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Review paper

Use of corticosteroids in neuro-oncology

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Glucocorticosteroids (GC) play an important role in the treatment of neuro-oncologic patients. GC are used for the management of malignant brain tumors, either primary of secondary, neoplastic epidural spinal cord compression (NESC), as adjuvant chemotherapy of some central nervous system tumors and perioperatively in brain surgery. GC are believed to exert their influence on brain tumors mainly by reducing the tumor-associated vasogenic edema, probably by decreasing the increased capillary permeability of the blood–brain barrier (BBB). Experimental as well as clinical studies applying computed tomography, magnetic resonance and PET have supported these theories. However, other mechanisms have been proposed and investigated, such as a reduction of cerebral blood flow and oncolytic effects, the latter being controversial. The effect of GC is best observed in patients with cerebral metastases and gliomas. Studies on the effect of non-steroidal anti-inflammatory drugs (NSAIDs) gave conflicting results. Although some prefer methylprednisolone, dexamethasone is the GC given in the majority of neuro-oncologic patients, at an empirically chosen dosage of 4 mg qid. Dose–effect studies in patients with cerebral metastases as well as in patients suffering from NESC have been performed and lower doses in a twice daily regime may be sufficient. Side-effects may be divided in three groups: those originating from the mineralocorticoid activity, the withdrawal of the drug and the chronic excess GC administration. Steroid myopathy is the most frequent occurring serious side-effect in neuro-oncologic patients. Others include gastrointestinal perforation and hemorrhage, opportunistic infections, steroid diabetes, and skin and facial changes. The most important interaction is that with phenytoin. The influence of dexamethasone on the effects of chemotherapy and radiotherapy is also discussed. New developments in GC treatment include the local administration of dexamethasone.

Key words: Adrenal cortex hormones, brain edema, brain neoplasm, dexamethasone, spinal cord compression.

Introduction

Glucocorticosteroids (GC) are often used in oncological patients in general. They are of importance in the treatment of hematological malignancies, as well as in combined treatment regimes for solid tumors. GC also play a substantial part in the treatment of neuro-oncologic patients. They are used for the management of malignant brain tumors, either primary or secondary, neoplastic epidural spinal cord compression (NESC), as adjuvant in chemotherapy of some central nervous system (CNS) tumors, and perioperatively in brain surgery. The main purpose of treatment with GC is the improvement of symptoms and signs, awaiting further treatment with radiotherapy (RT), surgery or chemotherapy.

Although Addison conducted his clinical studies on the effect of adrenal disease in 1855, and Brown-Séquard found, in 1856, that mammals die within 12 h after the removal of the adrenals, the preparation of active adrenal cortex extracts had to wait until 1930.[1,2] Within the subsequent 12 years, the structures of 28 steroids from the adrenal cortex, found to be more important than the adrenal medulla, were elucidated.[3] In 1949 the dramatic effects of cortisone and adrenocorticotropic hormones were demonstrated in rheumatoid patients by Hench and his colleagues.[4]

At the beginning of the 20th century, the treatment of brain edema in neurosurgical patients, and of patients with elevated intracranial pressure, was commenced with mannitol.[5] Although most showed improvement, metabolic and other problems led to the search for other agents. Ingraham found a remarkable effect of corticosteroid replacement therapy on postoperative edema in patients being operated on for craniopharyngioma in 1952.[6] The beneficial effect of prednisolone in patients with cerebral metastases was demonstrated 5 years later.[7] The reason for applying this drug was the observation of adrenalectomy being effective in disseminated breast carcinoma.[8]

Whereas disappointing results were obtained with relatively low dosages of cortisone, high doses of prednisolone, sufficient to cause adrenal suppression, appeared to be effective. One of the first

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patients with brain metastases thus treated showed dramatic improvement of neurological symptoms. In 1961 it was shown that dexamethasone had a favorable effect on cerebral edema resulting from brain tumors and brain surgery.[9] The beneficial effect of corticosteroids in spinal metastasis was reported 7 years later.[10] Since the late 1950s a large amount of research has been performed and many articles on the effect of GC published, but many questions remained unsolved or were only partially answered, such as: how does it work, what is the optimal dosage and treatment scheme, and what factors play a role in toxicity. Research has particularly concentrated on the pathophysiology of peritumoral brain edema, the effect of GC and tumoral steroid receptors.

In this review article, several aspects of GC treatment in neuro-oncologic patients are discussed. Brain tumors, NESC, other indications of GC, side-effects and interactions are dealt with successively.

Brain tumors

Cerebral edema

Whereas many authors use the term peritumoral edema, arguments have been raised to apply the term tumor-associated edema: the former would deny the fact that the edema may be present at considerable distance from the tumor, even across the corpus callosum in the opposite cerebral hemisphere.[11] Furthermore, the so-called peritumoral edema may contain tumor cells, particularly in the case of primary brain tumors.[12]

Many symptoms and signs from intracranial tumors result from tumor-associated edema, the reason why research has focused on the elucidation of the pathogenesis and treatment of this problem.

