 24 hour period; ultimately we are able to set the rates to suit the individual's metabolism.

### Examples

The following data are examples of two patients, Example One and Example Two, before using the pump method and then using the pump with the rates worked out to suit their individual metabolism using the Peter Hindmarsh Formula.

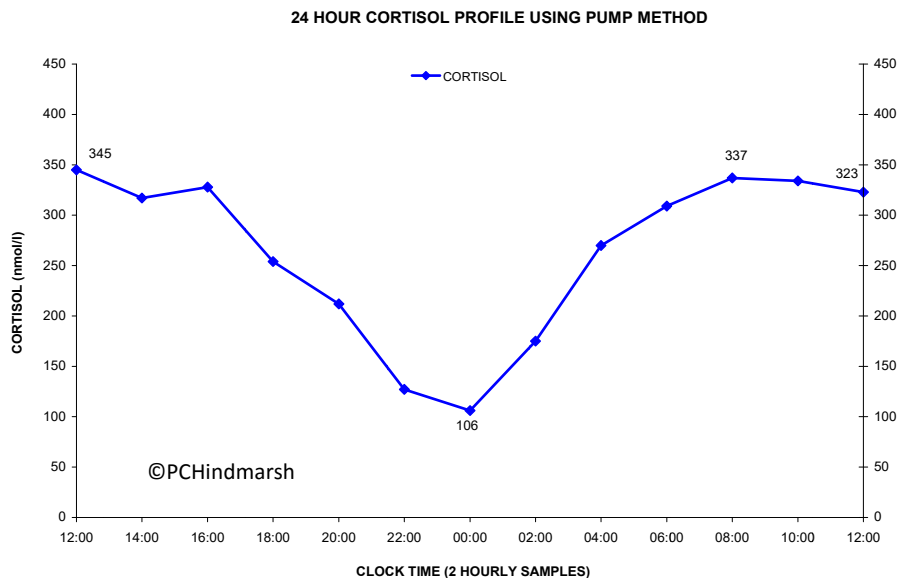
### Example One

The data in the graph below (Figure: 1) shows the result of a 24 hour profile done whilst the patient in Example One was taking hydrocortisone tablets. This patient has a reasonably normal clearance rate of cortisol. We can see that the cortisol distribution (solid blue line) over the 24 hour period does not follow the circadian rhythm (dashed light blue line).



**Figure:1 24 hour cortisol profile on oral hydrocortisone**

The data in graph below (Figure: 2) shows the result of a 24 hour profile done whilst the same patient, in Example One is using the pump with the rates worked out using the Peter Hindmarsh Formula.

