A 10 Year Retrospective Observational Study on The Utility and Prescription Standards of Dexamethasone in Pediatric Neuro-oncosurgery in a Tertiary Care Centre.

Abstract

Object

This study aimed to retrospectively assess dexamethasone utility in pediatric CNS tumor patients over a 10-year period, to better understand dosing variability, and highlight optimal practice.

Methods

All pediatric CNS tumor cases managed operatively for a ten year period at a single center were reviewed. Information was gathered on demographics, dexamethasone doses, course durations, weaning regimes, PPI co-prescription, adverse events, and route of administration. Comparison within these groups was analyzed through use of statistical testing.

Results

127 patients received 193 dexamethasone courses. Median age was 7 years, with a median weight of 27.9kg. Most common tumor type was astrocytoma (24.8%). Median daily dose was 8mg, with twice daily dosing most common. Median course duration was 8 days, ranging from 1 to 1103 days. Median weaning duration was 11.5 days. Daily dose was not correlated with patient weight and the median daily dose per kg was 0.2319mg/kg. Dexamethasone dose per kg was significantly inversely correlated with age. 44.9% of patients received intravenous dexamethasone only. 32.7% received oral dexamethasone only. 22.4% received multiple different routes of administration throughout their course. Intravenous dexamethasone was more commonly used in young age groups. Incidence of adverse effects was 14.5% with Cushing's syndrome most common. The 15+ age group had the highest incidence of adverse effects at 23.8%. Dexamethasone dose per kg was not significantly different between patients with and without adverse effects; however, average dexamethasone course duration was significantly different between these groups. No relationship was noted between adverse effects incidence and administration route. 64.2% of patients received concurrent PPI with 35.8% receiving no PPI.

Conclusions

Large variation was seen in practice, with prescriptions appearing based on clinician preference and symptom severity rather than patient age or weight. Dexamethasone administration route interestingly showed no relationship with incidence of adverse effects. Future guidelines should consider lower dose regimens with less frequent dosing as these may benefit quality of life. A

multi-centre prospective observational study would be the optimal next step, allowing assessment of national practice, and greater patient numbers. This could facilitate evidenced guideline development, through discussion between clinicians in both neurosurgery and neuro-oncology.

Key Words: Dexamethasone, Pediatric, Neurosurgery, Oncology, CNS Tumors, Guidelines, Standardization

What's already known about this topic?

- Dexamethasone is an effective drug treatment used for symptomatic treatment in pediatric patients with central nervous system tumours.
- Current prescription practices are varied between physicians and institutions.
- Adult guidelines on dosing have been proposed but formal pediatric guidelines do not exist.

What does this article add?

- This study aimed to assess dexamethasone utility in pediatric central nervous system tumor patients to better understand dosing variability, and highlight optimal practice.
- The study has shown current prescription practices in a tertiary care centre with regards to demographics, dexamethasone doses, course durations, weaning regimes, PPI co-prescription, adverse events, and route of administration.
- Possible practice recommendations are suggested which may be beneficial.

Introduction:

Central nervous system (CNS) tumors are the most commonly occurring solid tumor in the pediatric population and represent the second commonest cause of cancer in patients 0-19 years of age.[1, 2, 3] These tumors unfortunately still represent the most common cause of cancer-related death in children, with a 5-year mortality of 30%.[1, 4]

CNS tumors have heterogeneous presentations, but common symptoms include headache, nausea, vomiting and disco-ordination.[5] These are largely due to raised intracranial pressure exerted by the mass effect of the tumor itself, and tumor-related vasogenic oedema.[6]

Neurosurgical tumor resection represents the primary management modality for curative treatment.[7] However, tumor resection is not possible in many cases, dependent on a number of factors. For these patients, and for those awaiting surgery, effective symptomatic treatment is vital. Corticosteroids have been the cornerstone treatment for symptomatic management in cerebral tumors since their benefits were first noted in 1957.[8] These benefits originate from corticosteroids' abilities to reduce tumor-associated vasogenic edema, thus decreasing overall intracranial pressure.[9] Dexamethasone is the principal corticosteroid in this role, due to its high potency, long half-life and low mineralocorticoid activity.[10, 11] Dexamethasone's benefits are not purely symptomatic, and it has been shown in certain cases to extend lifespan.[12] However, dexamethasone use comes with numerous side-effects, such as: hyperglycemia; hypertension; immunosuppression; gastrointestinal (GI) problems; anxiety and mood disorders; issues with bone formation and maturation; Cushing's syndrome; and muscle weakness.[13, 14, 15, 16]

