Issues related to the pharmacological management of patients with brain tumours and epilepsy

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Summary

The patient affected by epilepsy related to brain tumours presents certain features linked to the summation of his cancer-related problems and his epilepsy-related problems. Furthermore, epilepsy in brain tumour patients is often refractory to pharmacological treatments and can complicate the therapeutic management of these patients due to the increased incidence of pharmacological interactions and adverse effects.
Analysis of the data in the literature suggests that it is opportune, when planning antiepileptic therapy in these cases, to choose the new-generation drugs, as these show a lower incidence of pharmacological interactions with the therapies used in brain tumour patients (chemotherapies, radiotherapy and support therapies), have fewer adverse effects, and have less impact on neuropsychological functions, all factors that strongly influence the patient's quality of life.
Of the new antiepileptic drugs, the following seem to be promising in the treatment of cancer-related epilepsy: oxcarbazepine, topiramate and levetiracetam (the latter as an add-on therapy). The pharmacokinetic features of these drugs, their effectiveness in controlling seizures, and the reduced incidence of adverse effects make them useful in this particular group of patients.

KEY WORDS: adverse effects, AEDs, brain tumours, epilepsy, interactions.

Introduction

In spite of the considerable progress made in diagnostics and in the fields of chemo- and radiotherapy, in the ambit of therapies for primitive brain tumours, palliative treatment of symptoms continues to be the key medical intervention for improving quality of life. The most common symptom in patients with brain tumours is epilepsy: it is the presentation symptom in 20-40% of cases, and will occur subsequently in 20-45% of the remaining cases (1-4). Overall, the incidence of epilepsy in brain tumours, considering all histological types and sites, ranges from 35 to 90% (2,5,6). The patient affected by epilepsy related to brain tumours presents certain features linked to the summation of his cancer-related problems and his epilepsy-related problems. Indeed, during the course of his disease, a cancer patient undergoes many treatments, pharmacological (chemotherapy and support therapy) surgical, and radiological; he may present neurological difficulties attributable to the tumour and psychological difficulties linked to the fact of having a disease with a probably unfavourable prognosis. Added to this, he has to deal with his epilepsy, which necessitates recourse to other pharmacological treatments (antiepileptic drugs, AEDs), and also live with the unpredictability of seizures, and the psychological distress caused by this diagnosis.
Epilepsy in brain tumour patients is often refractory to pharmacological therapies, both for reasons linked to the tumour itself, and because of poor efficacy of the drugs as a result of pharmacological interactions. Furthermore, the pathophysiological mechanisms underlying the epileptic seizures in patients with brain tumours are still unclear (7), whereas the correlations with several other factors, such as the histology of the tumour, its site, and the patient's age at tumour onset, seem to be better understood. The incidence of epilepsy at onset of tumour is inversely correlated with the degree of malignancy of the tumour: higher (ranging from 65 to 95% of cases) in those with a low degree of malignancy (astrocytomas, oligodendrogliomas, WHO grade I and II mixed astrocytomas and meningiomas) and lower (15-25% of cases) in malignant gliomas (5). A young age at tumour onset is more frequent in slowly-growing tumours and is associated with a higher incidence of epilepsy. A very important feature determining the appearance, or non appearance, of seizures is the site of the tumour: seizures are more frequent in supratentorial (as opposed to subtentorial) tumours whose site is cortical or superficial (as opposed to deep seated). The presence of epileptic seizures as an onset symptom of the tumour seems to be a favourable prognostic factor: this may be due to earlier diagnosis, to better surgical access (more superficial sites), or to the presence of more favourable histotypes (slowly-growing tumours). As regards the type of epileptic seizures occurring in brain tumour patients, they are, in most cases, simple-partial or complex seizures; partial seizures with secondary generalization are also frequent, but their focal onset is often difficult to detect clinically because of the

suddenness of the generalization phenomena due to the rapid diffusion of the epileptogenic discharge from the focus ipsilateral to the lesion, which can be detected only on EEG. Primary generalized seizures are more rare in patients with brain tumours.
Epilepsy and brain tumour implies the summation of many drug therapies, making the therapeutic management of affected patients particularly difficult. There are two fundamental reasons for this: i) an increased probability of pharmacological interactions, and ii) a higher incidence of adverse effects of the various drug treatments. Therefore, the neuro-oncologist, who has to make the therapeutic choices, must be equipped with in-depth knowledge of the problems linked to the pharmacological interactions and the adverse effects of the drugs used.

