

## **The use of steroids in vasculitis and the safe stopping of treatment once in remission.**

### ***What are 'steroids' and what do they do?***

Patients often refer to their treatments for vasculitis as “steroid therapy”. There are many type of “steroids” and if you want to learn more, Wikipedia is a fairly accurate source of information. There are three classes of steroid that differ very slightly in their chemical structure but have very different actions in the body. The first is a ‘glucocorticoid’ which is commonly used to treat inflammatory conditions and is the one you would have been prescribed. Common names for these type of steroids include ‘prednisolone’, ‘hydrocortisone’ or ‘dexamethasone’ and they differ mostly in their duration of action and potency. The second is a ‘mineralocorticoid’ (controls blood pressure) and the third class are sex steroids such as testosterone or oestrogen.

### ***What are the adrenal glands?***

The normal adrenal glands measure <1cm and are found sitting above each kidney. They make glucocorticoids of which ‘cortisol’ is the most biologically active (<http://www.yourhormones.info/hormones/cortisol.aspx>), and mineralocorticoids (aldosterone <http://www.yourhormones.info/hormones/aldosterone>). Cortisol levels normally climb when the body is under “stress” and by this we mainly refer to physical ‘stress’ such as severe illness or a major operation. Aldosterone rises when you have low blood pressure and acts to increase blood pressure by retaining salt in the circulation. Both hormones together coordinate the ‘stress response’, so that your circulation does not effectively collapse when you are unwell. This life-threatening scenario is what doctors often refer to as an ‘Addisonian crisis’.

### ***Diseases affecting the adrenal glands***

Diseases can arise in the adrenal glands and this can affect their ability to function normally. I work with a group of patients who often have their adrenal glands removed because of adrenal tumours. One group of them have a genetic cause of these tumours, and so at some point they have their adrenals removed. (<http://www.amend.org.uk/>). We also have patients with a condition called “Addison’s disease” which is where the adrenal glands are destroyed either by tuberculosis (Described by Thomas Addison at Guy’s hospital in 1855) or by destruction by the immune system.

### ***Commonly used steroid tablets when the adrenal gland stops working***

Patients who have no functioning adrenal glands need both cortisol and aldosterone to be replaced. Tablets of cortisol and aldosterone do not last long enough for once daily administration, so you either need to take the tablets several times a day, or use a modified molecule that lasts longer. Fludrocortisone is a modified version of aldosterone that can be administered once a day. Similarly for cortisol, you can either use cortisol (tablets are called “hydrocortisone”) three times a day, or use prednisolone once daily. It is the fluorine atom in fludrocortisone and the double bond in prednisolone makes them last longer (Fig 1).

Patients without functioning adrenal glands usually need 100mcg of fludrocortisone and 3mg-4mg of prednisolone daily to replace the steroid they lack and so feel normal and to prevent an Addisonian crisis when unwell.

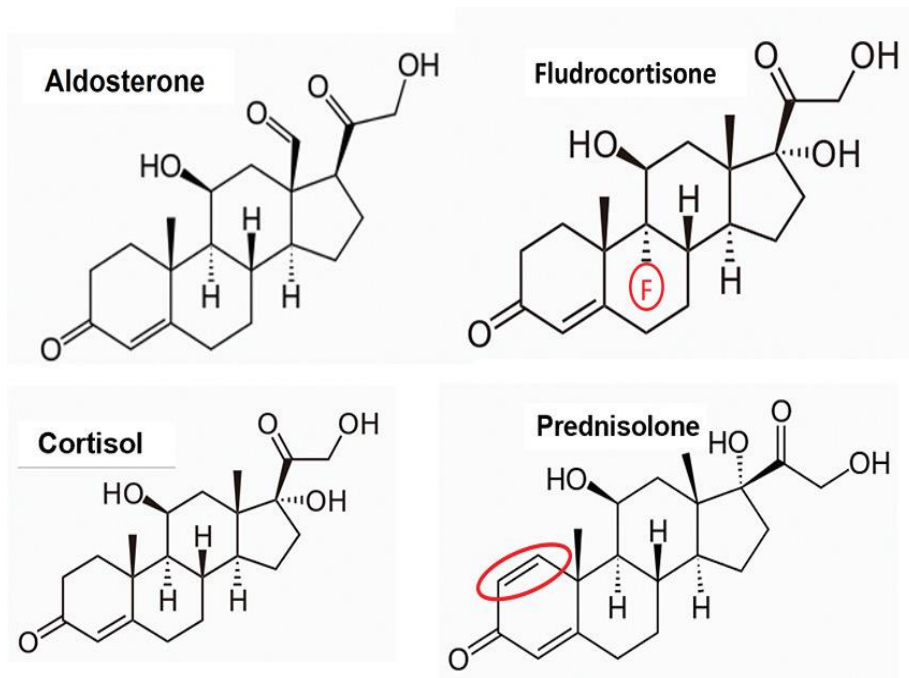


Fig 1. Molecular structure of aldosterone, fludrocortisone, cortisol, and prednisolone.