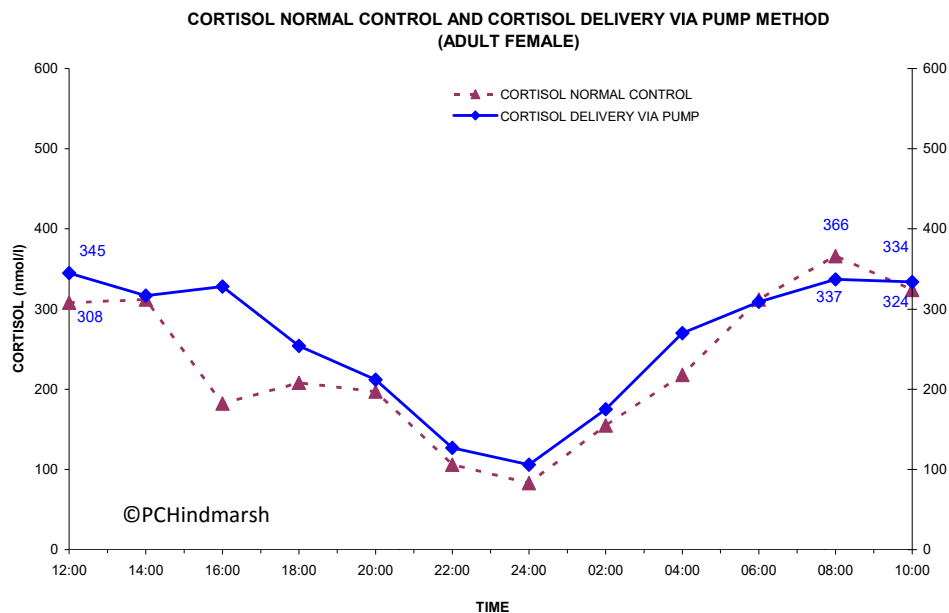


**Figure: 2 24 hour profile showing the cortisol levels delivered via the pump using the Peter Hindmarsh Formula**

The results in Figure 2 show us: -

1. The patient now has right distribution of cortisol over the 24 hour period.
2. The highest cortisol peak using the pump method is far less than that on the profile done when taking hydrocortisone orally, thus helping to prevent the side-effects that can be caused by over treatment.
3. The higher cortisol levels are occurring at the time of day when the body should naturally produce cortisol thus preventing under treatment.

Now if we add in a cortisol profile of a female without any adrenal problems (normal control) and plot it against the pump delivery cortisol levels that the pump using the Peter Hindmarsh formula, we can see that the pattern is the same.



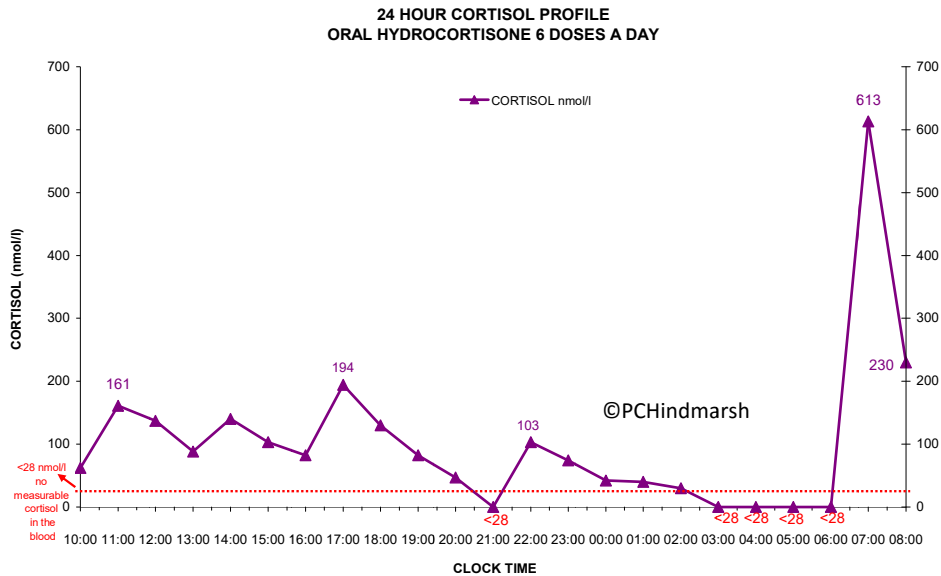
**Figure: 3 24 hour profile showing cortisol levels of someone without adrenal insufficiency and cortisol levels of an adult female using the pump method programmed using the Peter Hindmarsh formula**

This optimal control not only greatly improved the patient's general health and well-being, but side effects such as headaches and lethargy disappeared. This patient also suffered from severe gastritis which has now cleared up as the pump delivery bypasses the gut.

The patient reported "Since starting on the pump, their health has improved tremendously; no longer feels unnaturally tired, has energy and generally feels much better. Rarely gets a headache and no longer has problems with gastritis. The patient has found wearing the pump to be very easy having enjoyed skiing and a school trip abroad. The patient is now doing things they had not felt well enough or had the stamina to do before starting the pump."

