MANAGEMENT OF PERITUMORAL EDEMA

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INTRODUCTION

Peritumoral or localized edema occurs in most intrinsic and extrinsic brain and epidural tumours. Although the pathogenesis of peritumoral brain edema is not fully understood, it is believed to find its origin primarily in an increase of extravascular space secondary to the leakage of plasma constituants across an injured blood-brain barrier i.e. across altered or newly formed capillaries characterized by an absence of tight junctions, fenestrations and decreased number of pinocytic vesicles. The increased capillary permeability is also mediated by the release of vasoactive cytokines and mediators of tumour associated angiogenesis.

Within individual brain tumours there are significant quantitative regional variations in capillary permeability. In epidural metastases the dura provides an effective barrier to the neoplastic spread and the pathophysiology of spinal cord edema is probably different. However, the edema is *vasogenic* in both cases and responds to appropriate treatment. Brain edema accumulates preferentially within the white matter. Radiologically, the edema roughly corresponds to the hypodense area on CT and hypointense area on T1W or hyper-intense zone on T2W-MRI, that surrounds the contrast-enhanced part of the tumour. While this assumption is often largely correct in metastases, in primary brain tumours this area is usually extensively infiltrated by malignant cells.

Glucocorticosteroids are presently the first choice drugs in the treatment of vasogenic CNS edema (1, 2). Other drugs are either less active or more difficult to use for prolonged therapy in the every day clinical practice.

INDICATIONS OF CORTICOSTEROIDS (CS) IN NEURO-ONCOLOGY

1) BRAIN TUMOURS

Up to 70% of all brain - tumour patients will demonstrate a significant clinical improvement which may start 24-48 hours after the initiation of treatment and keeps improving gradually over several days (1,2). The clinical benefit is often correlated with the decrease of white matter edema and of the mass effect. In some cases there is an attenuation, sometimes even a complete vanishing of contrast enhancement. When optimal CS-doses are used, radiological changes are maximal after 15 days of treatment (3). There is no indication that CS may posses any anti-neoplastic activity in human brain tumours at concentrations used *in vivo* except in primary CNS lymphoma. In patients with suspected CNS-lymphoma CS, should not be administred before diagnostic biopsy is performed.

2) EPIDURAL METASTASES

In patients with epidural metastases, CS relieve rapidely and effectively the spinal pain and to a lesser extent, improve the neurological deficit (1). Their effectiveness on the neurological deficit is partially based on experimental data. CS have an established anti-tumoral effect only in tumours with lymphocytic component. Note : in some centers, a 24-hour perfusion of CS is given during operation of medullary tumours, but utility of this procedure remains unproven.

MECHANISMS OF ACTION OF CORTICOSTEROIDS

Naturally occuring corticosteroids are of two types :

1 - *Mineralocorticosteroids* (aldosterone) increase renal resorption of Na, decrease the resorption of K, and favour systemic hypertension. They have no effect on vasogenic brain edema.

2 - *Glucocorticosteroids* : hydrocortisone (or cortisol) and cortisone (active only when metabolized in cortisol) have multiple effects. They decrease vasogenic brain edema mainly by reducing the permeability of tumour capillaries, and by restoring the blood-brain barrier. CS exert some mineralocorticoid activity which is considerably decreased in synthetic CS. The mineralocotricoid and the glucocorticoid activity of the main CS are compared to cortisol (=1) in Table 1.

In patients treated with dexamethasone or methylprednisolone, mineralocorticoid effects, particularly hypokalemia, are rarely severe. Routine supplementation with potassium is unnecessary, but serum levels should be checked regularly in patients on prolonged therapy. However, serum level does not reflect intra-cellular concentrations of K, and patients comp-laining of cramps should be supplemented with K.

Low sodium intake may help to reduce systemic hypertentension and peripheral edema.

SIDE-EFFECTS

Anti-edematous activity of CS cannot be dissociated from their multiple side effects, presumably because they are mediated by the same receptors. The use of CS is therefore hampered by a cohort of toxic effects which are summarized in Table 2. All are related to the total administered dose and to treatment duration. Low serum albumin (< 2.5g/100 ml) is a risk factor for CS toxicity. Several side effects may be either prevented or minimized by appropriate prophylaxis and treatment (Table 2).

Behavioural disorders respond to dose tapering or drug discontinuation. In patients with persistent disorders benzodiazepines, antidepressant or antipsychotic drugs may be necessary, for more information see guidelines for treatment of psychiatric disorders.Insomnia may be minimized by avoiding CS-administration late in the day. Prophylactic adminisration of lithium carbonate to avoid psychotic episodes is based on few observations and is currently not recommended.