The beneficial effect of GC in patients with brain tumors has been attributed to the reduction of cerebral edema, although other mechanisms, such as oncolytic effects and an early reduction of cerebral blood volume, may also play a part.[13]

A large amount of research has been performed to analyze the pathophysiology of brain edema. Several types of brain edema have been discerned as based on the pathogenesis: cytotoxic and ischemic edema are observed in patients with cerebral infarcts, hemorrhage and trauma, and GC are much less effective in those types of edema.[14–16] In brain tumor patients, the edema is vasogenic: it is localized in the extracellular space of mainly the white matter and it is caused by changes in the blood–brain barrier (BBB). Plasma proteins, other large molecules and water-soluble polar compounds may move into the extracellular spaces of the brain parenchyma in this situation.

Four inter-related processes have been conceptualized for the origin of tumor-associated edema:[11]

(1) Increased microvascular permeability due to factors produced by the tumor.
(2) The permeability of new microvessels associated with tumor angiogenesis.
(3) Immunological factors.
(4) Increased microvascular permeability associated with the inflammatory process involved.

Human biopsy material from glioblastomas, gliomas, meningiomas and metastases has been investigated to establish the components of vasogenic edema.[17] Positive correlations were found between water content, on the one hand, and serum protein levels and sodium content in tumors and tumor-associated edema, on the other, except in metastases. Probably protein and sodium both play a role in edema formation.

Capillary permeability in tumor-associated brain edema has been investigated extensively. Increased capillary permeability of the tumor appeared to be a major source of edema.[18] Experimental brain tumors, as well as human malignant gliomas have been shown to secrete diffusible factors that are responsible for capillary endothelial leakage.[19–24] Macrophages and leukotrienes also play an important role in the formation of peritumoral edema,[25] although some have denied the action of leukotrienes with this respect.[26] Prostaglandins, arachidonic acid in particular, have been examined and were found to mediate the alteration of the BBB permeability.[27]

Tumor-associated edema, its production and propagation, and the effect of steroid therapy can be examined by regional imaging techniques.[28] Magnetic resonance (MR) longitudinal relaxation time (T1) was found to be highly correlated with water content of the cerebral cortex and white matter in man.[29,30] The time-course of propagation of extravasated contrast medium from small brain metastases into the peritumoral edematous white matter was studied by computed tomography (CT). The formation rate of edema fluid was 0.5–32 ml/h, whereas the speed of edema spreading measured 1.9 mm/h.[31,32]

Experimental studies with GC: glioma and metastases

GC may exert their effects on cerebral edema in several ways: dexamethasone decreases the normal permeability for large molecules in mice, which suggests that it influences cerebral edema in some way.[33]

It was found that GC may decrease the capillary permeability of tumors.[34] In rat glioma dexamethasone resulted in an 83% reduction of vascular permeability to intravenous Evans blue, an increased percentage of vessels expressing GLUT1 (a marker of barrier endothelium, linked to permeability restrictions), lower vascular density and smaller tumor size.[35]

Water and serum protein content in edematous tissue of glioblastomas was found to be decreased with increasing dexamethasone concentration in biopsy material.[17] This could not be demonstrated in gliomas and meningiomas. The increased permeability can be reduced by GC within 1 h.[36]

In another study it was found that the clinical improvement with dexamethasone was not likely to be due to a non-specific reduction in tumor vessel permeability to polar substances, as demonstrated with mannitol.[37] Recently the decreasing effect of dexamethasone on capillary permeability in brain tumors has been argued, whereas the reduction of tumor extracellular space was confirmed. The authors stated that decreased tumor edema and size after dexamethasone treatment would not depend on changes in capillary permeability.[38] Thus, controversies on this subject remain to be solved.

Imaging studies of the effect of GC in cerebral edema

CT scan. Steroid treatment has been shown to improve midline shift, ventricular compression, edema, enhancement intensity and the size of the enhancing mass in 11 patients with recurrent malignant glioma.[39] The effect of GC on vasogenic edema in several tumors was investigated with CT. In five cases with meningiomas, reduction of edema could hardly be detected; in four cases with glioma, reduction was considerable; whereas in three cases with metastases it was most remarkable: a reduction to approximately 25% of the original edema volume within 2 weeks. Some decrease was also noted in one patient with acustic neurinoma.[40]

The formation and propagation of cerebral edema surrounding metastases has been studied by CT. Following treatment with dexamethasone the formation rate of edema fluid appeared to be reduced by 30–50%.[31]

MR scan. GC treatment leads to a reduction of the visualized tumor on MR scan, whereas the solid core, represented on the T1 weighted images, is hardly influenced. GC may mask the (lack of) effectiveness of any simultaneous therapy.[41]

It is remarkable that the water content of peritumoral white matter, as measured by T1 relaxation time, did not change during the first 6 days after the administration of dexamethasone. Mannitol did reduce T1, and consequently peritumoral white matter edema, within 15 min.[29] Therefore, the clinical improvement observed shortly after the administration of GC cannot be attributed to the decrease of tumor-associated edema.

