

AMEND 2024 Webcast 1

Corticosteroids

With Professor Karim Meeran

Introduction:

Welcome to the first in a series of webcasts that AMEND will be producing over the coming months, looking at a wide variety of topics of interest to our patients communities. Today I'm delighted to introduce Professor Karim Meeran, who will be discussing corticosteroids, a class of medicines that we receive many queries about from our patient community.

Professor Meeran is Professor of Endocrinology at Charing Cross Hospital in London, as well as the Deputy Director of Medical Education and Lead Clinician for Endocrinology at Imperial College. He qualified at the Royal Free Hospital then trained in Endocrinology at Hammersmith Hospital and St Bartholomew's Hospital. I am also pleased to say that Prof Meeran has been a Trustee of AMEND for many years now, as well as a volunteer at many of our Annual Patient Information Days.

Questions:

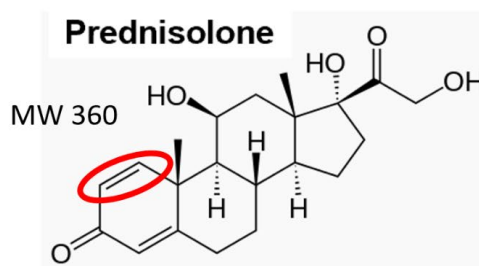
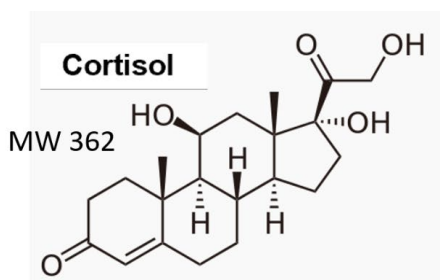
- 1. Can you give us a quick overview of corticosteroids and why they may be prescribed in patients generally, as well as for those with endocrine conditions?**

Okay, so corticosteroids – the word 'cortico' comes from cortex which is the adrenal cortex and the adrenal cortex makes the hormone cortisol which is a natural human corticosteroid which we all need to survive and it's very carefully controlled by the pituitary gland and the level of cortisol in your body depends on time of day, so it seems to be very important in informing all your cells about what time of day it is, and basically makes them all synchronise driving what some people call 'clock genes'. So, all your cells know that it's time to wake up or that it's time not to be awake. So that's what normally happens. Now, it was discovered in about the 1940s, that if you take adrenal extracts and concentrate up what we now know is cortisol, it has a very good anti-inflammatory affect on people with inflammation. So, for example, asthma or colitis, or any of those autoimmune diseases, if you give a huge dose of adrenal extract, or 'steroids' as people call them, you can treat those conditions that have, in the past, been life-threatening. So, using extra steroids, or glucocorticoids, saves lives, especially in conditions like asthma and so on. So, there are two separate uses that we now have, in 2024. One is, if you have no adrenal glands, you need some hydrocortisone or an analogue* of a steroid to survive, but also if you have a condition like acute asthma, we can give you a short course of very high dose of steroids which will treat the asthma and keep you alive. They are the two main roles of these steroids.

**a drug that differs in minor ways in molecular structure from its parent compound*

- 2. Historically, hydrocortisone has been the go-to corticosteroid, while prednisolone has had something of a bad reputation. This is changing now, so can you explain why this is?**

Hydrocortisone is cortisol. In fact, if you look at the molecular structure in the image, on the left is a molecule of cortisol, and it's a steroid structure, so those four rings are what makes it a steroid. If you look at hydrocortisone, it's got various random bonds on it. On the right-hand side is an artificial version of that, made in laboratories in the 1940s, and the only difference between that and hydrocortisone is the double bond that's circled in red. So, this was one of the first manufactured steroids and this would have been before we understood the molecular structure, but now we know that prednisolone is the same as hydrocortisone, except that it's got that double bond. Now what that double bond does is make it slightly different, and what that means is that it's a bit stronger, it's a bit more potent, you need fewer milligrams to have the same affect, and best of all, it lasts longer. And so, instead of taking hydrocortisone more than once a day, you can take prednisolone once daily.



