TITLE

Pre-operative dosing of dexamethasone for the management of children with posterior fossa tumours: are we getting it right?

AUTHORS

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KEYWORDS: Corticosteroids, dexamethasone, paediatric tumours

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ABSTRACT

INTRODUCTION

Posterior fossa (PF) tumours are associated with vasogenic oedema causing symptoms of raised intracranial pressure. Preoperatively this is managed with dexamethasone. To minimise steroid related complications, the lowest effective dose should be administered. No neurosurgical guidelines exist for pre-operative dosing of dexamethasone in PF tumours.

METHODS

A retrospective review was performed of surgically managed cases for patients under 16 years of age between 2013 and 2018 to ascertain the initial dose of dexamethasone with symptomatic PF tumours.

RESULTS

Thirty-six patients were identified of which 30 notes were available. Sixteen were male. Median age was 6 years (range 10 months - 15 years). Twenty-two (73%) were referrals from DGH and 8 (27%) presented to our neurosurgical centre.

All patients presented with symptomatic PF tumours including headache (97%), vomiting (93%), gait disturbance (43%), and nystagmus (17%). Four (13%) had papilloedema. Average initial stat dexamethasone dose was 9.15mg; 0.31mg/kg (range 1mg-16.7mg; 0.05mg/kg - 1.77mg/kg). Stratified according to weight, average dose (and range) was 8.8mg;0.94mg/kg (1mg-16.6mg; 0.13mg/kg - 1.77mg/kg) in those weighing <10kg; 9.7mg;0.66 mg/kg (4mg-16.7mg; 0.21mg/kg - 1.35mg/kg) in 10-20kg; 12.3mg;0.52 mg/kg (8mg-16.7mg; 0.27mg/kg - 0.73mg/kg) in 20-30kg and 7.8mg; 0.17mg/kg (2mg-16.7mg;0.05mg/kg - 0.39mg/kg) in >30kg up to a maximum of 16.6mg in any 24h period. These results suggest that dosage was higher in those children weighing less. PPI was used in 24 (80%) of cases. All doses were reduced after review by the neurosurgical team and a PPI added.

CONCLUSION

Pre-operative dexamethasone dosing does not always reflect the severity of clinical symptoms for PF tumours. Guidelines are required to correlate clinical symptoms with a suggested suitable dose of dexamethasone to prevent overdose and complications associated with corticosteroid use. We recommend a weight-based regimen as provided by the Food and Drug Administration. The current advice is for 0.02-0.3mg/kg/day in 3-4 divided doses

INTRODUCTION

Posterior fossa (PF) tumours in children typically present with clinical features of raised intracranial pressure. In most cases this is as a result of mass effect from the tumour itself and/or vasogenic oedema effacing the fourth ventricle leading to hydrocephalus.[30]. Preoperatively, dexamethasone is utilised to reduce oedema and in turn manage related symptoms such as nausea, vomiting, headache and neurological deficit[2,3,22,25].

To minimise steroid-related complications, the lowest effective dose should be administered. No national guidelines exist for pre-operative dosing of dexamethasone in children with PF tumours. Despite a lack of any prospective trial evidence, best practice guidelines for management of most brain tumours in adults[1,26] suggest corticosteroids be tailored to symptomatic patients and then tapered slowly[27].

Anecdotal evidence from our unit suggests that initial doses are high in the paediatric population. This is particularly evident in referrals we receive from district general hospitals (DGH). Patients who have moderate or severe symptoms may be commenced on an initial dose of dexamethasone often guided by reference to the British National Formulary (BNF)[15]. In the absence of any current guidelines this dose can be variable.

We reviewed doses of dexamethasone given to children referred to our unit who had a PF tumour with the aim of understanding current dosing regimens and establishing a standardised guideline.

