

From NZAN's Medical Advisor 1998-2000, Dr Geoff Braatvedt

NZAN Update Number 5, November 1998

Hormones and the adrenal gland

Addison's disease is usually due to autoimmune destruction of the outer layer of the adrenal gland – for some reason, patients develop antibodies against themselves, which attack and destroy this layer of the adrenal. The adrenal gland is responsible for 4 main sets of hormones: the inner layer or core, secretes adrenaline, and this is usually not affected by Addison's disease. The outer layer secretes cortisol, aldosterone and androgens-more about androgens later. Prednisone, hydrocortisone, cortisone acetate and dexamethasone are all synthetic tablets that are converted by your body into cortisol and can be taken to replace deficient cortisol levels. Fludrocortisone (Florinef) effectively replaces the aldosterone you require. Cortisol and aldosterone have totally separate control systems and assessment of the adequacy of dose replacement of cortisol and fludrocortisone by your doctor are thus separate.

Cortisol

Cortisol is under the control of a messenger hormone called ACTH (adrenocorticotrophin hormone), which is released from the pituitary gland. This is a master control gland and is situated behind your eyes. When your body does not have enough cortisol the pituitary senses this, and increases the amount of ACTH production to try and correct this. Of course Addison's patients' adrenal glands do not work and so the amount of ACTH in the blood rises (if the patient is not taking enough cortisol) and can be measured. Symptoms of too little cortisol are often non specific and include tiredness, weakness, dizziness and because ACTH causes pigmentation of the skin, patients notice increased pigmentation of skin creases or the inside of their mouths, or may note that they tan easily, especially in winter. Measurement of ACTH levels is not usually needed and is certainly not a routine test. Which cortisol tablet is best is debatable, and will be discussed in the next issue of Addison's update.

Aldosterone

Fludrocortisone (Florinef) tablets replace the aldosterone that your body cannot produce. Aldosterone is normally needed to control blood pressure by causing your kidneys to retain salt (sodium). Aldosterone is under very complex control systems. Chemicals in your kidney and blood stream are converted into an aldosterone release promoting messenger hormone called angiotensin 2 by an enzyme called renin. So if aldosterone levels are low, renin levels rise to try and send more angiotensin 2 to the adrenal glands so that more aldosterone can be produced. Again, Addison's patients cannot produce aldosterone and so renin levels will be high if the dose of

fludrocortisone in your blood is not right. Measuring the salt (potassium and sodium) concentrations in the blood, and lying and standing blood pressure (which should not be more than about 10 mm mercury lower than the lying blood pressure), are usually all that is required to assess adequate dosing with fludrocortisone. Measuring the renin levels can sometimes be helpful if the blood pressure and salt levels are not satisfactory but again, they are not often "routinely" measured. Too much fludrocortisone can cause the blood pressure to be high and you can retain salt and water and develop swelling around your ankles.

Androgens

Androgens are male-like hormones. Men produce most androgens from their testicles as well as some from the adrenal glands. Most men with Addison's disease do not have any change in testosterone levels when they develop Addison's disease, as their testicles do the job properly. Furthermore, testosterone levels in male Addison's patients do not tend to be much different from normals as they get older – testosterone levels often do reduce a little as we all get older. Some men with Addison's can however develop testosterone deficiency as a separate autoimmune disorder and this is more common in Addison's sufferers. So if your sex drive or erection quality is not as good as it used to be, get your doctor to check your testosterone level.

Women also produce androgens, both from their ovaries and from the adrenal glands. These hormones are in much lower concentration than in men, and are thought to be needed for normal functioning of ovaries, maintenance of healthy bone thickness, clear thinking and possibly sexual behaviour. The androgens are often converted into oestrogens and testosterone. The androgens from the adrenal gland have got long names and are called DHEA (dehydroepiandrosterone) and androstenedione. As stated above, testosterone is also produced from the ovary and in premenopausal women with Addison's disease, the amount of circulating androgens is therefore not that much different from normal as the ovaries are working okay. However after the menopause, the ovaries do not produce androgens and coupled with the already failed adrenal glands, post menopausal women with Addison's disease do have lower total androgen levels than normal women of the same age. How this affects these patients is poorly understood and most post menopausal women with Addison's disease on adequate cortisol and fludrocortisone and especially hormone replacement therapy (HRT), usually do not feel any different from other women their age. Trials of androgen replacement treatment in women with Addison's disease are few and far between. The results are conflicting and there is no real consensus about the benefits of such treatment. Some studies using DHEA tablets show that bone thickness is improved and possibly that sexual function and thought processes may be improved. There are however potential downsides to treatment with androgens, as they can increase the risk of heart disease via adverse effects on cholesterol levels, as well as causing excess hair growth on the face, and acne. DHEA is not available in New Zealand and the prescribing of androgens to women with Addison's disease is not part of my practice.