There's another advantage to this, so when you measure the level of prednisolone, if you measure the level of cortisol in a person who has adrenal glands, it goes up in the morning just before you wake up, and then the adrenal glands keep on making cortisol but less and less through the day, so the levels slowly fall over time. Now, if you take a hydrocortisone tablet, it's not like an adrenal gland, because you get the whole thing in one big blast and then it's consumed and all gone by about 11am, so you've got none left at all, and you're forced to take hydrocortisone 2 or 3 times daily in order to have enough to have a good quality of life. Now if you take prednisolone, you can take a much smaller dose, say 3mg of prednisolone, it's more potent, and lasts for the whole day, and then finally disappears in the evening when it should be low, and that really tells your body what time of day it is. So if you think about taking it in the morning, that's the clock telling your body it's time to wake up, so we advise people to take whichever drug first thing in the morning for their first dose, and the problem is, if you're on hydrocortisone, you need a second and a third dose, and so the timing of that can be very difficult and also, we tend to use a little bit too much. It's actually very hard to get the exact dose of hydrocortisone when you need it more than once a day. So that's the basic difference between them.

3. Can you tell us about the research study you've been working on to compare hydrocortisone with prednisolone?

My interest in this started in about 2014 when we were looking at these two molecules, and some patients were saying that hydrocortisone was very inconvenient to take because they can't remember to take two or three doses, so that was the first problem. The second problem was that the cost of hydrocortisone for some reason rose astronomically, and so we then started looking at alternatives. Then we discovered that prednisolone is, a) more convenient, but then, in about 2016, we also made an assay for prednisolone and discovered that the levels of steroid were very similar to normal, healthy people. So, we worked out that, in fact, if you take prednisolone once daily you actually get a closer mimic of a normal circadian rhythm than hydrocortisone. The minute you take a second dose you're going to

overshoot. Everyone said that hydrocortisone was the 'natural thing' and they've always used hydrocortisone (and I was taught as a junior doctor to use hydrocortisone) because it is the same as cortisol, and prednisolone is artificial. Of course, we're now finding that artificial drugs have benefits, and we use artificial drugs in many things. Insulin, for example, we use analogues of insulin now because they're better. They're better because they're more convenient, and it's the same with steroids. If you can modify it to make it more convenient but keep the shape of that curve - the level of it in the blood the same as a healthy volunteer - that would be better. In order to decide that I'm right, we had to do a proper trial. We can't just say that it looks right, so what we've done is asked a large number of people, in fact with AMEND's help, we've got healthy people who are healthy except they've got no adrenal glands and therefore they needed hydrocortisone. They've been on hydrocortisone for many years and they've been quite well, and we said, let's do a trial of between 4-6 months on prednisolone and let's measure everything like blood sugar, blood pressure, and bone turnover, because one of the problems with too much steroid is that you become hypertensive, you might become diabetic or have a higher glucose, you have a higher cholesterol, and you might have osteoporosis in the long run. These are all 'long-run' things, so you don't tend to notice a difference on a day-to-day basis, but if you want to prevent trouble in the future, we need to know which drug is better. So, we got a large number of people, and in fact we're just finishing the last patient at the moment, and we're measuring prednisolone levels and we're also measuring their bone turnover, blood sugar, blood pressure, and other things, to see which one is better. I don't know the answer because all of them are blinded. In other words, neither I, nor the patient, knows whether they're on hydrocortisone or prednisolone. Now, you might ask, how are we doing this? We're going this because the hydrocortisone is typically 10mg in the morning, 5mg at lunchtime, and 5mg at 4pm, and in the second half of the study, we're giving them the same number of tablets, a single prednisolone of 3mg and then 2 placebo tablets. That means that I don't know whether they're on the prednisolone and placebo or the hydrocortisone, and that's to avoid the bias of the advantage of saying, well I like this, so I want to stay on it. So, we're making it equally inconvenient, and looking at how people feel and lots of other things, and to see what happens to all the other markers. We will know this probably in another two or three months, so by the summer of 2024, we will have some answers, and we hope to publish a paper saying which one is better, but at the moment I can't tell you which one is better. I will say that we have got another study ongoing which is not blind, and patients know what they're on, and it seems that they're reporting that when they're on prednisolone, they find it easier to keep the weight under control, it might be easier to keep blood sugar under control, and so my thought is that we will probably find that prednisolone is better, but let's wait until the results come out before we really say that.

