PK/PD considerations for corticosteroids

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National Veterinary School, Toulouse, France
Wuhan October 2015
Anti-inflammatory drugs

- Corticosteroids
- NSAIDs
Glucocorticoids: main properties

• Glucocorticosteroids (GCS) are broad and potent anti-inflammatory drugs.
• They are extensively used to mitigate or suppress inflammation associated with a variety of conditions especially joint and respiratory system inflammation.
• GCs are not curative:
  • GCs are only palliative symptomatic treatments and chronic use of GCs can be, in fine, detrimental
• GCs possess many other pharmacological properties (not reviewed in this presentation)
The cortisol or hydrocortisone
Cortisol:
An endogenous hormone and a surrogate endpoint of the duration of the GCS effects; it physiology should be understood to use properly GCS
Cortisol synthesis

- All GCs used in therapeutics are synthetic derivatives of cortisol.
- Cortisol (hydrocortisone) is synthesized in the adrenal cortex and it is the main corticosteroid hormone in most species.
Steroids synthesis by the adrenal gland

- **Aldosterone**
- **Cortisol**
- **Androgens**
- **Epinephrine (adrenalin)**
Cortisol ou Hydrocortisone structure – activity relationship

Three structural properties are required for a GC activity (i.e. for cortisol to bind to GC receptor)
Cortisol (hydrocortisone)

- Minimal information on cortisol physiology (secretion, distribution & elimination) needs to be known to understand the clinical pharmacology of GCS
Plasma cortisol

• Cortisol levels are very different in domestic species
• Pattern of secretion
  – Circadian rhythm (h)
  – Pulsatility (minute)
Plasma cortisol level

Plasma concentration (ng/mL)

- Series 1

[Bar chart showing plasma cortisol levels for different species, with the x-axis labeled from 1 to 5 and the y-axis labeled from 0 to 600.]
Plasma cortisol levels: circadian rhythm & pulsatility

Circadian Rhythm of Cortisol Secretion in Dogs of Different Daily Activities

J. KOLEVSKÁ, V. BRUNCLÍK, M. SVOBODA

**All dogs**

**Rest dogs**
Plasma cortisol levels: circadian rhythm & pulsatility

• The cortisol secretion is pulsatile with minute-to-minute variations in the plasma cortisol concentrations making the interpretation of snapshot plasma samples difficult.
Modeling of circadian cortisol

Mathematical Modeling of Circadian Cortisol Concentrations Using Indirect Response Models: Comparison of Several Methods

Abhijit Chakraborty,¹ Wojciech Krzyzanski,¹ and William J. Jusko¹,²

Received December 14, 1998—Final March 29, 1999
In mammalian plasma, cortisol binds to a specific alpha-glycoprotein: corticosteroid-binding globulin (CBG).

Binding to CBG is saturable (Bmax)

\[
Total = Free + \frac{B_{\text{max}} \times Free}{K_d + Free} + NS \times Free
\]
Binding of synthetic GCS to plasma protein

• Prednisolone also binds to transcortin
• Other synthetic GS only bind to albumin

WARNING!

Prednisolone cannot be used for an adrenal suppression test
**Adrenal suppression test**

**Prednisolone vs. Dexamethasone (IV)**

**Prednisolone**

(600µg/kg)

Immediate decrease of cortisol due to the displacement of cortisol from the CBG by prednisolone

**Dexamethasone**

(50µg/kg)

Delayed decrease due to the suppression of ACTH secretion

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*Cortisol concentration (ng/ml)*

- **Prednisolone**
  - 0 hours: 60 ng/ml
  - 1 hour: 40 ng/ml
  - 2 hours: 30 ng/ml
  - 4 hours: 20 ng/ml
  - 8 hours: 10 ng/ml
  - 12 hours: 5 ng/ml
  - 24 hours: 2 ng/ml
  - 48 hours: 1 ng/ml

- **Dexamethasone**
  - 0 hours: 80 ng/ml
  - 0.16 hours: 75 ng/ml
  - 0.5 hours: 70 ng/ml
  - 1 hour: 65 ng/ml
  - 2 hours: 60 ng/ml
  - 3 hours: 55 ng/ml
  - 4 hours: 50 ng/ml
  - 6 hours: 45 ng/ml
  - 24 hours: 40 ng/ml
  - 48 hours: 35 ng/ml
  - 72 hours: 30 ng/ml
  - 96 hours: 25 ng/ml