PET scan. Blood-to-tumor transport of ^{82}Rb has been measured by PET in patients with primary or metastatic cerebral tumors, before, at 6 h and at 24 h after a 100 mg intravenous bolus injection of dexamethasone. A 29% decrease in blood-to-tumor transport rate constant could be established at 24 h, as well as at 5–6 h, supporting the hypothesis of a positive effect of dexamethasone on tumor capillary permeability.[42,43]

Changes after dexamethasone treatment, as observed with PET scans of 10 brain tumor patients, were consistent with a direct vasoconstriction of cerebral blood vessels.[44] This may be due to the inhibitory effect of GC on endothelium prostacycline production, resulting in vasoconstriction.[45,46] Vascular volume in tumor tissue of experimental RG-2 gliomas was reduced after dexamethasone therapy, in contradistinction to tumor-free brain regions.[47]

Effects in tumors, other than gliomas and metastases

GC have been demonstrated to exert much less influence on cerebral edema surrounding other tumors than gliomas or metastases: the edema in acustic neurinomas decreases in the order of 10–20%, whereas the effect on meningiomas is also small.[40,48] Tumor-associated edema is observed in different tumors and is possibly not related to one single mechanism, as discussed above. Meningiomas have an unpredictable degree of edema.[49] In supratentorial meningiomas, the amount of edema was found to be correlated with the prostaglandin

level. There was no detectable effect of dexamethasone on tumor prostaglandin levels nor on water concentration at surgery. Steroid treatment did not correlate with prostaglandin levels, which might explain the inconsistent effects of GC on the edema surrounding meningiomas. It was hypothesized that the balance among several prostanoids, with opposing effects on vaso-activity, determines the net vascular homeostasis.[50]

Effects of other anti-inflammatory drugs

As GC have considerable adverse effects, the effect on tumor-associated edema of other drugs have been investigated. Reichmann demonstrated in the rat C6 glioma sphenoid implantation model that tumor-induced protein extravasation was diminished by steroids as well as by non-steroidal anti-inflammatory drugs (NSAIDs).[51]

In a C6 spheroid tumor implantation model, long-term high dose ibuprofen resulted in decreased tumor growth.[52] The same drug was able to improve the Karnofsky scale of approximately 40% of patients with brain tumors and tumor-associated edema.[53]

This anti-edema effect of NSAIDs has not been confirmed by others.[54] The effects in experimental neoplastic epidural spinal cord compression will be discussed below.

Other possible mechanisms of action of GC

An inhibitory effect of GC on cultured human astrocytoma cells has been established.[55,56] More recent studies in experimental brain tumors, using local delivery techniques with GC, have also demonstrated an effect on tumor volumes.[57,58]

Dexamethasone at high concentrations shows growth inhibition in tissue cultures from neuroepithelial tumors and meningiomas.[59] Dexamethasone and methylprednisolone have been found to promote cellular differentiation, supporting a cytostatic role for GC in the treatment of brain tumors.[60] GC receptors have been determined in normal brain and several tumors.[61–63] These receptors were found to modulate the growth of cultured neuroepithelial tumors. In some *in vitro* studies, glioma cell cultures with GC receptors were found to be stimulated in growth.[62,64] Thus, the cytotoxic effect of GC remains a controversial subject and seems to be clinically relevant only in lymphoproliferative disease and some types of breast carcinoma.

The lethal dose of dexamethasone in human glioblastoma cell cultures has been determined and it was found that this is probably higher than can be tolerated by systemic delivery. Interstitial administration, however, might be considered to overcome this problem.[65]

Treatment

Clinical studies with GC. If left untreated, the median survival of patients with cerebral metastases is approximately 1 month.[66,67] By using GC, the median survival increases to approximately 2 months.[68] However, as these data emanated from older series, and from a period when tumors were detected later in the course of the disease, and often treated less effectively, these results may be to pessimistic for the present situation.[69] Additional whole brain radiation therapy (WBRT) increases the median survival to 3–6 months.[66,70]

In patients receiving RT combined with GC, symptoms were demonstrated to decrease earlier than in those treated with RT only.[71] However, overall neurologic outcome did not differ between the two treatment groups. Improvement in patients with cerebral metastases may be observed within a few hours after administration of GC and approximately 70–80% will show significant clinical improvement.[67,72] Improvement following the institution of dexamethasone therapy is more dramatic in patients with symptoms of generalized cerebral disease and signs of herniation than in those with focal symptomatology. Probably this is due to the fact that steroids exert their major effect on brain edema, which is supposed to be more present in the first group.[73]

The dosage of dexamethasone usually administered has been chosen empirically at 4 mg qid,[74] but patients that are not responsive to this dosage may benefit from doses up to 100 mg/day,[75] although this may lead to more side-effects, as will be shown further on.