Questions and answers

Jocelyn wrote *'I find living with Addison's not very easy at all. I took seriously ill with a total physical breakdown in January 1993 and was diagnosed with Addison's at the end of February 1993. I found that in time my health has never come back to 100% and it has taken me five years to be able to cope with an ongoing spate of symptoms including bad heads, head pains, dizzy spells and sometimes, small turns. Although I do not let these feelings control my outlook on life I always try to remain bright and cheerful. I would like to hear your comments and answers on this ongoing condition. I have recently been changed from cortisone to prednisone and found this to be helpful.'*

Dear Jocelyn

Patients with Addison's disease on the correct dose of cortisol and fludrocortisone should feel normal and do not have a reduced life expectancy. Finding the right dose and type of cortisol tablet can be tricky and the fact that prednisone makes you feel better suggests that this suits you more than cortisone. Prednisone is a much longer acting drug than hydrocortisone and probably results in less variability in cortisol blood levels. Some patients find they feel weak and head-achy first thing in the morning before taking their tablets, and taking the prednisone at bed time can sometimes solve the problem. This occasionally causes patients to have difficulty in going to sleep. I suggest you get your doctors to check your salt and blood pressure levels; potentially an ACTH level as well; and to look out for other hormone deficiencies, particularly thyroid deficiency or even diabetes, which are more common in patients with Addison's disease.

Shirley writes *'regarding treated primary Addison's disease and plasma renin tests, will you kindly explain (1) the purpose of the test, (2) how frequently should the test be ordered, (3) how the test should be taken at the medical laboratory, (4) what the range of figures are for a normal test, (5) the significance of an abnormal test, and (6) why it can take as long as a month before the doctor receives the test results;'*

Dear Shirley

I hope I have answered most of your questions in the above discussion. The renin test should be taken in the morning with the patient standing. There is no need to be fasting. It has to be taken into a special tube and transported to a laboratory very quickly. A normal test result in Auckland is 5-76 mμ per litre. If the level is very high, say greater than 100 mμ per litre, this suggests you need more fludrocortisone. However, striving to get the renin level into the normal or even the low-normal range by increasing the dose of fludrocortisone can make the blood pressure go unacceptably high and result in salt and water retention, and is not usually necessary. The test costs about \$60 and is done every 2-3 weeks in our laboratory, depending on workload; hence the delay in your doctor getting the result. Renin levels are not absolutely necessary tests at all if everything is going well otherwise.

