Serious drug reactions to carbamazepine in oncologic patients after x-ray treatment.

Report of four cases

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SUMMARY

Carbamazepine is a valuable and widely used drug for treatment and prevention of epileptiform fits and further neurological conditions. Milder general symptoms like dizziness or drowsiness or cutaneous side effects like rashes, pruritus, urticaria, or multiform erythema are not unusual. Sometimes serious cutaneous adverse reactions e.g., Stevens Johnson syndrome, generalized erythroderma or even toxic necrolysis may appear.

We report on four cases: in three female patients, who have been operated for malignant brain tumors and were given carbamazepine for prevention of seizures, partial erythroderma developed; the fourth died from toxic epidermal necrolysis. All were treated with x-rays, in the female patients cutaneous manifestations disappeared after systemic treatment with corticosteroids and replacement of carbamazepine with other anticonvulsive drugs.

KEY WORDS

Carbamazepine, drug reactions, brain tumor, x-ray treatment, erythroderma

Introduction

Carbamazepine (CBZ) (Tegretol[R], Novartis), is a valuable and widely used anticonvulsant, but also antineuralgic, antimanic and antidepressant drug. It is used for treatment of partial seizures, both simple and tonic-clonic. It is preferred over phenobarbital for children because it has fewer adverse effects on behavior and alertness. The drug is also effective in treating pain of neurological origin (neuralgia), psychiatric disorders, including schizophrenia (1) manic depressive illness (2) and even aggression due to dementia. These numerous indications explain the wide spread use of the drug. On the market it is available under a score of trade names e.g. Carbatrol[R] (Shire Richwood), Epitol[R] (Tave) as well as others.

A number of usually not dangerous side effects are known. General symptoms like dizziness, drowsiness, vomiting, diplopia, abnormal liver function or bone-marrow suppression may disappear after continued treatment at reduced dosage. Very rare side effects are aplastic anemia, agranulocytosis or thrombocythopenia. The frequency of cutaneous drug reactions due to carbamazepine (CBZ) is generally assessed at 3 to12 %

(3,4). Cutaneous adverse effects like rashes, urticaria, pruritus, erythema, alteration of skin pigmentation, hirsutism or alopecia are not rare. More serious events like: syndrome Stevens Johnson, erythematous lupus, generalized erythroderma, purpura Henoch-Schönlein or even toxic necrolysis are also described. CBZ hypersensitivity syndrome includes fever, lymphadenopathy and rash. Photosensitivity, pseudolymphoma are also mentioned. Cross sensitivity to oxacarbazepine, phenytoine or barbital is possible. In his manual Litt mentioned 326 references on cutaneous side-effects to CBZ (5).

We report on severe drug reactions in four patients. Three females were operated because of malignant brain tumors and were given CBZ (Tegretol^{R}) for prevention of seizures. All three were after the brain operation treated with x-rays. A further patient was given carbamazepine because of brain metastases due to malignant melanoma.

Case reports

Case 1.

The 51-year-old female patient BB underwent a radical operation for a brain tumor located in right parietal hemisphere on November 11, 2000. The diagnosis was confirmed by magnetic resonance imaging (MRI). After the operation she received methylprednisolone (Medrol^{R}, Pharmacia & Upjohn) 32 mg daily. Due to symptomatic epileptic fits carbamazepine (Tegretol^{R}, Pliva), 200+200+400 mg was given. X ray treatment was also introduced.

About a week after the first X-ray dose a rash started to appear. Dermatologic examination revealed erythema and edema of the face as well as large areas of erythematous skin on the chest, around the waist and on the gluteal area. Similar lesions were on the extensor sites of arms, while on the distal parts of the extremities a macular and papular rash was visible. Figures 1 and 2. An increase of the methylprednisolone dose to 64 mg daily and the replacement of carbamazepine with valproic acid (Apilepsin^{R}, Krka & Sanofi) 450+300+450 mg was suggested. At five weeks after the operation all cutaneous symptoms were gone.

Case 2.

