Adrenal Insufficiency & Asthma

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Asthma Nurse Specialist
RHSC Edinburgh
NPRANG 5th October 2013
Topics to explore

- History behind adrenal function testing
- The role of cortisol
- What goes wrong
- Testing
- Management
- School plans
- Practical tips
Emma Agnes Frame died on 24 November 2001 at Wishaw General Hospital in Lanarkshire. She was five years old.

Known to have asthma – on high dose fluticasone 1500mcg = 3000mcg BDP

She presented at Wishaw General (DGH) with abdominal pain and vomiting

She had a seizure

Despite medical care she continued to deteriorate and died

Cause of death initially was inconclusive
Callum Frame

- 7 year old Sibling of Emma
- Known to have asthma, on high dose ICS
- developed sore stomach and vomiting
- Parents took him to GP – Hospital
- Deteriorated – found to have cerebral oedema – ventilated but improved
- Abnormality on a random cortisol
- Attended for Short Synacthen Test as an outpatient
Findings – adrenal insufficiency due to drug treatment used to control his asthma.

Emma’s death was attributed to adrenal insufficiency. (Adrenal glands very small on PM.)
CURRENT PROBLEMS
in
Pharmacovigilance

COMMITTEE ON SAFETY OF MEDICINES

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MEDICINES CONTROL AGENCY
Inhaled corticosteroids and adrenal suppression in children

Adrenal suppression may be under-recognised

Prescribers are reminded that the presenting symptoms of adrenal suppression and crisis are non-specific and include anorexia, abdominal pain, weight loss, tiredness, headache, nausea, vomiting, decreased level of consciousness, hypoglycaemia and seizures. Situations which may potentially trigger acute adrenal crisis include infection, trauma, surgery or any rapid reduction in dosage.
**Box 1: Maximum licensed doses of inhaled corticosteroids in children**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose</th>
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<tbody>
<tr>
<td>Budesonide</td>
<td>800 mcg/day (under 12 years)</td>
</tr>
<tr>
<td>Fluticasone</td>
<td>400 mcg/day (4 - 16 years)</td>
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</tbody>
</table>

1. CSM/MCA *Current Problems in Pharmacovigilance* 1998; 24: 8
Adrenal Gland

Cortisol is a steroid hormone and is vital for health.

Main functions include:
- Helping to regulate blood pressure
- Helping to regulate the immune system
Helping to balance the effect of insulin in regulating the blood sugar
Helping the body to respond to stress
Steroid burden

Mouth and pharynx

10–50% Deposited in lung

Lung

Complete absorption from the lung

Systemic circulation

Orally bioavailable fraction

Liver

40–90% Swallowed (reduced by space or mouth rinsing)

Absorption from gut

GI tract

First-pass inactivation

Systemic side effects
- High dose inhaled steroids
- Prednisolone (repeated courses or maintenance)
- IM Triamcinolone

But need to consider overall steroid burden:
- Nasal
- Topical
- Occular
Pathophysiology

- Pituitary gland senses circulating cortisol (natural or synthetic – can not differentiate)
- If the circulating levels are high then its sends a message to ACTH (Adrenocorticotropic hormone)
- ACTH sends a message to Adrenal cortex to reduce production of cortisol
Adrenal glands reduce/ stop producing cortisol

The adrenal glands shrivel

This process can only be reversed when steroid load is reduced

BUT

We need to maintain good asthma control so it’s maintaining a balance
Good asthma control v normal adrenal function

Asthma Control

Adrenal function
Insulin Tolerance Test (ITT) is the gold standard investigation for adrenal insufficiency: correlates with adrenal response to surgical stress.

BUT:

unpleasant and potentially dangerous

Short Synacthen Test is main challenger

Cortisol at 0 and 30 mins ± 60 mins

Concordance between ITT and SST widely reported, with peak cortisol at 30 mins correlating, but discordance found.
Why has this test been arranged?
Your child has been prescribed a high dose of inhaled steroid and/or oral steroids, as their asthma has not been well controlled on lower doses.

Occasionally, when children have been on these higher doses for a while their bodies can stop making cortisol.

It is important that we are aware of this, as your child may need some additional treatment if they become unwell or have an accident.

What is cortisol?
One of the hormones produced in the body is called CORTISOL, which is a really important hormone because it helps the body cope with serious stress, such as infection and injury.