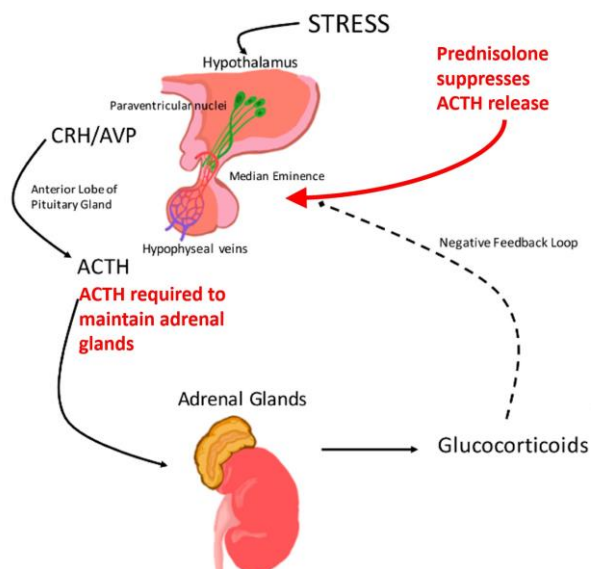
### ***Why is the steroid “prednisolone” so commonly used in certain diseases?***

When these different steroids were discovered in the 1940s, it was also discovered that high doses of prednisolone magically enabled people with severe rheumatoid arthritis to walk. We now know that prednisolone when used in high doses, is a potent immunosuppressant and anti-inflammatory and still today remains the most effective and widely used anti-inflammatory drug.

### ***What happens to your adrenal gland when you take your steroid treatment?***

Human endocrinology has a system of negative feedback, so that normal adrenal glands produce exactly the right amount of cortisol under the control of the pituitary gland. So when you take a large dose of prednisolone for your vasculitis, the pituitary detects this and stops stimulating the adrenal gland to make cortisol (Fig 2). This doesn't matter because you have a large excess of prednisolone, so you won't have an Addisonian crisis.

If you stay on high dose prednisolone for several days the ACTH will be fully suppressed and the adrenal glands won't make any cortisol for that whole period. If you stay on prednisolone for several weeks, the adrenal glands will start to shrink, and waste away.



*Fig 2. The negative feedback loop that occurs in normal people. ACTH stimulates the adrenal to make cortisol which suppresses the pituitary gland from making ACTH. Large dose of prednisolone suppress the pituitary production of ACTH. If you slowly reduce the prednisolone dose, then the pituitary will start to stimulate the adrenal gland, but if it has atrophied (wasted away) then it will take several weeks to wake up.*

### ***Why can it be dangerous to stop steroid treatment suddenly?***

Suddenly stopping your prednisolone can be dangerous if your adrenals have wasted away, because they might not make sufficient cortisol in time. They might take some time to recover. This can give you a mild form of an Addisonian crisis, although it won't be as bad as patients with no adrenal glands because you may still be producing aldosterone (not affected by prednisolone) that helps to maintain your blood pressure.

### ***What are the side effects of prednisolone treatment?***

High doses of prednisolone usually works very well for vasculitis and other auto-immune disease, but we recognise that side effects occur if you take prednisolone for too long. One good thing about prednisolone is that although it has side effects, we know what they are, and can watch out for them. These include diabetes, weight gain, osteoporosis and high blood pressure (also called "Cushing's syndrome"). As soon as the vasculitis is under control, we therefore need to cut the dose to the minimum required. Your rheumatology specialist will reduce the dose as much as possible but you might need some prednisolone to keep the vasculitis at bay. As you reduce the dose, careful monitoring of your vasculitis (or other condition) is required and the rate at which you cut the dose depends on how severe your condition is.

### ***What if my vasculitis goes completely into remission? Can I stop the prednisolone?***

The answer is that you can, but very slowly and cautiously because as we have mentioned your own adrenal glands may have been 'asleep' for some time. We know that patients who have no adrenal glands feel fine on 3mg-4mg prednisolone so that is the equivalent of what your adrenal glands make daily. If you feel unwell as you cut the dose before you reach 4mg, that would suggest that your primary vasculitis is not fully in remission. However if you get down to 3mg, then reducing the dose further requires your own adrenal glands to be in working order. If you don't have enough cortisol, then it is likely that you will feel rather tired. If you have a bit too much (many people stay on 5mg), then your adrenals will stay asleep.

## ***Practically-speaking how do I reduce my prednisolone when I am in remission?***

If your rheumatologist wants to stop your prednisolone, either because you are in remission, or because you have had a newer treatment for your vasculitis, you have a choice. You can either stay on a small replacement dose forever (just over 3mg) or you can deliberately cut the dose so that the adrenal glands slowly awaken but risk feeling a bit tired and under the weather for a while. Almost all vasculitis patient's adrenal glands will recover if the dose is cut by 0.5mg every month. This is hard work for patients because for most of that time, you have to run on less glucocorticoid that you need in order to wake up the adrenal. This is the reason that some of you might choose to stay on 3mg daily even if your vasculitis is in remission.