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Urine cortisol

• The advantage of urine cortisol is due to the fact, that unlike plasma sample, a snapshot urine sample is representative of the total cortisol secretion over the entire preceding period of time separating two micturitions, i.e. it is not subjected to time-to-time variation like plasma cortisol.
Urine cortisol

• Diagnostic of Cushing syndrom

**Urine Cortisol**: cushing: 118 ± 15 ng/mL; Sensitivity of the test 100%. Spécificity= 22% (confusion with dogs having a poluuuric/polydipsic syndrom)

Feldman, JAVMA 1992, 200 : 1637
Urine cortisol
(doping control)

• International threshold: 1µg/ml or 1000ng/mL
Urine cortisol
Population investigations (n=254)

Log Transformation

<table>
<thead>
<tr>
<th>Probability exceeding</th>
<th>Urine concentration ng/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>$10^{-3}$</td>
<td>611</td>
</tr>
<tr>
<td>$10^{-4}$</td>
<td>1025</td>
</tr>
<tr>
<td>$10^{-5}$</td>
<td>1606</td>
</tr>
</tbody>
</table>

Average (geometric) 48ng/mL
maximum 388

Popot & al EVJ 1997 29 220-229
Regulation of cortisol secretion to be understood to predict the suppressive effect of GCS
Suppressive effect of corticosteroids on the hypothalamic pituitary adrenal axis (HPA)

ACTH

- Stimulation of cortisol synthesis (no storage)
- Trophic action on the zona fasciculata and reticularis
Suppressive effect of synthetic GC

Control

Short term

Long term

SNC → CRF → ACTH

ACTH → COR

SNC → CRF → ACTH

ACTH

CS

SNC → CRF → ACTH

ACTH

COR

COR

Cortic 00A.27
Inactive glucocorticoid receptors (GR) are located in the cytoplasm; after binding to cortisol, the GR is activated and translocated into nucleus; then, GR bind the glucocorticoid response element (GRE) in the DNA and regulate the responsive gene (activation). The GR can also inhibit transcription by a direct protein/protein interaction.
Corticosteroid Mechanism of action

Lipocortin

Corticoids

NSAIDs

PLA₂

Inhibition of phospholipase A₂ (PLA₂)

Plasma membrane

Arachidonic acid

cyclooxygenases

PG, TXA₂

lipoxygenase

Leucotrienes

Ferguson In: Adams, 1995
Métabolisme du cortisol

20α et 20β dihydrocortisone

Cortisone

11-Ketoetiocholanolone

11β - hydroxy etiocholanolone

11 ß - déshydrogénase

CORTISOL

20β dihydrocortisol

6β hydroxy cortisol

20β dihydrocortisol
Cortisol metabolism is used as a biomarker of drug metabolism (polymorphism associated to CYP3A)

RESEARCH ARTICLE – Pharmacokinetics, Pharmacodynamics and Drug Transport and Metabolism

Evaluation of 6β-Hydroxycortisol and 6β-Hydroxy cortisolone as Biomarkers for Cytochrome P450 3A Activity: Insight into Their Predictive Value for Estimating Oral Immunosuppressant Metabolism

XI LUO,1,2,3 LIYUN ZHENG,2 NINGFANG CAI,4 QING LIU,2 SHUANG YANG,5 XIAOAI HE,6 ZENENG CHENG2

1School of Life Sciences, Central South University, Changsha, Hunan, China
2School of Pharmaceutical Sciences, Central South University, Changsha, Hunan, China
3The State Key Laboratory of Medical Genetics, Central South University, Changsha, Hunan, China
4Department of Pharmacy, Zhangzhou Municipal Hospital of Fujian Province, Zhangzhou, Fujian, China
5The Third Xiangya Hospital, Central South University, Changsha, Hunan, China
6Haikou People’s Hospital and Affiliated Haikou Hospital of Xiangya Medical School, Central South University, Haikou, Hainan, China
Corticosteroids - Filiation -
Synthetic glucocorticosteroids (GCs)

- Chemical modification of cortisol have generated derivatives with:
  - Greater separation of glucocorticoid and mineralocorticoid activity (selectivity)
  - Higher potency
  - Longer duration of action

- Chemical modification of cortisol do not have generated derivatives with:
  - Separation of AI effect from effect on carbohydrates, lipids and proteins metabolism or without adrenal suppression
The main CS used in veterinary medicine for systemic administration

