

CONTINUOUS SUBCUTANEOUS HYDROCORTISONE INFUSION – PUMP THERAPY AS A WAY TO MIMIC NORMAL CORTISOL PROFILES

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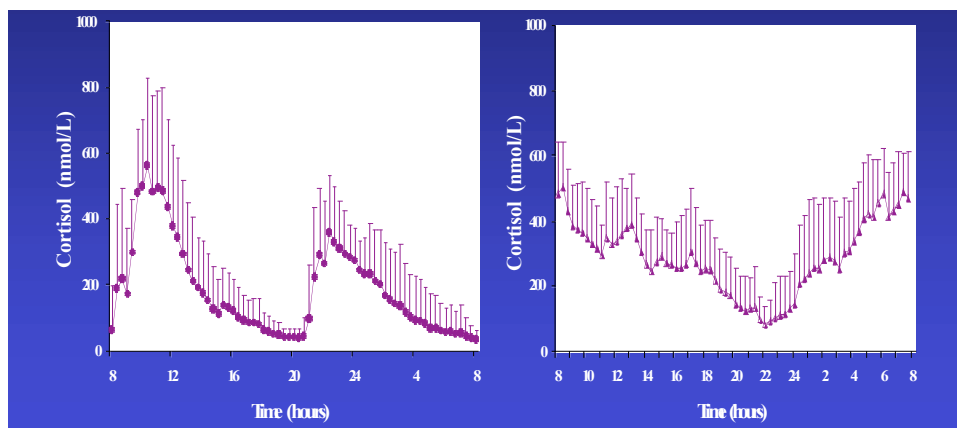
Narrative:

For as long as I can remember, I've always suffered from bad headaches which were the bane of my life and as I grew older, they became more frequent and debilitating. I also battled with my weight which affected my self confidence and even though I was very careful with what I ate, it did not seem to matter, my weight steadily increased. The specialist I was under at the time told me I was fat and said, 'you are what you eat'; having CAH was simply a matter of replacing what was missing and my headaches were psychological. During puberty my 17 OHP levels spiralled out of control, the doctors increased the dose and of course I grew fatter. They tried me on prednisolone which made me feel so angry and caused such mood swings which I found very hard to control, I hated the way I felt. They tried dexamethasone which again increased my weight and caused my skin to break out in acne which yet again led to me feeling extremely despondent and depressed. Both the prednisolone and the dexamethasone caused me to have really bad gastritis; it was then decided to switch me back to hydrocortisone. I was at this stage suffering from a continuous headache and felt ill and exhausted. I started to lose weight rapidly although my diet had not changed, I became weak, frail, extremely dizzy and found the simplest tasks extremely hard to achieve. My growth plates had almost fused and I was told I would be lucky to reach 5' 7" which I was really upset about at the time, as despite everything my growth had always been good. It was suggested I was not taking my tablets, which really made me mad, why on earth would I want to feel this way, more than anything I longed to be normal and headache free. I became so ill I could not attend school; in fact I had very little quality of life.

Comment:

The treatment of CAH in children and young people consists of hydrocortisone therapy to suppress ACTH production and adrenal androgen generation and fludrocortisone to prevent salt loss. One of the central rules of endocrinology is to replace hormones as closely as is possible to their physiological production. Cortisol has a circadian rhythm with high concentrations measured in the blood in the early hours of the morning and low almost undetectable values around midnight. Figure 1 shows this rhythm and it is this pattern that hydrocortisone therapy tried to copy.

Figure 1 Circadian Rhythm of Cortisol on the right and what is delivered by Hydrocortisone therapy on the left



Although the values attained in the morning are similar to the chemistry of hydrocortisone and the fact that children go to bed earlier than adults means that in the evenings cortisol concentrations are high between 8 and 12 pm when they should be low and low thereafter when they should be high to prevent the normal rise in ACTH. It is not surprising therefore that 17OHP values in the mornings are often high.

Generally three times per day hydrocortisone keeps children and young people reasonably well controlled although problems of weight gain are common. Prednisolone and dexamethasone therapy in children is problematic because of the growth suppressing effects of these medications as well as the weight gain and gastritis.

What is described by Chris is a loss of glucocorticoid effectiveness. How does this happen? In fact Chris is telling us when he made the observation that it was something to do with the pubertal years. It is very easy to say that it is just being adolescent and maybe they are not taking the medicines. Actually something other than that may be taking place.

Narrative:

By now I was in big trouble. My skin had tanned from such high levels of ACTH, and everyone thought I was anorexic, I was eating, felt hungry but I felt full quickly and nauseous most of the time. My headache was continuous and I wanted to sleep most of the time. My growth had stopped, I had no muscle tone, I was often so dizzy I couldn't stand, I felt terribly ill and totally exhausted. My friends thought I was dying. After loads of tests we found that although I was swallowing all the tablets, they gave me; I did not absorb the hydrocortisone properly and I was metabolising the hydrocortisone I did absorb very quickly. At last a reason was found, the relief to both my mum and I, was immeasurable.

Comment:

Poor control in young people with congenital adrenal hyperplasia is often observed in adolescence because in part the handling of hydrocortisone by the body changes and it is removed more quickly from the circulation. This can lead to problems with getting the right dose for the individual. In Chris's case not only was hydrocortisone removed from the circulation more quickly but in addition the absorption of hydrocortisone from the stomach was reduced.

