Add-on Gabapentin for Refractory Seizures in Patients With Brain Tumours

James R. Perry and Carol Sawka

ABSTRACT: Background: Seizures associated with intracranial neoplasms are occasionally refractory to conventional anti-epileptic drugs. Gabapentin (GBP) is one of several novel anti-epileptic drugs effective as an add-on therapy for intractable seizures but has not been studied in patients with cerebral tumours. Patients and Methods: We used GBP in a open-label add-on fashion to treat 14 patients with intractable seizures associated with intracranial tumours including four glioblastomas, four metastases, three recurrent glioblastomas, and one each of anaplastic and low grade astrocytoma and meningioma. GBP was added if optimization of pre-existing therapy failed and was titrated until seizures were controlled. Results: One patient experienced adverse drowsiness. Follow-up ranged from 3-24 weeks during which time 7 patients died from disease progression. Concurrent therapy included dexamethasone in eight, cranial irradiation in four, and radiosurgery in one. Responder rate (number with at least 50% fewer seizures) was 100% and persisted throughout follow-up. Complete resolution of seizures occurred in 8/14 patients. Conclusions: GBP was well tolerated in patients with brain tumours. Seizure frequency was reduced in all patients and efficacy persisted over time; however, the mechanism of this improvement is unclear. Concurrent therapy, regression of frequency to the mean, and the lack of controls may account for apparent benefit. In addition, because GBP may interact with a leucine-related neuronal binding site we also speculate that this novel mechanism of action may have been enhanced in our patients due to the abnormal blood-brain barrier associated with cerebral tumours. Further investigation and a controlled trial are warranted.

RÉSUMÉ: La gabapentine comme adjuvant dans le traitement des convulsions rebelles chez les patients atteints de tumeur cérébrale. Introduction: Les convulsions associées à une néoplasie intracrânienne sont occasionnellement refractaires aux antiepileptiques (AEs) conventionnels. La gabapentine (GBP) est un des nouveaux AEs qui sont efficaces comme adjuvant dans les cas de convulsions rebelles. Cependant, elle n'a pas été étudiée chez les patients qui ont une tumeur cérébrale. Patients et Méthodes: Nous avons utilisé la GBP comme adjuvant dans une étude ouverte pour traiter 14 patients avec convulsions rebelles associées à une tumeur cérébrale, dont quatre étaient des glioblastomes, quatre des métastases, trois des récidives d'un glioblastome, un astrocytome anaplasique, un astrocytome de bas grade et un méningiome. La GBP était ajoutée s'il y avait échec du traitement optimal et la posologie était ajustée jusqu'à ce que les convulsions soient contrôlées. Résultats: Un patient a présenté de la somnolence comme effet secondaire. Le suivi a duré de 3 à 24 semaines et 7 patients sont morts à cause de la progression de leur maladie. Les patients recevaient d'autres traitements, soit la dexaméthasone chez 8, la radiothérapie crânienne chez quatre et la radiochirurgie chez un. Le taux de répondeurs (patients ayant 50% moins de crises convulsives) était de 100% et a persisté pendant tout le suivi. Une disparition complète des crises a été observée chez 8 patients sur 14. Conclusions: La GBP a été bien tolérée chez les patients avec tumeur cérébrale. La fréquence des crises convulsives a diminué chez tous les patients et l'efficacité s'est maintenue; cependant, le mécanisme en cause est obscur. Le traitement concomitant, la régression de la fréquence vers la moyenne et l'absence de contrôles peuvent être responsables d'un bénéfice apparent. De plus, parce que la GBP peut interagir avec un site de liaison neuronal apparent à celui de la leucine, nous spéculons que ce nouveau mécanisme d'action puisse avoir été accru chez nos patients à cause des anomalies de la barrière hémato-encéphalique associées aux tumeurs cérébrales. Des recherches plus poussées et un essai clinique contrôlé sont justifiés.

