PERSONAL PRACTICE

Corticosteroids in the management of central nervous system tumours

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Central nervous system (CNS) tumours account for 20% of childhood malignancy.[1] Long term survival is still only 50%.[2 3] Hence, symptomatic management remains a key area of specialist care during treatment, rehabilitation, and terminal care. A key component of adjunctive treatment is the use of corticosteroids to control symptoms related to peritumoral oedema and consequently raised intracranial pressure (ICP).

Rationale for glucocorticoids

Kofman *et al* first reported the beneficial role of glucocorticoids in managing brain tumours in 1957 after prednisolone was given to 20 adults with brain metastases.[4] These drugs are now routinely administered to children with symptomatic CNS tumours.[5] The rationale for their use is to improve neurological function by reducing associated brain or spinal oedema, although the mechanism by which this occurs is unresolved.[6 7] Glucocorticoids increase membrane stability and thereby correct flux of sodium, potassium, and water across the cell membrane.[8] There is evidence that they may reduce vascular permeability.[9 10]

Whether glucocorticoids are tumoricidal remains contentious. Inhibition of glioma cells by dexamethasome was reported for in vivo and in vitro studies.[11–13] A process involving membrane modification leading to alteration of cell-cell interactions and reduction in their malignant potential has been postulated.[14] For the clinician, however, concern exists that corticosteroid induced membrane stabilisation may decrease permeability of the blood-brain barrier and inhibit entry of water soluble cytotoxic agents into the tumour.[15]

Clinical dilemma

Few attempts have been made to systematically study the optimum corticosteroid dose regimen and the incidence of short and long term side effects in children with CNS tumours. Consequently, the risk-benefit ratio remains undetermined.

Lack of consensus regarding steroid treatment is exmplified by the wide variance of doses and duration of courses prescribed by clinicians between and within treatment centres. This issue is potentiated by the complex pattern of presentation of children with CNS tumours. The mean time from onset of clinical history to diagnosis may be up to 20 weeks, with the involvement of a range of specialties before this occurs.[16] Several studies have found a significantly prolonged lag time from symptom onset to diagnosis for CNS tumours compared with that for other malignancies in childhood.[17 18]

Approximately 25% of children presenting with CNS tumours to regional neurosurgical units have clinical features of raised ICP.[16] It is often appropriate to provide symptomatic relief while the logistics of transfer to these centres are arranged. A rational, standardised approach to glucocorticoid administration is required so that all clinicians, wherever their practice, can manage these individuals optimally.

The initial response to steroids may be dramatic. In association with the lack of other treatment options this experience frequently fuels parents' demands for their use at later stages of the disease process. In such circumstances a rational approach must be adopted as corticosteroids are a potential source of acquired neurological handicap.

Indications

An audit of steroid prescribing in our regional neuro-oncology unit (excluding patients having radiotherapy) found that 62 patients received 130 courses of corticosteroid over a one year period.[19] The indication was raised ICP in 68%. Steroids in the remaining third were administered for the treatment or prevention of allergic and anaphylactic reactions, as hormone replacement therapy and as preparation for neurosurgery.

Adverse effects

Once started, the glucorticoids are frequently administered for long periods (fig 1). In our review approximately one in four courses was for longer than four weeks. More than one third of children receiving treatment for raised ICP were included in this group. Adverse effects are frequently seen with this pattern of drug administration. This is in agreement with the findings of other clinical services utilising long term corticosteroid treatment. These side effects are legion and well documented.[20] Some of these, however, warrant particular attention when dealing with children with CNS tumours.

The beneficial effects of relief of symptoms attributable to raised ICP must be balanced by the frequently observed severe mood and

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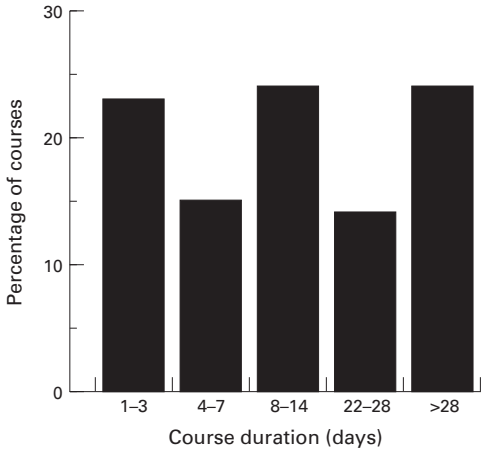

Figure1 Duration of treatment used on a regional neuro-oncology unit.

behavioural changes. These are not without significant impact on the individual child and his or her family. Indeed, cyclical use of prednisolone as maintenance treatment for acute lymphoblastic leukaemia has been documented to produce a specific morbidity burden and a reduction in health related quality of life.[21] Insatiable appetite and weight gain are disturbing. It is our experience that this burden is not confined to the patient; back problems secondary to very overweight children are a common finding even among carers of young children receiving steroid treatment.

The development of a moon face presents a practical problem for the radiotherapist. A well fitting face mask is required to ensure that the patient's face is correctly positioned for optimal delivery of cranial radiation. An increase in facial adipose tissue may require the moulding of a new mask: an unpleasant experience for the child and one that delays administration of essential treatment. Additionally, altered body habitus may add to the distress experienced by the patient and his or her family during terminal care.[22]

Peptic ulceration and gastritis are complications of steroid administration causing severe morbidity and are associated with the risk of haemorrhage and perforation.[23]

Mucocutaneous candidiasis is an additional common finding in young people with CNS tumours receiving steroids as they are often receiving immunosuppressive chemotherapy.