NZAN Update Number 6, March 1999

Questions and Answers

- Q1 Do patients with Addison's disease produce adrenaline? Can they get a 'high' from bungy-jumping?**
- A1** Why anyone wants to go bungy-jumping is beyond me but that's a separate question! For most patients in New Zealand (80-90%), Addison's disease is due to an auto-immune process that specifically attacks the outer layer of the adrenal gland, leaving the inner layer that produces adrenaline unharmed. Therefore, normal adrenaline responses can be expected in most situations. In any event, a large amount of adrenaline is produced at the nerve endings of our automatic nervous system which is unaffected by Addison's disease. So you can expect the normal terror of a bungy jump if you dare.
- Q2 Should patients with Addison's disease take more vitamin C than usual?**
- A2** I know of no reason why vitamin C levels should not be normal in Addison's patients and so no particular advice regarding vitamin C or any other vitamin is necessary – see calcium advice below.
- Q3 Lidy asks "I have been prescribed Serzone as an anti-depressive which works via adrenaline activation. Will I get the full benefit of this, being an Addison's patient?"**
- A3** As described above, your adrenaline responses should be fine. The drug (Nefazodone is its pharmacological name) does not quite work via adrenaline release in any case, but blocks the breakdown of a chemical called serotonin in the brain and so should work perfectly normally.
- Q4 Which steroid replacement is best?**
- A4** There is no right or wrong answer here. Some patients do better on long acting once a day tablets like Prednisone or Dexamethasone, and also find taking the tablet at night helps them start up better in the mornings. A normal person produces most cortisol in the very early hours of the night (3-6am). The standard dose of prednisone is around 5 mg/day but this dose does depend on other factors, such as if you are taking other medicine which can interfere with prednisone metabolism, and your body weight – obese people need more. Some patients on night time prednisone doses find they get tired in the late afternoon and a small boost of hydrocortisone eg; 5-10 mg mid afternoon, can be helpful. Giving prednisone at night time can also help reduce the amount of ACTH level, which causes pigmentation (see November 1998 article on hormones and the adrenal gland).
Many patients however, are quite happy on twice daily hydrocortisone which is usually taken in a dose of between 20-30 mg/day depending on your weight, and with about 2/3 of the dose taken in the morning. As long as things are going well, there is no particular need to change to prednisone.
The right dose of steroid is enough to make you feel well! This can be estimated by checking the ACTH level – the test should be done in the morning and if the ACTH level

is too low, then this suggests you are taking too much steroid and if it is more than 2-3 times the upper limit of normal, you are taking too little steroid replacement. You should discuss this with your own doctor if you are concerned.

Q5 What about bone density in Addison's disease? Should I take more calcium?

A5 There are many diseases that require steroids for their treatment eg; very severe asthma and some inflammatory conditions. We know that some of these patients who are on large doses of steroids (10 or 15 mg prednisone daily) lose bone density and can develop thin bones (osteoporosis) and even develop bone fractures over quite short periods of time (within 6-12 months in some patients). What is uncertain however, is how much prednisone per day is safe ie; is 5 mg or 7.5 mg/day safe? There are four or five previous studies looking at bone density in patients with Addison's disease and the message from these studies is a bit conflicting and confusing. Some studies suggest there is an increased risk of osteoporosis in patients with Addison's disease but other studies including our own from Auckland, suggest that this relationship is quite complex. There may be a relationship with how much prednisone or hydrocortisone you take, such that those patients with the highest dose and longest duration of Addison's disease tend to have slightly lower bone densities than patients on smaller doses. However there are many factors that influence this, including whether or not you are post menopausal or if a male, have low testosterone levels. Furthermore, post menopausal female patients with Addison's disease not only lack estrogen and potentially take too much prednisone, but also have lower than normal amounts of male hormone (because of Addison's disease stopping their adrenal produce male hormone, and the menopause stopping normal male hormone production from their ovaries). All these factors can have additive and adverse effects on bone density.

The overall summary of the evidence is that for most patients on sensible amounts of prednisone (or hydrocortisone), their bone density is probably not much different from if they did not have Addison's disease in the first place. However because of the potential adverse effects of very subtle over-dosage with prednisone, which would not be easily recognised, and because of all the other adverse effects described above, it is sensible to discuss the value of a bone density measurement with your own doctor. Correction of low estrogen levels in post menopausal women or testosterone levels in men with hormone replacement treatment should be considered, as well as maintaining a good calcium intake in your diet – dairy products are the main source of this. Other treatment options if low bone density is discovered are available, and are no different in patients with Addison's disease eg; bisphosphonate treatment with drugs such as Alendronate (fosamax) or Etidronate (didronal), to name just two.

NZAN Update Number 7, July 1999

Question What is the difference between an adrenaline response and cortisol response in people with normal adrenal glands?

The adrenal gland has an outer layer that produces cortisol (and aldosterone - see Nov '98) and an inner core producing adrenaline and noradrenaline. Most noradrenaline is produced by our automatic nervous system and is released from nerve endings that supply almost every part of our body.

When faced with danger, our automatic nervous system is activated and noradrenaline and adrenaline is released which causes a myriad of effects - heart rate rises, blood pressure increases, muscles tense and you get ready to "run" away from the danger.