Although many patients with cerebral metastases die within 6 months, mostly resulting from systemic progression of the tumor, some patients may benefit from intensive therapy. This includes surgery (particularly in the case of single metastases)[76,77], radiotherapy, in some cases brachytherapy[78] or radiosurgery,[79] and chemotherapy, the latter in particular for breast cancer.[80] Lifetime may be prolonged with improved quality in some cases.[81]

Which steroid and what dosage? The adrenal cortex produces corticosteroids and androgens. The first group can be divided in glucocorticoids (e.g. cortisol) and mineralocorticoids (e.g. aldosterone). This division is based on the potencies of sodium retention and hepatic glycogen deposition. The synthetic prednisone has some sodium retaining properties, and as dexamethasone has lower mineralocorticoid activity than other GC, it is preferred. The dosage of dexamethasone was empirically established at 16 mg/day in the 1960s.[74] It may be administered orally, intramuscularly or intravenously. If no response to lower doses is observed, doses up to 100 mg of dexamethasone or 2000 mg of methylprednisolone may be given in some instances.[75,82] The dosage of 16 mg is usually given in four doses, but considering its prolonged plasma half-life, it may be given twice daily.[73] This regime might also prevent prolonged hypothalamic–pituitary axis (HPA) suppression.[83] For the same reason others preferred methylprednisolone in an alternate-day regime. Dexamethasone was supposed to suppress the HPA axis too long, because of its longer half-time.[84] Ehrenkranz and Posner, however, did not find anti-edema effects with an alternate-day regime.[85] One way to find out the best drug would be to conduct a randomized controlled trial with both drugs.

Dose–effect studies have hardly been performed until recently. Experimental studies addressing this issue have been performed, but these concerned neoplastic epidural spinal cord compression.[86,87] In two randomized studies in patients with metastatic brain tumor, it was demonstrated that a daily dose of 8 mg was as effective as 16 mg after 1week of treatment, and that 4 mg/day resulted in the same degree of improvement as 16 mg/day after 1 week of treatment. However, the 4 mg dosage had to be tapered more slowly than the other two dose regimes (8 and 16 mg), as an increase of neurologic signs during tapering was more frequent in this group, than in the other two, and the 4 mg dosage had to be reinstituted. The latter dosage of 4 mg/day was recommended, if no signs of impending herniation were present.[88]

Duration of treatment and tapering. Considering the side-effects, that will be discussed below, the treatment should last as short as possible. In most instances it has been common practice to continue GC treatment until the end of radition therapy. A regime of twice daily administration of dexamethasone (8 mg bid), tapering the dosage every 4 days with 50% and continuing with 2 mg bid until the last day of RT, provided good clinical results with minimal morbidity.[89] The incidence of side-effects from RT with the fraction dose regimes in use at present is low if GC are used.[90] However, if patients receive RT without GC, toxicity is not more common. In one study 30% of patients did not receive GC during RT for brain metastasis. No toxicity was reported from this group.[71] The continuation of GC until the end of RT may be particularly valuable in patients with elevated intracranial pressure or in those with cerebellar metastases.

Long-term steroid dependency after the completion of RT occurred in 20% of 183 patients from a retrospective study.[90] In patients with cerebral glioma, GC dependency appeared to be a reliable prognostic indicator in terms of survival.[91]

NESC

The beneficial effect of GC in patients with NESC was first demonstrated by Cantu in 1968. He observed striking neurologic improvement within 24 h after the administration of methylprednisolone in two patients, one with metastasis from an endometrial carcinoma and the other from an ovarian tumor.[10] GC and radiotherapy have become the mainstay in the treatment of NESC.[92]

Pathophysiology

The pathophysiology of NESC is different from that in brain tumors, not in the least because there is no actual contact between the epidural tumor and the spinal cord, which is prevented by the dura.[93] Besides the well-known vasogenic cord edema (caused by compression of the venous plexus and the mechanical cord compression leading to blood-cord barrier disruption),[94,95] venous hemorrhage, loss of myelin, and ischemia seem to play an important role, as has been demonstrated in animal models.[86,92,95,96] The amount of edema has been correlated to the neurological deficit.[86,94]

As pencil-shaped softenings have been found at autopsy, a combination of neural compression and circulatory disturbance may be responsible.[97] Prostanoids play a role in the processes involved with NESC. Increased production of prostaglandin E_2 (PGE_2) was demonstrated in experimental NESC. PGE_2 synthesis, vascular permeability and spinal cord edema could be reduced by the administration of the serotonin antagonist cyproheptadine.[98] PGE_2 synthesis can also be inhibited by GC and NSAIDs.