Pharmacological interactions

A pharmacological interaction occurs when one drug modifies the activity of another, increasing or reducing its effects (8). It is positive, if it increases the efficacy of the other drug, or negative, if it increases adverse effects or reduces its efficacy. There are two types of interaction between drugs.
Pharmacodynamic interactions occur between drugs that have similar or different mechanisms of action. They take place at cellular level (either at the site of action of the drug or elsewhere) and they are not associated with alterations of the plasma levels of the two drugs. At present, they can be demonstrated only by means of *in vitro* studies.
Pharmacokinetic interactions occur when one drug interferes with the distribution in the organism of another drug, altering its concentration at the site of action. This results in changes in the plasma levels of both drugs and of their metabolites. These interactions can occur at any stage during the drug's passage through the organism.
In the drug *absorption phase*, some drugs can alter the absorption of others. For example, antacids reduce absorption of phenytoin, phenobarbital, carbamazepine and gabapentin, by reducing gastric acidity and forming complexes that are insoluble with them.
The drug *distribution phase* concerns the binding with the plasma proteins and the free fractions of the active drug. For example, concomitant administration of phenytoin and valproic acid causes release of the phenytoin from the protein bond; this leads to increased phenytoin concentration and possible toxicity. Other AEDs, such as lamotrigine, levetiracetam, topiramate and vigabatrin, on the other hand, do not show a significant degree of protein bonding and are thus not prone to this type of interaction. The active metabolite of oxcarbazepine shows a low degree of plasma protein binding, making clinically significant competitive binding unlikely at this level (9).
During the *elimination phase*, a drug is eliminated from the organism through renal excretion (as in the case of vigabatrin, gabapentin, levetiracetam and felbamate), or hepatic excretion. Elimination by the hepatic excretion route, which is associated with the most clinically significant pharmacological interactions, may occur by means of glucuronidation (as in the case of lamotrigine) or by means of biotransformation of the drug mediated by CYP isoenzymes belonging to the cytochrome P450 system. These isoenzymes catalyze the oxidation reactions both of drugs and of endogenously produced substances, and their function can be modified by the concomitant administration of other substances (6). This means that P450-enzyme-inducing drugs provoke faster elimination of a second concomitantly administered drug and thus a reduction of its efficacy, or at least of its concentration at the site of action. Since induction of the CYP enzymes involves the synthesis of numerous proteins (the same CYP enzymes), it can be days or weeks before the effects on the pharmacokinetics appear. CYP-enzyme-inhibiting drugs decrease the metabolism of the second drug, increasing the risk of toxicity and of the appearance of adverse effects. Of the AEDs, phenobarbital, primidone, carbamazepine and phenytoin act as enzyme inducers, and thus enhance the metabolism of corticosteroids (drugs routinely administered to patients with brain tumours) and of many chemotherapeutic agents, including nitrosoureas, paclitaxel, cyclophosphamide, etoposide, topotecan, irinotecan, thiotepa, adriamycin and methotrexate. This means that the administered doses of these drugs could be inadequate, and therefore less effective (1,8,10) (Table I). On the

Table I - Anti-epileptic drugs reduce the activity of chemotherapeutic drugs.

