Dental management of patients on steroids and other immunosuppressive therapies

Joel J. Napeñas DDS FDSRCS(Ed)
Associate Professor of Oral Medicine
Director, Oral Medicine Residency Program
Carolinas HealthCare System
Statement of Disclosure

I have no actual or potential conflict of interest in relation to this presentation
Outline

• Systemic Steroid Therapy
• Biological Agents
Systemic Steroid Therapy
Adrenal Glands and Stress Response

Stress Response: Short Term
- Heartbeat and blood pressure increase.
- Blood glucose level rises.
- Muscles become energized.

Stress Response: Long Term

<table>
<thead>
<tr>
<th>Glucocorticoids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein and fat metabolism occur instead of glucose breakdown.</td>
</tr>
<tr>
<td>Inflammation is reduced; immune cells are suppressed.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mineralocorticoids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium ions and water are reabsorbed by kidney.</td>
</tr>
<tr>
<td>Blood volume and pressure increase.</td>
</tr>
</tbody>
</table>

http://ascharlihara.blogspot.com/
Secretion and regulation

- **Glucocorticoids - Cortisol**
  - Daily Secretion: 15~30 mg/day
  - May be up to 200 mg under stress
  - Regulated by ACTH (HPA axis)
  - F=M

- **Mineralcorticoïds - Aldosterone**
  - Daily Secretion: 50~250 µg/day
  - Secretion regulated by renin-angiotensin system (AT II)
  - Net effect: Na reabsorption (Na/K pump) at distal tubules of kidney
  - Minor influence of ACTH
  - M>F

- **Androgen**
  - Regulated by ACTH
Cortisol and ACTH - Circadian Rhythm
Physiology of Glucocorticoids

- Immunologic
- Anti-inflammatory
- Metabolic
- Connective tissue
- Calcium and bone
- Circulatory
- Renal
- CNS
- Eye
- Growth and developmental
Glucocorticoids - Anti-inflammatory activity

Hench (1949) – high dose cortisol in Cushingoid patients ameliorated RA symptoms

- Only in supraphysiological doses
- Inhibit phospholipase → dec. PG (bradykinins) and LT → dec. leukocyte migration
- Synthesize ACE, which degrades bradykinin
- Block histamine, interleukin-1 and 2, plasminogen activating factor (PAF)
- Decrease vascular permeability
- Increase WBC (ANC), platelet, WBC and RBC (dec. erythrophagocytosis)
- Decrease circulating eosinophil, basophil, and lymphocyte counts
Glucocorticoids - Immunologic activity

- Impairs cell-mediated immunity (T-lymphocyte dependent)
- Lymphotoxic
- Little effect on humoral immunity
  - no decrease in existing Ab levels
  - B-cell response to antigen not inhibited
### Systemic Corticosteroid Use

**Conditions with evidence-based benefits include:**

<table>
<thead>
<tr>
<th>Asthma</th>
<th>Eczema</th>
</tr>
</thead>
<tbody>
<tr>
<td>Croup</td>
<td>Otitis externa</td>
</tr>
<tr>
<td>Crohn's disease</td>
<td>Pemphigus</td>
</tr>
<tr>
<td>Ulcerative colitis</td>
<td>Dermatomyositis</td>
</tr>
<tr>
<td>Giant cell arteritis (temporal arteritis)</td>
<td>Minimal change glomerulonephritis</td>
</tr>
<tr>
<td>Polymyalgia rheumatica</td>
<td>Acute leukemia</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>Acquired hemolytic anemia</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>Idiopathic thrombocytopenic purpura</td>
</tr>
<tr>
<td>Polyarteritis nodosa</td>
<td>Cerebral edema</td>
</tr>
<tr>
<td>Wegener's granulomatosis</td>
<td>Cluster headache</td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td>Congenital adrenal hyperplasia</td>
</tr>
<tr>
<td></td>
<td>Anaphylaxis and allergic reactions</td>
</tr>
<tr>
<td>Name</td>
<td>Glucocorticoid potency</td>
</tr>
<tr>
<td>-------------------------------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>Hydrocortisone (cortisol)</td>
<td>1</td>
</tr>
<tr>
<td>Cortisone acetate</td>
<td>0.8</td>
</tr>
<tr>
<td>Prednisone</td>
<td>3.5-5</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>4</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>5-7.5</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>25-80</td>
</tr>
<tr>
<td>Betamethasone</td>
<td>25-30</td>
</tr>
<tr>
<td>Triamcinolone</td>
<td>5</td>
</tr>
<tr>
<td>Beclometasone</td>
<td>8 puffs 4 times a day = 14 mg oral prednisone once a day</td>
</tr>
<tr>
<td>Fludrocortisone acetate</td>
<td>15</td>
</tr>
<tr>
<td>Deoxycorticosterone acetate (DOCA)</td>
<td>0</td>
</tr>
<tr>
<td>Aldosterone</td>
<td>0.3</td>
</tr>
</tbody>
</table>
Adrenal Insufficiency