Siegal demonstrated a positive effect of the treatment with indomethacin and dexamethasone in experimental NESC, but it was not clear whether this was due to edema reduction. Specific gravity (a characteristic of the tissue that is not only influenced by the water content, but probably also by tissue blood volume and dry matter composition, reflecting complex pathophysiological processes) changes were corrected by dexamethasone treatment, whereas water content did not change. Treatment with indomethacine reduced both elevated water content and specific gravity values back to normal levels.[99] Indomethacine compared favorably with dexamethasone in delaying the onset of paraplegia in experimental NESC.[100] Thus, the mechanism of action by GC in NESC needs further elucidation. Posner suggested oncolytic effects to be partly responsible for the improvement of four patients with NESC. However, two had a lymphocytic component in the tumor.[101]

Treatment

In patients with NESC, GC may result in improvement of neurological symptoms and alleviate pain. Treatment should be started as soon as the diagnosis has been confirmed by myelography, CT or MR. In some instances, however, it will be sensible to start it at the suspicion of the diagnosis, before the diagnostic imaging is performed, in particular if serious cord compression is suspected. In any case it should be instituted before the start of radiotherapy, as symptoms and signs may worsen by radiation.

A standard dose of dexamethasone 4 mg qid has usually been given, comparable to the situation in brain tumors.[93,102,130] However, as laboratory studies demonstrated a dose–effect relationship with dexamethasone usage,[86,87] a loading dose of 100 mg, followed by 24 mg qid, has become current in many centers.[104,105] Clinical research has been undertaken to elucidate this issue. In a randomized controlled trial with patients suffering from NESC, an initial bolus of 10 mg was compared with 100 mg, in both regimes followed by 16 mg daily. No differences could be established between the two groups as for the effect on pain-relief, ambulation and bladder function.[103]

Despite these results, some prefer an initial bolus of between 10 and 100 mg, depending on the severity of neurological signs and symptoms. The higher doses are administered to patients with profound and rapidly progressive neurological signs.[92] The relief of pain, in particular, may occur within a few hours of the administration of GC and the first radiotherapy session. It is not known if the use of GC contributes to overall neurological outcome,[93] although in a recent study, comparing high-dose dexamethasone with placebo, in patients with NESC treated by radiotherapy, ambulation after treatment and after 6 months was better in the dexamethasone group. Median survival was identical in both treatment groups.[106] The most important prognostic factor is the neurologic function at the time of diagnosis.[107,108] Non-ambulant patients will rarely become ambulant after treatment.[107]

Duration of treatment and tapering

GC therapy is mostly continued until the end of radiotherapy to prevent radiation-induced spinal cord edema.[92,93] In an experimental study, however, radiation induced edema did not seem to play an important role.[109] Sometimes tapering is started before or during RT. The duration of treatment should be chosen on an individual basis. In patients with minor symptoms and signs, combined with minor NESC on imaging studies, GC may be tapered earlier than in severe compression with paraparesis. An example of a tapering schedule may be: 16 mg, reducing by 4 mg every 3 or 4 days.[92]

Some patients have been treated by dexamethasone in combination with chemotherapy. NESC in patients with breast carcinoma, in particular, may respond to this treatment.[101,110,111]

Other indications for GC

Primary CNS non-Hodgkin lymphoma (pCNS-NHL)

pCNS-NHL represents less than 1% of all primary brain tumors.[112] Despite the low incidence, the issue is discussed here because of the important implications of the use of GC in these patients and because the occurrence of pCNS-NHL has gradually increased during the past decades. This cannot only be attributed to improved detection methods, AIDS or other forms of immunosuppression. The prognosis is poor.[112,113]

Striking results have been obtained with GC in these patients. The tumor may even disappear temporarily.[114–116] In some cases this remission lasted for a considerable period.[117,118] The rapid action of GC has often posed problems at surgery, particularly in the case of stereotactic biopsy, when tumors seemed to have disappeared on the planning CT

scans. Therefore, if a pCNS-NHL is suspected on CT or MR (homogenous contrast enhanced tumors in the subcortical white matter, often close to the ventricles), rapid diagnosis should be obtained, prior to the administration of GC.[119,120] In modern chemotherapy regimes for pCNS-NHL, dexamethasone is often used.[121–123]

GC are sometimes used for the palliative treatment of radionecrosis, which may occur after brachytherapy or, less frequently, following stereotactic radiosurgery of brain metastases. Additional surgery may be necessary.[81] Radionecrosis may be difficult to discern from tumor growth, although PET with fluorodeoxyglucose may be helpful in this respect. Sometimes stereotactic biopsy may be required, as PET is rarely available. Symptoms related to swelling from inflammation in radiation myelopathy, a rare condition, may also respond to GC.[124]

Addendum

During the processing of this article an important study was published reporting the possibly favourable action of heparin and warfarin for the treatment of CNS radiation injury.