- Prednisolone
- Méthylprednisolone
- Dexaméthasone
- Triamcinolone acétonide
- Fluméthasone
- Isoflupredone
The main CS used for systemic inhalation

**Fluticasone** propionate

**Beclométhasone** 17 monopropinate

**Budesonide**
The two main group of CS

Cortisol

Non halogenated - derivatives

Prednisolone
Methylprednisolone
budesonide

Halogenated-derivatives

With mineralocorticoid activity
Isoflupredone

No mineralocorticoid activity
Dexamethasone,
betamethasone
triamcinolone acetonide
betamethasone
Synthetic derivatives of cortisol

• All therapeutic GCs have a 21-carbon cortisol skeleton

• A variety of GCs have been developed to increase the potency of the anti-inflammatory effect and to decrease or even suppress the mineralocorticoid effects of cortisol
Cortisone $\rightarrow$ Prednisone

Cortisol $\rightarrow$ Prednisolone

Methylprednisolone

Fluoroprednisolone (Predef 2X)

Cortisol $\rightarrow$ Prednisolone

GC filiation

Triamcinolone acetonide

OH - TRIAMCINOLONE

CH3 - Dexamethasone

CH3 - Betamethasone

CH3 - Flumethasone

PROPERTY

ANTI-INFLAMMATORY - GLUCOCORTICOID

MINERALOCORTICOID
The 2 main PD parameters:

- **Efficacy**
  - Emax 1
  - Emax 2

- **Potency**
  - ED\(_{50}/EC\(_{50}\) 1
  - ED\(_{50}/EC\(_{50}\) 2

**Issue for vets**

**Potent drug=low LOQ**
Relative potency of corticosteroids

<table>
<thead>
<tr>
<th>Substances</th>
<th>glucocorticoid action</th>
<th>Minéralocorticoid action</th>
<th>Duration action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortisol</td>
<td>1</td>
<td>1</td>
<td>12h</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>5</td>
<td>0.8</td>
<td>24h</td>
</tr>
<tr>
<td>Méthylprednisolone</td>
<td>5</td>
<td>0.8</td>
<td>24h</td>
</tr>
<tr>
<td>Isoflupredone</td>
<td>25</td>
<td>25</td>
<td>48-72h</td>
</tr>
<tr>
<td>Triamcinolone</td>
<td>5</td>
<td>0</td>
<td>24h</td>
</tr>
<tr>
<td>Triamcinolone acétonide</td>
<td>30</td>
<td>0</td>
<td>48-72h</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>25</td>
<td>0</td>
<td>48-72h</td>
</tr>
<tr>
<td>betamethasone</td>
<td>25</td>
<td>0</td>
<td>48-72h</td>
</tr>
<tr>
<td>Flumethasone</td>
<td>120</td>
<td>0</td>
<td>48-72h</td>
</tr>
</tbody>
</table>

Order of potency of the different corticoids is now internationally accepted and cannot be reconsidered even if there are some discrepancies in the literature.
Relative anti-inflammatory (AI) potency of topical GC used for inhalation (1=dexamethasone)

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<th>Substances</th>
<th>AI Potency (1=dexamethasone)</th>
<th>Comments</th>
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<td>Beclomethasone dipropionate</td>
<td>0.5</td>
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</tr>
<tr>
<td>Beclomethasone 17-monopropionate</td>
<td>13</td>
<td>Active moiety of beclomethasone dipropionate</td>
</tr>
<tr>
<td>Beclomethasone</td>
<td>0.5</td>
<td>Metabolite of beclomethasone monopropionate</td>
</tr>
<tr>
<td>Fluticasone propionate</td>
<td>18</td>
<td>Active substance</td>
</tr>
<tr>
<td>Budesonide</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Triamcinolone acetonide</td>
<td>50</td>
<td></td>
</tr>
</tbody>
</table>
Corticoïds :
esters & Formulations
Corticoïdes :

Substance active vs. esters

Substances

(principes actifs)

alcohol

Hydrosolubles

Esters

(prodrogues)

Non hydrosolubles
Most GCs are administered as esters
Most GCs are administered as esters

