

## Dexamethasone: An All Purpose Agent?

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### SUMMARY

Dexamethasone is a synthetic glucocorticosteroid which has minimal mineralocorticoid activity. It is a potent anti-inflammatory drug with 25-50 times the potency of hydrocortisone and is up to sixteen times as potent as prednisolone. Dexamethasone is utilised frequently in the perioperative setting, including prophylaxis against postoperative nausea and vomiting, reduction of airway and cerebral oedema, and it may be useful in the management of acute and chronic pain.

This review is intended to outline some of the perioperative uses of dexamethasone and elucidate areas where further research is needed.

### PHARMACOLOGY

Like all glucocorticoids, dexamethasone acts on the glucocorticoid receptor which is a member of the nuclear receptor superfamily, subfamily 3C. Multiple signalling pathways are involved following binding of the steroid to the receptor, including direct DNA binding which results in changes to gene transcription. This results in changes to carbohydrate, protein and fat metabolism as well as changes to gluconeogenesis. Of interest in the perioperative setting is the decreased release of bradykinin, tumour necrosis factor, interleukin-1, interleukin-2 and interleukin-6 and decreased production of prostaglandins<sup>1</sup>. There is decreased transmission of impulses in C fibres. Binding of steroid ligands to the glucocorticoid receptor also alters the half life of mRNA which have already been produced within the cell<sup>2</sup>. For example, dexamethasone decreases both bradykinin receptor mRNA expression as well as the response to bradykinin binding<sup>3</sup>. The absence of the receptor in homozygous mice results in rapid demise due to respiratory failure as steroids play an important role in lung development in utero. These mice also have enlarged adrenal glands which do not produce adrenaline. Knockout mice also exhibit immunosuppression due to T cell and thymocyte impairment<sup>2,4</sup>.

Dexamethasone is most frequently administered intravenously by anaesthetists, although patients may be commenced on oral dexamethasone preoperatively. The biological half life is about 3 hours<sup>5</sup>, although the duration of action may be much longer. Dexamethasone is bound to plasma proteins in much lower levels than other glucocorticoids. Hepatic metabolism (both glucuronidation and sulfation) occurs to produce inactive metabolites, with 65% of the dose of dexamethasone excreted in the urine within 24 hours<sup>5</sup>, with less than 3% unchanged. Intramuscular injection results in maximal plasma concentrations within one hour.

### Antiemetic prophylaxis: dose and timing

Dexamethasone is used for prevention and treatment of chemotherapy related and postoperative nausea and vomiting (PONV). It has been recommended as first line for PONV<sup>6</sup> at a dose of 5-10mg prior to induction (level IIa evidence)<sup>7</sup>. In children, doses from 0.05-1.5mg/kg have been used. The guidelines published by Gan<sup>7</sup> recommend a dose of 0.15mg/kg.

Multiple theories have been proposed for the mechanism of action of dexamethasone: reduction of 5-hydroxytryptophan in neurones by reduction of tryptophan, decreased serotonin release from the gut and increasing the response to other antiemetics at a receptor level<sup>8</sup>. In addition, there may be decreased 5HT3 turnover in the central nervous system or central inhibition of prostaglandin synthesis<sup>9</sup>.

There is some evidence for smaller doses of dexamethasone (4mg) in surgery which has been considered lower risk for PONV. In some circumstances, such as dental surgery<sup>10</sup> or to decrease vomiting with PCA use<sup>11</sup>, 8mg is more effective than 4mg. However, over a wide range of operations, with a baseline incidence of PONV of 60%, dexamethasone 4mg was as effective as ondansetron or droperidol as a sole antiemetic<sup>6</sup>. This is in contrast to other literature which suggests that there is increased effect at higher doses, with a plateau at 8-10mg<sup>10,11</sup>.

The literature available was reviewed in 2000<sup>8</sup>. Since then, a multicentre trial<sup>6</sup> and consensus guidelines<sup>7</sup> have been published, although this remains the most up to date review focussed on dexamethasone in the literature. For the studies incorporated in the review, the dose of dexamethasone was 8mg. When a 5HT3 antagonist was used, granisetron 20-40mcg/kg or 3mg and ondansetron 4mg were used. Unless stated, the number needed to treat was compared to placebo. This data was from pooled trials where approximately one-third of the participants experienced early PONV and nearly 50% experienced late PONV<sup>8</sup>.

**Table 1: Number needed to treat to prevent postoperative nausea and vomiting**

Indication	Number needed to treat (NNT)
Adults, nausea (overall)	4.3 (95% CI 2.-26)
Adults, vomiting (overall)	7.1 (95% CI 4.5-18)
Children, vomiting	3.8 (95% CI 2.9-5)
Adults (versus 5HT3), nausea	7.8 (95% CI 4.1-66)
Adults and children (versus 5HT3), vomiting	7.7 (95% CI 4.8-19)
Adults and children (with 5HT3)	~ 4*

Summarised from text of: Henzi I et al. Dexamethasone for the Prevention of Postoperative Nausea and Vomiting: A Quantitative Systematic Review. *Anesth Analg* 2000; 90:186-94<sup>5</sup>

\* Early and late nausea and vomiting data average.