These side effects are dose-dependent in both severity and frequency.[10, 17, 18] Furthermore, dexamethasone has to be carefully weaned to prevent acute adrenal insufficiency crisis or withdrawal syndromes.[19] Dosing recommendations for the adult population have been proposed.[10, 20] However, despite ubiquitous use in the pediatric population, there is a paucity of evidence with regards to appropriate prescription practices for children; noted by other authors previously.[21, 22]

Dexamethasone dosing is therefore currently guided by the patients' clinical factors and physician judgement, resulting in a growing disparity in treatment regimens between individual

physicians and various centres.[21, 22] Guidelines for dexamethasone prescription in pediatric CNS tumor patients would hopefully allow for expedited control of symptoms, with optimal dosing, balancing benefit and risk. Our team has previously noted this, and colleagues internationally have also recognized the paucity of evidence.[23]

The aim of this study was to perform a retrospective observational study assessing dexamethasone utility in pediatric CNS tumor patients managed in a tertiary care centre over a 10-year period, to better understand variability in dosing, and possibly highlight optimal dosing regimens.

Methods:

Patient selection:

Patients were identified from a database of all pediatric patients undergoing CNS tumor-related neurosurgical procedures at a tertiary centre within the United Kingdom between January 2011 and December 2020. Patients with CNS tumors not undergoing surgery were not listed on the database, and therefore not included.

Data collection:

Data for each patient was retrieved via the local electronic patient record system. Demographic factors of age, sex, weight and tumor type were assessed. For data analysis, patients were divided into 4 age groups (0-4, 5-9,10-14, 15+ years).

Dexamethasone doses and daily regimens were collected. Where doses had been varied, the dosing regimen maintained for the longest period was used.

Changes in dexamethasone dose, and route of administration were reviewed. Dexamethasone dose duration was calculated from recorded dexamethasone start and end dates. Where no specific dates were able to be defined, course duration was not calculated. Weaning regimen duration was also reviewed.

Adverse effects reported to be directly or likely associated with dexamethasone were reviewed and categorized.

PPI co-prescription for GI side effect mitigation was also assessed for drug, dosing and route of administration. If no PPI was recorded, it was recorded as such.

In all other cases where data could not be sourced or confirmed, data points were not recorded and intentionally excluded from statistical analysis.

Statistical analysis:

Data points were analyzed to calculate means, medians, modes, maximums, minimums, interquartile ranges, standard deviation and N numbers where appropriate. Statistical significance was defined with a confidence interval of 95% ($p<0.05$). Correlation analysis was performed to assess association between daily dose and patient weight, dose per kg and age. Mann-Whitney-U test assessed differences between median doses per kg for males and females. ANOVA and post-hoc tukey test were utilized to assess the difference between mean dose per kg, age groups, and tumor types. Binomial test was used to assess frequency of intravenous and oral dexamtheasone administration. Chi-squared test was used to assess relationship between age group and incidence of adverse effects, and presence of adverse effects and route of administration. Independent-samples T-test assessed differences in mean daily dexamethasone dose per kg and dose duration for patients with and without adverse effects. All analyses were carried out on SPSS. Outliers were included in analysis but not represented on graphs and figures for data presentation.

Results:

Patient variables:

Total number of patients reviewed was 164. 101 (61.6%) were male and 63 (38.4%) were female. 37 (22.6%) patients did not receive dexamethasone. 127 (77.4%) patients received 193 courses of dexamethasone. 87 (53.0%) patients received 1 course, 25 (15.2%) received 2, 8

(4.9%) patients received 3 courses while 7 (4.3%) patients had 4 or more courses. The median number of dexamethasone courses received was 1 [1,1](n=164).

The median age of patients receiving dexamethasone was 7 years [4,12](n=193) with a median weight of 27.9kg [16.2,43.7](n=168). Most common tumor types were astrocytomas (24.8%) (n=57), medulloblastomas (11.3%)(n=26), and ependymomas (10.0%)(n=23)[Fig.1].