This is largely the cause of the so called adrenaline rush (actually a noradrenaline and adrenaline rush). Adrenaline itself is mostly released from the core part of the adrenal gland and not from the nervous system. This core part is usually not affected by Addison's disease which tends to attack the outer layer only and so adrenaline and noradrenaline responses in most patients with Addison's disease are normal.

Cortisol on the other hand is released exclusively from the outer layer of the adrenal gland. Cortisol is also released during danger and stress, but also in varying quantities during the day and night according to an in-built body clock. Most is produced at about 6 in the morning. Cortisol is under a totally different control mechanism to noradrenaline and adrenaline and is released from the adrenal gland under the action of a messenger hormone called ACTH (adrenocorticotrophic hormone) which is released from the pituitary gland in your brain. Cortisol is vital for all sorts of important things and is critical in regulation of glucose, fat and protein production in your body, but also is needed for the proper functioning of all your body organs. The sudden release of cortisol in response to major stress, eg a car crash, severe illness or operation does not result in any particular symptoms as such - there is no cortisol rush like an adrenaline rush. Cortisol just quietly gets on with its job in helping you recover from such stressful events as mentioned above. That's why patients with Addison's disease need to take 3 x the steroid replacement dose (cortisone, hydrocortisone, prednisone, dexamethasone but not fludrocortisone) during severe illness as outlined in a previous Newsletter.

Question: Does the normal adrenaline response decline with age?

The automatic nervous system that produces noradrenaline as outlined above, is largely responsible for the "butterflies in stomach" feeling you get when anxious. Little has been written about whether ageing per se reduces the sense of anxiety - of course, as you get older you may have reduced anxiety under stressful circumstances due to being more practised and more confident! Having said this, the automatic nervous system certainly does not respond as well with ageing and many normal fit elderly people have quite abnormal blood pressure and heart rate responses to eating and standing up, which confirms some malfunction of this system with ageing.

Question: What is an ACTH test? What controls ACTH?

As discussed above, ACTH is a messenger hormone released from the pituitary gland which controls cortisol release from the adrenal gland. ACTH is itself very sensitive to the amount of cortisol circulating in the blood, such that if cortisol levels are high, ACTH is switched off and vice versa! ACTH

and cortisol are therefore usually in a very delicate balance. ACTH levels do fluctuate according to a 24 hrs built-in body clock with levels highest at about 6 in the morning and lowest in the late evening. Patients with untreated Addison's disease, thus have low cortisol levels because their adrenal gland cannot produce cortisol. This feeds back to the pituitary gland which senses the low cortisol levels and sends out more messenger hormone-ACTH. ACTH is therefore high and cortisol low. The high ACTH causes pigmentation.

When Addison's patients are finally diagnosed and placed on adequate hydrocortisone or prednisone replacement dose, the pituitary senses this and so ACTH levels return back to normal.

When patients are adequately replaced therefore, ACTH levels are usually in normal or just above normal range. Whenever the dosage of hydrocortisone replacement is too high, ACTH levels are suppressed and are low. Conversely, when the hydrocortisone is too low, then ACTH levels rise and this can be measured.

As ACTH levels normally fluctuate during the course of a 24 hr day, the best time to measure the response is in the morning between 8-10 am so that the result can be interrupted as high, low or acceptable. As stated in previous Newsletters, measuring ACTH level is not however a routine test and does not necessarily need to be done regularly. It can however be helpful if patients or their doctors are concerned about the adequacy of the steroid placement dose.

Question: Should cortisol in the blood or urine be measured as a test of replacement dosage?

Some doctors find repeated blood cortisol levels during a day (a cortisol day curve) helpful or even measuring a 24-hour urinary cortisol level. However prednisone and hydrocortisone tablets are converted into cortisol and do show up as cortisol levels in blood and urine tests, which can make interpretation of blood and urine cortisol levels difficult. The best way to test the adequacy of prednisone or hydrocortisone dose replacement in patients is to ask the patient how they feel. If they are feeling really well and the blood pressure response to lying and standing is OK and simple blood tests of salt levels are normal, there may be no need to check any more complicated tests. If in doubt however, an ACTH level can be checked and this is quite a useful and reproducible way to test the adequacy of cortisol replacement therapy. (Renin is the one to check if you are worried about the fludrocortisone dose replacement as previously described)

Question: Does the calcium intake of patients with Addison's disease matter?