Systematic reviews of the literature comparing combination therapy with dexamethasone and a 5HT3 antagonist to either alone have consistently demonstrated a decrease in PONV with combination therapy<sup>12</sup>.

### INFLAMMATORY EFFECTS

Research on clinically significant anti-inflammatory effects of dexamethasone in humans is predominantly in dental or ear, nose and throat procedures (adenoidectomy and tonsillectomy). Dexamethasone (0.5mg/kg up to 8mg) has consistently decreased oedema compared to placebo and also reduced time to first oral intake over a number of studies<sup>13</sup>. Steroidal anti-inflammatory drugs, as distinct from non-steroidal anti-inflammatory drugs, reduce chemotaxis in areas of inflammation as a glucocorticoid receptor mediated effect<sup>14,15</sup>.

Administered in the setting of cardiac surgery in children, dexamethasone is used in much larger doses than in adults (1mg/kg). At this dose, levels of interleukin 6 and tumour necrosis factor alpha are decreased to less than a third of placebo, and postoperative pyrexia, fluid requirements, ventilatory and oxygen requirements are decreased<sup>16</sup>. Mechanical ventilation was reduced from 3 days to 5 days<sup>16</sup>. Dexamethasone also reduces T-cell proliferation in rats<sup>4</sup>, a component of the inflammatory response which may also have implications for wound healing. However, chemokine expression and inflammatory cell infiltration may also lead to injury. The implications of a single dose perioperatively are uncertain in terms of this effect.

Ventilation induced lung injury (tidal volume 35ml/kg) in rats was attenuated by dexamethasone 6mg/kg. This dose resulted in no change in peak inspiratory pressure, no decrease in the PaO<sub>2</sub>/FiO<sub>2</sub> ratio and lower levels of markers of inflammation, although still higher than controls<sup>17</sup>.

Bronchial hyper-reactivity may be modulated by dexamethasone. In mice, dexamethasone inhibits cytokines involved in airway inflammation, suppresses airway reactivity in response to antigens and mucus accumulation by altering metabolism within the airway cell. This resulted in decreased airway hyper-reactivity, decreased mucus production and decreased eosinophilia<sup>18</sup>.

Wound healing following a single dose of dexamethasone has been studied in rats, at a dose of 1 mg/kg administered intraperitoneally. This dose decreased the usual inflammatory response

to wound healing, including collagen formation and migration of inflammatory cells to the wound<sup>19</sup>. There is minimal data on bone healing in the animal model following a single dose of dexamethasone and no evidence supporting an increase in postoperative wound infections. There is insufficient evidence however to draw conclusions as to the benign nature of dexamethasone with regards to these endpoints.

Patients are procoagulant after surgery, which is mediated in part through inflammation. Dexamethasone eluting drug stents have been developed for the management of acute coronary syndrome. These have demonstrated decreased events at six months in a non randomised trial, but do not decrease restenosis<sup>20</sup>. There have been no studies examining the incidence of postoperative thromboembolism following a single perioperative dose of dexamethasone.

### **OTHER METABOLIC EFFECTS**

As a potent glucocorticoid, dexamethasone causes suppression of the hypothalamic-pituitary-adrenal axis. Dexamethasone 1mg administered intravenously suppresses the diurnal variation in cortisol production by the adrenal gland of normal controls in the dexamethasone suppression test for Cushing's disease. A pilot study is underway to examine the effect of a single perioperative dose of dexamethasone administered at induction on cortisol levels, as this has not yet been studied.

Following dexamethasone 10mg in non-insulin dependent diabetics and non-diabetics, blood glucose concentrations increased by 30% to a peak at 120 min. There was correlation between peak blood glucose and both HbA1C body mass index<sup>21</sup>. Obese patients, particularly those with poorly controlled diabetes, are more likely to experience elevation of blood glucose following a single dose than lean non-diabetic patients. Of note, none of the non-diabetic group had a blood glucose level greater than 10 mmol/L.

### **ANALGESIA**

Limited research has taken place regarding the effects of dexamethasone on postoperative pain. Much of the available literature is in dental surgery and tonsillectomy.

As an adjunct to regional analgesia, intravenous dexamethasone (8-10mg) has demonstrated prolongation of IV regional anaesthesia<sup>22</sup>, and brachial plexus blocks<sup>23</sup>. Administered during general anaesthesia, dexamethasone has proven beneficial in reducing pain from tonsillectomy in adults(10mg)<sup>24</sup>, and dental surgery (4-16mg)<sup>25</sup>. It is even more effective when combined with a non-steroidal anti-inflammatory, particularly for tonsillectomy<sup>26</sup>. In anorectal procedures, dexamethasone 4mg decreased time to readiness for discharge with no increase in wound related complications<sup>27</sup>.