Narrative:

What now? The team wondered whether a pump system to deliver the hydrocortisone might work. I was a bit apprehensive but I felt so terribly ill that all I wanted was to feel better, go back to school and live, so I was desperate to try it. I found the thought of inserting the cannula into my stomach a bit daunting but like most things in life, the thought was actually far worse than the deed. My mum and I were very afraid that the pump may not work but after several days on the pump, after years of battling with my levels, they were normal and stable. I cannot put into words how wonderful I felt, to wake up and not have a headache, to be able to think clearly, to actually have some energy to enjoy life.

Comment:

Having tried to increase both the dose and frequency of oral hydrocortisone it was clear that it was not possible to easily control the CAH. Although there were pubertal changes these were due to the adrenal androgens rather than testosterone from the testes.

We decided with the family to see if we could by-pass the stomach problem and get better cortisol delivery by using an insulin pump to continuously deliver hydrocortisone under the skin.

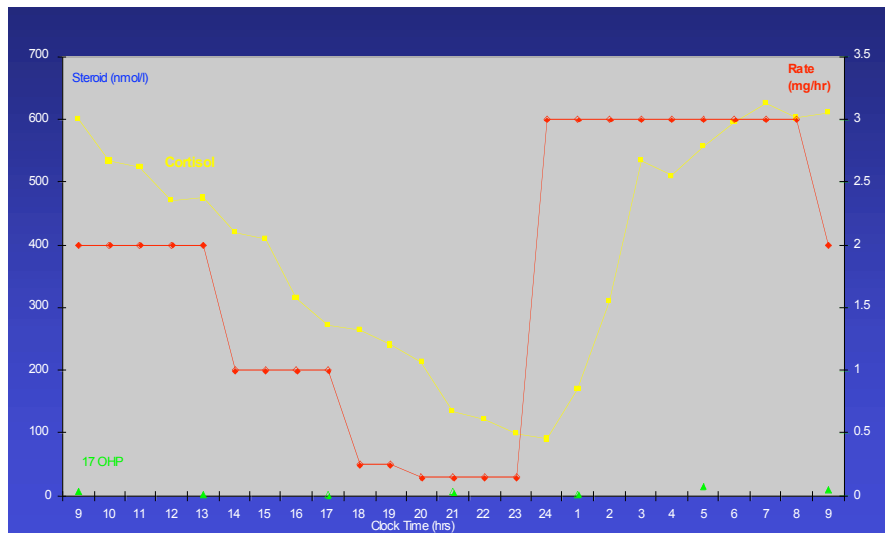
The system we chose was a Minimed Medtronic continuous insulin infusion pump and this connects to the patient using an inserter which places a small flexible tube under the skin. The components are shown in the picture below

- Medtronic Generation 2 -2003
- 3 ml volume reservoir
- 100mg/ml Efcortisol[®]
- Quick-set[®] Teflon catheter
 - a 90° insertion angle
 - an at-site disconnect
 - an insertion device
 - a soft, tapered cannula



The pump allows a variety of infusion rates to be programmed in as well as emergency rates that double the infusion rate if unwell. The system works well and after some refinement delivers a normal cortisol profile (Figure 2) and has normalised parameters of control.

Figure 2. Cortisol concentrations in yellow following hydrocortisone infusion at different rates during the day shown in red.



Over the first 6 months of treatment ACTH fell from 331 ng/ml to undetectable and 17OHP fell from 265 nmol/l to 2.8 nmol/l as did androstenedione from 40.3 nmol/l to 2.8 nmol/l which is within the normal range.

Narrative:

Now I am at University, only my close friends know I have a pump, and know that I have CAH. I am confident in the fact that I am able to use the bolus function which Prof H has worked out and tested, this delivers enough hydrocortisone to get me out of any potential problems by simply pressing a button. The pump also has a remote control which I can use to activate this function too. I never have to worry about having to take tablets at certain times of the day, and people seeing me do this. I hated going to the office at school every day to do this, and worse was when I would forget, they would send for me! This singled me out as being different and made me self conscious, if I was feeling unwell, I would have to go and ask for tablets. At University this is of course different as you can carry tablets on you which you are not allowed to do at school, however if I am not feeling well, I am able to again give myself a smaller bolus dose and discretely switch my pump to double. I have found this bolus function and switching to double or even triple dose really handy and have used this on several occasions when I have felt I have needed extra hydrocortisone, for example during exams and giving presentations. I have learnt over the years and through my experiences to know when I need extra hydrocortisone which is easy to achieve with the pump, I do not even have to have a drink to do this. The pump has given me a greater independence in the way I can manipulate the dose when needed and for a long as I require. I am able to swim although I do not wear it when swimming, tests have shown that even off it for several hours, my levels soon return to normal and are stable.

So how is and what can we use it for?

I have been on the pump for over two years now; I think I probably have the best controlled CAH in the world. Another bonus is that I started to grow again, yeah I think Prof Hindmarsh, never really expected this but I am still growing and am over 5' 9". I go to the gym as often as I can. My weight is stable, everyone says I am very lean, I do battle with accepting that I am not fat and worry about my weight but I

realise now that my weight was not my fault. Of course you have to be careful with what you eat but I am now certainly eating more than I ever did in the years where I battled with my weight, even though I am on the same dose. I think it is the way the hydrocortisone is delivered, slowly and continuously at a rate which has been specifically tailored by Professor Hindmarsh to suit my body's needs. It took some getting used to having it attached to me all the time, especially at night but I am now so used to it, that I feel strange without it.

You have to be disciplined in changing the site regularly, but really this is a very small price to pay when I consider what advantages this method has given me. The pump gave me my life back and I will always be so grateful to Professor Hindmarsh and of course my mum, as I could not have got through any of this without her constant love and support.

The continuous subcutaneous delivery of hydrocortisone may prove useful in managing some people with congenital adrenal hyperplasia.