Dexamethasone Dosing:

Median dexamethasone dose per single administration was 4mg [2,4](n=126). Most common dosing regimen was twice daily (BD) (74.8%)(n=95), second most common was three times daily (TDS)(12.6%)(n=16), followed by once daily (OD)(8.7%)(n=11), 4 times daily (QDS) (3.1%)(n=4) and 8 times daily (0.8%)(n=1).

Median daily dose was 8mg [4,8](n=126), ranging from 1.1mg to 26.4mg[Fig.2].

Daily dose was not correlated with patient weight ($r=0.157$, $p=0.094$). Median daily dose per kg was 0.2319mg/kg [0.1443,0.3588](n=115) and ranged from 0.0260mg/kg to 1.664mg/kg[Fig.2].

Median daily dose per kg for males and females were 0.2319mg/kg [0.1417,0.3535](n=79) and 0.2432mg/kg [0.1809,0.4072](n=36) respectively, which were not significantly different ($U=1219.5$, $p=0.222$).

Dexamethasone dose per kg was significantly correlated with age ($r=-0.482$, $p<0.01$). The age group that averaged highest dexamethasone dose per kg was 0-4 years (0.4385mg/kg)(SD+/-0.2457)(n=30). This was followed by the 5-9 age group (0.3186mg/kg)(SD+/-0.2637)(n=38), then 10-14 (0.1803mg/kg)(SD+/-0.0942)(n=36), and 15+ (0.1341mg/kg)(SD+/-0.0942)(n=11) [Fig.3]. Differences between age groups were statistically significant as determined by one-way ANOVA ($F(7,76)=3.187$, $p=0.05$). Tukey post-hoc test showed doses received in 0-4 age group were significantly greater than those received in the 10-14 ($p<0.001$) and 15+ age group ($p<0.001$). 5-9 age group also received significantly higher doses than those in 10-14 ($p=0.024$) and 15+ age groups ($p=0.05$). Differences between 0-4 and 5-9 age groups ($p=0.087$) and 10-14 and 15+ age groups ($p=0.915$) were non-significant.

Throughout the 10-year period, no obvious trends in dose prescribed were noted.

Of the 8 most common tumor types, patients with craniopharyngioma (0.6066mg/kg)(SD+/-0)(n=1), ependymoma (0.4267mg/kg)(SD+/-0.2266)(n=11) and medulloblastoma (0.4077mg/kg)(SD+/-0.3535)(n=17) received on average the highest doses of dexamethasone per kg. Patients with Ewing's sarcoma received the lowest dexamethasone dose per kg (0.1495mg/kg)(SD+/-0.0572)(n=3)[Fig.4]. Differences observed between tumor types were statistically significant as determined by one-way ANOVA ($F(7,76)=3.187$, $p=0.005$). Post-Hoc Tukey test demonstrated that patients with medulloblastomas significantly received higher dexamethasone doses than those with unspecified gliomas ($p=0.049$).

Dose duration:

Median dexamethasone dose duration was 8 days [4,28](n=125), ranging from 1 to 1103 days. The most common duration was 3 days (n=13).

There were no obvious trends in dose duration over the 10-year period. Across age groups, no obvious trends were identified also.

Route of administration:

44.9% (n=44) of patients received intravenous (IV) dexamethasone only. 32.7% (n=32) received oral (PO) dexamethasone only. 11.2% (n=11) initially received IV dexamethasone then switched to PO. 2% (n=2) received IV dexamethasone then later changed to nasogastric tube (NG). 2% (n=2) received IV dexamethasone initially then switched to PO then back to IV. 2% (n=2) received PO dexamethasone initially then switched to IV. 2% (n=2) of patients received PO dexamethasone at first, switched to IV and then switched again to NG. 1% (n=1) of patients received IV initially then switched to NG then back to IV. 1% (n=1) received NG dexamethasone then IV and 1% (n=1) received dexamethasone PO then NG.

A binomial test showed proportions of IV and PO dexamethasone were 0.58 and 0.42, not significantly different from 0.5 ($p=0.207$).

IV dexamethasone was most commonly used in young age groups and less common in older patients. In 0-4 age group, 76.7% (n=23) received IV dexamethasone as part of their administrative regimen. In 5-9 age group, 65.7% (n=23) received IV dexamethasone. In 10-14 age group, 58.3% (n=14) and in 15+ age group, 55.6% (n=5) received IV dexamethasone during their course of treatment. PO dexamethasone was used more in older age groups but was used relatively more consistently throughout all age groups[Fig.5].