• Most GC are administered as esters,
• Esterification considerably alters the disposition and duration of the GC action.
  – Esterification with a monoacid (like acetic acid) at C-21 gives non-hydrosoluble drugs that can be used as long-acting formulations when administered by the intramuscular, subcutaneous or IA routes.
  – Esterification of the same parental drug by a diacid (such as succinic acid) can give a hydrosoluble ester enabling a salt to be formed (e.g. a sodium succinate). Phosphate esters are also hydrosoluble.
Formulations of corticoïds

Méthylprednisolone (medrol)

Methylprednisolone sodium succinate (Solumedrol®)

Methylprednisolone acetate (Dépomedrol®)

Méthylprednisolone sodium succinate (Solumedrol®)

Methylprednisolone acetate (Dépomedrol®)

\[ C_{22}H_{30}O_5 = 374.5 \]

\[ C_{26}H_{33}O_8Na = 396.5 \]

\[ C_{23}H_{30}O_6 = 402.5 \]
Corticoids

Esters

Esterification en $\text{C}_{21}$ et/ou $\text{C}_{17}$ des OH
Par des monoacides : formes insolubles

- acetate (21-acétate)
- dimethylbutyrate (21)
- phenylpropionate
- dipropionate ($\text{C}_{17}, \text{C}_{21}$)
- valerate, pyvalate
- benzoate ($\text{C}_{17}$)
Esters are prodrugs

• Practically all esters except beclomethasone 17-monoprpionate and fluticasone propionate are inactive prodrugs and have to be hydrolyzed to release their active moiety because an OH radical at C-21 is necessary for the binding of corticoids to their cellular receptors.
Near all ester are prodrugs
Prednisolone & prednisolone acetate

Prednisolone

Prednisolone acetate
A prodrug
Hydrolysis by esterases

- Hydrolysis by esterases may occur either in different body fluids such as blood or synovial fluid (as for methylprednisolone acetate for which the half-life is about 1h in synovial fluid) or mainly in liver (as for succinate), meaning that for a local administration, the judicious selection of an appropriate ester is in order.
Fluticasone propionate & beclomethasone monopropionate are not prodrugs

- Fluticasone propionate
  - Active drug

- Beclomethasone 17,21 dipropionate
  - A prodrug

- Beclomethasone 17-monopropionate
  - Active drug
Corticoïds : Route of administration
Route of administration

systemic
- IV, PO, IM.....

Local
- GCS also use for systemic administration
- GC specifically developed for local administration
  - Intra-articular
  - Intramammary
  - Percutaneous
  - inhalation
PK of corticoids
Disposition of méthylprednisolone

- Méthylprednisolone succinate (MPS) vs. méthylprednisolone acetate (MPA)

Plasma Concentration (ng / ml)

Prednisolone succinate vs. prednisolone acetate

• illustrates the differences between the disposition of prednisolone after administration of prednisolone succinate by the IV and IM routes and after prednisolone acetate administration by the IM route.
Disposition of prednisolone: hydrosoluble vs. Unsoluble formulation (0.6 mg/kg)

Pharmacokinetic parameters of GCs

<table>
<thead>
<tr>
<th>Substances</th>
<th>CL (mL/kg/min)</th>
<th>Vd (mL/Kg)</th>
<th>HL (h)</th>
<th>F%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocortisone (tritiated cortisol)</td>
<td>2.28</td>
<td>229</td>
<td>1.55</td>
<td></td>
</tr>
<tr>
<td>Hydrocortisone (after HC succinate, 1g)</td>
<td>2.56</td>
<td>600</td>
<td>10.1</td>
<td></td>
</tr>
<tr>
<td>Prednisolone</td>
<td>3.91</td>
<td>561</td>
<td>1.65</td>
<td>IM:92</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>15</td>
<td>3600</td>
<td>2.85</td>
<td></td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>7.33</td>
<td>2060</td>
<td>10.7</td>
<td></td>
</tr>
<tr>
<td>Triamcinolone acetonide</td>
<td>8.1</td>
<td>5300</td>
<td>12</td>
<td></td>
</tr>
</tbody>
</table>
DXM disposition: rest vs. exercise

Clearance: -25%
VSS: -17%
Half-life: no change
Adrenal suppression:
Plasma cortisol levels and synthetic corticoid treatment
Adrenal suppression of cortisol secretion by synthetic GCs

• Synthetic GCs are able to inhibit the production of cortisol
  – negative feedback on ACTH secretion.
• The duration of the AI effect of a synthetic GC for a systemic administration is generally similar to the duration of suppression of endogenous cortisol
Adrenal suppression of cortisol secretion by synthetic GCs

