Hypopituitarism

EXTRA HYDROCORTISONE DOSE AT 04:00 HOURS (4 AM) IN ILLNESS

By Professor Peter Hindmarsh and Kathy Geertsma

We now recommend during periods of illness that an **extra double/triple dose** of hydrocortisone is given around 04:00 hrs **(4 am)**.

* The dose should be the *same dose* as the *usual double/triple morning dose*.
* The double/triple doses should be given as usual, as the 04:00 hrs **(4 am)** dose is an ***additional*** dose.
* You should give this dose even if you have given a double dose at 01:00 hrs (1 am)

REASON

The reason why we are now advocating this extra dose at 04:00 hrs (4 am) is because at this time in someone who does not have Hypopituitarism, the circadian rhythm shows us there is usually a lot of cortisol in the system (see Figure: 1) This cortisol helps keep the blood glucose levels up whilst we are asleep.

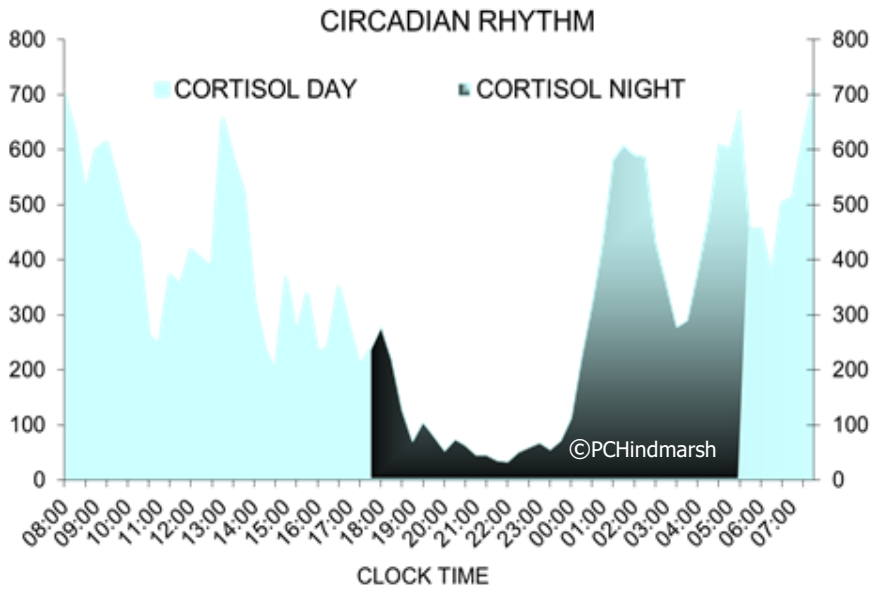

Figure: 1 The natural cortisol distribution over 24 hours is known as the Circadian Rhythm

When we are using hydrocortisone to replace cortisol, the evening dose or the last dose taken in that period will have dropped to a low level of cortisol at this time and in illness this can cause hypoglycaemia - low blood glucose levels. Low blood glucose levels can be dangerous and lead to unconsciousness and adrenal crisis.

Professor Peter Hindmarsh Professor of Paediatric Endocrinology http://www.cahisus.co.uk
Divisional Clinical Director for Paediatrics and Adolescents at UCLH

Below we give some examples of what happens to cortisol levels when hydrocortisone is taken at specific times.

Example 1

In the graph below (Figure: 2) we can see that the patient took their evening dose at 20:00 hrs (8pm) and that by 04:00 hrs (4am) the cortisol level is very low and by 06:00 hrs (6am) there is no traceable cortisol left to measure in the blood, this could lead to dangerously low blood glucose levels.