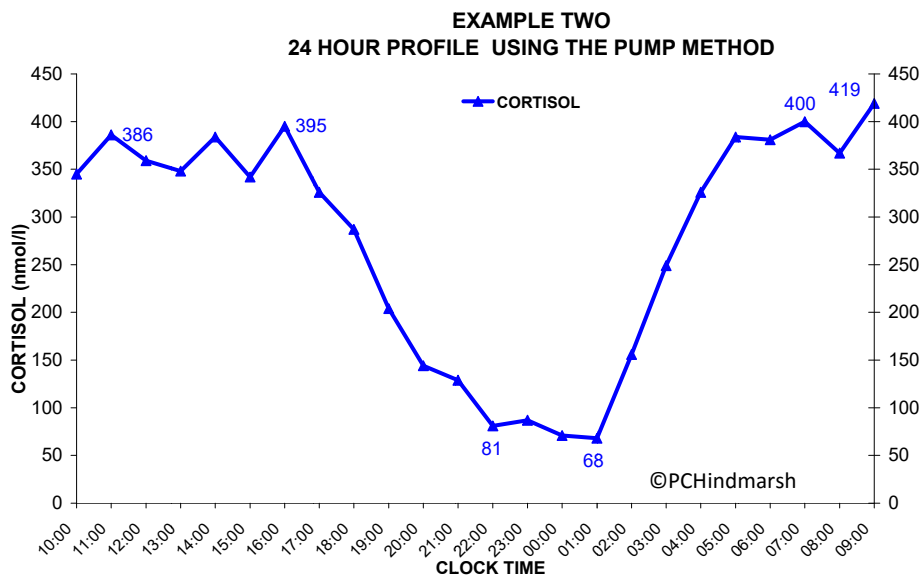
### Example Two

The data in the graph in Figure: 4 shows the cortisol results of a 24 hour profile of a patient (Example Two) was taking oral hydrocortisone tablets in six doses a day.



**Figure: 4 24 hour cortisol profile of a patient (Example Two) taking oral hydrocortisone 6 times per day**

The data in the graph in Figure: 4 shows that this patient clears cortisol rapidly. This is more common than we think in AHC and even though the patient was taking 6 doses of hydrocortisone a day, there are still periods where no cortisol can be measured in the blood. The patient had multiple symptoms of under treatment. If a one off blood sample had been taken at 11:00 or within an hour of taking a dose of hydrocortisone the problem this patient has in handling oral hydrocortisone would not have been evident.



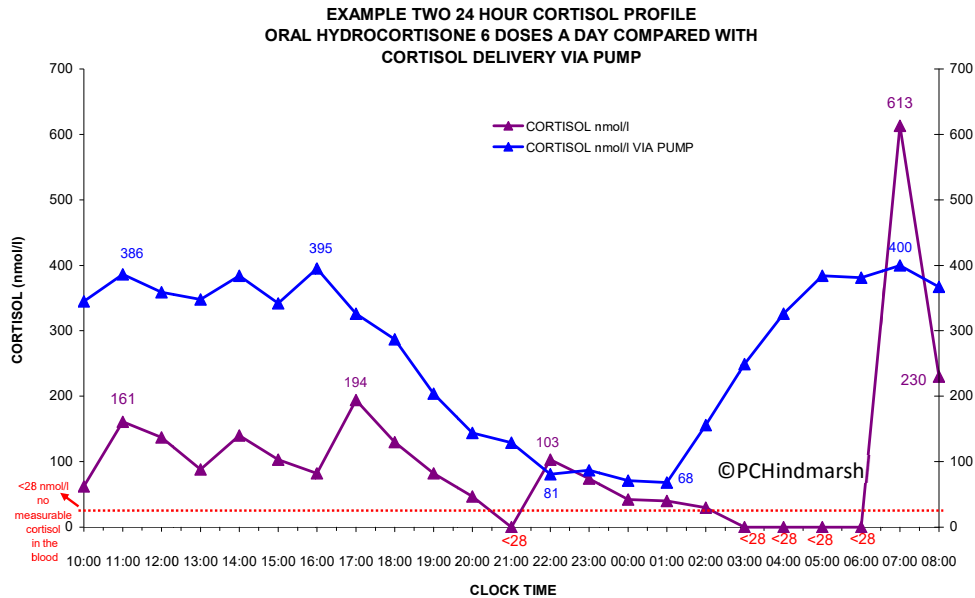
**Figure: 5 Example Two 24 hour profile showing the cortisol delivered via the pump method using the Peter Hindmarsh Formula**

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

The data in the graph Figure: 5 shows the result of a 24 hour profile done on the same patient (Patient Two) using the pump delivery method with the Peter Hindmarsh Formula. We now compare both sets of data (Figure: 3 and Figure: 4) in Figure: 6.