Glantz MJ, Burger PC, Friedman AH, Radtke RA, Massey EW, Schold SC, Jr. Treatment of radiation-induced nervous system injury with heparin and warfarin, *Neurology* 1994; 44: 2020–2027.

Side-effects and complications of GC treatment

GC have many effects: they stimulate lipolysis, gluconeogenesis, glycogenolysis, protein degradation and inhibit protein synthesis in musle and adipose tissue. The effect on lymphocytes is of importance too: GC decrease lymphocytic reaction, impair immunity, in particular cellular immunity, and bring about decreased inflammation.[3] The side-effects of exogenous GC may be divided into three main categories:

(1) Effects from mineralocorticoid activity.
(2) Effects from withdrawal of GC
(3) Effects from chronic GC excess

Complications from mineralocorticoid activity

As dexamethasone is the most frequently used steroid in neuro-oncology and has minor mineralocorticoid effects, these problems, such as hypokalemic alkalosis, sodium and fluid retention, edema and hypertension, are rarely observed. Peripheral edema may be severe and require therapy with diuretics.

Complications of withdrawal

The following problems may occur on tapering or discontinuation of GC.

(a) Symptoms may develop from the side of the tumor itself: too rapid withdrawal may lead to recurrent tumor-associated edema in the brain or spinal cord, resulting in cerebral symptoms, such as increasing lethargy or paraparesis. Increasing the dosage of GC is the treatment of choice in this situation.

(b) Steroid pseudorheumatism may occur. This syndrome embraces acute myalgias and arthralgias.[125] Sometimes it may be difficult to discern the syndrome from radicular pain and paresis in NESC.[126] It should be treated either by increasing the dosage of GC, followed by slower tapering, or by the administration of aspirin or NSAIDs.[125]

(c) Corticosteroid withdrawal syndrome, including anorexia, nausea, lethargy, arthralgia, weakness, desquamation and weight loss, may occur, even in the absence of adrenal insufficiency.[127] It is obvious that part of these symptoms may also be due to recurrent brain tumors and may confuse the physician.[126]

(d) Sudden withdrawal following prolonged GC treatment may result in serious complications, even in death.[128,129] Intercurrent acute illness during GC treatment may sometimes require temporary increase of the dosage, particularly if the patient has received GC for a prolonged period and is using a low dosage at that particular moment. Gradual tapering from the physiologic dosage may be necessary, sometimes with control of the plasma cortisol level.[129] In some instances the use of cortisol (30 mg: 20 mg in the morning and 10 mg in the evening) or cortisone acetate (37.5 mg in two doses) is preferred above dexamethasone.[130] Despite the high doses of dexamethasone used in neuro-oncologic patients, adrenal insufficiency occurs less often than expected, probably because of the rapid elimination of dexamethasone, the adrenals not being continuously suppressed. A twice-daily administration is probably preferable, as discussed above.[131]

(e) In children GC withdrawal has been associated with the syndrome of benign intracranial hypertension.[126,132]

Toxicity from GC excess

Many toxic effects of GC treatment have been described,[126,133,134] but not all are observed in neuro-oncologic patients. Some are not serious, such as facial and skin changes, or even beneficial, as for instance increased appetite and feeling of well-being. Night sweats, hiccups, tremor and insomnia may be inconvenient for the patient. The risk of side-effects increases with the duration (more than 3 weeks) and total dose given (more than 400 mg).[133,135] In a retrospective study, 30 of 59 neuro-oncologic patients (51%) developed at least one steroid toxicity and 11 (19%) required admission to a hospital.[133] In another retrospective study of 100 patients with glioma, who had been treated with dexamethasone in doses up to 96 mg daily, remarkably less toxic effects were found, steroid myopathy (SM) being the most frequent (6%).[136] The author studied a different patient population and this is the reason why comparison between studies is difficult. In 121 consecutive neurosurgical patients receiving dexamethasone combined with an antacid agent, three major complications (2.4%) occurred, two in patients with previous or concurrent gastrointestinal disease. It is remarkable that in 19 patients with prolonged use (mean 206 days) of dexamethasone (more than 40 mg/day) no complications occurred.[137]

In another series of 28 consecutive patients treated for NESC with high-dose dexamethasone (starting with 96 mg, tapered to zero in 14 days), eight patients had side-effects (28.6%), four of them considered as serious (14.3%)—one fatal ulcer with hemorrhage, the other three also gastrointestinal complications. After changing to an initial dose of 16 mg, no serious side-effects were observed in the following 38 consecutive patients.[134] In a group of 40 NESC patients, of whom duration of GC treatment was known, more steroid dependent complications were observed, if they were treated for more than 40 days.[107]

Low serum albumin has been identified as a possible risk factor for GC toxicity.[93,138] When serum albumin concentration is less than 2.5 g/100 ml the occurrence of GC toxicity is doubled. Elevated levels of free GC partly explain this increased frequency of side-effects.