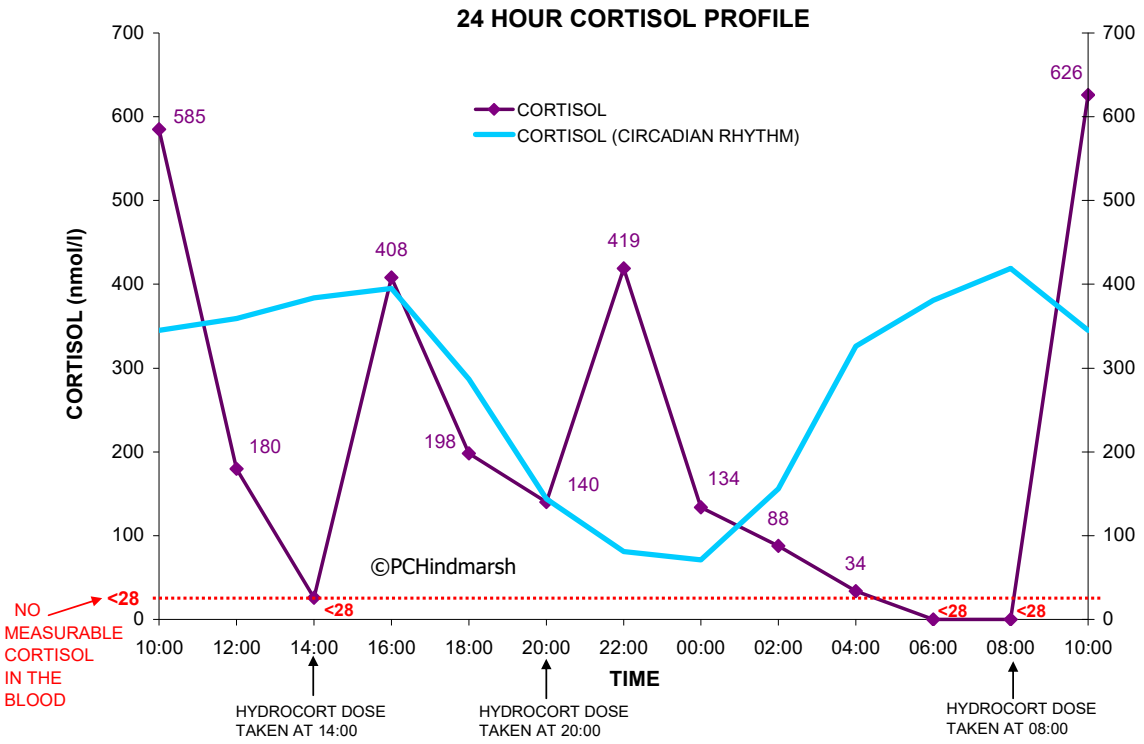

Figure: 2 Example 1 Last evening dose of hydrocortisone taken at 20:00 hrs (8pm)

If you look at the light blue line which represents the body's own natural production of cortisol there is normally a significant amount of cortisol present and although it is not the actual values of cortisol we try to replicate when using replacement therapy it is the pattern/distribution of cortisol we try to mimic. At this time of the morning one of the important roles cortisol plays is to regulate the blood glucose level and in illness the body would naturally produce even higher levels of cortisol at this time.

Example 2

Example 2 (Figure: 3) shows a patient having their last dose at 20:00 hrs (8pm) and as they metabolise hydrocortisone at a different rate to the patient in Example 1, they are left without any cortisol in the system for almost 6 hours.