• It should be stressed that adrenal suppression is not only associated with a given substance but also with a particular ester of that substance and for a particular ester, the route of administration and the administered dose.
Adrenal suppression
Prednisolone vs. Dexamethasone (IV)

Prednisolone (600µg/kg)
Short action

Dexamethasone (50µg/kg)
Longer duration of action

Cortisol concentration (ng / ml)

Adrenal suppression of prednisolone (600µg/kg) succinate vs. Acetate (IM)

Succinate (IM)  
Short action

Acetate (IM)  
long action

Cortisol concentration (ng / ml)

# Duration of adrenal suppression (IV route)

<table>
<thead>
<tr>
<th>Substances</th>
<th>Anti-inflammatory potency</th>
<th>Mineralocorticoid potency</th>
<th>Adrenal suppression (h, days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>hydrocortisone</td>
<td>1</td>
<td>1</td>
<td>About 24h</td>
</tr>
<tr>
<td>Hydrocortisone hemisuccinate</td>
<td>0</td>
<td>0</td>
<td>A prodrug of cortisol</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>5</td>
<td>1</td>
<td>About 24h</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>5</td>
<td>1</td>
<td>About 24h</td>
</tr>
<tr>
<td>isoflupredone</td>
<td>25</td>
<td>25</td>
<td>No data</td>
</tr>
<tr>
<td>Triamcinolone</td>
<td>5</td>
<td>0</td>
<td>No data</td>
</tr>
<tr>
<td>Triamcinolone acetonide</td>
<td>30-50</td>
<td>0</td>
<td>24h</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>25</td>
<td>0</td>
<td>72-96h</td>
</tr>
<tr>
<td>Betamethasone</td>
<td>25</td>
<td>0</td>
<td>Likely similar to DXM</td>
</tr>
<tr>
<td>Flumethasone</td>
<td>120</td>
<td>0</td>
<td>Likely longer than for DXM</td>
</tr>
</tbody>
</table>
Adrenal suppression of cortisol secretion by synthetic GCs

- For local administrations, the fraction that gains access to the blood can be too low to impact on the adrenal gland function.
Adrenal suppression for an intra-articular methylprednisolone acetate administration

Autefage et al., Equine Vet J 1986
IC\textsubscript{50} for cortisol suppression

<table>
<thead>
<tr>
<th>Substances</th>
<th>IC50 (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortisol</td>
<td>8</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>1.2</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>0.52</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>0.17</td>
</tr>
</tbody>
</table>

• (Mager et al., 2003)
Corticosteroid esters and local routes of administration
Intra-articular administration
Intra-articular administration

• Two technical issues:
  – Selection of a joint;
  – Technic of administration:
    • Blind or not?
Pro:
mostly of non scientific nature

- To help the horses perform the job they were bred for and to prolong their careers and lives
- Postoperative administration may be beneficial in protecting the cartilage and improving the cosmetic appearance of the joint
CONS:
mostly of scientific nature and rather well documented

– Lack of curative effect
– joint flare
– Risk for further injury
– Articular cartilage degenerative/steroid chondropathy
Musculoskeletal injury following local corticosteroid injection in Thoroughbred racehorses

- Veterinary records for 1911 thoroughbred
- Thoroughbred racehorses receiving local corticosteroid injection (LCI) suffer musculoskeletal injury MSIs at approximately 4.5 times the rate of horses not receiving treatment, and for horses receiving multiple LCI the rate is approximately twice that of horses receiving single LCIs.

*Whitton, C., et al 2012*Faculty of Veterinary Science, University of Melbourne, Victoria, 3030, Australia.
Accuracy of IA administration: blind vs. ultrasound-guided injection

**TABLE 1: Ultrasound-guided (UG) vs. ‘blind’ injection of the infraspinatus bursa, bicipital bursa and scapulohumeral joint**