There were no obvious trends in route of administration over the 10 years.

Weaning regimens:

Median weaning regimen duration was 11.5 days [4,20.25](n=40), ranging from 2 to 129 days. The most common weaning period was 2 days (n=5).

Adverse effects:

Overall incidence of adverse effects was 14.5% (n=28) with Cushing's syndrome (3.6%)(n=7), adrenal suppression (3.1%)(n=6), and weight gain (3.1%)(n=6) being most common[Fig.6].

The age group with the highest incidence of adverse effects was 15+ at 23.8% (n=5). The 0-4 age group experienced the least side effects (11.1%)(n=6). However, relationship between age and incidence of adverse effects was not significant (X^2 (3, N=193)=1.962, p=0.580).

An independent-samples T-test revealed that mean daily dexamethasone dose per kg were not significantly different (t(113)=-114, p=0.909) between patients with (0.2841mg/kg)(SD+/-0.2036)(n=24) and without adverse effects (0.2902mg/kg)(SD+/-0.2395)(n=91). However, average dexamethasone dose durations were significantly different (t(123)=2.486, p=0.014) between patients with (90.9 days)(SD+/-138.3)(n=22) and without adverse effects (24.22 days) (SD+/-108.6)(n=103).

A Chi-square test of independence showed no significant relationship between presence of adverse effects and route of administration (X^2 (2, N=98)=2.0, p=0.368). Relationship between presence of adverse effects and tumor type was also non-significant (X^2 (7, N=158)=8.919, p=0.258).

Proton pump inhibitor (PPI) co-prescription:

64.2% (n=124) of patients received PPI during their dexamethasone treatment with 35.8% (n=69) not receiving any PPI. 49.7% (n=96) received omeprazole. 7.8% (n=15) received ranitidine. 3.1% (n=6) received both omeprazole and ranitidine. 0.5% (n=1) received lansoprazole and ranitidine and 3.1% (n=6) received an unspecified PPI[Fig.7].

The most common Omeprazole dose was 20mg (63.4%)(n=40) which also represented the median dose [10,20](n=63).

Discussion:

Patient factors:

Most common tumor types receiving dexamethasone were astrocytomas, brain stem gliomas, unspecified gliomas and medulloblastomas. Although exact incidence may differ, these findings were commensurate with descriptive epidemiology from current literature.[1] The larger male proportion of patients also reflect the propensity for CNS tumors to be more common in males.[1]

Dexamethasone dosing:

There seems to be preference for 4mg BD dexamethasone prescription which is in-line with some of the guidelines proposed for adults.[11, 24] Regardless, the range of daily doses was wide (1.1-26.4mg). When adjusted for weight, this wide range was still noted (0.0260-1.664mg/kg). This may be attributed to heterogeneous symptom severity that this study was unable to assess.

Doses per kg for male and female patients were not significantly different ($U=1219.5$, $p=0.222$), suggesting patient sex was not significant in determining dosing.

There was no correlation between patient weight and daily dexamethasone dose ($r=0.157$, $p=0.094$). This was surprising, with weight often being determinant for dosing in pediatrics. Dexamethasone dose per kg was negatively correlated with age ($r=-0.482$, $p<0.01$), implying younger patients received higher doses relative to their body weight. This may be due to younger

patients having more severe symptomatology requiring increased doses to control. However, the correlation could reflect clinicians prescribing fixed dexamethasone regimens in patients of varying weights. This may be further evidenced by the fact no correlation was noted between patient weight and daily dexamethasone dose.

These findings suggest dosing decisions may be based on clinician preference, and symptom severity, overlooking or taking into minor consideration patient weight, age and sex.

Dexamethasone doses per kg were significantly different between tumor types ($F(7,76)=3.187$, $p=0.005$). Though only the difference between medulloblastoma and unspecified gliomas was statistically significant, it is likely that with increased patient numbers, significant differences between other tumor types would become apparent. This suggests different tumor types may require different dexamethasone doses for symptomatic relief, warranting further investigation.