Cortisol levels in the body vary a lot throughout the day and can be difficult to measure. This means it is necessary to stimulate the body to release cortisol, so that the amounts produced can be accurately measured. The Short Synacthen test is considered a painless and efficient way of doing this.

About the test
In this test, a harmless substance called Synacthen, which closely resembles a natural hormone called ACTH (Adrenocorticotropic hormone), is given to stimulate the body into producing cortisol. The levels of cortisol your child produces can then be measured by taking regular small blood samples during the test.

Procedure
If your child is having a Synacthen test only, he/she will not need to be fasted and can remain up and about throughout the test. If your child is currently on oral steroids (prednisolone) on a daily basis, please omit the dose the morning of the test.

After arrival in the ward, the doctor will insert a very small plastic tube (called a cannula) into your child’s arm, or in the back of their hand. The tube will remain in place until the test is finished, and will be used to give the Synacthen and to take small blood samples throughout the test (approximately two hours).

Your child can have Emla cream (which numbs the skin) applied an hour before the cannula is put in – this really helps to make the procedure as painless as possible.

Symptoms
Your child should not experience any symptoms or side-effects from the Synacthen.

Follow-up
Your child should already have an appointment to be seen in the Asthma Clinic. The Asthma Nurses will contact you with the results of the test as soon as they are available.

Contacts
Please do ask the doctors any questions you may have, or contact the Asthma Nurse Specialists, Ann McMurray or Julie Westwood, Monday to Friday on 0131 536 0773 or via switchboard on 0131 536 0000 bleep 9323.
Procedure

- Insertion of cannula
- Rest for 30 mins
- Baseline blood
- Administer synacthen
- Blood samples at 30 minute intervals

- Rearrange test if the child is unwell
- Withhold oral steroids on morning of test
The short Synacthen test: a questionnaire survey of current usage

Charlotte Jane Elder, Pooja Sachdev and Neil Peter Wright

Arch Dis Child 2012 97: 870-873 originally published online July 11, 2012
doi: 10.1136/archdischild-2012-301713
National Questionnaire through BSPED

- 39 of 92 centres responded = 42% response rate
- 46% DGHs, 54% tertiary centres
What dose of synacthen?

250 mcg supraphysiological
5 mcg gives similar response to 250mcg
1 mcg probably maximally stimulates too, with same peak at 30 mins but ? less at 60 mins

- No real evidence to support the reliability of Low Dose test
- Advocates of LDSST say it may detect more subtle defects
- Detractors say may give false positive results
Standard Short Synacthen test v Low dose SST

- 3 meta-analyses
- Agreed SSST has no advantage over LDST
- 2 of the 3 thought LDST may have advantages

- Increase in SST test since alert re risk of adrenal suppression of high doses inhaled corticosteroids (HDICS): guidance advocates LDSST
The low-dose ACTH test is considered to provide a physiological stimulation of adrenal responsiveness but it is not known how useful such a sensitive test is at predicting clinically relevant adrenal insufficiency.

LDSST or SSST?
Questionnaire Survey

Evaluate current usage

- Only 250mcg currently available commercial preparation
- If centres do LDSST then also asked re method of dilution
Use of SST

- 82% use LDST
- 87% use SSST
- 69% use both
- 18% use SSST only
- 13% use LDST only
Marked variability in reporting how make up drug for LDST
- 14 different methods by 23 (72%) of centres
- Single dilution method n = 8
- Double or triple dilutions n = 6
- Diluent volume varied from 10 ml to 1 litre
- Volume of synacthen vial varied from whole 1ml vial; 0.5 ml or less was used in 5 of methods described
Conclusions

- Very varied practice! (except baseline and 30 min samples)
- Quite good correlation re peak results
- Assay variability must be used when determining cut offs
- 14 different methods for LDST will cause marked variation in dose given
  - synacthen is inherently unstable at room temp, degrades with light, sticks to plastic etc
What do we do in Scotland?

In SPEG guideline – only SST.

- Bloods at 0, 30, 60 mins
- Pass = peak of > 650 if < 6yrs
- Pass = peak of > 470 if aged 6 – 18 yrs
  (RHSC use >400)

- About to change so all children regardless of age will be expected to achieve lower peak value
Testing

- Know your analyser! Results are interpreted according to equipment specific reference ranges
- Two types -
  - Abbott Architect Cortisol Assay (peak 400)
  - Siemens advia centaur cortisol assay (peak 470)
Results

- Borderline
- Suptoptimal response – sick day cover only
- Complete lack of response – maintenance dose & sick day cover
- Presumed to be adrenally suppressed
Table 1: Dose of hydrocortisone for patients with known or suspected adrenal insufficiency during intercurrent illness.

