The Management of Seizures in Brain Tumor Patients

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ABSTRACT

The diagnosis of a brain tumor requires healthcare providers to examine the best course of treatment for each individual patient. Unfortunately, seizures are a common occurrence in those with brain tumors. Seizures can contribute to many undesirable life-altering consequences that can greatly impact quality of life. Healthcare providers are inconsistent in the use of prophylactic antiepileptic drugs. Despite published guidelines, prophylactic use of antiepileptic drugs is still practiced for patients who have never experienced a seizure. Because of the many side effects of first-generation antiepileptic drugs, this practice should be discouraged. Furthermore, drug interactions between antiepileptic drugs and antineoplastic treatments can cause life-threatening complications. Since the 1990s, newer antiepileptic drugs, which have fewer drug interactions, have been introduced and show promise as first-line therapy and adjunct treatment of epilepsy. Although reports have demonstrated their promise, prospective randomized controlled trials are needed to determine their reliability in this population of patients. Managing seizures in brain tumor patients requires diligent comprehensive care by healthcare providers to help limit unnecessary side effects and improve quality of life.

The occurrence of seizures in brain tumor patients is quite common (Sperling & Ko, 2006). Seizures contribute to increased morbidity and a decreased quality of life in this already-vulnerable population. Loss of independence, depression, and anxiety are some of the psychosocial problems that can transpire (Batchelor & Byrne, 2006; Thompson, Takeshita, Thompson, & Mulligan, 2006). Although only 3%–5% of individuals have seizures that are directly related to brain tumors, it is estimated that 30%–50% of patients with supratentorial tumors will present with or acquire epilepsy (Bromfield, 2004). The location and pathology of the tumor ultimately contribute to the risk of developing seizures (Sperling & Ko, 2006). Unfortunately, seizures in brain tumor patients are often more complicated to treat than those of the typical epilepsy patient. Explanations for these complications include the lack of control over a tumor's progression and the pathophysiological nature of the tumor itself, which can lead to uncontrollable disturbances to the brain (Sperling & Ko, 2006). An additional obstacle to treatment of seizures in brain tumor patients is the various side effects of antiepileptic drugs (AEDs). These drugs typically have numerous side effects when used alone; however, the synergistic effects of the combination of AEDs with radiation, chemotherapy, and steroid treatments have the potential to cause life-threatening complications for patients with brain tumors. These interactions can produce central nervous system toxicity, changes in pharmacokinetics, and drug toxicity (Hildebrand, 2004). Typical management of seizures in brain tumor patients has included phenytoin, carbamazepine, and valproic acid (Thompson et al., 2006). Recently however, newer second-generation AEDs have been introduced and approved for the treatment of seizures. These second-generation AEDs, which include oxcarbazepine, levetiracetam, lamotrigine, and topiramate, have been shown to be effective in treating seizures and cause fewer known adverse events than the previous generation of AEDs (Stevens, 2006). With this introduction comes the demand for more clinical trials that focus specifically on the use of these AEDs in brain tumor patients. Not only can these newer medications treat the underlying seizure disorder, but research has shown them to be effective in the treatment of pain, anxiety, and mood disorders, all of which are common in this population of patients (Thompson et al., 2006). As a result, healthcare providers must take careful consideration when selecting antiepileptic therapy for brain tumor patients as the antiepileptic choice can decrease unnecessary side effects and may benefit more than just the underlying seizure disorder.

The Central Brain Tumor Registry of the United States (CBTRUS, 2005) compiles statistics on primary malignant and nonmalignant brain tumor cases. Their statistics are used to promote awareness; provide incidence, mortality, and survival rates; compare treatment options; and ultimately help in the prevention of brain tumors. Their report issued in 2005 analyzed information from 18 different states and

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Myriad reasons underlie the difficulty inherent in treating seizures in patients with brain tumors. Unlike typical patients with epilepsy, patients with brain tumors experience physiologic changes and other treatment modalities that complicate seizure management.

predicted approximately 43,800 new cases of primary brain and central nervous system tumors for that year (CBTRUS, 2005). These annual reports have shown that the incidence of these tumors continues to rise. Unfortunately, the mortality rate has also risen consistently, with 12,760 deaths attributed to brain tumors in 2005 (CBTRUS, 2005). Because of this high mortality rate, care must concentrate on decreasing comorbidities, with the main goal of increasing quality of life. All patients with brain tumors are at an increased risk of developing a seizure or epilepsy. Consequently, healthcare providers must be educated regarding variables that make certain brain tumor patients more prone to seizures than are others.

Seizures consist of atypical firing of neurons at high frequencies, which in turn can cause irregular behaviors or experiences in an individual (Blumenfeld, 2002). Epileptogenesis, the process that leads to the development of epilepsy, in brain tumor patients is considered to have multiple variables and may be different in each individual (van Breemen & Vecht, 2005). Cortical or structural irritation, genetic abnormalities, and metabolic disturbances may all contribute to this process (Amidei, 2005; Blumenfeld, 2002). Secondary epileptogenesis is also common in brain tumor patients. This occurs when the epileptogenic focus does not correlate with the tumor location, and a new epileptogenic region is formed away from the initial site of the tumor (Vecht & Van Breemen, 2006).