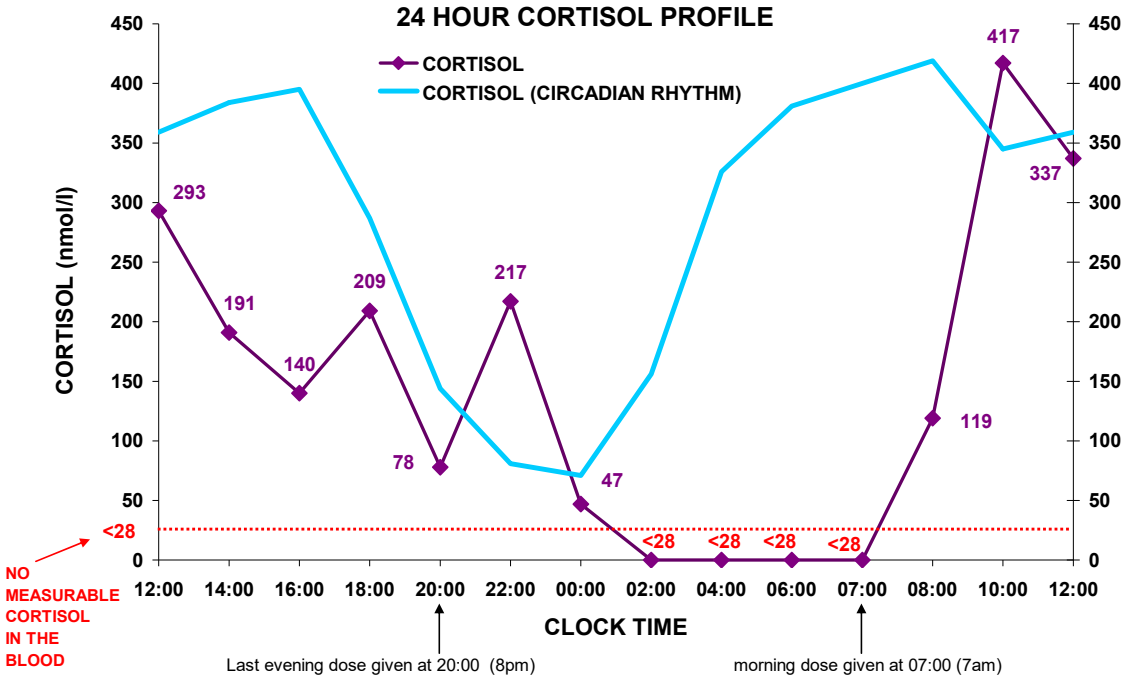

Figure: 3 Example 2 Cortisol levels in someone who metabolises hydrocortisone very quickly

Example 3

In the graph below (Figure: 4) we can see that the patient has taken their evening dose at the later time of 22:00 hrs (10 pm). The profile shows that because the duration of hydrocortisone is 4 to 6 hours, the cortisol level drops low and there is little around in the early morning and in fact no measurable cortisol from around 06:00 hrs (6 am).