The joint formulary committee published recommendations for dexamethasone prescription for children in the British National Formulary for Children (BNFc), however it only concerns patients with life-threatening cerebral oedema.[20] It recommends for those <35 kg of weight an initial dose of 16.7 mg and a maintenance dose of 26.4 mg daily (3.3mg every 3 hours) for 3 days which can then be tapered. For those >35kg, an initial dose of 20.8 mg is recommended followed by a maintenance regime of 39.6mg (3.3mg every 2 hours) daily for 3 days, after which dosing can gradually be tapered. Even though dexamethasone prescribed in this center was primarily for acutely non-life-threatening cases of cerebral edema, comparison was still of interest. The mean doses in this study were significantly lower than these recommendations for both <35kg ($t(68)=-38.189$, $p<0.001$) and >35kg ($t(45)=-60.079$, $p<0.01$). For those <35kg, the average doses were 73.9%(n=69) lower than the BNFc recommendation. For patients >35kg, average doses were 80.6%(n=46) lower. This is concordant with literature from the adult population, claiming lower doses of dexamethasone may be sufficient for symptomatic management of CNS tumors in non-severe cases.[11, 15, 25] Literature also suggests less frequent dosing regimens – such as BD – may be associated with better sleep and improved quality of life. This is especially pertinent in a population where maximizing quality of life is of paramount importance.[24]

Dose duration:

There was large variation in dexamethasone dose duration (1 – 1103 days). This may reflect differences in symptom severity between patients, and also reflects varied periods awaiting surgery. The skew of data may also represent the patients that have passed away affecting apparent dose duration. It is important that adequate symptomatic palliation is given in cases where necessary and should not be compromised in pursuit of minimizing dose duration. However, where possible, minimizing dose duration is beneficial to reduce incidence of dexamethasone related adverse effects.

The wide variation in dose duration emphasizes the importance of guidelines to encourage consistent dexamethasone prescriptions to minimize superfluous dexamethasone treatment. In this study, incidence of adverse effects increased noticeably after dexamethasone was given for greater than 16 days. For those prescribed dexamethasone for >16 days 42.5% (n=17) experienced adverse effects compared to 5.9% (n=5) in those given dexamethasone for <16 days.

Route of administration:

The most common routes of administration were IV and PO. The difference in frequency of these routes was not statistically significant (p=0.207). Therefore, it can be inferred that these routes of administration were favored equally. IV routes were more commonly used for younger patients, likely illustrating the inability of younger patients to tolerate oral medications. A small proportion of patients received complex administration regimens, and represent a group of individuals with complex pathology and highly fluctuant disease course.

Weaning Regimen:

A wide range of weaning regimens were recorded (2-129 days). Long tapering periods were mainly used in complex cases where dose reduction risked symptom recurrence. The most common tapering regimen was 2 days (all dexamethasone weaned over two days). This seems acceptable, with no serious adverse events reported or attributed to the short weaning regimen. However, adult studies have shown risk of adrenal insufficiency to be as high as 48.7% upon discontinuation of oral corticosteroids.[26] Given this risk, a more gradual tapering scheme may prove beneficial. Further studies addressing this will be crucial to gain insight into ideal tapering schemes. Given the complexity of these patients, the optimum regimen will likely require an

element of individualization. Nevertheless, this should not discourage the development of recommendations that can serve as starting points to be adapted as required.

Adult guideline recommendations have suggested a tapering regimen over a period of 2 weeks which can be extended for symptoms.[11] Perhaps these recommendations can be explored further and adapted to the pediatric population.

Adverse effects:

No life-threatening adverse events related to dexamethasone were reported. The side effects observed were in keeping with the common adverse effects reported in the literature, with Cushing's syndrome being most common.[15, 24] Although, the incidence of these were lower than those reported by other authors.[13, 27] This may reflect under-reporting of adverse effects or occurrence of adverse effects not directly ascribed to dexamethasone.

The mean dexamethasone dose per kg for patients with and without adverse effects were not significantly different (P=0.909). This implies that the incidence of adverse effects were not dose dependent, contrasting existing literature.[10, 11, 17, 18] Due to small sample sizes, the study is likely underpowered for assessing adverse effects of drugs. Recording incidence of adverse effects that allows for scale or severity analysis would enable more accurate assessment of correlation between variables. Optimizing these factors may reveal similar results as published by other authors.

