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

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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 réfractaires aux antiépileptiques (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 apparenté 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.

Can. J. Neurol. Sci. 1996; 23: 128-131

Adult-onset seizures are caused by intracranial neoplasms in 6-21% of patients and seizures are the first manifestation of 50% of all brain tumours.[1] Although most brain tumour related seizures are easily managed, occasional patients experience frequent seizures intractable to conventional anti-epileptic drugs (AEDs) such as phenytoin and carbamazepine. This problem has not been extensively studied. Based upon early anecdotal success, we evaluated the new AED gabapentin in an open-label, add-on study for patients with intractable seizures associated with benign and malignant intracranial neoplasms.

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RECEIVED AUGUST 10, 1995. ACCEPTED IN FINAL FORM JANUARY 11, 1996.
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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 clobazam. 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.

	Pathology[a]	seizure type[b]	prior drugs[c]	GBP dose (mg)	Seizures/wk[d] before	Seizures/wk[d] after	follow-up (wks)[e]	other treatment[f]
1	GBM-rec	focal+/–G	PHT	900	3	0	16, dod	decadron
2	GBM	focal status	PHT->CBZ	900	status	1	12	ativan, decadron, XRT
3	breast	focal	PHT	900	2	0	4, dod	decadron
4	GBM	focal	PHT,CBZ, CLB	1200	3	0	12	XRT
5	AA	focal+/–G	CBZ	1200	9	2	24	XRT
6	GBM-rec	focal+G	PHT->CBZ	1200	2	0	3, dod	
7	GBM-rec	focal+/–G	PHT	2400	6	1	7, dod	decadron
8	lung	focal+G	PHT	1200	2	0	4, dod	decadron
9	lung	focal+G	PHT	900	2	0	3, dod	decadron, XRT
10	GBM	focal+/–G	PHT	2400	4	1	8	
11	breast	focal	PHT->CBZ	900	4	2	3, dod	decadron
12	meningioma	CPS	CBZ,CLB	2400	2	0	16	radiosurgery
13	GBM	focal+/–G	VPA	900	1	0	12	decadron, XRT
14	low grade	CPS	CBZ	900	daily	1	20	

[a] GBM = glioblastoma multiforme, rec = recurrent, AA = anaplastic astrocytoma
[b] G = generalized, CPS = complex partial seizures
[c] PHT = phenytoin, CBZ = carbamazepine, CLB = clobazam, 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 frequency may also decrease following surgery, particularly for benign tumours associated with chronic epilepsy.[3,12,13]

Seizures impair quality of life (QOL) in chronic epilepsy;[14] however, patient utilities 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 investigation 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 neoplasia, neo-vascularization, and reactive astrocytosis 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 administration in the peri-operative period. In general, for patients without a history of seizures, no benefit of prophylactic phenytoin has been demonstrated.[8,17,18] Several authorities recommend the use of AEDs for these patients only if a clinical seizure has occurred;[18-20] 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 properties of the "ideal" AED because of its pharmacokinetic properties.[2,21] 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 probably 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 transport across the BBB and may therefore serve as a true or functional leucine antagonist. After BBB transport, various amino acids are metabolized within brain by aminotransferases to create 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 mechanism 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 improvement 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 subject of a large randomized controlled trial because of the rarity of the problem. For this reason, we plan single patient ("n=1") randomized trials[26] for individuals with a relatively stable disease course.

Acknowledgements

Dr. Perry is supported by the McEachern Travelling Fellowship of the Canadian Cancer Society and the Gordon E. Richards Fellowship of Ontario Division of the Canadian Cancer Society.

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