METHODS

A prospectively gathered database was interrogated for all PF tumours in children under 16 years of age referred to our unit between 2013 – 2018. Data was collected from patient notes, the oncall referral database and electronic systems. The data collected included demographics, referring DGH, presenting symptoms and signs, weight in kilograms (kg), blood results, dose of dexamethasone prescribed in mg/kg and proton pump inhibitor (PPI) use. All data was captured using a secure excel spreadsheet. Data is presented using descriptive statistics. No ethical approval was required.

A retrospective review was performed of surgically managed cases for patients under 16 years of age between 2013 and 2018 to ascertain the initial dose of dexamethasone with symptomatic PF tumours. Data was collected regarding demographics, referring DGH, presenting symptoms, weight (kg), initial dosing of dexamethasone in mg/kg and proton pump inhibitor (PPI) use.

RESULTS

Thirty-six patients were identified for which 30 notes were available. Baseline characteristics are presented in table 1. Sixteen (53%) were male and 14 (47%) were female. Median age was 6 years (range 10 months - 15 years). Twenty-two (73%) were referrals from DGH in South Wales and 8 (27%) presented directly to our neurosurgical centre.

All patients presented with symptomatic PF tumours including headache (97%), vomiting (93%), gait disturbance (43%), and nystagmus (17%). Four (13%) had papilloedema on examination. None of the patients in this cohort presented with life threatening cerebral oedema or had clinical symptoms that warranted high doses of dexamethasone.

Average initial stat dexamethasone dose was 9.15mg or 0.31mg/kg (range 1mg-16.7mg or 0.05mg/kg - 1.77mg/kg). Stratified according to weight, average dose (and range) was 8.8mg or 0.94mg/kg (1mg-16.6mg or 0.13mg/kg - 1.77mg/kg) in those weighing <10kg; 9.7mg or

0.66 mg/kg (4mg-16.7mg or 0.21mg/kg - 1.35mg/kg) in those between 10-20kg; 12.3mg or 0.52 mg/kg (8mg-16.7mg or 0.27mg/kg - 0.73mg/kg) in those between 20-30kg and 7.8mg or 0.17mg/kg (2mg-16.7mg or 0.05mg/kg - 0.39mg/kg) in those >30kg up to a maximum of 16.6mg in any 24h period. These results suggest that dosage was higher in those children weighing less.

PPI was used in 24 (80%) of cases. All doses were reduced after review by the neurosurgical team and a PPI added if not already prescribed. Doses over the next 24 hours were adjusted after discussion with the neurosurgical team. Average continued dexamethasone dose over a 24-hour period in divided doses stratified according to weight, average dose (and range) was 8.0mg or 0.82mg/kg (4.0mg-12.0mg or 0.37mg/kg – 1.28mg/kg) in those weighing <10kg; 9.9mg or 0.58mg/kg (2.0mg-24.0mg or 0.10mg/kg – 1.83mg/kg) in those between 10-20kg; 10.6mg or 0.47mg/kg (8.0mg-16.0mg or 0.27mg/kg – 0.78mg/kg) in those between 20-30kg and 12.0mg or 0.27mg/kg (4.0mg-16.0mg or 0.06mg/kg – 0.49mg/kg) in those >30kg.

We saw no significant fluctuation in average serum white cell count (WCC) 9.9x10/L (range 1.0x10/L – 19.1x10/L) or blood glucose 6.2mmol/L (range 4.3mmol/L – 7.9mmol/L), although both measurements were taken within 24h of admission. Variations in WCC and blood glucose are common after administration of dexamethasone[24]. Whilst our results did not demonstrate any significant change, they remained a snapshot taken at 24h. Perhaps a longer duration of testing would have shed light on the effects of dexamethasone in this population, clinically, however, blood tests were not warranted and repeated tests on paediatric patients would not be deemed ethical.