The 50-year old female patient M.Z. was operated on November 8, 2000 because of an expanding brain tumor of the left temporal lobe. The tumor was removed completely, histopathology showed a glioblastoma. The patient was given methylprednisolone (Medrol^{R}) 32 mg and CBZ (Tegretol) 2 times 200 mg. Additionally she received also X-ray treatment.

About two weeks later a maculo-papular rash was observed, which in a few days expanded into a pruritic erythema covering mainly the chest and extremities. Figure 3. The consulting dermatologist diagnosed a drug eruption, most probably due to CBZ. He suggested an increase of the methylprednisolone dose to 64 mg and the replacement of CBZ. The neurologist proposed 4 mg of diazepam (Apaurin^{R}, Krka) as replacement therapy. When the patient came for a reexamination four weeks after the operation, the rash has almost completely faded away.

Case 3.

The 31-year-old female patient G.K. suffered for about one year from seizures and spasms. Valproic acid relieved her of seizures, but spasms persisted. MRI disclosed an expanding brain tumor of the left frontal lobe. October 14, 1999 the tumor was surgically removed and histopathology confirmed a malignant oligodendroglioma. The patient was additionally treated by x-rays.

After the operation CBZ and later on also phenytoine (Difetoin^{R}, Pliva) were introduced. Shortly after the introduction of the antiepileptics a pruritic rash with signs of a beginning erythroderma appeared. When CBZ was replaced with valproic acid 3 x 450 mg and primidone (Primidon^{R}, Pliva) the cutaneous symptoms disappeared.

Case 4.

This case is mentioned only shortly as an extended publication is scheduled to be published elsewhere.

The 55-year old male patient was operated March 7, 2000 for a Clark IV, Breslow V stage malignant melanoma on his back. In January 2001 computerized tomography disclosed a melanoma metastasis in his brain. He was treated by x-rays, on January 7, CBZ 2 x 200 mg was given to prevent epileptic seizures. Four weeks later a macular rash started to appear on the lower half of his trunk, which continuously spread all over the body. Soon the whole skin of the face and chest became red and large erosions started to appear. On February 15 the diagnosis of toxic necrolysis was made. Although he obtained all the necessary care he died soon afterwards.

Discussion

In three instances the developing erythroderma was recognized early enough, so that after a moderate dose of methylprednisolone daily and replacement of CBZ with valproic acid or other anticonvulsives, the patients recovered. The fourth patient with melanoma brain metastases, in whom toxic epidermal necrolysis developed, has died. It is interesting to note that the four patients underwent an x-ray treatment for various ma-

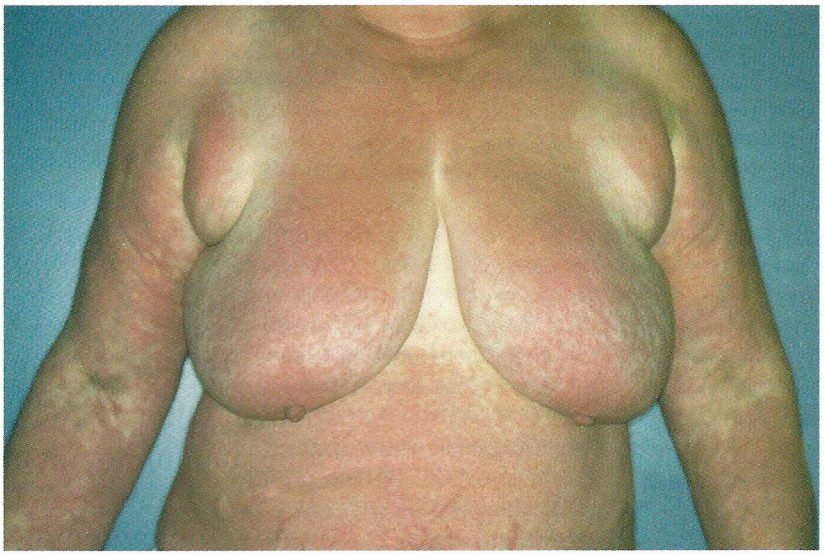


Figure 1. Patient BB. Partial erythroderma due to carbamazepine (Tegretol®). Large areas of erythematous skin appeared during Carbamazepine treatment, about one week after x-ray treatment for cerebral tumor.