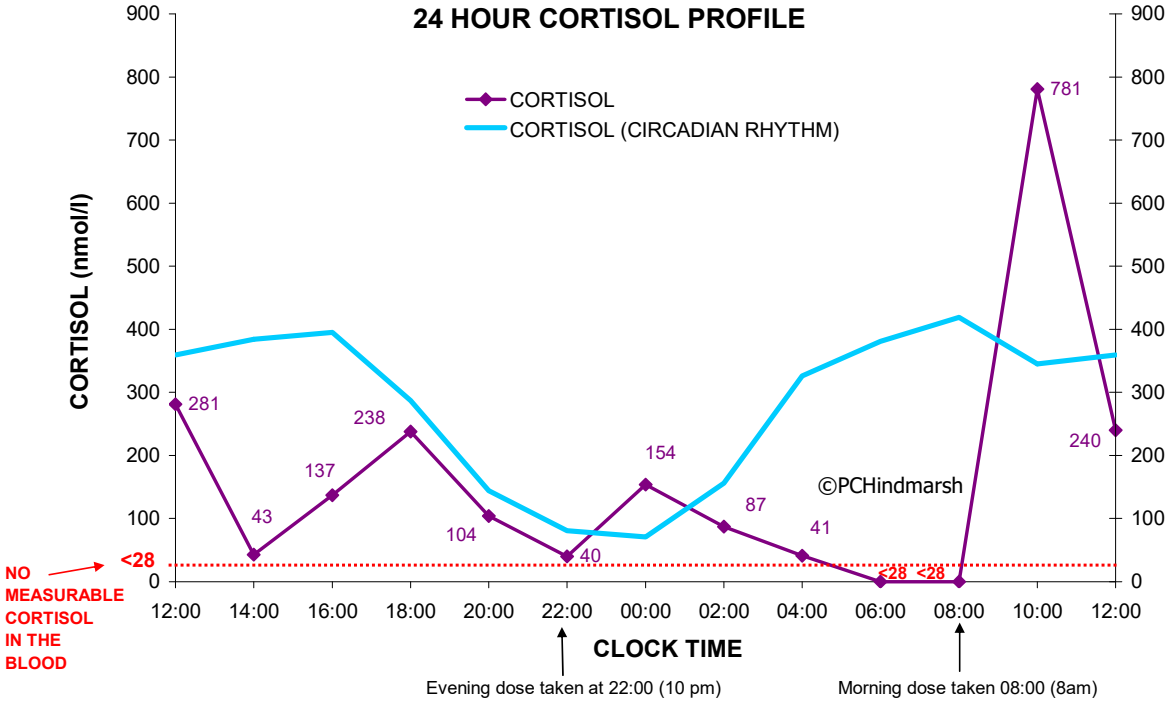

Figure: 4 Example 3 Last evening dose taken at 22:00 hrs (10 pm)

Does a double dose last longer?

Due to the half-life of hydrocortisone, a double dose does not last much longer in the system at all, in fact it peaks much higher and excess cortisol is passed out in the urine. The graph below Figure: 5 illustrates this effect of half-life on the cortisol levels obtained after the peak has been reached.

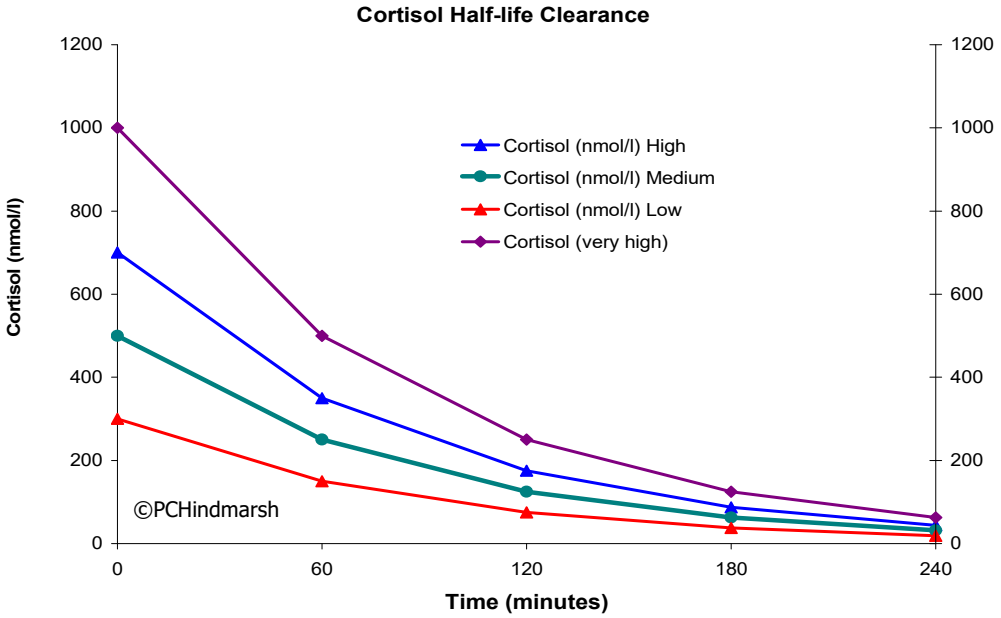

Figure: 5 The effect on cortisol levels after 240 minutes when starting cortisol ranges between 300 and 1000 nmol/l

The clearance of cortisol, which is related to the half-life in the graph above (Figure: 5) is based on normal clearance; however there are some patients that clear cortisol faster than others. The graph below (Figure: 6) shows the results of 4 patients of a similar age and size, who took a higher than their usual dose of hydrocortisone.

