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...
Pharmacokinetic interactions

At present, they can be demonstrated only by means of alteration of plasma levels of the two drugs. Pharmacological interactions can 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. 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. 

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 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.

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

<table>
<thead>
<tr>
<th>Phenobarbital</th>
<th>Phenotyin</th>
<th>Carbamazepine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclophosphamide</td>
<td>Busulfan</td>
<td>Methotrexate</td>
</tr>
<tr>
<td>Ifosfamide</td>
<td>Methotrexate</td>
<td>Vinocristine</td>
</tr>
<tr>
<td>Thiotepa</td>
<td>Vincristine</td>
<td>Paclitaxel</td>
</tr>
<tr>
<td>Nitrosoureas</td>
<td>Paclitaxel</td>
<td>9-aminocamptothecin</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Irinotecan</td>
<td>Teniposide</td>
</tr>
<tr>
<td>Vincristine</td>
<td>Topotecan</td>
<td>9-aminocamptothecin</td>
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<tr>
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<td>Topotecan</td>
<td>9-aminocamptothecin</td>
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<tr>
<td>Doxorubicin</td>
<td>Topotecan</td>
<td>9-aminocamptothecin</td>
</tr>
<tr>
<td>Procarbazine</td>
<td>Topotecan</td>
<td>9-aminocamptothecin</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>Topotecan</td>
<td>9-aminocamptothecin</td>
</tr>
</tbody>
</table>

(Source: ref.s 1,11,13)
The pharmacological management of epilepsy in brain tumours

other hand, many chemotherapeutic agents, too, are in-
ducers of the CYP enzymes and can therefore alter the
efficacy or increase the toxicity of many AEDs adminis-
tered 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 an-
ti-epileptic drugs.

<table>
<thead>
<tr>
<th>Phenytoin</th>
<th>Valproic acid</th>
<th>Carbamazepine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleomycin</td>
<td>Methotrexate</td>
<td>Cisplatin</td>
</tr>
<tr>
<td>Nitrosoureas</td>
<td>Cisplatin</td>
<td>Adriamycin</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>Adriamycin</td>
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<tr>
<td>Etoxside</td>
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<tr>
<td>Dacarbazine</td>
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<tr>
<td>Adriamycin</td>
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<tr>
<td>Carboplatin</td>
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<td>Vinblastin</td>
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<tr>
<td>Methotrexate</td>
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</tbody>
</table>

(Source: ref. 1)

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

<table>
<thead>
<tr>
<th>Valproic acid</th>
<th>Phenytoin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin</td>
<td>Fluorouracil</td>
</tr>
<tr>
<td>Nitrosoureas</td>
<td>Tegafur</td>
</tr>
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<td></td>
<td>Tamoxifen</td>
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</tbody>
</table>

(Source: ref. 1)

Adverse effects

The adverse effects of a drug can be divided into three
type: 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 se-
vere 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 qual-
ity of life, make it difficult to assess correctly the re-
sponse to chemotherapy, and even mimic a progress-
sion of the tumour (11). A recent study showed that can-
cer 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 confirm-
ing 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 pa-
tient:

1. Phenobarbital seems to be associated with the
worst cognitive profile (sedation, behavioural prob-
lems, cognitive deficits, depressed mood) (7), and its
use is thus not recommended in patients with brain tu-
mour and cognitive deficits (11). It can also cause
meagaloblastic anaemia and scapular-humeral peri-
arthritis: the latter often causes pain and functional im-
potence, which can aggravate the tumour-related dis-
ability.

2. Carbamazepine can cause dizziness, diplopia and
sedation, whereas its most feared idiosyncratic effect,
although 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 reac-
tions; it can cause agranulocytosis (which does re-
quire suspension of the drug) and acute encephalopa-
y with psychological and neurological problems that,
in the absence of the classic signs of toxicity, can
seem to suggest a progression of the tumour. Com-
bined use of phenytoin or carbamazepine during radio-
therapy 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 radiother-
agy (12,13).

4. Valproic acid can, in some cases, cause acute en-
cephalopathy whose symptoms may suggest a pro-
gression 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 manu-
ual writing speed (16). The most frequent CNS-related
adverse effects, usually only moderate, are somno-
ence, headache and dizziness. Although oxcar-
bazepine therapy has been associated with hypona-
triaemia, this is usually asymptomatic and does not ne-
cessitate 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 func-
tions, 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, esophinophilia 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.

References

The pharmacological management of epilepsy in brain tumours