**Figure: 6 Comparison of the distribution of cortisol from oral hydrocortisone dosing six times a day and delivery via pump method using the Peter Hindmarsh formula**

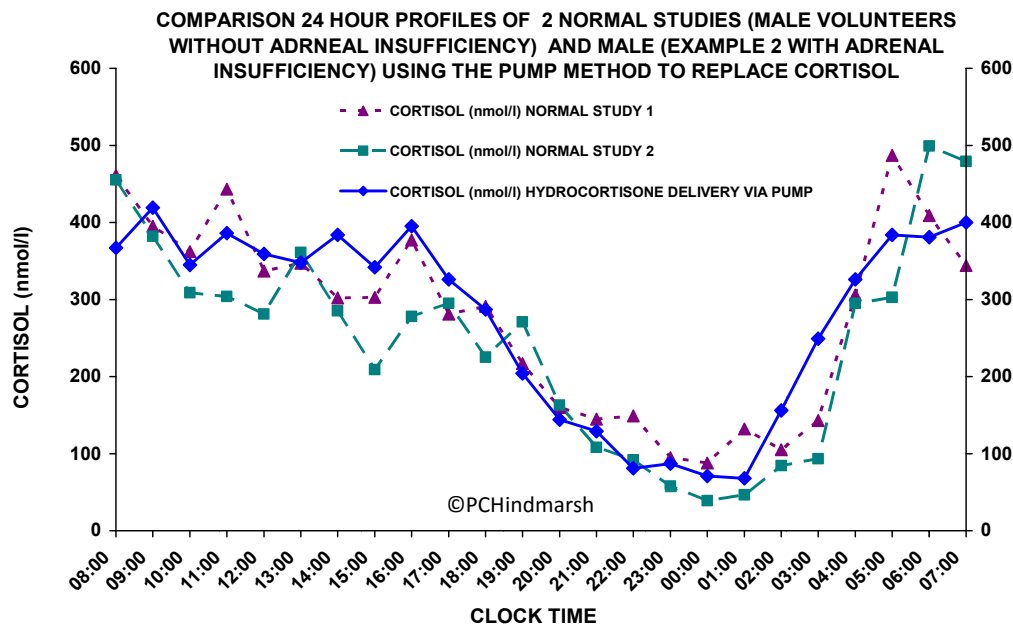
The results in Figure: 6 show us: -

1. Despite the patient clearing cortisol rapidly the cortisol delivered via the pump method has been carefully calculated using the Peter Hindmarsh formula and now mimics the circadian rhythm.
2. There are no periods where the patient is cortisol deficient or where the cortisol drops too low using the pump method.
3. Using the pump method there is no excessive cortisol peak of 613 nmol/l at 08:00 which the oral dose gives.
4. The pump delivers normal concentrations of cortisol in the early hours of the morning, thus preventing hypoglycaemia and providing the cortisol the body would normally have when waking to start the day.

An important factor to note is that the overall daily dose of hydrocortisone delivered by using the pump in the profile Figure: 5, is significantly lower than the overall daily oral dose taken in the profile Figure: 4! This shows that with the right rates suit to this patient, the pump delivery of cortisol is using a smaller amount of hydrocortisone over the 24 hour period and giving a perfect distribution of cortisol.

The patient's well-being and general health improved dramatically. The patient's weight issues resolved and the patients' BMI remains normal. Headaches, severe gastritis and lethargy disappeared. The patient also noticed a marked increased stamina when partaking in sport.

*"The pump has given me my life back, I am now fit healthy and live a full life. I swim and surf whilst wearing my waterproof pump, go to the gym and also run. I no longer have severe gastritis. I prefer using the pump as I do not have to worry about taking tablets at certain times; I can sleep in over weekends without worrying about taking the morning dose as soon as possible and I wake up feeling ready for the day. For me the pump has proved miraculous".*



**Figure: 7 Comparison of the distribution of cortisol from two normal (without adrenal insufficiency) controls and cortisol delivery via pump method using the Peter Hindmarsh formula in patient (EXAMPLE 2) who has cortisol deficiency.**

We can see in that the cortisol distribution throughout the 24 hour period in patient (Example Two) using the pump delivery method mimics the natural circadian rhythm as can be seen in both normal controls.