Because of the high incidence of seizures in these individuals, it is important to recognize different tumor types with their associated risk for developing seizures. Understanding the World Health Organization's grading of brain tumors is essential, as there is quite a remarkable difference in survival rates between the tumor types. Tumor grading is used as a method to group different cancer cells into separate categories according to their appearance, growth, and variability. The World Health Organization's grading system classifies brain tumors from Grade I, which is the most benign, to Grade IV, which is the most malignant (Demonte, Gilbert, Mahajan, & McCutcheon, 2007).

Determining the Risk of Seizures

Tumor Pathology

One variable proven to have a significant correlation with acquiring seizures is the pathology of the tumor. The lower the grade of the glioma, the more likely seizure activity will develop (van Breemen & Vecht, 2005). In one study, seizures were present in an estimated 80% of low-grade glioma patients, compared with 30% of patients with higher grade gliomas (Hildebrand, 2004). Although the pathology of a brain tumor and its related effects on seizures is not completely understood, the higher incidence of seizures in individuals with low-grade gliomas may be due in part by their longer rate of survival.

The 5-year survival rate after the diagnosis of all primary malignant brain or central nervous system tumors is about 30% (CBTRUS, 2005). There is a striking contrast though when comparing survival rates in low- versus high-grade glioma patients. In one study evaluating the survival rates and patterns of care for patients with low-grade gliomas (Grades I and II), there was a 59.9% 5-year survival rate among patients (Claus & Black, 2006). Unfortunately, the average survival for high-grade gliomas (Grades III and IV) is much different. Grade III anaplastic astrocytomas have an estimated survival of 24−36 months, whereas there is only a 12-month average survival for those suffering from Grade IV glioblastoma multiforme (Giovagnoli, Silvani, Colombo, & Boiardi, 2005). Evidently, low-grade tumors have a longer survival rate and thus a longer time period for the production of more focal or remote cell changes to produce a seizure focus (van Breemen & Vecht, 2005). Dysembryoplastic neuroepithelial tumors and gangliogliomas are two different types of low-grade tumors most commonly associated with seizures. These tumors actually contain a neuronal component that may in fact be able to directly generate seizures. Purely glial tumors are unable to directly cause a seizure because they lack this neuronal component, but indirect effects on neurons eventually can cause seizures to take place (Bromfield, 2004). Those with high-grade gliomas who have developed seizures are thought to have acquired this added comorbidity from complications of different treatments rather than from cellular changes (van Breemen, & Vecht, 2005). Some of these complications include necrosis, edema, scar tissue formation, tumor progression, medication interactions, and hemosiderin deposits. These variables are all thought to contribute to the development or

increased susceptibility of seizure activity in high-grade glioma patients (Amidei, 2005; van Breemen & Vecht, 2005).

Tumor Location

The location of a brain tumor also plays a crucial role in determining the risk of seizures. Tumors located within the cortical gray matter will most commonly generate seizures, as compared with a lower prevalence among tumors within the deep cerebral white matter (Bromfield, 2004). It is unusual for infratentorial or pituitary tumors to cause a seizure, unless the tumor bulk is especially large with resulting mass effect. Tumors located in the parietal, frontal, and temporal lobes have the highest incidence of producing seizures (Sperling & Ko, 2006). It is thought that the closer a lesion is located to the central sulcus, the more likely a seizure can occur. The central sulcus is an important landmark in neuroanatomy. This sulcus, also known as the Rolandic fissure, separates the parietal lobe from the frontal lobe as well as the primary motor cortex from the primary somatosensory cortex (Blumenfeld, 2002).

The type of seizure that the patient presents with may give an indication as to where the brain tumor is located, unless secondary epileptogenesis has occurred. When tumors are located in the motor cortex, unilateral focal motor symptoms usually occur (Sperling & Ko, 2006). Auras often precede seizures correlated to temporal lobe tumors. Auras may include unpleasant sounds or smells, fear, déjà vu, or merely an overwhelming, indescribable feeling. Tumors in the temporal lobe typically produce complex partial seizures. These seizures manifest as oral or manual automatisms, staring, or unresponsiveness (Sperling & Ko, 2006). Parietal tumors initiate seizures that usually have focal sensory symptoms, and visual hallucinations are often seen with occipital lobe tumors (Sperling & Ko, 2006). Although it may be possible to link these symptoms to the location of the tumor, this may not be true if generalized seizures develop. The severity of the seizure depends on how it travels throughout the brain. If the seizure remains confined to the area or lobe of the brain in which the tumor is contained, then a simple partial seizure is most likely to develop. If extensive spreading of the seizure occurs, complex partial or generalized tonic–clonic seizures are seen (Sperling & Ko, 2006). Evidently, the production of seizures in brain tumor patients is multifactorial. This variability leads to treatment strategies that are inconsistent, especially in the use of prophylactic AEDs.