4. What are the sick day rule differences, if any, between hydrocortisone and prednisolone?

If you get diarrhoea and vomiting, then neither oral drug will be very useful. If you're vomiting, then nothing will work – neither oral hydrocortisone nor prednisolone works – so you need an injection of hydrocortisone. That has always been the case, so if you are very sick and you get something like norovirus and you're vomiting, you need your steroids to survive and so you need to have an injection of hydrocortisone, ideally at home, but if not, if you've not got it available, get to casualty and tell people you've got adrenal failure, and they will give you some hydrocortisone to keep you alive. If you don't have quite such an illness and you're keep things down, when you become sick, your body needs more steroid. If I become sick, say with pneumonia, my adrenal glands double their output of cortisol, and

that's been shown. If I have an operation, my adrenal glands will tend to increase their output of cortisol, and we want to mimic that. So, in the case of both drugs, you will double the dose for three days. Now I say three days, and that depends on how long the illness lasts, but a typical serious illness will cause cortisol to rise for three days. So, typically, for both drugs, we say double your hydrocortisone, or double your prednisolone for three days, but if you're unable to keep it down, you need an injection. So, in effect, they're both the same – you double your drug for three days. I know some people have said triple, and if you're very sick, that might be appropriate but when that is the case, you should be thinking about going to casualty at that point rather than struggling on at home which I think would be a mistake.

5. Are there any other steroid medicines available in the UK?

Yes, there are, and I should be careful not to confuse people. The word 'steroid' means any molecule that looks like those four circles (in the above diagram) and that basically, is the structure of cholesterol, so all steroids come from cholesterol. I think what you mean is, are there any similar glucocorticoids – that class of steroid. Just to be clear, testosterone and oestrogen are also steroids and, of course, they're also abused by other people in different ways, so when you say 'steroid', we don't mean those ones (e.g. anabolic steroids). We're talking about glucocorticoids, and we've talked now about hydrocortisone and prednisolone. The other one that many of you will know since covid is dexamethasone. Now dexamethasone is a very, very potent excellent steroid which gives a really, really large dose. The evidence came out about 4 months after covid had been causing so much trauma in the world that dexamethasone (a very, very large dose of glucocorticoid) saved lives. So, people were dying of inflammatory lung problems were saved by having a huge dose (6mg) of dexamethasone. Dexamethasone is 7 times more potent than prednisolone, and prednisolone is 7 times more potent than hydrocortisone, so 6mg of dexamethasone is like 40mg of prednisolone, so an enormous dose, but that's what you need when you have covid – you need to suppress your immune system so that the inflammation doesn't cause lung failure – and it worked. We also use dexamethasone for patients who are very unlucky to have large brain tumours where you really want to suppress and oedema (swelling) around the brain. So, there is a much more potent steroid around and that's dexamethasone, however, I wouldn't advise its use as a replacement as it's so potent and so long-lasting that even the smallest dose available of about 0.1mg tends to cause some cushingoid affects over time because it has a very long half-life, like 2 days. You could argue that you could have it every other day, but the levels are very, very high in terms of the outcome. So use it appropriately. All these drugs have got good uses and in the long run they'll have side effects of course but if you want to save your life, there's no question you would take your dexamethasone for the 10-day period that's been proven to save lives.

6. What might be the reasons that a patient is moved from one steroid medication to another?

Traditionally, I'd always started patients on hydrocortisone, and now, I always start them on prednisolone because, a) it's more convenient, and b) I think the evidence is about to come out that it's actually better for the metabolism. But, there may be patients who metabolise the drug very slowly, and so for example, we have an experimental research tool that measures levels of prednisolone, that showed that we have one or two patients who seem to need only 1mg of prednisolone which is a bit peculiar. And then we measured their levels, and it seems that they break it down really slowly, and some of those patients are on just