PATIENTS AND METHODS

Patients were referred to the study neurologist through our regional cancer centre in a university hospital setting. Fourteen consecutive patients were seen and are all included in this report. All had intractable seizures (with or without secondary generalization) defined as continuing seizures despite maximal tolerated doses of at least one appropriate AED. Dose adjustments to existing AEDs or substitutions to more appropriate drugs were made prior to consideration of GBP. GBP was added to existing treatment and titrated until seizures were controlled or adverse effects encountered. Seizure counts were obtained by means of patient and care-giver diaries completed on a weekly basis. Electroencephalography was not routinely performed. We treated 12 patients with malignant tumours (4 glioblastoma multiforme (GBM), 3 recurrent GBM, one malignant astrocytoma, 4 metastases) and one patient each with meningioma and low grade astrocytoma (Table). The majority of patients had seizures since the time of tumour diagnosis but were referred to us because of worsening seizure control over a period of days to weeks. Prior AEDs included phenytoin, carbamazepine, and cllobazam. GBP was started at 300 or 400 mg three times daily (single capsule on day one, twice daily on day two, and three times daily thereafter) and the final dose ranged from 900 to 2400 mg per day. The primary AEDs were maintained in the standard therapeutic range and not dose-adjusted during the study period unless toxicity occurred. Only one patient experienced adverse drowsiness attributable to gabapentin. Follow-up ranged from 3-24 weeks during which 7 patients died from disease progression. Concurrent therapy included dexamethasone in 8 patients, external beam cranial irradiation in 4, and stereotactic radiosurgery in one. Steroid doses were held constant and usually were a maximum of 16 mg per day prior to study entry. Radiotherapy was completed prior to study entry (range 1 week to 3 months). The pre-treatment seizure frequency was obtained from patient and caregiver reports and ranged from a minimum of 1 seizure per week to continuous seizures (partial status epilepticus).

RESULTS

The responder rate (number with at least 50% fewer seizures) was 100% and persisted throughout the study. Mean response ratios (RR) were calculated whereby RR equals the (number of seizures per week after GBP minus seizures per week before GBP) divided by the total number of seizures.2 Seizure reduction results in negative numbers; for example, RR = -0.33 implies 50% reduction and RR = -1.0 implies perfect control. For our patients with malignant tumours the mean RR was -0.81 (median -0.93, range -0.33 to -1.0). No differences in response or adverse effects were noted between pathological subtypes of tumour.

DISCUSSION

In an early study, Penfield found that 37% of patients with intracranial tumours had seizures.3 Seizure frequency was highest for low grade lesions (astrocytoma 70%, meningeal tumours 68%) and lowest for malignant tumours (GBM 37%). In addition, frontal location (closer to primary motor cortex) was associated with a higher seizure frequency. These figures were confirmed in subsequent series.4-9 Supratentorial location and the presence of focal neurological signs correlate with seizure frequency in patients with brain metastases from solid cancer.10 Seizures were the presenting symptom in 18% of patients while

Table: Results from treatment using add-on gabapentin (GBP) in 14 patients with intracranial tumours.

<table>
<thead>
<tr>
<th>Pathologya</th>
<th>seizure typeb</th>
<th>prior drugs</th>
<th>GBP dose (mg)</th>
<th>Seizures/wk before</th>
<th>follow-up (wks)c</th>
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<tbody>
<tr>
<td>GBM-rec</td>
<td>focal +/-G</td>
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<tr>
<td>meningioma</td>
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<td>2400</td>
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<tr>
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a GBM = glioblastoma multiforme, rec = recurrent, AA = anaplastic astrocytoma
b G = generalized, CPS = complex partial seizures
c PHT = phenytoin, CBZ = carbamazepine, CLB = cllobazam, VPA = valproic acid
d patient or caregiver reported seizure frequency before GBP and at last follow-up
e dod = died of disease
f XRT = cranial irradiation
a further 10% developed seizures on follow-up (median survival
time was 13 weeks). Several authors have examined the influence
of intracranial surgery upon subsequent seizures.5,9 Shaw
found no increase in the incidence of seizures following surgery
but did note that open craniotomy was associated with a higher
seizure rate (20%) than biopsy only (9%).9 The Toronto
Hospital experience found that 40% of patients with GBM had
seizures prior to diagnosis and a further 16% developed seizures
after conventional surgery and radiotherapy.11 Seizure frequen­
cy may also decrease following surgery, particularly for benign
tumours associated with chronic epilepsy.2,4,12,13

Seizures impair quality of life (QOL) in chronic epilepsy;14
however, patient utilties for the various health states associated
with brain tumours (including freedom from seizures) are
unknown.15 Seizures often cause a sense of loss of control and
helplessness and lead to otherwise unnecessary hospital investi­
gation and occasionally admission. Improved seizure control by
administration of simple, non-toxic medications may improve
QOL and reduce direct hospital costs for these patients. Two of
the 20 items in a brain tumour specific self-administered QOL
questionnaire (FACT-BR) are seizure-related.16 The FACT-BR
items were generated using patient, family, and content expert
input and with further reliability and responsiveness testing this
instrument may help to elucidate important QOL concerns for
brain tumour patients.