Most of the complications are dose-dependent and reversible. The following side-effects will be discussed in more detail.

Myopathy

SM is probably the most frequently occurring complication of prolonged GC use in patients with primary cerebral tumors. However, it may also occur soon after the start of treatment. It should be realized that SM frequently occurs without elevation of serum creatine kinase (CK) or the well-known myopathic findings on electromyography.[126] It may cause serious handicap and recovery may be slow and incomplete.[3] It may be difficult to discern this complication from the symptoms of brain tumor progression or, more particularly, from epidural spinal cord compression, paraneoplastic Lambert Eaton myasthenic syndrome and polymyositis or leptomeningeal metastasis. In a retrospective study SM occurred in 10.6% of 216 patients with primary brain tumors following daily dexamethasone treatment for 2 weeks or more.[139] Although SM occurred over a wide range of peak and cumulative doses, two-thirds of the patients developed their weakness during the third month of treatment. It was suggested that substitution of dexamethasone by a non-fluorinated GC may be useful, if patients have become steroid-dependent.[139] This is based on experimental studies.[140,141] A remarkable fact from Dropcho's study was his finding that SM occurred less often in patients taking phenytoin. The interaction between dexamethasone and phenytoin will be discussed below.

In a prospective study of 97 neurosurgical patients, SM was not observed. However, in this study approximately 80% of the patients took GC less than 1 month.[137] Two other studies with neuro-oncologic patients reported frequencies of 19 and 59%.[133,142]

Gastrointestinal complications

Perforation. Perforation of the intestinal wall in patients receiving GC is a serious complication, involving high mortality rates.[143,144] In one study of 107 patients receiving 16 mg/day dexamethasone, three (2.8%) developed gastrointestinal perforation, and in a group of 226 patients tapered from 100 mg/day, it occurred in six (2.7%).[145] There was no difference between high- and low-dose GC treatment in the two groups. In another study, perforations were only observed with the high-dose regime.[134] Weissman found one sigmoid perforation in 59 neuro-oncologic patients receiving GC, whereas Heimdal observed two perforations in 28 (7.1%) and Weiner five in 719 (1.7%) (one lethal).[133,134,146] It has been suggested that it occurs

more often in bedridden, constipated persons with epidural spinal metastases and prevention of constipation might be important in this particular group of patients.[145] Age over 50 years and known diverticular disease were also identified as risk factors. Special care is required for the latter condition, in particular if the patient is complaining of abdominal discomfort, has fever or shows unexplained leucocytosis. Lower doses should be considered in these patients.[146] In a study of 125 patients with gastrointestinal perforations, 33% was associated with steroid use, the indication being a neurologic disease in 60%.[145]

Hemorrhage. Gastrointestinal hemorrhage was observed in 1.9% of 107 patients receiving low-dose (16 mg/day) and 3.5% of 226 following high-dose GC (tapering from 100 mg/day).[145] It occurred as frequent as gastrointestinal perforation, but appeared to be less serious. Heimdal observed 21 gastrointestinal hemorrhages in 719 neurosurgical patients (3.7%), one of them lethal[134] and Weissman four in 59 patients (6.8%).[133] The difference between the latter two groups was probably due to the difference in duration of treatment.

The association between GC use and peptic ulcer or gastrointestinal hemorrhage has been controversial. In a retrospective analysis of a large number of prospective, controlled investigations, this association was challenged.[147] However, pooled data from 71 controlled clinical trials strongly suggested a relationship.[148] In an editorial of the latter study the prophylactic administration of H2-blockers was recommended in those patients who are using other medications, that may promote the formation of ulcers, such as NSAIDs.[149] The concommittant use of GC and NSAIDs has been associated with a 10-fold increase in the risk of gastrointestinal hemorrhage.[150] In a study of 120 patients with brain tumors being treated with high-dose GC and stomach-protective agents, only one patient developed GI symptoms and a positive hemoccult test. However, there was no placebo group in this study.[151]

Opportunistic infections

The most common opportunistic infection in patients receiving GC is *Candida* pharyngitis and esophagitis, occurring in eight (13%) and six patients (10%), respectively, in one series of 59 neuro-oncologic patients.[133] Other infections have been observed, such as *Listeria monocytogenes*, *Pseudomonas aeruginosa cellulitis*, suppurative parotitis, pneumocystic carinii pneumonia.[133,152] Additional chemotherapeutics and the existence of steroid diabetes may attribute to the risk of this complication.