<table>
<thead>
<tr>
<th>Weight in kilograms</th>
<th>Double dose hydrocortisone for mild illness</th>
<th>Treble dose of hydrocortisone for moderate illness</th>
<th>IM dose for severe illness</th>
</tr>
</thead>
<tbody>
<tr>
<td>15-24.9 (0.7m² - 0.85m²)</td>
<td>5mg tds</td>
<td>7.5mg tds</td>
<td>50mg</td>
</tr>
<tr>
<td>25-39.9 (1.0m² - 1.2m²)</td>
<td>7.5mg tds</td>
<td>10mg tds</td>
<td>100mg</td>
</tr>
<tr>
<td>40 - 69.5 (1.3m² -1.8m²)</td>
<td>10mg tds</td>
<td>15mg tds</td>
<td>100mg</td>
</tr>
<tr>
<td>70+ (1.9m² -2.0m²)</td>
<td>15mg tds</td>
<td>20mg tds</td>
<td>100mg</td>
</tr>
</tbody>
</table>
When it gets confusing...

- If a child is on maintenance prednisolone of varying doses or triamcinolone

Table 2: Minimum dose of prednisolone below which a patient (by weight) would commence oral hydrocortisone during intercurrent illness.

<table>
<thead>
<tr>
<th>Weight in kilograms</th>
<th>Oral prednisolone dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>15-24.9</td>
<td>5mg</td>
</tr>
<tr>
<td>25-39.9</td>
<td>7.5mg</td>
</tr>
<tr>
<td>40-69.9</td>
<td>10mg</td>
</tr>
<tr>
<td>70+</td>
<td>15mg</td>
</tr>
</tbody>
</table>
Patient information

Following the short Synacthen test carried out in PIU, the results have revealed that your child’s body does not produce an adequate amount of cortisol to cope with periods of illness. This has been caused by the high dose inhaled steroids and/or the oral steroids your child has to take to keep their asthma under control. It is very important that your child continues to take their prescribed steroid medication especially when they are unwell.

What is hydrocortisone?
Hydrocortisone is a steroid medication which closely resembles the natural steroid your body produces called cortisol. This medication is necessary as your child is currently unable to produce a sufficient amount of their own cortisol. They should continue to take the hydrocortisone until they are feeling better. The dose given depends on the severity of the symptoms.

Mild illness
A mild illness would include a sore throat, bad cold or just feeling generally unwell and are not keen on eating. Your child should take their hydrocortisone tablet or melt three times a day until they feel better.

Plan: Hydrocortisone ___ mg three times a day. Stop when feeling better.

Moderate Illness
A moderate illness would include high fever (over 38.5 °C or very hot to touch), vomiting and/or severe diarrhoea. Your child should take their hydrocortisone tablet or melt three times a day until they feel better.

Plan: Hydrocortisone ___ mg three times a day. Stop when feeling better.

If your child is unable to take their hydrocortisone you must seek medical advice from your GP or attend A&E.

Severe illness
A severe illness would include a vomiting bug were your child is unable to tolerate any food or fluids or if your child is involved in a bad accident.
Your child will need an injection of hydrocortisone. As this would be a task which would be unfamiliar to you, especially in an emergency, it is safest to have this done in hospital. An alert has been placed on the Scottish Ambulance Service system and also on the hospital computer system which will alert staff that your child has adrenal insufficiency. Your child will be treated promptly when they arrive in A&E.
If you are going abroad or to a remote area in the UK please discuss this with the Asthma Nurse Specialists as they can discuss an appropriate plan should this arise whilst away from home.

Exceptions
If your child requires oral steroids for asthma symptoms they do not require any additional hydrocortisone at this time. The prednisolone must be reduced over 7-10 days and never given as a 3 day course.

Children often have bumps and grazes which occur during play. If your child appears to be well then they do not routinely need to have hydrocortisone for this type of minor injury. It is important to note however that giving hydrocortisone will never do your child any harm so if you think it is required then you should use it.

If you have any queries please do not hesitate to contact Ann McMurray or Julie Westwood, Asthma Nurse Specialists at RHSC on 0131 536 0773.
How to give an emergency injection of liquid Hydrocortisone

REMEMBER

If the injection is required then the child must go to hospital
IM Hydrocortisone
School

Adrenal Insufficiency
A Guide for School Nurses and Teachers

This leaflet has been created to give the school more information they may need about Adrenal Insufficiency in a child.

