

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 constituents 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 possess 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 administered before diagnostic biopsy is performed.

2) EPIDURAL METASTASES

In patients with epidural metastases, CS relieve rapidly 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 occurring 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 mineralocorticoid 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 complaining of cramps should be supplemented with K.

Low sodium intake may help to reduce systemic hypertension 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 administration 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-inflammatory 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 osteoporosis, 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 and vitamin D3 plus calcium. Biphosphanates, (e.g. alendronate 10 mg daily or 70 mg weekly p.o. , or resindronate 5mg daily or

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-inflammatory 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 \pm Ca . Hip prothesis
INFECTIONS		. Mainly fungal & gram negative . \uparrow 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