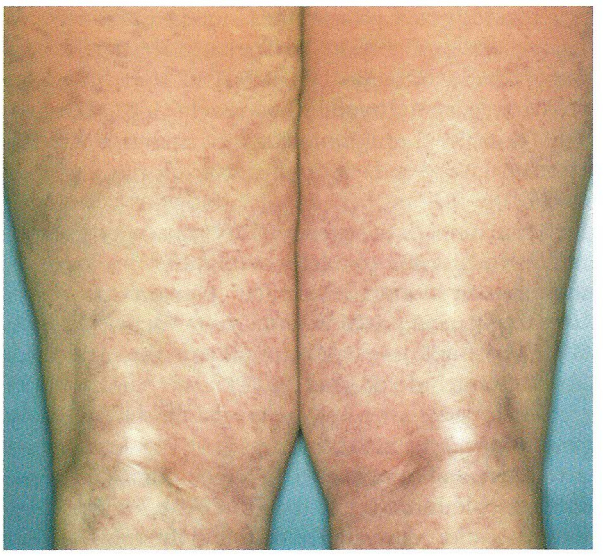
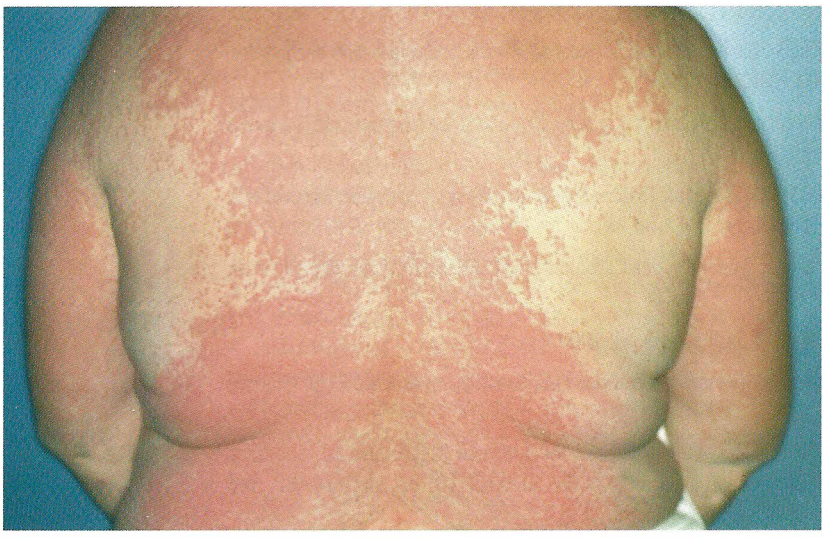


Figure 2. Same patient

lignant brain conditions, before or during the treatment with carbamazepine.

CBZ is lipophilic and is distributed in CSF, brain, duodenal fluids, bile and saliva. The drug is 76% protein bound in adults. The plasma half-life is 25 to 65 hours and falls to 12-17 hours after repeated dosing.

Figure 3. Patient M.Z. Pruritic erythema covering mainly the chest and extremities, triggered by carbamazepine. The lesions appeared about 2 weeks after the x-ray treatment.



CBZ is metabolized in the liver by oxidation to an active metabolite, the carbamazepine 10,11-epoxide, which is subject to further hepatic metabolism. It is a potent enzyme inducer and can induce its own metabolism, probably via CYP3A4 isoenzyme. Onset of enzyme induction is at about 3 days, with maximum effect at about 30 days. There is a high variability between individuals, concerning the extent to which induction occurs. CBZ is excreted in the urine, 72% as unconjugated metabolites and only about 3% as unchanged drug, the rest is excreted in the feces (6,7).

Unluckily, the diagnostic tests used for assessment of drug eruption like the blastic transformation of lymphocytes, macrophage inhibition and even determination of specific IgE are not reliable enough to confirm the diagnosis, and did not fulfill the expectations. There are some reports on positive patch tests to C BZ in patients suffering from eruptions due to this drug. It has been reported, however, that patch testing may reintroduce erythroderma (3,8). Mesec and cow. were able to prove contact hypersensitivity to. CBZ in a female patient with hypersensitivity syndrome (8).