DISCUSSION

Steroids such as dexamethasone are associated with adverse effects that may manifest systemically as an increase in appetite, weight gain, cushingoid facies, hypertension, lymphopenia, hyperglycaemia, depression or other mood and behavioural changes. Complications are also seen in multiple organ systems including gastrointestinal, endocrine and musculoskeletal[24,29] and these are both dose and duration dependent[24]. Furthermore, the presence of dexamethasone-induced leukocytosis has been shown to decrease overall survival in patients with glioblastoma multiforme[9] and the resultant hyperglycaemia seen in this cohort of patients has been shown to affect overall survival[17]. A recent meta-analysis of 8752 within 22 studies, patients has shown that in patients treated with radiotherapy or chemotherapy for GBM, association with steroids significantly reduced survival (HR=1.54, 95% CI 1.37-1.75; p<0.01) and progression free survival (HR=1.28, 95% CI 1.1-1.49; p<0.01)[20] suggesting that the lowest dose of steroids be used and for the shortest period. Whilst GBM is a different disease entity to paediatric PF tumours; the long-term effects of dexamethasone in use paediatric PF tumour populations is unknown and warrants further investigation.

Patients with posterior fossa tumours who are symptomatic often benefit from short courses of dexamethasone to alleviate symptoms of raised intracranial pressure and where evidence is available in the adult population, this is between 4-8mg per day[22,27]. Previous studies[21] and a recent meta-analysis[20] looking at dexamethasone use in brain tumours and the resultant demonstrated poor outcome both in terms of overall survival and progression free survival, we thought the dosing regimen was an important topic to address.

Pharmacodynamics and mechanism of action of dexamethasone

Dexamethasone is standard for management of peritumoural oedema because of its lack of mineralocorticoid activity reducing the potential for fluid retention[5]. It is a long-acting corticosteroid It decreases inflammation by suppression of neutrophil migration, decreased

production of inflammatory mediators, and reversal of increased capillary permeability. It also suppresses normal immune response.

The mechanism of action of dexamethasone is related to transcriptional and direct effects after passing the cell membrane and binding to the glucocorticoid receptor. Dexamethasone upregulates angiopoietin-1 which is known to stabilise the blood-brain barrier (Kim et al., 2008). It also downregulates vascular endothelial growth factor (VEGF) limiting the capillary permeability which would otherwise enable vasogenic oedema as well as altering tight junctions leading to a reduction in the overall permeability of the blood brain barrier[18]. Dexamethasone also inhibits the production of interleurkin-1 from macrophages associated with tumours[12].

Intravenous administration produces a rapid response, but the plasma concentration is short lived. Absorption via an oral route is typically between 61-86%[7]. The metabolism is predominantly hepatic, and the excretion is renal. Peak serum concentration when given orally is 60-120 minutes[7], IM is 30-120 minutes and IV is 5-10 minutes[10,13]. Half-life elimination varies amongst age groups. Typically, in low birth-weight infants it is: 9.2 ± 3.3 hours (range: 5.8 to 16.1 hours)[6] and children 4 months to 16 years: 4.3 ± 4.1 hours (range: 2.3 to 9.5 hours)[14,23].

The variability seen in our results is not unusual. Previous reports[8] have called for more study into the effects of dosing dexamethasone and a recent report in adults suggests that lower doses may be just as effective for managing gliomas as higher doses[28]. With no available guidance, many clinicians use guidance printed in the BNF to commence an initial dosing regimen. However, the dose suggested (16.6mg), whilst appropriate for life-threatening cerebral oedema, is not required for mild symptoms of raised intracranial pressure where a smaller, weight adjusted dose would be more appropriate.

Stat doses of dexamethasone are often prescribed and given by local clinicians prior to contacting the neurosurgical team. Following discussion with neurosurgery, doses are often

refined to a lower level. Our results demonstrate that whilst there is a refinement in the dose according to weight, there remains a high degree of variability. The dosing regime is decided on a case-by-case basis and considers the underlying cause being treated, the symptoms and their severity, and a comprehensive assessment of the individual patient. The need for a more standardised approach to steroid management in newly diagnosed PF tumour patients is needed to prevent potential harm.