The mean dose durations for patients with and without adverse effects were significantly different (p=0.014), suggesting the incidence of adverse effects was dependent on dose duration. This is in line with findings from existing literature where extended treatment duration was associated with increased frequency and severity of side effects as well as reduction in symptomatic control.[13, 15, 25, 28] This further highlights the importance of minimizing course duration and redundant dexamethasone prescription where possible to reduce incidence of dexamethasone-associated adverse effects.

Despite older patients receiving lower dexamethasone doses per kg, the incidence of adverse effects was higher, although not statistically significant. This may represent higher susceptibility

of older patients to adverse effects, but more likely reflects the ability of older patients to report side effects with younger patients not able to distinguish or vocalize concerns as well. Therefore, it is imperative that adverse events are adequately screened in younger patients.

There was no significant relationship between incidence of adverse effects and route of dexamethasone administration or tumor type. Appearing to highlight that the ideal route of administration would be the one that the patient tolerates best. It will be interesting to assess if different routes of administration are associated with greater symptomatic relief or better outcomes. This was not possible to assess in the bounds of this study.

Proton Pump Inhibitor (PPI) co-prescription:

Current guidelines in adults do not detail PPI co-prescription recommendations.[29, 30] Some authors have suggested routine co-prescription is not recommended due to low incidence of GI side-effects (0.4-1.8%).[31] However, when non-steroidal analgesics are used, as is common in these patients, PPI prescription is indicated. Many adverse effects of PPIs on gut microbiome, immune function and bone fractures have been noted in the pediatric population, however these are relatively rare.[32] In this study, PPIs were commonly co-prescribed to 64.2% of patients. It is possible there was under-reporting of PPI prescription. The lower incidence of GI side effects in this patient group (0.5%) relative to other research populations (0.4-1.8%) may be due to PPI co-prescription, demonstrating their possible benefit. Further large-scale studies would be ideal to assess the value of PPIs in these patients. Nevertheless, PPIs seem relatively safe and incorporation into formal guidelines could be considered with advice on safe practice.

A small group of patients were prescribed ranitidine. Ranitidine has been withdrawn with advice from Royal College of Pediatrics and Child Health due to presence of NMDA, a likely carcinogen, and should no longer be used.[33]

Practice recommendations and future considerations:

One study highlighted 80% of sampled institutions in Canada lacked formal guidelines, leading to large discrepancies in prescription practices, and this lack of guidelines has been noted elsewhere for many years.[21, 22] This lack of standardization between centers and clinicians may be

leading to variable time to effective treatment, and increased risk of adverse effects and suboptimal symptom control. Formulation of standardized guidelines would represent a step toward more reproducible, easily understood, and safe pediatric CNS tumor management.

Current recommendations from BNFc only reference life-threatening cases of cerebral edema and moreover, they divide a continuous spectrum of patients into only two heterogenous groups based on weight. Reviewing existing evidence, and findings from this study, it seems any guidelines developed in the future should consider lower dose regimens of 4-8mg daily with higher doses reserved for severe cases. Lower doses of 2mg per day may even be efficacious in smaller or less symptomatic children. It also appears less frequent dosing such as BD as opposed to TDS or QDS should be favored as these may be associated with better quality of life. Guidelines should also consider stratification of patients based on age, weight, tumor type and severity of symptoms. As dose duration has been shown to be directly associated with increased incidence and severity of side effects, clear recommendations on optimum dexamethasone course lengths should be formed. Recommendations should also guide weaning to limit withdrawal syndromes. Preferably, guidelines should also detail optimum PPI co-prescription regimens to mitigate GI side effects. Recommendations should also advise on principles of increasing dosage or extending treatment where necessary to tailor therapy to severe individual cases. Before this can be achieved, further work is required to establish current understanding.

This study highlighted route of dexamethasone administration appears to have no effect on incidence of adverse effects. This may alleviate clinician concern that with the increased bioavailability of IV dexamethasone versus oral preparations there may be an increased risk of adverse effects.[34] This result requires further validation through reinforced study power from increased patient numbers, but does provide useful clinical information. These findings should also be reflected in future guideline, with an allowance to – as previously stated – utilize the method of administration best tolerated by the patient.

A multi-centre prospective observational study would likely be the best forward course from this study. This would allow assessment of practice not purely reflecting local or regional patterns, and would provide greater patient numbers. It would also allow evidenced guideline

development, through discussion between multiple clinicians in both neurosurgery and neuro-oncology.