Primary
- Pituitary necrosis
- Bilateral adrenalectomy
- Removal of a functioning adrenal tumor that had suppressed the other adrenal
- Injury to both adrenals (trauma, hemorrhage, infection, anticoagulant, thrombosis or metastatic carcinoma)
- Thyroid hormone replacement is given to a patient with adrenal insufficiency

Secondary
- Administration of exogenous steroids
Adrenal Insufficiency

- **Chronic adrenal insufficiency (Addison’s disease)**
  - Primary - adrenal function↓, ACTH↑, MSH
  - Secondary - ACTH↓
    - glucocorticoid deficiency, mineralcorticoids relatively maintained
    - 2-3X more common than primary

- **Acute adrenal insufficiency**
  - Adrenal crisis (Addisonian crisis)
Adrenal Crisis - Causes

May occur in the course of treatment of chronic insufficiency or as its presenting manifestation

Primary adrenal insufficiency >> secondary

Stressors:
- Infection
- Surgery
- Trauma
- Prolonged fasting
ADRENAL INSUFFICIENCY

ADRENAL CRISIS - PATHWAY OF EVENTS

Life Sustaining Cortisol replacement therapy needed with either:- Hydrocortisone, Prednisolone or Dexamethasone

ADRENAL GLANDS
Defective production of

GLUCOCORTICOIDs

CORTISOL IMPAIRED OR NO PRODUCTION

LIVER
Function decreases

Hypoglycaemia
Low blood glucose

Seizures, convulsions
Loss of consciousness

Shock

BRAIN COMA
ORGAN FAILURE

DEATH

MINERALCORTICOIDs

ALDOSTERONE IMPAIRED OR NO PRODUCTION

KIDNEY
Water and Sodium loss

Hyponatremia
Low sodium level

Hyperkalaemia
Increase in potassium

Heart
Irregular output

CARDIAC ARREST

Vital Aldosterone replacement therapy with Fludrocortisone is needed to maintain a proper balance of body salts and fluid i.e. electrolytes and blood volume

http://www.cahisus.co.uk/pdf/Adrenal%20Crisis%20Pathway%20Professor%20Peter%20Hindmarsh.pdf
Scenario

• 65 y/o female
• PMH:
  – Rheumatoid arthritis
  – Hypertension
• Medications:
  – Prednisone 10 mg daily (5 years)
  – HCTZ
  – Captopril
  – Meloxicam
1. Perio – S/RP
2. Extract non restorable teeth
3. Implants vs. removable or fixed prosthodontic therapy
Dentistry and Steroid Supplementation
Areas of confusion

Do we cover or not cover?

If we decide to cover, then:

Which appointments do we cover?
How do we cover? (when, how much, how long?)
Rule of Twos

Adrenal suppression may occur if:
• patient is taking 20 mg of cortisone or its equivalent daily
• for 2 weeks
• within 2 years of dental treatment

Steroid cover regimen:
**Doubling** the dose of current regimen on the day of surgery
Case reports (N=6)
• ‘suggestive’ of adrenal crisis – 4
• ‘consistent’ with adrenal crisis – 2
• prophylactic steroid supplementation - 4
• First 3 cases between 1964-1973
  – All ‘suggestive’
  – All involved general anesthesia
  – All involved prophylactic steroid supplementation
• No fatalities
Case reports (N=6)