Muscle atrophy (4) predominates in pelvic and quadriceps muscles. It may be minimized by physical training and possibly by high protein intake. Important respiratory distress due to diaphragmatic involvement may occur even in the absence of proximal weakness.

Epidural lipoma possibly responds to low -calorie diet, but symptomatic patients usually require surgical removal.

It remains uncertain whether CS increase the risk of gastric or duodenal ulcer when used alone. However, CS clearly increase the risk of gastro-intestinal perforation particularly in bedridden and constipated patients, e.g. in patients with epidural cord metastases (5, 6). CS also exacerbate ulcers induced by nonsteroidal anti-inflamatory drugs (NSAID). The combination of CS and NAIS must be avoided, but if used requires the co-administration of proton pump inhibitors (PPI).

The following instructions should minimize the gastrointestinal toxicity of CS :

- In patients without symptoms or history of peptic ulcer, drug prophylaxis is not necessary.
- Symptomatic ulcer does not contradict CS-treatment, but requires the administration of a PPI such as omeprazole or an anti H2 drug and the performance of a control gastroscopy one month after the initiation of treatment.
- In asymptomatic patients with a past history of ulcer, gastroscopy and biopsy for Helicobacter pylori should be performed. No treatment is needed in patients without ulcer and negative for Helicobacter pylori. Patients with a positive serology for Helicobacter pylori must be treated with antibiotics (clarithromycine 2 x 0.5 g and amoxicilline 2 x 1 g) for 7 days and IPP for 8 weeks. Patients with asymptomatic ulcer who are negative for Helicobacter pylori should receive either PPI or anti-H2 drugs and control gastroscopy should be performed one month after drug discontinuation Gastric pain without ulcer usually responds to anti-acid drugs.

Hyperglycemia occurs in 1-5 % of patients with normal pancreatic endocrine function receiving CS, and routine low carbohydrate diet is not necessary in these patients. But individuals presenting with glucose intolerance (i.e. fasting glucose > 110 mg/100 ml) or patent diabetes require low carbohydrate intake and usually either an institution or an intensification of insuline therapy. In some patients with moderate hyperglycemia and stable CS-doses, oral antidiabetic agents may suffice, but the use of stable CS-doses is uncommon in neuro-oncology. In case of clinical deterioration, glycemia should be checked in brain-tumour patients which are on CS and antidiabetic treatment should be adapted if necessary.

The aim of treating CS-induced osteoporosis (7,8) is to prevent bone fracture, mainly vertebral and femoral. The main risk factors for developing osteoporosis are postmenopause, aging, low bone mineral density,and dose and duration of CS treatment To minimize osteo-porosis, patients should be encouraged to have physical activity, to stop smoking, and to moderate alcohol intake. Medical prophylaxis is recommended when CS-administration is anticipated to last three months or longer in patients without risk factors, and one month in patients with increased risk, particularly low bone calcium mass. The recommended drugs are biphosphanates andvitamin D3 plus calcium. Biphosphanates, (e.g. alendronate 10 mg daily or 70 mg weekly p.o. , or resindronate 5mg daily or

35mg weekly p.o.), must be taken in one morning dose before the intake of any food or drug. Recumbent position is prohibited during 30 minutes following biphosphanate administration. Biphosphanates are usually well tolerated. However, they cannot be used in patients with gastric ulcer or oesophagitis. Biphosphanates may cause hypocalcemia and, when given i.v., fever.

Vitamin D3 (800 IU daily) combined with calcium supplementation (1.5 g daily, in patients with low dietary calcium intake). Calcium alone is insufficient to prevent rapid bone loss in patients on high CS-dose.

Opportunistic infections include oral candidosis, which may be easily detected by routine mouth examination, tuberculosis and pneumocyctis carini. However, except in immuno-compromized individuals, routine prophylaxis with anti-tuberculous drugs or trimethoprim plus sulfamethoxazole is not used.

ROUTES, DOSES AND DURATION FOR CS-ADMINISTRATION

There are no demonstrated and widely accepted rules for the best use of CS in neuro-oncology. The dominant rule is *to achieve and maintain a satisfactory effect while using the lowest possible doses for the shortest time.* To achieve this goal we suggest the following :

1. Use mainly dexamethasone (DXM) as it has the lowest mineralocorticoid activity. For the same reason, consider methylprednisolone (MPR) as the second best choice. In some countries (France, Spain…) only 0.5 or 1.0 mg pills of DXM are available, and MPR may be prefered for practical reasons when high doses of CS are needed.
2. Start with a daily dose of either 16mg DXM or 96 mg MPR. In patients with impaired consciousness or impending herniation, give an intravenous bolus of either up to 40 mg DXM or up to 240 mg MPR. Avoid intramuscular injection as the uptake varies markedly depending on the preparation.
3. If a satisfactory effect is achieved after a 7-day treatment , try to reduce CS-doses.

