Absorption of Steroids - what happens in the gut!

By Dr John W Honour

This is a very topical subject in an area of scientific research that has only developed over the last 15 years. In the media you will have read articles about the microbiome, which is the term for the bacteria in and on our bodies.

The bacteria in your gut can influence any treatment with steroids.

Some medications taken by mouth have instructions of when to take them in relation to meals or not to take with grapefruit juice and this is about all that is commonly considered in the link between steroids and the gut.

That is no longer the case

Steroid is a term used to describe hormones with a certain chemical structure that deal with sugar, salt and sexual characteristics in the human body.

The aim of this paper is for the reader to understand the what, how, where and when, of steroid treatment, particularly how the gut changes steroids influencing the impact of a treatment.
Figure 1

Figure 1 is a cartoon of the gut. The main parts of the gut start with the stomach, where acid and enzymes act to start the breakdown of complex sugars, fats and proteins. The stomach is not included in the cartoon but that is where hydrocortisone and other steroids taken by mouth are absorbed. When taken by mouth, some steroid will get to the duodenum and maybe ileum.

Food then goes from the stomach into the duodenum then on to the jejunum and ileum which is loosely referred to as the small intestine because in essence, it is a long narrow tube. Each zone has particular functions. The caecum is what we call the large intestine reflecting its size. Fats are emulsified, broken down and absorbed in the areas shown. Note the liver drains bile through the bile duct into the duodenum. Bile acids from the liver are important to fat breakdown. Bacterial degradation is shown in jejunum, ileum and caecum.
In the past 15 years we have had the technology to define the bacteria in our gut. This is achieved through analysis of the bacterial genes. Previously it was necessary to culture organisms, which was a long process as all experiments had to be performed in duplicate, in air and without air, because of the requirements of different bacteria. Recent research has shown there are 10 times more microbial cells than human cells in and on the body. There are 130 times more microbial genes.

Microbes influence the course of several diseases, heart, blood vessels, brain function, diabetes, obesity, arthritis and many others. Bacteria in our gut have been known for many years to be important for making some of our essential amino acids and vitamins.

In the years 2000 to 2016 the scientific literature has grown from less than 50 papers to more than 6000 papers. This indicates how much research is taking place in this area and we will be hearing about this for some time in the future.

What is the current view of how our gut influences the steroids we use in treatment?

**WHAT**

Patients may be prescribed steroids for different reasons and they encounter one or more of the following problems. Cortisol or hydrocortisone is well known to patients with congenital adrenal hyperplasia (CAH) and patients with adrenal insufficiency due to Addison's disease or hypopituitarism because cortisol is needed when production fails (Figure 2).
<table>
<thead>
<tr>
<th>Cortisol (hydrocortisone)</th>
<th>Replacement steroid in CAH, adrenal insufficiency, hypopituitarism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fludrocortisone</td>
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<td>Salt retaining steroid</td>
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<tr>
<td>(Substitute for aldosterone)</td>
<td></td>
</tr>
<tr>
<td>Fluticasone</td>
<td>Treat asthma</td>
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<tr>
<td>Becotide</td>
<td></td>
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<tr>
<td>(Anti-inflammatory steroids)</td>
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<tr>
<td>Oestrogen and progestogen</td>
<td>Oral contraceptives</td>
</tr>
<tr>
<td>Testosterone</td>
<td>Stimulate red blood cells</td>
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**Figure 2**

Some patients with CAH and adrenal insufficiency will also take fludrocortisone to stop the loss of salt in the urine. This replaces the natural steroid called aldosterone which was discovered in 1953, at the Middlesex Hospital in London.

Many children these days seem to be given steroid to treat asthma and respiratory conditions. Fluticasone and Becotide are commonly used as anti-inflammatory steroids. These are potent steroids applied locally to the airways.

Currently, only females take steroids for oral contraception. The only real use for testosterone beyond replacement therapy is to stimulate red blood cells in some patients, but we are all aware that anabolic steroids such as testosterone are used in sport to enhance performance and elsewhere to enhance physique. Anabolic steroids at high doses encourage muscle development but have many side effects.
HOW

Cortisol for most patients is taken by mouth as tablets (Figure 3). There are now delayed release forms of hydrocortisone being developed, hoping to better mimic the changes in concentrations of cortisol in the blood over a 24 hour period. Cortisol can also be taken per rectum when there are difficulties swallowing tablets.

<table>
<thead>
<tr>
<th>Cortisol (hydrocortisone)</th>
<th>Tablet</th>
<th>Delayed release</th>
<th>Cream</th>
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<td>Contraceptives</td>
<td>Tablet</td>
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<td></td>
<td>Coil</td>
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<td></td>
<td>Implant</td>
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<tr>
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<td>Tablet</td>
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<td></td>
<td>Injection</td>
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**Figure 3**
The plasma concentrations of cortisol (measured as 17-hydroxycorticosteroid in earlier studies) (Figure 4) increase rapidly when cortisol is taken by mouth (open circles), by injection (closed circles) and rectally (open squares). Note five times more steroid was used rectally to get concentrations of cortisol 10 times less than oral or injection cortisol. For those who take notice of blood and urine test results the numbers 10, 100, 1,000 mg/day equate to 27, 270 and 2700 nmol/day. So, rectal use of hydrocortisone is less effective than other routes of administration.