Cutting from 3mg to nothing can take 6 months, and some people can do this more quickly than others. It depends of course on how long you have had prednisolone, but many authors suggest cutting by half a milligram per month.

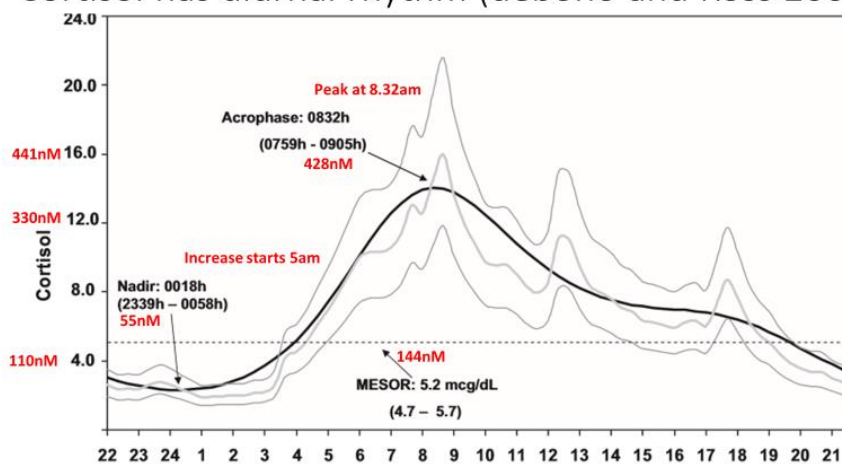
Patients with no adrenal glands need approximately 3mg (varies from 2-5mg) prednisolone as there is no hope of the adrenal gland waking up. Details can be found here on <http://www.imperialendo.com/prednisolone> and <http://dx.doi.org/10.1530/EC-17-0257>.

## ***How do you know whether your adrenals have recovered?***

Probably the best test is how you feel. However many patients want to try and measure their cortisol to see if there has been recovery. It sounds easy, but it isn't. The problem is that cortisol rises in response to stress, so if you are very calm on the day that the blood sample is taken, it might look like your cortisol is abnormally low, when in fact it is normal for the circumstances. The other problem is that cortisol levels vary during the day as cortisol is a diurnal hormone, with levels highest in the morning and lowest at night possibly because waking up is the most stressful part of the day.

The graph below demonstrates this. Blood was taken regularly through the day and night from healthy volunteers. The x-axis is the time of day and the y axis is the cortisol level. Providing you are not someone who is awake all night, then the peak level of cortisol usually occurs at about 8.30am, but there is a lot of variation between individuals.

Cortisol has diurnal rhythm (debono and Ross 2009)



### ***There must be a test I can have to check my adrenal function?***

Another method that some people use is a synacthen test. SynACTHen is synthetic ACTH which is a hormone that is produced from the pituitary gland (Fig. 2). When a patient is given a dose of ACTH, that dose rapidly stimulates the adrenal gland to make cortisol, and you can measure the cortisol response at the end. This tells us whether your adrenal glands have woken up.

However this is not an accurate test in patients who are on prednisolone, and it is really only used to check adrenal function in patients with Addison's disease to prove they have it.

### ***I really want to get my prednisolone dose below 3mg, how do I do this?***

The other way to reduce prednisolone below 3mg is to take 3mg on some days and 2mg on others. If you take 2mg for one day and 3mg for 6 days, and then slowly increase the number of days that you take 2mg for. It will in fact take 7 weeks to go from 3mg to 2mg. This should slowly help your adrenal gland to recover.

Table 1. Suggested regimen to reduce prednisolone from 3mg to 2mg over a 7 week period (doses in mg)

<b>Week</b>	<b>Mon</b>	<b>Tues</b>	<b>Wed</b>	<b>Thurs</b>	<b>Fri</b>	<b>Sat</b>	<b>Sun</b>
0	3	3	3	3	3	3	3
1	3	3	3	2	3	3	3
2	3	2	3	3	2	3	3
3	3	2	3	2	3	2	3
4	2	3	2	3	2	3	2
5	2	3	2	2	3	2	2
6	2	2	2	3	2	2	2
7	2	2	2	2	2	2	2

If you look at old textbooks and websites, you will see that in the past, people thought that 7.5mg was the equivalent amount of prednisolone that you need in a day, but we now know that this is too much and is much closer to 3mg. Even doses of 3-7.5 mg therefore have the potential to cause side effects.

### ***Any other tips?***

One other tip that some people might benefit from is that the enteric coating in prednisolone make the absorption a bit erratic. When I took it myself (as part of some healthy volunteer research) I did not absorb any at all, but when I took the plain tablets, absorption was absolutely fine. Therefore I tend to avoid the enteric coating.

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