   3.1 After extensive tumour resection or in patients with limited brain edema, CS should be tapered within 2-3 weeks, as symptomatic withdrawal syndrome is uncommon in patients treated for < 21 days. This can be achieved by decreasing the dose of CS by 50 % every 4 days untill reaching either a complete discontinuation or the minimal effective dose. In case of clinical deterioration return to the prior CS dose.

   3.2 In patients with poorly controlled tumours and/or extensive edema, this rapid rate of CS titration may result in a rapid clinical deterioration before specific treatment of the tumour is active. In such patients, CS should be tapered more progressively by reducing the dose by 25% every 8 days.

   3.3 In case of stress (infection, operation), CS dose may have to be temporarily Increased especially in patients on low CS-dose (equivalent to 30 mg hydrocortisone).
4. If the response to either 16mg DXM or 96mg MPR/day is unsatisfactory, escalation up to 96mg DXM and up to 500mg MPR/day helps in some cases (9), but leads to a significantly higher toxicity.
5. The administration (particularly the doses) of CS during the entire period of brain irradiation is controversial. The correlation between the use of CS and the completion of radiotherapy is uncertain (10). In most patients the principles for CS use during irradiation are similar to these

followed in brain tumour patients which are not irradiated, and are determined by neurological symptoms and signs. They are not recommended in asymptomatic patients, but should be used in patients with raised intracranial pressure, papilledema or progressive neurological deficit. CS may be used more intensively during the first and possibly the last week of irradiation as early radiation toxicity (attributed to brain edema) may be minimized by CS. In most patients with primary or metastatic (11) brain tumours CS may be safely maintained at 2mg bid during brain irradiation and discontinued shortly after its completion. Corticosteroids are recommended prophylactically on the day of radio-surgery and during the 48 hours following the procedure. CS reduce brain edema surrounding late radiation necrosis, which may require a prologed symptomatic treatment.

6. Alternate day therapy has been advocated to decrease toxicity while maintaining efficacy of CS. This procedure is considered to be effective in some diseases (myasthenia gravis, rheumatoid arthritis) but not in other (giant cell arteritis). There are no data supporting the use of alternate day therapy with CS in brain tumour edema.
7. In patients with epidural metastases CS doses are derived from those used in brain tumours : In patients with acute spinal compression, start with an i.v. bolus dose of either 10 mg DXM or 60mg MPR followed by p.o. administration of either 16 mg DXM or 96 mg MPR/daily An i.v. bolus of 100mg DXM does not seem to be superior to 10mg (12).

   Most patients with epidural metastases are treated either by irradiation or surgery plus irradiation in emergency manner. In patients with signs of severe spinal cord compression (such as impaired gait) either 16 mg DXM or 96 mg MPR/daily should be maintained throughout irradiation and rapidely tapered (by 50% every 4 days) thereafter.

   Lower doses of either 4 to 8mg DXM or 24 to 48mg MPR/daily may be used in patients with little or no signs of spinal dysfunction.

COTRICOSTEROID WITH DRAWAL SYNDROME

Symptoms and signs appearing in response to CS -withdrawal may be due to :

(a) recurrence or worsening of features related to the underlying tumoral disease,

(b) a relatively rapid drop in CS-serum concentration (arthralgias),

(c) adrenal insufficiency.

Clinical distinction may be difficult. The most prominent features of *secondary* hypothalamic-pituitary-adrenal depression such as anorexia, lethargy, weight loss, headache and fever may mimic tumour progression. On the other hand, acute myalgia and arthralgia may be mistaken for radicular pain. Manifestations of mineralocorticoid insufficiency (such as dehydration, hypotension, low Na and high K levels) are unusual in *secondary* adrenal depression. The degree of adrenal depression is related to the total dose and to the duration of CS administration. However, it varies considerably among patients, rendering it difficult to evaluate individual risk. Adrenal function recovery varies from days to over one year, and adrenal insufficiency may become symptomatic only during stress. Therefore the discontinuation of CS should be performed step by step after prolonged administration.

Even in such patients, the decrease of CS –dose can be quick in the beginning, but must be very slow when approaching the basal physiological daily need of 30mg cortisol. During stress (infection, operation,...) CS-doses should be increased, sometimes up to the equivalent of 100mg cortisol every 8 hours.

OTHER ANTI- EDEMA DRUGS

1. *Hyperosmolar solutions* of sugar, manitol or urea have been used to reduce brain edema,

mainly in patients undergoing neurosurgery or presenting with intracranial hypertension. The use of hyperosmolar solutions is made difficult by the shrinking of normal brain and rebound edema.