CBZ and its metabolite the 10,11-epoxide can be assayed in body fluids by immunoassay (9) and by high performance liquid chromatography (10), but these tests are not helpful for detecting allergy to CBZ. Thus the diagnosis of drug reaction to CBZ is still based mainly on the patient's history, on the clinical experience of the physician, and on data from the literature. There is increasing evidence that T cells play an important role.

The mechanisms of action of CBZ on the central nervous system are still not completely understood. It blocks sodium channels by slowing their rate of recovery from inactivation and thus inhibiting sustained repetitive firing. Like phenitoine CBZ reduces posttetanic

potentiation of synaptic transmission in the spinal cord. Pain relief is probably due to blockade of synaptic transmission in the trigeminal nucleus. CBZ also shows anticholinergic, antiarrhytmic, muscle relaxant, antidepressant (possibly through blockade of nor adrenaline release), sedative and neuromuscular-blocking properties (6,7).

Some authors believe that the CBZ acts on the central nervous system similarly to lithium, which reduces the turnover of arachidonic acid. Lithium down-regulates the gene expression and enzyme activity of cytosolic phospholipase A(2), an enzyme that selectively liberates arachidonic acid (11,12).

Maculopapular eruptions are the most frequent hypersensitivity reactions to drugs (13). *Erythroderma* is a serious condition, especially when it has developed into a stable form, it is difficult to treat. Various drugs like pyrazolon derivatives, gold and lithium salts, certain anticonvulsants phenitoin, phenobarbital, CZB, primidon and clonazepam may cause erythroderma (14). Usually even the most severe drug reactions start as a macular or papular exanthema. Sigurdsson et al observed drug related erythroderma in 5 out of 102 patients with erythroderma, CBZ was assumed to be the cause only in one case (15).Drugs are incriminated for triggering erythroderma in 5% (16) to 40% (17) of cases reported.

Toxic epidermal necrolysis (TEN) is probably more often provoked by drugs. Blum et al reported that in one of their10 TEN patients with toxic renal involvement, the disorder was triggered by CBZ (18). Bahamdan mentioned a TEN patient, who developed also the *toxic shock syndrome* (19). Contrary to this, Lemitaphong et al did not incriminate CBZ in none of their 16 TEN cases, but considered CBZ responsible for four of their 44 cases with the Stevens Johnsone syndrome (20).

The *anticonvulsant hypersensitivity syndrome* which is similar to toxic shock syndrome is characterized by high grade fever, ertythroderma, shock and involvement of two or more organic systems: gastrointestinal, renal, hepatic, musculoskeletal or central nervous system. The onset is usually between 4 weeks and 3 months after starting the drug. CBZ was incriminated in a few instances (21,22).

When an exanthema appears during the treatment with CBZ one has to proceed very carefully: If the therapeutist decides not to withdraw CBZ, systemic corticosteroids should be introduced and the patient monitored strictly. A better choice is to replace CBZ with another anticonvulsant, e.g.valproic acid, which seems to be safe.

CBZ should be used with care in patients with atrioventricular conduction abnormalities, or with a history of blood disorders, cardiac, hepatic or renal disease and also in patients with raised intraoccular pressure (4), as well as in patients simultaneously treated with x-rays.

Conclusion

CBZ is a widely used and efficient drug, but one has to bear in mind that serious complications like erythroderma, anticonvulsant hypersensitivity syndrome or TEN may develop. Every rash appearing during CBZ treatment should be carefully monitored. If the therapeutist decides not to withdraw CBZ, we suggest that systemic corticosteroids should be introduced. A better choice is to replace CBZ with another anticonvulsant, e.g.valproic acid, which seems to be safer and to introduce systemic corticosteroids.

We firmly believe that due to the early recognition of the imminent erythroderma in the three female patients, the immediate replacement of CBZ with other anticonvulsants as well as the introduction of systemic corticosteroids prevented a more serious drug reaction.

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