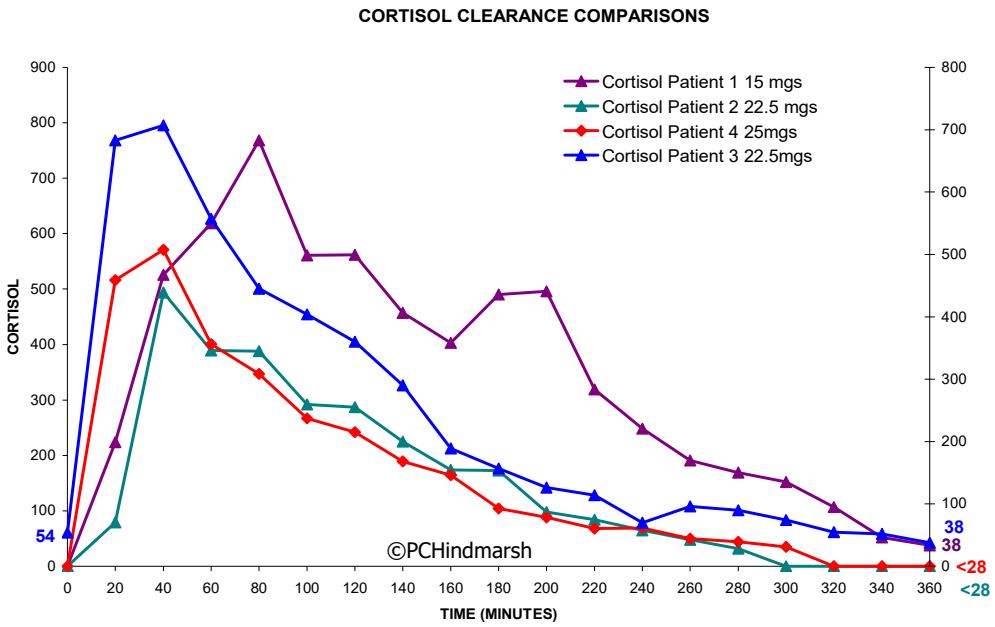

Figure: 6 Cortisol comparisons over 6 hours on 4 patients when taking higher than normal doses of hydrocortisone

In Figure: 6 Patient 1 (**purple line)** took 15 mgs of hydrocortisone at 08:00 hrs (8am) and 240 minutes later still had quite high cortisol levels (200 nmol/l) whereas Patient 4 **(red line)** who had 25 mgs of hydrocortisone had very low levels (38 nmol/l). Even the 200nmol/l level is still less than encountered in illness where values are over 500 nmol/l.

Patient 2 **(green line)** and Patient 3 **(blue line)** both took 22.5 mgs of hydrocortisone. We can see that Patient 3 had 54 nmol/ls of cortisol pre tablet and has a slower clearance rate than Patient 2. Patient 2 had no measurable cortisol in the system after 300 minutes whereas Patient 3 has only 38 nmol/ls at 360 minutes, which is low.

If we think however, what the situation might be if these were doses given at say 22.00 hrs then 6 hours later (360 minutes) for all of these patients they would have suboptimal amounts of cortisol.

This tells us that we need to be careful when dosing hydrocortisone and we should not assume that patients are well covered by their doses particularly during illness.

We can say:

1. The body normally has high cortisol levels in the early hours of the morning.
2. Using any of the glucocorticoid treatments means that there is less cortisol around in the early hours of the morning
3. When ill more cortisol is needed overall
4. We recommend that an **extra** 4am dose should be given. The dose should be the *same dose* as the *usual double/triple morning dose*.
5. The double/triple morning dose should be given as usual, as the 04:00 **(4 am)** dose is an ***additional*** dose.
6. You should give this dose even if you have given a double dose at 01:00 (1 am).