![Plasma concentration graph](image)

**Figure 4**

In 1957, an Endocrinologist at the Middlesex Hospital, John Nabarro, looked further at the use of cortisol rectally (Figure 5). He showed differences in
uptake between 2 patients. In 1957 cortisol was measured in a chemical reaction for 17-hydroxycorticosteroids. Male hormones were detected in those days as 17-ketosteroids. In one patient given 200mg hydrocortisone daily, concentrations of 40 milligrams/day of hydroxycorticosteroids were achieved which was four times what was measured before the treatment. About 5 milligrams of 17-ketosteroids/day did not change with treatment. A second patient again increased cortisol-like steroid in the urine. 17-hydroxycorticosteroids in urine were 4 times higher after rectal administration than before treatment. The urinary male sex hormones (ketosteroids) doubled to 20 mg per day.

Figure 5

Nabarro JD et al 1957
The fundamental differences in the 17-hydroxycorticosteroids and the 17-ketosteroids are shown in Figure 6. The steroids were thought to be broken down by bacteria. There are many other actions of bacteria on steroids but that would rather complicate this story. One such reaction is shown. Note the loss of OH in the chemical structure at C numbered 21.

![Metabolism of steroids by bacteria in the intestine](image)

**Figure 6**

Thinking that bacteria were involved in changing the hydrocortisone to ketosteroids, John Nabarro looked to see if he could reduce androgen excretion by giving an antibiotic (Figure 7). Neomycin was given by mouth to one patient and this killed the bacteria in the gut. Again the 17-ketosteroid output in urine after rectal hydrocortisone gave rise to more 17-ketosteroid excretion than oral hydrocortisone but this response to rectal hydrocortisone was less during antibiotic treatment. Those experiments have not been
repeated with modern hormone methods but from the limited experiments performed by Nabarro, rectal hydrocortisone is less effective than oral or injection cortisol and the response is variable due to the action of bacteria in the gut.

![Graph showing 17-ketosteroid excretion after 200 mg rectal hydrocortisone. Wade AP et al 1959](image)

**Figure 7**

The bacteria throughout the gut from oesophagus (your throat) to colon can now be analysed and many different species are found in each zone (Figure 8). In the orange blocks cfu stands for colony forming units which was the old standard for numbers of bacteria grown on agar plates. There are a lot more bacteria in the colon than the stomach. The gut changes from highly acidic to basic in the pH scale. The amount of bacteria increases from stomach to colon. The oxygen concentration decreases and this has a **huge impact** on the nature
of the steroids and what they can do. This microbiome makes the gut a factory for chemicals in the body. Bacteria such as Clostridia and Eubacterium are known to react chemically with steroids.

Figure 8

Hydrocortisone can be taken from an insulin pump to a small cannula under the skin (Figure 9). The delivery of hydrocortisone can be programmed to produce cortisol concentrations in blood during the day and night, exactly as would be seen in an individual with normal adrenal function.

This method bypasses the gut.
Figure 9

Cortisol when taken as a dual release capsule is delivered from the outer layer of the capsule and absorbed from the stomach. A layer has to be broken before the second dose of cortisol is released (Figure 10). Both absorption and clearance will affect the time this takes to get into and out of the blood stream.

Although cortisol delivery in the stomach comes from the outer layer the second delivery stage could be in the duodenum or jejunum, where increasing numbers of bacteria may act on the cortisol to release ketosteroids or other steroid products. This may alter delivery.
Figure 10

1. Absorption of drug and partial conjugates in gut wall

2. Further synthesis of steroid conjugates

3. Excretion of conjugates from liver in bile

4. Steroid conjugates arrive in colon

5. Hydrolysis of steroid conjugates by gut bacteria

6. Reabsorption of free steroid

Bacterial metabolism – side chain cleavage (Ketosteroids)

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Anti-inflammatory steroids for asthma are taken by inhalation which for some patients the co-ordination of spraying and breathing can be difficult (Figure 11).

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**Figure 11**

The drug can get on the wall of the mouth and into the saliva which is swallowed so the steroid gets in to the gut reducing the impact of the steroid on the lungs (Figure 12) and leading to potential side effects in the rest of the body.

**Figure 12**
Contraceptives can be taken by tablet over 21 or 28 days of a menstrual cycle (Figure 13). The steroids can also be supplied from a coil in the uterus or an implant under the skin in the arm. The scientific literature has shown that women taking antibiotics during the use of oral contraceptives were at risk of an unwanted pregnancy.

**Figure 13**
The oral contraceptive is less effective because bacteria in the gut alter the chemistry of the oral contraceptive and increase clearance from the body in the faeces (Figure 14).

Interestingly the oral contraceptive also increases the amount of cortisol binding globulin in the blood, leading to higher cortisol levels in those taking hydrocortisone. Another example, of how complex this whole system can be.