LONG TERM SEQUELAE

Several of the adverse effects of corticosteroids may be slow to resolve after cessation of treatment and recovery may be incomplete, especially for proximal myopathy, cataracts, and osteoporosis. The development of these complications compounds the difficulties of neurological rehabilitation.

The possibility of addisonian crisis requires the stepwise reduction in dose on completion of prolonged courses. The risk may persist for at least one year after cessation and exogenous steroid administration during periods of stress is necessary for those at risk.

Recommended approach to corticosteroid use

INDICATIONS

It is important to restrict the use of corticosteroids in patients with CNS tumours in order to maximise their quality of life. They should be prescribed only in situations in which their use will be of genuine benefit. Unfortunately, CNS tumours frequently present the clinician with few therapeutic options. It is tempting in these circumstances to resort to glucocorticoids.

Raised ICP secondary to peritumoral oedema

Steroid treatment for raised ICP should be started only if it allows time for a therapeutic intervention, which has a chance of treating the malignancy, to become effective. Such interventions include surgical resection and debulking in addition to radiotherapy. If these options are not available, then corticosteroids should be used sparingly to treat neurological symptoms secondary to progressive disease.

Preparation for neurosurgery

When prescribed in preparation for a neurosurgical procedure to reduce cerebral oedema corticosteroids should be reduced and stopped as soon as can be tolerated after the operation. Vigilance and awareness of the implications of long term administration are required to achieve this objective.

Antiemetic

Increasingly intensive trials of chemotherapy have increased the frequency of emesis in this cohort of patients. Glucocorticoids may reduce permeability of the blood-brain barrier to cytotoxic agents and should be used only if other treatments, including metoclopramide, prochlorperazine, and the 5-HT3 receptor antagonists as antiemetics,[24] have failed.

Prevention and treatment of allergic reactions and anaphylaxis

The same priniciple applies for these indications as for antiemetics. Chlorpheniramine should be used initially and steroids added if adequate control is not established.

Replacement treatment

Disturbance of the hypothalamo-pituitary-adrenal axis occurs after tumours in the vicinity of these structures and many patients require lifetime replacement treatment. Management should be shared with an endocrine service.

Special circumstances

Children with brain stem tumours present a special situation. Most of these patients will receive radiotherapy and are at high risk of developing peritumoral oedema during this treatment. Consequently, many will be given corticosteroids for the whole of the four to five week period of radiotherapy. Vigilance for side effects and adequate supportive care are required.

Table 1 Steroid regimen for children with CNS tumours

Indications	**(i) Raised ICP** **(ii) Preparation for neurosurgery** **(iii) Antiemetic**	**(i) Allergic reactions** Prevention Treatment **(ii) Anaphylaxis**
Drug	Dexamethasone	Hydrocortisone
Route	Oral, intravenous	Intravenous
Starting dose	5-10 mg/m^2/day *in divided doses* OR 0.5 mg/kg/day *in divided doses*	4 mg/kg bolus
Maximum	16 mg/day	200 mg bolus
Notes	Smaller doses if possible Trial of 3-5 day courses for raised ICP Only use as antiemetic if other drugs not effective	2 mg/kg 6 hourly if needed Only use if chlorpheniramine inadequate, or anaphylaxis

All patients prescribed steroids receive concurrent oral nystatin and an antacid (magnesium trisilicate preparation).

Despite our stated objective of only using corticosteroids to allow time for other therapeutic interventions to take effect humanitarian prescribing is essential. Their short term use in the terminal setting may be highly appropriate, enabling the patient to reach a much desired anniversary date or sought after meeting.

STEROID REGIMEN

Corticosteroid regimens for the treatment of cerebral oedema are based on 'conventional wisdom and use'. A literature review (*Medline* and *Bath Information and Data Services, 1985-1996*) reveals a paucity of studies. Although the steroid dose in the management of adults with metastatic brain tumours has been evaluated: Weissman *et al*[25] and Vecht *et al*[26] have reported that lower doses than the traditional 16 mg/day dexamethasone are equally as effective yet with many fewer adverse effects.

Alternate day steroid treatment for nephrotic syndrome has been shown to be effective with few long term side effects.[27] Unfortunately, our clinical experience suggests that this mode of administration has no value in the treatment of raised ICP. We have found short, sharp bursts of 10 mg/m^2/day dexamethasone for three to five days, however, useful in the control of symptoms for periods of up to four weeks.

Concurrent administration of an antacid, for example a magnesium trisillicate preparation, reduces the risk of gastrointestinal side effects. Similarly, the occurrence of oral thrush can be decreased by the prescription of an oral antifungal agent, for example nystatin. Neither of these interventions is expensive yet each may greatly improve the patient's quality of life and the palatability of steroids.

Table 1 shows our regimen for glucocorticoid use in children with CNS tumours.

Conclusions

Corticosteroids are exceptionally valuable in the management of children and young adults with CNS tumours. However, they are not a universal panacea and their administration is often associated with high levels of morbidity. Their use must be closely regulated. Adoption of standardised guidelines and the use of the lowest possible dose for as short a course as possible is essential if morbidity is to be minimised.

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