2. *Glycerol* 1.5g/kg given orally in four daily fractions is effective in patients with brain metastases but causes severe nausea and vomiting. Intravenous administration of glycerol favours phlebitis. Paradoxical increase in intracranial pressure may occur when it is given four hourly and this agent is no longer recommended by many authors.

3. *Corticotrophin (ACTH)* probably acts by stimulating CS production. Its use is no longer recommended as its pharmacological activity is less predictable than that of CS whereas the side effects are similar.

4. *Corticotropin-releasing factor* is a natural neuropeptide produced in the hypothalamus which stimulates the pituitary-adrenal axis. In a rat model hCRF showed substantial anti-edematous effect comparable to that of high-dose DXM and this activity was also found in a clinical study. The anti-edematous activity of hCRF is not mediated by a release of CS and differs from DXM. hCRF may be an alternative to CS. Its use is limited by systemic hypotension (13).

5. *Boswellic acid* is an active compound of Boswelia Serata gum used in the Eastern world to treat inflamatory diseases. Boswellic acid inhibits 5-lipoxygenase, an enzyme involved in the synthesis of cysteinyl leukotriene which is produced in large amounts by gliomas and contributes to the formation of peritumoral edema. In a group of 12 GBM-patients, Boswellic

acid reduced brain edema, prevented the use of CS, and had mild side effects. According to this preliminary observation, Boswellic acid could be a possible surrogate for CS in patients with mild to moderate (but not with severe) brain edema (14).

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Table 1 : Characteristics of Main Glucocorticosteroids

MOLECULE	DOSE EQUIVALENT TO 20 mg CORTISOL	BIOLOGICAL HALF-LIFE (hours)	ANTI-INFLAMMATORY ACTIVITY COMPARED TO CORTISOL (=1)	MINERALOCORTICOID ACITVITY COMPARED TO CORTISOL (=1)
HYDROCORTISONE or CORTISOL	20 mg	8 - 12	1	1
CORTISONE (Cortisol = active form)	25 mg	8 - 12	0.8	1
PREDNISONE (Prednisolone = active form)	5 mg	12 - 36	3.5	0.8
PREDNISOLONE	5 mg	12 - 36	4	0.8
METHYLPREDNISOLONE	4 mg	12 - 36	5	0.5
DEXAMETHASONE	0.75 mg	36 - 54	25 - 30	< 0.2

Table 2 : Main toxic effects of Glucocorticosteroids (GCS)

DISORDERS	INCIDENCE	MAIN FEATURES	FAVOURING FACTORS	THERAPY
MENTAL & BEHAVIOURAL	Common Rare (3 %)	. Anxiety, insomnia, euphoria . Depression, psychotic reaction	. More common with natural GCS . Psychiatric history	. Usually resolve with drug discontinuation, Benzodiazepines . Antidepressants, antipsychotics
MUSCULAR	20 %	. Type 2 fiber atrophy : proximal (mainly pelvic) weakness, dyspnea	. Lack of physical activity	. Physical training . High protein diet ≥ 150 g/d
FAT DEPOSIT	Common Very rare	. Facial, nuchal, truncal, abdominal, weight gain . Epidural : symptomatic spinal compression		. No therapy . Diet, Laminectomy
DIGESTIVE	≤ 3 %	. Gastrointestinal perforation . Gastric, duodenal ulcer	. History of ulcer . Use of anti-inflammotory drugs	. Anti-H2 drugs, avoid constipation . Proton pump inhibitors
HYPERGLYCEMIA	1-5 % in average population		. Glucose intolerance or diabetes (very frequent)	. Low carbohydrate diet . Insuline if diet fails
BONE LESIONS	. Up to 50 % . Rare	. Osteoporosis : causing fractures & pain . Ischemic necrosis (acute pain) mainly of femoral head	. Age, female gender (post menopausal)	. Biphosphanates .Vitamin D3 800 IU/d ± Ca . Hip prothesis
INFECTIONS		. Mainly fungal & gram negative . ↑ incidence & severity of tuberculosis	. Immunodepression . Leucopenia	. No prophylaxis . Treat symptomatic infections
HYPOKALIEMIA	. Rare with DXM		. Prolonged therapy	. No prophylaxis check serum level and add K
OTHER		. Hirsutism, hypertrichosis, altered body image, purple cutaneous striae, hypertension, oedema, cataract, renal calculi, glaucoma . reduced smell and taste . deep venous thrombosis		. No prophylaxis . Treat symptomatic hypertension and renal calculi . Low Na intake