In more painful procedures, however, dexamethasone does not have a clinically significant effect. In major gynaecological surgery 10mg of dexamethasone resulted in no better analgesia than placebo<sup>28</sup>. Mastoidectomy patients reported less nausea and dizziness but no benefits with respect to pain relief<sup>29</sup>.

Dexamethasone 1mg daily had no impact on the incidence or severity of chronic pain following cholecystectomy<sup>30</sup>. However, dexamethasone has been recommended as adjuvant therapy for cancer pain, particularly where oedema may be present<sup>31</sup>. Recommendations on an appropriate regime are variable, but 4-8mg twice to three times per day has been utilised with effect<sup>31</sup>. Larger doses are recommended where raised intracranial pressure occurs.

Central glucocorticoid receptors may play a different role to peripheral glucocorticoid receptors with respect to the development of chronic pain states. Increased expression of receptors occurs with repeated injury in adrenalectomised rats. This appears to occur in response to inflammatory markers within the cord as interleukin-6 and protein kinase C antagonists reduce expression. In rats the expression of GR centrally is believed to increase neuropathic pain<sup>32</sup>. Implications of this in humans remains to be examined.

### **ADVERSE EFFECTS**

Adverse effects reported in association with dexamethasone include perineal pain associated with intravenous injection<sup>33</sup>. The incidence of this complication is unclear, but could range from 25-100%, with females at increased risk compared to men<sup>34</sup>. The speed of injection and the dose may also influence severity. This discomfort ranges from an 'itching' sensation to 'excruciating',

lasting 25-30 seconds. It is also not known if a regional block reliably prevents this sensation. The mechanism of action of this effect is unclear but believed to be related to the use of a phosphate ester of the steroid, as it has also been reported with other phosphate esters.<sup>34</sup> This is a strong disincentive to administer dexamethasone to an awake patient. There may however be some benefits to administering dexamethasone prior to induction (in some studies up to 90 minutes prior). This may be related to the presumed mechanism of action (on an intracellular receptor in the central nervous system), allowing sufficient time for dexamethasone to reach the effect site. Dexamethasone administered at the conclusion of anaesthesia has effects on late nausea and vomiting which supports this theory<sup>8</sup>.

There is increased reporting of adverse effects when dexamethasone is administered with 5HT3 antagonists<sup>8</sup>. These include headache, dizziness, sedation, constipation and muscular pain. There was no statistically significant difference between dexamethasone or placebo with respect to these effects.

Avascular necrosis of both the humeral and femoral heads is a known complication of steroid use. It has been reported after dexamethasone use as part of chemotherapy regimes or to prevent chemotherapy induced nausea and vomiting<sup>35</sup>. Cumulative dose of dexamethasone was an independent risk factor for this complication. It has also been reported in neurosurgical patients after 'short' courses (days rather than weeks) of dexamethasone. Neurosurgical patients on oral dexamethasone have a risk of about 1:1000 patient-years<sup>36</sup>. Avascular necrosis has not been reported in the English literature following a single dose of dexamethasone in the perioperative setting. There are multiple case reports in the setting of malignancy or of courses of steroids. Recommendations to limit the dose and duration of therapy to minimise the risk have been made in these settings.

#### **AREAS FOR FUTURE RESEARCH**

There are a number of questions remaining around dexamethasone use in our clinical practice. Whilst there is good evidence for its use as an antiemetic, particularly in combination with a 5HT3 receptor antagonist, there have been few dose finding studies. Larger doses may be required in certain types of surgery. Dose finding studies may be relevant if side effects such as hyperglycaemia or avascular necrosis cause clinically significant effects. The increase in effectiveness with a 5HT3 antagonist may be synergistic or additive-this remains to be elucidated.

Dexamethasone may prove a useful steroidal adjunct in the management of acute pain and to decrease airway complications in patients with bronchial hyper-reactivity due to disease, tobacco abuse or airway manipulation. The clinical significance of the underlying alterations in the inflammatory response remains to be examined.

The stress response to surgery has been the subject of much research, particularly in cardiac surgery. The endocrine response to surgery or trauma may have both positive and negative implications. Wound healing may be impaired by administration of dexamethasone due to reduction in the inflammatory response. However, postoperative nausea and vomiting is significantly decreased following administration of dexamethasone, particularly in combination with a 5HT3 antagonist. This is an important outcome, improving not only postoperative recovery but also increasing patient satisfaction. Dexamethasone may also have unexpected benefits with respect to preventing procoagulant inflammation or improving lung function postoperatively. Further research is anticipated into the effects of dexamethasone on wound and bone healing in humans, as well as other metabolic effects.

In summary, dexamethasone has proven efficacy as a sole agent and increased efficacy when combined with a 5HT3 receptor antagonist. The most appropriate timing of administration appears to be prior to induction, however, it is still efficacious for late PONV when administered during anaesthesia. Adverse effects are likely to be minimal but may be dose related. The metabolic effects of a single perioperative dose of dexamethasone are the subject of current research.

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