<table>
<thead>
<tr>
<th></th>
<th>Infraspinatus bursa</th>
<th>Bicipital bursa</th>
<th>Scapulohumeral joint</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>UG</td>
<td>‘Blind’</td>
<td>UG</td>
</tr>
<tr>
<td>No. injections performed</td>
<td>8 (100)</td>
<td>8 (62)</td>
<td>8 (100)</td>
</tr>
<tr>
<td>No. valid injections (%)</td>
<td>8 (100)</td>
<td>5 (62)</td>
<td>8 (100)</td>
</tr>
<tr>
<td>Median time for injections (range)</td>
<td>62 s (32–190)</td>
<td>44.5 s (11–78)</td>
<td>77.5 s (37–210)</td>
</tr>
<tr>
<td>Median number of redirections per injection (range)</td>
<td>1 (1–2)</td>
<td>2 (1–2)</td>
<td>1.5 (1–3)</td>
</tr>
</tbody>
</table>
Disposition of methylprednisolone in the synovial fluid

- Disappearance of MPA within 6 days but a persistence of its active moiety for 5 to 39 days depending on the horse. The terminal half-life of MP was between 81 and 261h:
Origin of the sustained release of MP after a MPA administration

• the reason for the persistence of MP was most likely due to a precipitation of MPA that adheres to the synovial membrane and most likely acts as a foreign body.

• This likely explains why MPA is not well tolerated in horses (McIlwraith, 2010) and that other GC are now preferred for IA administration, namely betamethasone esters and triamcinolone acetonide
IA disposition of methylprednisolone (MP) in synovial fluid after an methylprednisolone actate administration (MPA, Dépomédrol®) (200 mg in toto)
Adrenal suppression following a methylprednisolone acetate (200mg in toto) IA administration in cattle assessed by a series of ACTH tests

Return to control value needs 3 months

HYDROCORTISONE plasmatique (ng / ml)
Triamcinolone acetonide

Mean synovial Triamcinolone acetonide (TA) concentration (ng/mL) vs. time (h) in the metacarpophalangeal joint after an administration of TA at a dose of 9mg in toto (16µg/kg)

Data were fitted with a biexponential equation to give the terminal half-life of TA in synovial fluid as 20.2h with an overall mean residence time of 13.8h.

(redrawn from raw data of Kay et al. (Kay et al., 2008))
Inhalation
Inhaled Corticosteroids: indications

1. Airways inflammation
2. Recurrent airways obstruction ou RAO or heaves
   • (formally named COPD)
Why inhalation?

• To ensure selectivity (no other effect)
  – Long-lasting treatments

• Specific GCS were developed for this application
  – Highly potent (small volume)
  – Slow eliminated from the airways
  – High systemic clearance for the absorbed fraction
Inhaled Corticosteroids (ICS)

- Inhaled corticosteroids (ICS) are now considered the first-line therapy in treating asthma and are approved for chronic use in children as young as 12 months of age.
Many devices: are they equivalent?
Relative anti-inflammatory (AI) potency of topical GC used for inhalation (1=dexamethasone)

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<td>Beclomethasone 17-monopropionate</td>
<td>13</td>
<td>Active moiety of beclomethasone dipropionate</td>
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<td>Beclomethasone</td>
<td>0.5</td>
<td>Metabolite of beclomethasone monopropionate</td>
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<td>Fluticasone propionate</td>
<td>18</td>
<td>Active substance</td>
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<tr>
<td>Budesonide</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Triamcinolone acetonide</td>
<td>50</td>
<td></td>
</tr>
</tbody>
</table>
Disposition of GG after inhalation

- **Inhalation**
  - **Atmosphere**
  - **User safety**
  - **Swallowing Digestive tract**
    - Possible Adrenal suppression
    - Yes for beclomethasone
    - No for fluticasone
  - **Lung disposition**
    - Possible Adrenal suppression
Inhalation treatment: an user safety issue?

• During exhalation, some degree of air pollution of the drug was evident and user safety was accounted for by ventilating the room sufficiently during administration.

• Q: Do we have a part of liability if releasing DT for inhalation while no marketing authorization exist in case of difficulties for staff who are at high risk of adverse effects from exposure (e.g., pregnant women or those with demonstrated sensitivity to the specific agent).
Systemic disposition of inhaled GS

• Drug deposited in the oropharynx, in up to 80% of horses and does not contribute to the therapeutic effect but is swallowed and contributes to the systemic exposure with possible systemic side effects.

• Inhaled GC are well absorbed by the lung parenchyma but have a rather low or very low bioavailability when ingested.
Pharmacodynamic of inhaled GS

- Such a progressive establishment of clinical effects and return to pretreatment status makes it difficult or even impossible to establish any PK/PD relationship useful for drug monitoring.
- In addition, the dose-effect relationship is flat and difficult to establish.