- secondary AI – 3
  - ‘suggestive’ of adrenal crisis – 3
  - pre and perioperative steroid supplementation – 3
  - type of secondary AI:
    - irradiated pituitary gland w/ steroid therapy (13 y) - 1
    - steroid therapy (4-5 y) - 2
      - general anesthesia - 2
Conclusions:

- Adrenal crisis in dental patients a rarely reported event (6 in 66 years)
- Very rare when attributed to secondary steroid supplementation
- Uncertainty regarding efficacy of prophylactic steroid supplementation
Surgery and Steroid Supplementation

Bromberg et al (1991, 1995)\textsuperscript{1,2}
- 5 to 10 mg prednisolone daily > than 3 months
- Renal transplant recipients undergoing surgery
- Moderate surgery
- Usual daily dosage with no additional adjustments
- No evidence of adrenal suppression
- Comparative cortisol levels between treatment and controls in response to stress
- No signs of adrenal crisis

Current Recommendations

Cochrane Review (2012) –
• 2 RCTs with N=37 - (High risk of bias)
• Unable to support or refute use of supplemental corticosteroids
• No adverse events from treatment and control groups
• Short courses (< 48 hours) of increased glucocorticoid therapy rarely cause significant problems
• Consider coverage for:
  • glucocorticoid therapy patients suspected of having iatrogenic adrenal insufficiency (AI)
  • patients who have received glucocorticoid therapy for more than 3 weeks by any route.

Risk Assessment

Health Status
- Disease Control
- Infection
- Pain

Stress
- Patient anxiety
- Invasiveness
- Pain
- Drugs that affect cortisol

Steroid regimen
- How much?
- How long?
- Last taken?
Risk Assessment – Health Status

Specific risk factors increase the risk of an adverse event in patients with AI

- presence of oral infection
- hypovolemia
- inadequate circulating cortisol due to adrenal insufficiency
- fasting state
Surgical stress

- **Minor surgical stress:**
  - surgical extractions, multiple extractions

- **Moderate surgery procedures:**
  - mandible, zygoma

- **Major oral surgery procedures:**
  - multiple extractions, quadrant periodontal surgery, extraction of bony impactions, osseous surgery, osteotomy, bone resections, cancer surgery, surgical procedures involving GA, procedures lasting > 1 hour, procedures assoc with significant blood loss
  - orthognathic surgery, severe facial trauma, head and neck, orthognathic surgery

Cortisol equivalents – Salem (1994)

Review of multiple studies

75-150mg/24hr cortisol secretion after major surgery

cortisol level rarely exceed 200mg/24hr

(50mg prednisone)
Perioperative Steroid Supplementation Guidelines

• No need for mineralocorticoid supplementation\(^1\)
• Insufficient evidence to support or refute the use of supplemental perioperative steroids in patients with adrenal insufficiency\(^2\)
• Administration of the patient’s daily maintenance dose may be sufficient\(^2\)
• Supplemental doses may not be required\(^2\)

Perioperative Steroid Supplementation Guidelines

General Dental Procedures

Does not warrant supplementation with additional glucocorticoids¹

Minor surgery under LA

Patients are at very low risk, if any, for developing adrenal crisis¹
Supplementation is unnecessary¹
Maintain their usual dose of glucocorticoids¹

Surgery under GA

No evidence that supplementation is beneficial¹
Should be determined by the severity of the surgery and the preexisting glucocorticoid dose¹

Major oral surgery under LA?

Treat like surgery under GA
Recommended cortisol equivalent doses
Salem (1994) –

Daily physiologic – 10-20 mg

Minor stress – 25 mg on day of procedure (5 mg prednisone)
Moderate stress – 50-75 mg for 1-2 days (10-15 mg prednisone)
Major stress – 100-150 mg daily for 2-3 days (20-30 mg prednisone)
Conclusions

• Adrenal crisis from dental treatment of patients on supplemental steroids is rare
• Adverse events from short term courses of steroids is rare however a concern
• Steroid supplementation rarely indicated for routine dental treatment
• Consideration based on individual risk assessment of patient (medical, surgical stress, steroid regimen)
• Control of pain and stress peri and post operatively
• Monitoring post operatively for high risk patients (BP)
Biological Agents (BA)

• Manufactured in or extracted from a biological source (i.e.: blood, stem cells, vaccines, DNA recombinant technology)