We found that PPI was not always given. The importance of PPI use with steroids is well documented in adult patients who are at high risk[16]. Absence of PPI with dexamethasone is likely to reflect a deficiency in local protocol. Interestingly, recent guidance from the National Institute of Clinical Excellence (NICE) suggests that corticosteroids do not greatly increase the risk of peptic ulceration in low-risk populations including children. Therefore, PPIs are not routinely indicated for prophylaxis of peptic ulceration in people using oral corticosteroids[19]

Limitations

There are several limitations to this study. It is retrospective, limited to a small cohort of patients in a local population group presenting to a single tertiary centre. We did not capture the full duration of dexamethasone for these patients peri-operatively. This may have provided more insight into prescribing behaviour and the rationale for it. However, given the absence of guidelines, we would hypothesise that the perioperative dosing of dexamethasone is likely to have been equally variable and dependent on the clinical condition of the child.

Recommendation

Guidance from the Food and Drug Administration suggests a weight-based regime for dosing dexamethasone. The current advice is for 0.02-0.3mg/kg/day in 3-4 divided doses[11]. Based on this advice we suggest using the range shown in table 2 together with the clinical picture. This is broadly in line with new guidelines suggested by Caruthers et al.[4] The burden of disease may dictate a higher dose of steroid and may be used at the discretion of the treating

clinician; however, the suggested guidance would serve to minimise the harmful effects of large doses in most of the cases that present to local hospitals. A more robust clinical guidance is required which is likely to be achieved through an expert panel.

CONCLUSION

Pre-operative dexamethasone dosing does not always reflect the severity of clinical symptoms for PF tumours. Referring clinicians are often guided by the dosing schedule in the British National Formulary. Guidelines are required to correlate clinical symptoms with a suggested suitable dose of dexamethasone to prevent overdose and complications associated with corticosteroid use. We suggest using the FDA dosing regimen guided by the weight of the child.

CONFLICT OF INTEREST

On behalf of all authors, the corresponding author states that there are no conflicts of interest.

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FIGURES AND TABLES

Table 1.

Demographics	
Male	*16*
Female	*14*
Median age in years (range)	*6 (10months – 15y)*
Referrals	*n (%)*
District General Hospitals (DGH)	*22 (73)*
University Hospital of Wales	*8 (27)*
Symptoms	*n (%)*
Headache	*29 (97)*
Vomiting	*28 (93)*
Gait disturbance	*13 (43)*
Nystagmus	*5 (17)*
Papilloedema	*4 (13)*
Dexamethasone Dosing	*(stat dose and range in mg); [stat dose and range in mg/kg]*
Average Stat dose (mg) (range)	*(9.15; 1.0-16.7); [0.31; 0.05-1.77]*
Stratified by weight kg:	
<10	*8.8 (1.0-16.6); [0.94; 0.13-1.77]*
10-20	*9.7 (4.0-16.7); [0.66; 0.21-1.35]*
20-30	*12.3 (8.0-16.7); [0.52; 0.27-0.73]*
>30	*7.8 (2.0-16.7); [0.17; 0.05-0.39]*
Average dosing after discussion with Neurosurgical team (mg) (range)	
Stratified by weight kg:	
<10	*8.0 (4.0-12.0); [0.82; 0.37-1.28]*
10-20	*9.9 (2.0-24.0); [0.58; 0.10-1.83]*
20-30	*10.6 (8.0-16.0); [0.47; 0.27-0.78]*
>30	*12.0 (4.0-16.0); [0.27; 0.06-0.49]*

Table 2. Recommendations for stat and continued dosing of dexamethasone in patients presenting with symptomatic posterior fossa tumours.

Weight	10kg	20kg	30kg
Dose at 0.02-0.3mg/kg/d	0.2 – 3mg	0.4-6mg	0.6-9mg