## Conclusion

The primary aim in treating adrenal hypoplasia congenita is to try and replace cortisol as closely as possible to the way the body would normally produce it. Hydrocortisone is a synthetic form of cortisol and it is the mildest steroid that can be used to replace cortisol. It is important to try to get the dose as accurate as possible in order to avoid the side-effects caused by replacing with either too much or too little cortisol as this can cause long term damage to the body.

In AHC it is important to replace the early morning levels of cortisol to stop the risk of hypoglycaemia and using the pump method achieves this. The body naturally produces cortisol in the early hours of the morning and the reason for this is thought to be because it is a period where no food or drink is consumed, so it is the body's natural way of keeping blood glucose levels normal.

As we can see from the profiles in Figure: 2 and Figure: 5, whilst using the pump with the Peter Hindmarsh Formula, this method can achieve perfect cortisol replacement on the minimum dose of hydrocortisone. However it is important that the rates are worked out for each individual patient as the pump can only deliver what it is programmed to do and does not have generic rates. There are important steps to be taken when working out the rates, which include doing a clearance study.

## **General Information**

Pumps are becoming smaller and wireless pumps are now available on the market and a new slim, versatile, discreet rechargeable pump is due to be released soon. The auto inserters are so good it makes inserting the small cannula virtually painless. The site only needs to be changed every three to four days.

## **Bolus Function**

There is also the option of using a bolus button, which infuses a bolus dose of hydrocortisone directly into the blood stream. The bolus can be given in various doses by the simple press of a button; some pumps have a remote control device.

## **Double and Triple Rates for Illness**

Double and triple doses can be achieved very easily by switching over to the desired rate (these rates are worked out and programmed into the pump). Although the pump method also ensures the patient is getting cortisol during vomiting illnesses, it is still important to have the emergency injection on hand at all times and remember to increase fluid intake.

It is important when ill to give a bolus when switching over to double/triple rates; this gives the cortisol level an immediate boost.

Temporary Basal Function can be used to set a specific rate for a certain period of time. For example, the temporary basal rate can be set to deliver 150% which is the normal dose (100%) and an increase of half the normal dose (50%). The pump will deliver one and a half times the daily rate for as many hours as you set it to do this. This function is handy to use in exam situations or a situation where the patient feels they may need a little more cortisol, it is also very easily cancelled and the pump automatically reverts to deliver normal rates.

The pump gives the patient more independence as there is no forgetting or missing doses, no doses taken late, no having to wake up to take a dose and also not having to take a tablet at inconvenient times.

The pump is driven by batteries; the type depends on the manufacturer of the pump. Most Animas pumps use one AA lithium battery and most Medtronic pumps use two AAA lithium batteries. When using the pump for cortisol replacement the batteries last several months and as soon as the pump senses a low battery an alarm alerts you to this.

When the reservoir is running low, the pump will alarm. You can see exactly how much the pump has delivered by looking at the history. Many pumps come with software, which allows you to download the delivery information.

If there is a problem with delivery, which is rare, the pump will alarm to alert you.

The Animas pumps are waterproof and can be used whilst doing water based activities such as swimming. All other pumps are very robust and are used by diabetics whilst doing all kinds of sport.

**We recommend using Solu-Cortef in the potency 100 mgs to 1 ml of sterile water.** For more information on how to do this, have a look at the pump video on our CAH website

<http://www.cahisus.co.uk/> PUMP VIDEO

It is important to note that the pump delivery using hydrocortisone to replace cortisol will only be as good as the rates are set to deliver. These rates need to be very carefully worked out and to achieve this 24 hour profiles and clearance rate need to be factored in the Peter Hindmarsh formula. Blood sampling must be used for this. Saliva sampling is not suitable because saliva is not the cortisol level that is going to the organs, which is the measurement we are interested in. Saliva is rather like a 'by product' and it can also be influenced by other factors, such as caffeine from coffee, tea or certain sodas and fruit juices. What we want to measure is the level of cortisol in the blood that the hydrocortisone tablet provides, so we know that there is sufficient or an excess level of cortisol to be carried in the blood to all the organs in the body.



Waterproof Animas Pump



Medtronic Pump



Coming soon the rechargeable, wireless and waterproof Cellnovo Pump



Animas Inset



Medtronic MIO insets



Inset in the skin