A limitation of this study was the lack of recorded information from patient notation. For many patients, information such as dose or administration route were unobtainable. This limited inclusion of patients in data analysis. Due to the retrospective nature of this study, certain data points were unable to be assessed due to lack of formal data collection in specific areas. For example, adverse effects were treated as categorical variables and severity of these side effects could not be measured to assess correlation. Furthermore, degree of symptomatic relief achieved and effects on patient outcomes or mortality could not be assessed. A larger prospective study would provide higher quality evidence with broader scope of analysis.

Steroid-sparing agents represent a rapidly-evolving area in the field that should be further considered for inclusion in any new guidelines developed. Corticorelin acetate has shown to reduce steroid requirement as well as incidence and severity of side effects in patients.[35] Incorporation of such agents into routine practice may confer further benefit in quality of life for these patients.

Conclusions:

Overall, dexamethasone was generally well tolerated and doses used in this centre were considerably lower than the doses recommended by the BNFC. Although, there was large variation of doses, course length and tapering schemes utilized. Significant differences in dexamethasone doses between tumor types were observed which require further investigation. It seems prescribing practices have been based on clinician preference and symptom severity rather on patient age or weight. Incidence of dexamethasone -associated adverse effects were lower than those reported by other authors and was closely related to dexamethasone course duration. PPIs were also inadequately co-prescribed. A final principal finding was that mode of dexamethasone administration had no effect on incidence of adverse effects. The findings of this study highlight the necessity of implementing uniform dosing protocols to help standardize treatment. Given the heterogeneous nature of pediatric neuro-oncology, therapy tailored to individual cases will always be necessary. However, utilization of a standardized guideline in conjunction with clinician judgment to individualize treatment will yield optimal results.

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Figure Legends:

Figure 1

Bar chart representing frequency of the most common tumor types for patients receiving and not receiving dexamethasone (DEX). All patients receiving and not receiving DEX (n = 164) are included. This chart also represents the sometimes multiple courses of DEX received by individual patients (i.e. if patient received 3 courses of DEX for same tumor type, 3 cases of that tumor type were recorded); allowing assessment of the true case burden. Therefore, total cases assessed = 230.

Figure 2

Box plot representing the distribution of daily dexamethasone (DEX) doses and daily DEX dose per kg given for all patients. Daily DEX dose n = 126. Daily DEX dose per kg n = 115 (weight unable to be assessed in 11 cases). Outliers were not represented within this graphic. Outliers in Daily DEX Dose category = 16, 16, 16, 16, 16.5, 26.4. Outliers in Daily DEX Per KG category = 0.7186, 0.7273, 0.8000, 0.9756, 1.2500, 1.6604.

Figure 3

Bar chart representing the average daily dexamethasone (DEX) dose per kg received across different age groups. One-way ANOVA ($F(7,76)=3.187$, $p=0.05$) was utilized to show significant differences between groups. Post-Hoc Tukey test was utilized to highlight specific significant differences, represented by * $p<0.05$, and ***$p<0.001$.

Figure 4

Bar chart representing the average daily dexamethasone (DEX) dose per kg received across different tumor types. One-way ANOVA ($F(7,76)=3.187$, $p=0.005$) was utilized to show significant differences between groups. Post-Hoc Tukey test was utilized to highlight specific significant differences, represented by *$p<0.05$.

Figure 5

Comparative bar chart representing intravenous versus oral administration routes of dexamethasone (DEX) between various age groups. Number of patients where route was able to

be assessed = 98. This chart records route utilized at any time in treatment, and therefore total percentage (IV% + PO%) for each group can be >100%.

Figure 6

Bar chart representing the full number of courses of dexamethasone (DEX), and the frequency of associated adverse effects. Number of courses reviewed = 193. In cases where one patient experienced >1 adverse effect, both of these were recorded (i.e. Cushing's syndrome and adrenal suppression).

Figure 7

Proportional bar chart representing the full number of courses of dexamethasone (DEX), and whether a concurrent PPI was prescribed. Number of courses reviewed = 193. Number given PPI = 124 (64.2%). Number not given = 69 (35.8%). Those given PPI were subdivided by PPI utilized. Unspecified PPI noted when PPI use recorded, but specific agent unable to be assessed, with number unspecified = 6.