As described in last month's Newsletter, bone thickness (or density) in patients with Addison's disease may be a little lower than normal, especially if the patient is a post-menopausal female with long duration disease. Ensuring

an adequate calcium intake in your diet (around 1,000 mgs per day) is however important, whether you have Addison's disease or not and good calcium intake should start in childhood - dairy products such as cheese, milk, ice-cream and yoghurt are good sources of calcium. Patients with ↓ bone density however, may need higher than normal calcium intakes and additional specific therapy for osteoporosis just like any non-Addisonian patient with osteoporosis.

Question: What happens to the adrenal gland in Addison's?

If tuberculosis is the cause of Addison's the gland can become very small and distorted. Most patients in New Zealand have auto-immune Addison's which means that you develop antibodies against your adrenal glands. This makes them become small and "scarred" up and this process is called "atrophy".

NZAN Update Number 8, November 1999

Question: Can patients with Addison's disease avoid jet lag on long distance, cross time zone travel by giving extra Hydrocortisone?

The cause of jet lag is not fully understood but may involve a hormone called Melatonin. This is usually secreted at night time and so sudden changes in time zones with altered day and night cycles may upset the usual Melatonin release rhythm. Some studies suggest that Melatonin replacement treatment may help jet lag. As I understand it cortisol rhythms are however not involved in the cause of jet lag and top up hydrocortisone has no effect on jet lag in patients with Addison's disease. However there is very little information on this point. Like all travellers on long distance flights, try to not drink alcohol, sleep as much as you can and walk around the plane during the flight. You may however need to take extra hydrocortisone on your arrival depending on the local time at your destination e.g. Europe is 12 hours behind New Zealand and long haul flights often arrive in the morning local time which is of course your own body clock night time. You may therefore need to take "another" morning dose of hydrocortisone on your arrival at the destination.

Does the dose of hydrocortisone change with age?

In general no. If you gain weight (which of course often happens with advancing age) you may need more hydrocortisone for that reason. Drugs that increase the speed your body breaks down cortisone can mean that you need extra dosing whilst taking those drugs. The common ones would include Phenytoin and Phenobarbitone (taken for epilepsy) and some antibiotics like Rifampicin (taken for TB).

Does Addison's disease affect your ability to cope when sleep deprived? Do patients with Addison's cope less well with night shift work?

There is no published literature that I can find about the subject. All night shift workers are chronically sleep deprived and have higher scores of sleepiness, tiredness and moodiness than day-time workers. I guess taking a longer acting steroid like Prednisone or Dexamethasone instead of twice daily hydrocortisone may be worth trying for those who think they aren't able to deal with shift work at night as well as prior to them developing Addison's disease. This may help reduce fluctuations in blood cortisol levels. Melatonin again may be involved in causing these "jet lag" like symptoms. However Melatonin replacement therapy is still not generally advisable particularly on a long term basis as there may be long term side effects or even dangers from such use. Clearly more research in this whole area is needed.

My bone density is low and my GP has started me on Rocaltrol and calcium tablets. I take 10 mg of prednisone for my Addisons disease. Are there any problems with this?

Rocaltrol is a vitamin D type tablet and may be effective in preventing bone loss in patients taking prednisone in high doses for the treatment of all sorts of medical conditions. In general it is not as effective as hormone replacement therapy in post-menopausal women or in men who have low testosterone levels. It is also not as good as tablets that reduce bone turnover called "bisphosphonates" (like Didronel or Fosamax). In patients with normal parathyroid glands (calcium controlling glands) Rocaltrol and calcium taken together can raise the blood calcium levels above normal and this can be harmful . Patients with Addison's and low parathyroids can however safely take Rocaltrol and calcium together- your calcium levels will be monitored regularly .

There are no studies examining the effects of these drugs on bone density in patients with Addison's disease – as pointed out in an earlier newsletter, bone density in Addison's has received little attention. Our Auckland Hospital endocrinology department's recent research suggests that bone density is probably normal in most Addison's patients, but may be lower than normal in women who are many years into the menopause or in patients taking high doses of steroids as replacement therapy.