Phenobarbital	Phenytoin	Carbamazepine
Cyclophosphamide	Busulfan	Methotrexate
Ifosfamide	Methotrexate	Vincristine
Thiotepa	Vincristine	Paclitaxel
Nitrosoureas	Paclitaxel	9-aminocamptothecin
Methotrexate	Irinotecan	Teniposide
Vincristine	Topotecan	
Paclitaxel	9-aminocamptothecin	
9-aminocamptothecin	Teniposide	
Teniposide		
Doxorubicin		
Procarbazine		
Tamoxifen		

(Source: ref.s 1,11,13)

other hand, many chemotherapeutic agents, too, are inducers of the CYP enzymes and can therefore alter the efficacy or increase the toxicity of many AEDs administered concomitantly (Tables II and III). There are, to date, no data in the literature suggesting that the new AEDs interfere with anti-tumour drugs (8).

Table II - Chemotherapeutic drugs reduce the activity of anti-epileptic drugs.

Phenytoin	**Valproic acid**	**Carbamazepine**
Bleomycin	Methotrexate	Cisplatin
Nitrosoureas	Cisplatin	Adriamycin
Cisplatin	Adriamycin	
Etoposide		
Dacarbazine		
Adriamycin		
Carboplatin		
Vinblastin		
Methotrexate		

(Source: ref. 1)

Table III - Chemotherapeutic drugs increase the toxicity of anti-epileptic drugs.

Valproic acid	**Phenytoin**
Cisplatin	Fluorouracil
Nitrosoureas	Tegafur
	Tamoxifen

(Source: ref. 1)

Adverse effects

The adverse effects of a drug can be divided into three types: i) idiosyncratic toxicity, which is dose-independent, unpredictable, and usually manifests itself in the early stages of consumption of the drug; ii) acute toxic effects, which are dose-dependent, very frequent, and can occur throughout the course of treatment with the drug (these effects are often due to pharmacokinetic modifications induced by concomitant therapies), and iii) chronic toxic effects, which instead arise after months or years of treatment, are linked to the total quantity of the drug consumed, are specific for each drug, and can even appear at therapeutic dosages.

Adverse effects of AEDs are more frequent in patients with tumour-related epilepsy than in the rest of the epileptic population (1,6,8); a recent meta-analysis (1) in fact showed the appearance of adverse effects severe enough to warrant suspension or modification of the AED therapy in 24% of patients affected by tumour-related epilepsy, as opposed to 0.5-12% of patients without tumour. In particular, many AEDs, in addition to the idiosyncratic, haematological, and systemic toxicity effects, also have effects on the central nervous system (CNS), which can strongly impact on the patient's quality of life, make it difficult to assess correctly the response to chemotherapy, and even mimic a progression of the tumour (11). A recent study showed that cancer patients who used carbamazepine, phenobarbital, valproic acid and phenytoin showed worse cognitive performances, with the exception of verbal memory, than those who did not use them (7). It is, on the other hand, probable (although there are no studies confirming this) that the new AEDs could have less frequent and milder effects on cognitive function. Every AED is associated with certain adverse effects, but some of these assume particular significance in the cancer patient:

1. Phenobarbital seems to be associated with the worst cognitive profile (sedation, behavioural problems, cognitive deficits, depressed mood) (7), and its use is thus not recommended in patients with brain tumour and cognitive deficits (11). It can also cause megaloblastic anaemia and scapular-humeral periarthritis: the latter often causes pain and functional impotence, which can aggravate the tumour-related disability.
2. Carbamazepine can cause dizziness, diplopia and sedation, whereas its most feared idiosyncratic effect, albeit rare, is haematological toxicity; it can also cause, just at the start of treatment, a mild and non-progressive leucopenia, which does not necessitate suspension of the drug.
3. Phenytoin rarely gives rise to idiosyncratic reactions; it can cause agranulocytosis (which does require suspension of the drug) and acute encephalopathy with psychological and neurological problems that, in the absence of the classic signs of toxicity, can seem to suggest a progression of the tumour. Combined use of phenytoin or carbamazepine during radiotherapy seems to be associated with a higher risk of developing severe cutaneous reactions (even Stevens-Johnson syndrome), a risk that must be taken into account by physicians prescribing these drugs to neuro-oncological patients about to undergo radiotherapy (12,13).
4. Valproic acid can, in some cases, cause acute encephalopathy whose symptoms may suggest a progression of the tumour. It can induce coagulation deficits and thrombocytopenia (and thus worsen the thrombocytopenia caused by the chemotherapeutic agents). Increased haematological toxicity has also been reported in combined therapy with valproic acid and nitrosoureas (14).
5. Oxcarbazepine does not significantly alter cognitive function (15); in some cases it even seems to improve psychomotor functions, in particular, attention and manual writing speed (16). The most frequent CNS-related adverse effects, usually only moderate, are somnolence, headache and dizziness. Although oxcarbazepine therapy has been associated with hyponatraemia, this is usually asymptomatic and does not necessitate suspension of the drug (17).
6. Topiramate can cause problems with language and memory. In particular, one double-blind study of healthy subjects showed a global deterioration of cognitive functions, especially language and memory, but not of motor performances (18). Conversely, a study in patients with epilepsy showed that topiramate administered as an

add-on therapy to carbamazepine was well tolerated and did not produce appreciable cognitive adverse effects (19).
7. The most frequent adverse effects of lamotrigine are CNS-related (headache, diplopia, nausea, ataxia, dizziness), but it can also cause rashes, eosinophilia and Stevens-Johnson syndrome (20).
8. Vigabatrin, gabapentin and levetiracetam are not metabolized by oxidation or conjugation: therefore they show little or no interaction with other drugs. Vigabatrin, however, can cause sedation, depressed mood and psychoses (21), as well as severe visual disorders. Gabapentin has few adverse effects (22), but its efficacy in controlling seizures has not, to date, been proven. Levetiracetam appears to be well tolerated, showing good efficacy and few adverse effects, but it can cause aggressive behaviours and agitation (23).
In short, all the GABAergic drugs (phenobarbital, benzodiazepine, vigabatrin, tiagabine and topiramate) have sedative effects and can induce depression; valproic acid and lamotrigine, on the other hand, have antidepressant properties (11). In addition, phenobarbital, phenytoin and carbamazepine are osteopenic, and thus associated with an increased risk of fractures, particularly of the hip and heel, whereas valproic acid is associated with reduced bone density (24).

Choosing the antiepileptic drug

The question of when to start antiepileptic therapy in patients with tumour-related epilepsy is highly controversial: in the USA, treatment is, in most cases, begun after a single seizure, whereas in Europe there is no common line of conduct; however, since patients with brain tumour are considered to be at a high risk of recurrent seizures, it is considered necessary (contrary to the recommendations in non tumour-related epilepsy) to initiate antiepileptic therapy immediately after the first seizure (11). Finally, as regards the type of drug to use, it is recommended, as in traditional antiepileptic therapy, to begin with a monotherapy and, in the light of what we have said above, to choose those new AEDs (oxcarbazepine, topiramate, lamotrigine) that are poor enzyme inducers, that have prevalently renal excretion, a low degree of plasma protein binding and a mild adverse effect profile, and that have already been approved by the *Food and Drug Administration* and by the Italian Health Ministry for use in monotherapy. Should a polytherapy be required, recent literature data (25,26) confirm the need to use AEDs that are poor enzyme inducers, such as the ones mentioned above, in combination with levetiracetam.

Concluding remarks

In the patient with tumour-related epilepsy, the choice of the best AED to use must be made bearing in mind both the other therapies already in use (with a view to achieving the best possible balance between efficacy and adverse effects), and the impact on neuropsychological functions, which may be particularly vulnerable in this group of patients. The ultimate aim must therefore be to guarantee and conserve a good quality of life, while still exploiting as fully as possible all the available therapies.

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