5mg hydrocortisone once a day. So we're all different. The way we all metabolise drugs is different, and there's a very small number of them who are slow metabolisers and then there are others like one patient of mine who is a very, very fast metaboliser, and he couldn't keep up. He was on hydrocortisone for Addison's Disease (adrenal failure, no adrenals that work) and his cortisol levels were always zero. He took his hydrocortisone as normal and he was on enormous doses, and then we switched him to prednisolone and I kept having to pop the dose up, and he's now happy and well on 12mg once a day, and his levels are the same as anyone else on prednisolone. It's unusual and most patients need 3mg, some need 4mg, very few need more than 5mg, and then there's one that needs 12mg! That is a very unusual anomaly but it's important to bear in mind that we metabolise drugs differently, so that may be why you want to change the drug. The other thing is, depending on how they feel and what patients are comfortable with, if patients want to have more level later on in the day, it might be that hydrocortisone is better. I haven't found any evidence of that but I'm certainly open to letting patients choose the drug that they feel better on, and I think that's an important difference. If we find in an individual that the blood levels are harmful we can inform them but if they say that they feel better on one than the other then that's an important finding.

7. Are there any reasons why a patient wouldn't be prescribed a particular corticosteroid medication?

I can't think of any reason why. They need one. If you've got no adrenal glands, without any steroid you will not survive so you need one or the other. They're the two that are available in the UK. In other countries there are other different analogues. There's cortisone acetate in some countries and that's just another modified molecule of cortisol. They all seem to work very similarly and until now, we've not found any evidence of difference, so if they're all the same, you can choose any one you like. If we find that one is better than any other then we might encourage people, explain to them that we're finding these differences and they might prefer one over the other. At the moment, I can't think of any reason any is contraindicated and you must have one if you need it. Dose is very important. Just to summarise the issue that you highlighted – if you have insufficient steroid you feel it, you feel unreplaced and unwell. If you have normal or too much you feel great, and the problem is, if you feel great on too much then the downside in the long-run is that you become slightly hyperglycaemic or diabetic, you become a bit hypertensive, and you can become a little osteoporotic, and in years to come you get a fracture and you think that's a mistake, but of course you don't know that's going to happen to you, and so I'm very keen that everyone does their best to take as little as possible without feeling ill – I'm not saying you need to underrun, you just need to keep it stable.

8. What do you see as the future for corticosteroid replacement in patients with adrenal insufficiency?

Pumps have got pros and cons. Pumps are very difficult in that you've got to carry it with you everywhere all the time. We use pumps now in diabetes and it has transformed lives, but they were on 3 or 4 injections a day to mimic that. The big advantage of steroids over insulin is that steroids can be taken by mouth because they're absorbed, whereas insulin, which is a protein, can't be. If it were taken by mouth your stomach acid would just destroy it, so we're stuck with injections which is why pumps work for them. Certainly, there are trials going on to see whether giving a pulse of hydrocortisone which is even more natural

than we're doing is better, and if we find that they're better then that might be the future. That would be balanced with the inconvenience of setting up your pump every morning, which is what the diabetes patients have to do. In the case of diabetes, the patients are very clear that they are much happier and much better on a pump and so they find the time every morning invested in setting it up is worth it for the rest of the day, whereas otherwise, they are on 3 or 4 injections a day which they need to draw up. That doesn't happen for people on prednisolone – you take one dose in the morning and then that's it, so it needs to be as convenient as that probably, so I think it will be either hydrocortisone or prednisolone tablets; I think there will be some patients who would like to try a pump and might have some benefit from it, for example if they can't absorb it well, but I think in general we are going to stick to oral and working out the best one is going to be the future. There is one other steroid that I haven't mentioned and that is delayed release hydrocortisone that you take the night before. That is looking like it might have some advantages in that rising cortisol in the early hours, but I think the timing isn't perfect, so there needs to be a bit more work with that. One option I'm thinking about is whether we use that technology with prednisolone in that so that we have delayed release prednisolone which you take last thing at night and then at 5am it releases. That might be a really perfect once-daily treatment, but that's pie in the sky at the moment, but something to think about.

Thanks:

Thank you so much Professor Meeran for giving up your valuable time to discuss all things steroid today. I really believe that this will help our patient communities really understand the reasoning behind the prescribing and use of corticosteroids.