So there is no real right or wrong answer to the question of which drug is best for treating low bone density in patients with Addison's disease. However the following comments may be helpful. Firstly 10 mg of prednisone is quite a high dose –this may of course be needed in your case, but if a trial of a lower dose has not been tried, this may be worth-while –this must be done under careful supervision. If you are male, other causes of low bone density such

as low testosterone levels and vitamin D deficiency should be looked for and treated if necessary. If neither of these two points apply, then either a bisphosphonate or Rocaltrol can be tried. Care with the combination Rocaltrol and calcium supplementation should be taken (unless indicated for low parathyroid glands). If female and post-menopausal, then hormone replacement treatment is probably best unless there are contra-indications to this, followed by bisphosphonates and Rocaltrol as outlined above.

NZAN Update Number 9, March 2000

(Several questions included on the November 1999 Survey Responses, have been addressed under broad sub-headings.)

Q.1 Prednisone or Hydrocortisone?

Prednisone is a long lasting steroid that has a duration of action somewhere between 18-36 hours and an onset of action within an hour or two. Hydrocortisone lasts for a much shorter time – perhaps 8-16 hours and generally needs to be taken twice a day at least. Its onset of action may be quicker than prednisone. For patients who are well on either Prednisone or hydrocortisone, there is no need to switch from one to the other. There is no consensus on which drug is best – if patients don't feel well it is worth discussing switching from one to the other with your doctor – even taking prednisone at bed-time rather than in the morning can be useful for some patients.

Q.2) Alcohol and Addison's

There should be no adverse effects of sensible alcohol intake on steroid metabolism in patients with Addison's disease and so dose adjusting for modest alcohol intake is not necessary. High alcohol intake has major effects on all pathways in your body affecting the endocrine system and particularly the liver. This is highly likely to have unpredictable effects on salt and water metabolism as well as how your body responds to cortisone (prednisone, hydrocortisone and fludrocortisone).

Q.3) Faulty 'Thermostats' and Addison's

There is no known effect of properly treated Addison's on heat regulation. Thyroid over and under-activity are sometimes associated with Addison's and should be checked out if you do feel unusually hot or cold in a persistent way. If your steroid dose replacement is right and your male and female hormone levels and thyroid function are all appropriately sorted, you should be no different from non-Addisonian

patients. A number of patients did complain about abnormal 'thermostats' and I'm afraid I have no good explanation for you apart from what is said above.

Q.4 Emergency Hydrocortisone by Injection

Ian asks how important is it for Addison's patients in New Zealand to have an emergency dose of injectable hydrocortisone, as some doctors are reluctant to prescribe it. In general terms, assuming a patient is capable of self-injection or has a friend/partner who can do it for them, then I think most patients should have an emergency supply. This is particularly true if you live in or travel to remote areas. I guess if you live in a major city and never go away to the wilderness for a holiday, then you probably will have easy access to a doctor at all times, and thus a supply of injectable hydrocortisone at home is less important for emergency use.

Q.5 Emergency Treatment of Addison's – How Good is the Ambulance Service?

I have no idea how good our ambulance service is in dealing with patients with Addison's disease. I suggest that if ever you have reason to call an ambulance, you are probably doing so for a good reason and therefore are likely to be severely ill or injured. As such you should inform the emergency services immediately that you are on maintenance steroids and receive 100-200 mg of hydrocortisone intravenously or intra-muscularly. Wearing a Medic-Alert bracelet or necklace is also a good idea – you may be unconscious when the ambulance arrives!

Q.6 Lisa Laments About Weight Gain. She takes 25mg of Hydrocortisone and 50Ug of Fludrocortisone

Lisa, I'm sure you realise there are multiple reasons for gaining weight other than over-treatment with hydrocortisone. Clearly all patients should take the minimum amount of hydrocortisone that keeps them well, and that should be discussed on an individual basis with your doctor. As women approach the menopause weight gain commonly occurs. Addison's patients can sometimes have an early menopause, and this indirectly could contribute to weight gain. Finally, an under-active thyroid can be associated with Addison's and this can result in weight gain too. All these issues should be checked and with your doctor. Otherwise it's 'eat healthily and exercise' – a message for all of us!!