Figure 14

Male hormones are taken as oral tablets, patches on the skin or by injection (Figure 15). There are differences in the effects of the oral tablets through bacterial action in the gut.

These steroids can damage liver function.
**Figure 15**

**WHY**

There are reasons why steroids are prescribed (Figure 16). Without cortisol we are open to infection and have problems maintaining a normal glucose concentration in the blood. Glucocorticoid (like cortisol, hydrocortisone, prednisolone) steroids are very potent and at high doses in children there are reports of slowing of the growth rate. This can be seen, particularly, when taking synthetic anti-inflammatory steroids. Many children with CAH are short as adults because of this issue. They also have problems with body weight.

If cortisol is taken rectally as a suppository, there will be direct interaction with the bacteria in the lower intestine, reducing the amount of cortisol available and if testosterone like steroids are produced as a result, this will lead to
increased androgen like products in the blood, less of an effect of cortisol replacement and increased effect of androgens around the body.

![Table of Hormones and Their Functions](image)

**Figure 16**

Fludrocortisone acts on the kidney to retain salt but at high doses it will act like cortisol again contributing to slow growth of patients with CAH. It is important that the lowest dose of fludrocortisone is taken and regular monitoring of plasma renin activity as well as blood pressure measurements are undertaken.

Progesterone is needed to maintain a pregnancy. Synthetic steroids with progesterone-like activity are part of some oral contraceptive preparations.

Estradiol is the female hormone that induces breast development and prepares the uterus for implantation of an embryo. The oral contraceptive can be ineffective when taking antibiotics. Discuss this situation with your GP.
Male hormones are taken by men to enhance muscle growth and increase red blood cell numbers that increases oxygen delivery to the tissues. There are other side effects (Figure 17) such as deepening of the voice and testicular shrinkage making the males infertile.

![Harmful effects of anabolic steroids](image)

**Figure 17**

There is the risk of heart attack because of cardiac muscle growth. There can be changes in behaviour with increase in violence. Breast development is due to conversion of male hormone to female hormone, bacteria in the gut may contribute to this process. It's not good for sport as steroids can make for easy bruising and weak tendons.

Acne is often an early sign of anabolic steroid use, (Figure 18) and body builders get big bellies. This is attributed to the increased appetite and food intake from the steroid use, with growth of the muscles of the gut and the overlying muscles.
WHEN

The time and frequency of when you take steroids depends on the desired effect and its duration (Figure 19). Hydrocortisone is given up to four or more times per day, with different doses taken at different times, in an attempt to mimic the pattern of cortisol concentrations in the blood. An agreement on the best practice is desperately needed. Individualised dosing based on clearance and absorption and careful monitoring with profiles should be offered.
Figure 19

Fludrocortisone is only taken once a day at very low dose. This is to mimic the actions of aldosterone which is about one thousand fold less in concentration than cortisol. High doses of cortisol can also cause salt and water retention by acting like fludrocortisone.

Testosterone is usually taken as a monthly injection into a muscle. Some synthetic male hormones are taken by mouth daily. These are particularly dangerous for damaging liver function.

A skin patch will deliver enough testosterone to achieve normal blood concentrations so could not be used to build muscle. However, if a child were to stick on the patches there could be some effect on muscle growth, acne and penile growth similar to puberty.

Oral contraceptives are daily tablets or slow release implants and coils.
When doses of hydrocortisone are taken too frequently and the second dose is taken before the cortisol from the previous dose has dropped to an appropriate level, the cortisol is ‘stacked’ onto the remaining cortisol resulting in an accumulation of cortisol in the blood, taking cortisol levels into unwanted high concentrations. This is called ‘over stacking’.

In Figure 20 at the red circle an extra dose of hydrocortisone has been given too soon. Instead of cortisol declining as shown by the solid blue line, higher values result (dashed line).

![OVER STACKING](image_url)

*Reproduced with permission from Elsevier’s publication ‘Congenital Adrenal Hyperplasia – A Comprehensive Guide’*

**Figure 20**
TAKE HOME MESSAGES

Cortisol can be taken by mouth, skin cream, injection or from the rectum. Always follow the instructions and discuss any concerns with your GP or endocrinologist.

Figure 21

Steroids get into the gut at points from mouth to anus depending on what and how steroids are taken. Bacteria can act on steroids to affect bioavailability of cortisol.
Be **aware** that Herbal medicines may contain steroids such as hydrocortisone to blend Western medicine with complimentary practice.

If you take oral contraceptives they may not work if you are prescribed antibiotics, check with your GP and use barrier method of contraception to be safe. You can stop sperm by use of male or female condoms or the cap inserted in the female urogenital tract.

If you take inhaled steroids, be careful of the technique, otherwise a lot of the steroid may be swallowed. Check your technique with your GP or nurse.

Anabolic steroids are rarely prescribed and only for male hormone deficiency or problems with the red blood cell count. Anabolic steroids are illegal and can be very dangerous, particularly for children. This is a new area of scientific research but there are expectations that modification of the processes in the gut can help us understand disease processes and lead to new treatments using the knowledge base of the gut.

*In conclusion, your gut (and especially the bacteria therein) can affect your use of steroids!*