The mechanism by which brain tumour-associated seizures
occur is poorly understood. The presence of tumour, active neo­
plasia, neo-vascularization, and reactive astrogliosis may cause
abnormal excitation of neurons in paratumoural cortex but this
hypothesis remains unconfirmed.7 Few studies of the effect of
AEDs on seizures in brain tumour patients exist. Largely, those
that have been published concern prophylactic phenytoin admin­
istration in the peri-operative period. In general, for patients
without a history of seizures, no benefit of prophylactic pheny­
toin has been demonstrated.8,17,18 Several authorities recom­
 mend the use of AEDs for these patients only if a clinical
seizure has occurred;18,19 however, others recommend routine
AEDs post-craniotomy.1 There is some evidence to suggest that
patients with metastatic melanoma and terminally ill patients
with advanced intracranial disease should receive prophylactic
AEDs as they form a higher risk subgroup for seizures.20

Three new generation AEDs have been introduced for use as
add-on therapy for intractable partial seizures: gabapentin
(GBP), lamotrigine, and vigabatrin. All are at least moderately
effective at reducing partial seizure frequency. We chose to
study gabapentin because it was readily available, had simple
dosing, and may become available in parenteral form.
GABapentin has a unique but poorly understood mechanism of
action. Like the other drugs in its class GBP shares many prop­
erties of the "ideal" AED because of its pharmacokinetic prop­
erties.2,22 It has no protein binding, no effect upon hepatic
enzyme induction, no significant drug interactions, it is not
metabolized and has high water solubility and easy dosing.
Very few adverse effects were noted when GBP was used in an
add-on fashion.2 Although GBP was designed as a GABA­
mimetic drug, no activity has been demonstrated at GABA
receptors in the nervous system. In addition, no relevant action
was found at sites associated with the mechanism of other AEDs
including voltage-sensitive sodium channels, glutamate and
glycine receptors, and benzodiazepine receptor complexes.22 A
high-affinity GBP binding site was found but remains poorly
characterized.22 This site is associated with neurons and proba­
ably the L-neutral amino acid transporter at the level of the
blood-brain barrier (BBB). GBP shows strong three dimensional
similarity to l-Leucine and may act by altering amino acid trans­
port across the BBB and may therefore serve as a true or func­
tional leucine antagonist. After BBB transport, various amino
acids are metabolized within brain by aminotransferases to cre­
ate the excitotoxic amino acid glutamate. It is possible therefore
that GBP acts by effectively reducing activity at excitotoxic
amino acid receptors such as the N-Methyl-D-Aspartate
(NMDA) receptor.22

In our experience with 14 patients we found GBP to be safe,
well tolerated, and easily dose-adjusted in patients with brain
tumours. All of our patients experienced a reduction in seizure
frequency with disappearance of seizures in over half. The
mechanism of this improvement is unclear. Many patients had
concurrent therapy with steroids or radiotherapy and these alone
may account for improved seizure control.23 The unique mech­
anism of action of GBP may also be relevant. It is well known
that the BBB surrounding brain tumours is abnormal with
"leaky" tight junctions, disrupted endothelium, and complex
ultrastructural changes.24 As GBP may act by crossing the BBB
and binding specifically to a neuronal site associated with an
amino acid transporter, we speculate that this mechanism of
action may be altered, and possibly enhanced, in patients with
an abnormal BBB. Autopsy study of GBP concentration in
tumourous cortex,25 and radiolabelling studies would help to
answer this question.

While our data indicate that GBP may benefit patients with
intractable seizures due to brain tumours, a controlled trial is
required for several reasons. First, there exists uncertainty as to
the role of concomitant treatment with steroids and radiotherapy.
Second, these patients were treated with GBP at a time when
seizures were relatively problematic and the apparent improve­
ment in seizure frequency may simply have been caused by
regression to the mean. Third, our patients were not blinded,
were subject to placebo effect, and may have wished to please
their physicians by reporting fewer seizures. The effectiveness
of AEDs in patients with brain tumours is unlikely to be the sub­
ject of a large randomized controlled trial because of the rarity
of the problem. For this reason, we plan single patient ("n=1")
randomized trials26 for individuals with a relatively stable
disease course.

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