Other side-effects

Steroid-diabetes is a well-known complication occurring in 19% of 59 neuro-oncologic patients.[133]

Steroid-induced spinal epidural lipomatosis has been reported several times, mostly in people taking GC for an extended period, usually several months or years.[153,154] Slowly progressive paraparesis over months may develop, although acute, irreversible paraplegia has been observed as well.[154] In most cases the indication for GC use was other than neuro-oncologic.

Osteoporosis and avascular osteonecrosis are common complications of prolonged GC use. Avascular necrosis of the femoral and, less frequently, humeral heads after short-term GC treatment for brain edema has been described.[156] If present in the femur, it may be confused with spinal cord compression.[126]

Severe *psychiatric reactions* occur in approximately 5% of patients treated with GC, many of them developing affective or psychotic symptoms. It often occurs early in the course of treatment.[157] Most of the 14 patients from one series were using prednisone, one was taking dexamethasone and suffered from lung cancer. Steroid-induced psychosis is probably a rare complication if dexamethasone is used.[126]

Ophthalmologic complications, such as glaucoma and cataract, are rarely observed in neuro-oncologic patients, depending on the duration of treatment.

Interactions

GC treatment may interfere with other drugs, the most important being *phenytoin*, which is often used in patients with cerebral tumors. The mean bioavailability of dexamethasone in neurological patients, including neuro-oncologic patients, was 0.53,[158] which is lower than previously reported in healthy volunteers. This is probably due to the higher clearance by prior phenytoin or dexamethasone use.[159]

Liver enzyme induction from phenytoin results in decreased levels of dexamethasone.[160,161] Elevated phenytoin concentrations in patients receiving dexamethasone simultaneously have also been reported.[162] Interactions between these drugs may be rather complicated.[163] The less frequent occur-

rence of SM in patients using phenytoin has been addressed above.[139] A higher dosage of GC may be needed if phenobarbital or diazepam are used, comparable to the situation of Phenytoin.[164]

Paradoxically, reports have appeared on the negative effect of GC in patients receiving *chemotherapy*. As GC may decrease the increased capillary permeability in brain tumors, it might also inhibit transport of antineoplastic agents. Steroid treatment has indeed been found to decrease the delivery of methotrexate in experimental brain tumors, after the BBB had first been opened with mannitol.[165] Combined treatment of carmustine (BCNU) and high-dose methylprednisolone tended to be less effective than BCNU alone in patients with cerebral glioma with poor prognosis.[166] On the other hand, the positive effect of antineoplastic agents in brain metastasis and NESC from several tumors has been reported from clinical studies, as was mentioned above.[80,110,167–169]

Interaction between GC and *radiation therapy* has been described in experimental models. Dexamethasone has been found to be radioprotective in several non-glial cell lines.[170–172] This effect of dexamethasone, however, has not been established in rat glioma or human glioma cell lines.[172,173] At clinical concentration, dexamethasone was found to inhibit the C6 astrocytoma cell line and did not significantly alter the survival of the irradiated cells.[174]

Prospect

Interstitial drug delivery within the CNS, using controlled-release polymers, has been tried in experimental animals, the goal being to prevent side-effects and obtain higher local levels of GC in the tumor. High concentrations of dexamethasone in brain tissue could be achieved with minimal plasma concentrations, and tumor-associated brain edema could be treated effectively.[58,65] In a study with experimental brain tumors in rabbits, systemical and short-term local delivery of dexamethasone by osmotic pump were found to be equally effective for inhibition of tumor volume as well as on reduction of brain edema.[175] However, in comparison with systemic steroid therapy, a reduction in toxicity could not be proved in this study.

Dexamethasone may be of importance in gene-therapy. Tumor necrosis factor (TNF)-α-production was found to be stimulated in rat glioblastoma containing a TNF-α gene.[176]

The addition of vasopressin to GC has been investigated and may be favorable.[177] Further research to demonstrate a clinical effect of this combination is needed.

Conclusions

Although the origin of tumor-associated edema and the action of GC in brain tumors have been studied extensively, the knowledge increasing considerably during the past decade, not all questions are solved and new ones have been posed. Some controversies, in particular concerning the factors responsible for the altered permeability of the BBB, have arisen. GC are particularly effective in the treatment of brain metastases, primary cerebral tumors and NESC. Aside from the effects on tumor-associated edema, an effect on permeability of the BBB and cerebral blood flow seems likely. Not all patients suffering from the mentioned conditions require GC. It should be used if important neurological symptoms or signs have occurred. Furthermore, it should be considered if RT is planned, although even then, it may be omitted in some cases. If possible, GC should not be used for a period longer than 2–3 weeks. It may be reinstituted if symptoms reoccur. In some steroid-dependent patients it may be given for a more prolonged period. Particular attention for the side-effects should be paid in patients with NESC, as they are at risk for the development of gastrointestinal perforation.

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