• Target immunocytes or their products and steps in pro-inflammatory pathways
Biological Agents – Immune Mediation

Binding to:
- immunocytes (T lymphocytes, B cells, granulocytes, APCs, etc.)
- immune mediators (cytokines, chemokines, growth factors)

Objectives:
- Depletion
- Suppression
- Prevent binding to lymphoid organs or inflammatory sites
- Create unresponsiveness
Biological Agents

1. Biologics
   - Erythropoeitin
   - CSFs
   - GH

2. Monoclonal antibodies
   - Counteract or block a biologic substance
   - Target and/or damage a cell type
Monoclonal Antibodies (mAbs)

1. Human derived – ‘-mab’
2. Humanised – ‘-zumab’
3. Chimeric – mouse-human – ‘ximab’
Monoclonal Antibodies (mAbs)

- Expensive
- IV or SC administration due to size
- Adverse Reactions:
  - infusion reactions
  - fatigue
  - arthralgias
  - immunosuppression
  - autoimmunity
  - infections
  - malignancies
Main Biological Agents

- TNF-α inhibitors
- Interleukin inhibitors (e.g.: basiliximab)
- T-cell modulators
- T-cell co-stimulators (e.g.: abatacept)
- B-cell modulators (e.g.: rituximab)
- Cluster of differentiation (CDs)
- Others (anti-coagulant, anti-epidermal GF, NF-KB blockers, interferons, vaccines, anti-microbials)
<table>
<thead>
<tr>
<th>BA Targets and Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TNF-α</strong></td>
</tr>
<tr>
<td>Crohn’s, RA, psoriasis</td>
</tr>
<tr>
<td><strong>CDs</strong></td>
</tr>
<tr>
<td>Transplant rejection, RA,</td>
</tr>
<tr>
<td>AML, NHL,</td>
</tr>
<tr>
<td><strong>VEGF</strong></td>
</tr>
<tr>
<td>Cancers</td>
</tr>
<tr>
<td><strong>ILs</strong></td>
</tr>
<tr>
<td>RA, Transplant rejection,</td>
</tr>
<tr>
<td>Juvenile arthritis,</td>
</tr>
<tr>
<td>Lymphoma, other</td>
</tr>
<tr>
<td>autoinflammatory disease,</td>
</tr>
<tr>
<td>Psoriasis</td>
</tr>
</tbody>
</table>
Biologic Uses in Oral Healthcare

Mainly TNF-α inhibitors

• Behcet’s disease, RAS - infliximab, etanercept, adalimumab
• Vesiculobullous disease – rituximab, etanercept (pemphigoid)
• Lichen Planus – etanercept, adalimumab
• Crohn’s disease – infliximab, adalimumab
• Sjogren’s syndrome – infliximab, etanercept, rituximab
Dental Management of Patients on BAs

No official guidelines

Main concerns:
1. Infections
2. MRONJ
3. Impaired wound healing
4. Other (bleeding, drug eruption)
BAs and Infection

Post-transplant patients undergoing active therapy (anti IL-2, anti-CD3 agents)¹

- Pre transplant evaluation
- Conservative treatment of infections during therapy

Cutaneous infections²

Increased incidence of oral candidiasis³

³ Moen K et al. OOOOE 2005; 100: 433–440.
BAs and Other Adverse Effects

Bleeding - One case report of gingival bleeding due to abciximab related thrombocytopenia

Cutaneous or mucosal drug eruptions - varies and may manifest as a lichenoid reaction, vesicle/bullae, or ulcer

BAs and MRONJ

RANKL inhibitors (denosumab)
• Final mediator of osteoclastic bone resorption

Angiogenesis inhibitors (bevacizumab, sorafenib, sunitinib)
• VEGF inhibitor
BAs and Impaired Wound Healing

- VEGF inhibitors
- Bevacizumab – $T_{1/2} = 20$ days (11-50)

Recommendation to reduce risk of wound complications (surgical oncology, plastic surgery)$^1$:
  - 6-8 week interruption before surgery
  - Resume 4 weeks after surgery

Conclusions

• Rapid development of biological agents → > 900 agents in development
• Discontinuation of agents is often not an option
• Definitive recommendations and guidelines for dental management are lacking
• Consideration for management of adverse effects individually as they relate to dental management