Should you have any queries then please discuss with the School Doctor or Nurse in the first instance.

For the purpose of this document a child will refer to a young person.
Action Flowchart for Adrenal Suppression

Name has adrenal insufficiency and is therefore cortisol deficient. Her body cannot cope well with illness or trauma.

Is Name illness or trauma mild, moderate or severe?

- **Mild Illness**
  - Bad cold
  - Sore throat
  - Generally feeling unwell
  - May well be planned in the morning as part of recovery from an illness
  - Name is to have 5mg of hydrocortisone (half tablet) at school if needed

- **Moderate Illness or trauma**
  - High fever (over 38.5°C)
  - Vomiting
  - Flu
  - Injury to limb
  - Knock to head
  - May well not be planned: probably sudden onset of an illness or following a moderate accident
  - Name is to have 10mg of hydrocortisone (1 tablet) as soon as possible
  - Contact parents
  - Name won’t necessarily need to go home following moderate trauma

- **Severe Illness or Trauma**
  - Persistent vomiting, unable to tolerate any fluids
  - Broken bone
  - Bad accident
  - Injury requiring medical attention
  - Dial 999 stating that NAME is adrenal insufficient and has symptoms/injuries that require him/her to have an injection of hydrocortisone
  - Follow instructions given by ambulance control staff
  - Stay with NAME
  - Contact parents
Points to consider

- Adherence
- Poor adherence
- Respiratory Team
- Endocrine Team
Impact of adherence

Strategies to screen for adrenal suppression in children with asthma should take account of compliance with inhaled corticosteroids.

Brodie M, McMurray A, Crofton PM, Bath L, Cunningham S.

European Journal of Pediatrics. 2007 May;166(5):493-4
Measured adherence with treatment via GP repeat prescribing and the dose taken was approximately half.
Listed on NHS Lothian risk register
Recognised as a risk in the British Guideline on the Management of Asthma.
Alerts on TRAK (hospital IT programme)
Scottish Ambulance Service (will not give IM hydrocortisone unless they have an individualised plan)
Healthcare plan for school
MHRA statement 2006

- High dose inhaled steroids: new advice on supply of steroid treatment cards
- Patients who require prolonged high dose inhaled steroids
- are at risk of systemic side effects and should be issued
- with a steroid treatment card
Practical tips

- Joint working approach with endocrine team
- Decide which patients need to be seen by endocrine and which patients you can manage within respiratory
- Ongoing monitoring
- If child is suppressed – regularly review plan and reiterate message about hydrocortisone replacement
Be aware of prescribing practice of other colleagues in primary and secondary care

Be aware of steroid burden and rationalise treatment to lowest possible doses to maintain control
Minimising the steroid load with inhaled corticosteroids

Optimising patient care with inhaled corticosteroids (ICS) requires symptom control with minimised side-effects and harm. This table shows how ‘standard’ beclometasone doses compare to the equivalent dose of most corticosteroid inhalers. Please note, these are not treatment recommendations.

<table>
<thead>
<tr>
<th>Standard beclometasone dose (micrograms)</th>
<th>Approved name</th>
<th>Brand name</th>
<th>Combination brand</th>
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<tbody>
<tr>
<td>Regular Standard Dose - BTS Steps 2 and 3 - when combined with Long Acting Beta Agonist (LABA)</td>
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<td>‘100 bd’</td>
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<tr>
<td>beclometasone 100 bd</td>
<td>Clniff® 100 bd</td>
<td>Qvar® 50 bd</td>
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<tr>
<td>budesonide 100 bd</td>
<td>Pulmicort® 100 bd</td>
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<tr>
<td>fluticasone 50 bd</td>
<td>Fludicort® 50 bd</td>
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<tr>
<td>‘200 bd’</td>
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<td>beclometasone 200 bd</td>
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<td>Qvar® 100 bd</td>
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<tr>
<td>budesonide 200 bd</td>
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<td>fluticasone 100 bd</td>
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<td>ADULT Regular High Dose - BTS Step 4 - STEROID CARD REQUIRED</td>
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<tr>
<td>Symbicort® 200/6 X3 bd</td>
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Thanks to Louise Bath and the Endocrine Team at RHSC

Julie Westwood, Asthma Nurse RHSC