Use of Prophylactic AEDs

Differing views exist among healthcare specialists concerning the use of prophylactic AEDs. Practice parameters were published in 2000 by the Quality Standards Subcommittee of the American Academy of Neurology (AAN) on anticonvulsant prophylaxis in patients with newly diagnosed brain tumors. Their recommendations were twofold. First, the committee advocated for tapering and then discontinuing AEDs after the first postoperative week after a tumor resection. They felt that this was especially important for those encountering side effects of the drugs who were medically stable. Agreement is seen among neurosurgeons with the use of perioperative and postoperative AEDs to prevent seizures during this precarious time. Seizures are common in the first several days after surgery; therefore, complications can possibly be excluded if seizure prophylaxis is ensured (Sperling & Ko, 2006). Although the use is of prophylactic AEDs is suggested during this time, their use is not recommended beyond the postoperative period if the patient has never experienced a seizure.

Excluding the postoperative use of prophylactic AEDs, this committee's other recommendation was to discourage the use of AEDs in brain tumor patients with no history of epilepsy because of their unproven efficacy in preventing initial seizures (Glantz et al., 2000). These guidelines are based on a meta-analysis of published research on this topic (Glantz et al., 2000). Four randomized clinical trials that provided Level 1 evidence and eight cohort studies that provided Level 2 evidence were included in their review. The results of their findings showed that none of these trials offered statistical evidence proving prophylactic use of AEDs to be effective in reducing seizure incidence or seizure freedom (Glantz et al., 2000).

In 2004, the Mayo Foundation for Medical Education and Research concurred with the AAN's suggestions. A systematic review was performed of prospective randomized controlled trials that consisted of brain tumor patients with no history of seizures who were randomly assigned an AED versus a placebo. Their review yielded five trials that met these criteria. The three AEDs that were used in these trials were phenytoin, valproic acid, and phenobarbital. Their use was analyzed collectively among 403 adults with a brain tumor diagnosis. Four of the five trials revealed no statistical benefit of seizure prophylaxis with these medications. Three tumor types, gliomas, meningiomas, and cerebral metastases, were also examined individually to determine if the use of the AEDs had any correlation between seizure occurrence and tumor type. The consensus of their review showed no statistical benefit in the use of AEDs strictly for the prophylaxis of seizures regardless of the tumor pathology. Therefore, healthcare providers who are prescribing AEDs for these patients have no

proven evidence of their benefit (Sirven, Wingerchuk, Drazkowski, Lyons, & Zimmerman, 2004).

In a survey completed prior to the AAN's 2000 guidelines by Glantz et al. (1996), the following percentages of 113 physicians were prescribing AEDs to brain tumor patients with no history of seizures: oncologists, 50%; neurologists, 53%; neurosurgeons, 81%; and radiation oncologists, 33%. Evidently, before this recommendation was published, there was widespread use of AEDs in brain tumor patients with no history of seizures. However, the practice patterns have yet to change even after these recommendations were proposed. In another more recent e-mail survey performed of all members of the American Association of Neurological Surgeons, almost 70% of the responders revealed that they were prescribing prophylactic AEDs to patients with all intra-axial (supratentorial and infratentorial) gliomas and those with brain metastasis (Siomin, Angelov, & Li, 2005). In a review of the Glioma Outcomes Project, it was apparent that AEDs were once again being prescribed without a previous history of seizure (Chang et al., 2005). The Glioma Outcomes Project was established to provide a database for the evaluation of practice patterns and outcomes among 565 high-grade glioma patients (Chang et al., 2005). One area of interest in this study was to review the use of AEDs among glioma patients. Results revealed that, although only 32% of the individuals in this study presented with seizures, 89% received AEDs (Chang et al., 2005). Thus, the recommended guidelines are not being followed, and further investigation into this matter is warranted.

Complications of Seizures

Seizures can cause neuronal and cell death and potentially increase morbidity in this fragile population. Enhanced blood flow from increased metabolism during a seizure can lead to elevated intracranial pressure (Sperling & Ko, 2006). This increased intracranial pressure can contribute to neuronal and cell death and may also result in bleeding into the tumor bed. Other complications of seizures can cause bodily harm depending on the seizure type and the environment of the individual at the time of the attack. Status epilepticus is not common in those with brain tumors, but if it does occur, mortality is estimated at 6%−35% (Batchelor & Byrne, 2006). These complications are probable explanations for why healthcare providers continue to prescribe AEDs to patients with no occurrences of seizures. Although this logic is noteworthy, studies have shown that prophylactic use of AEDs has been proven to be unsuccessful in preventing initial seizures. One randomized control trial aimed at determining if valproic acid was successful in preventing first seizures in individuals with brain tumors. Ninety-one patients were enrolled in this trial. Results revealed that 35% of those patients who were being treated with prophylactic valproic acid experienced a seizure, and 23% of those individuals had a seizure occurrence with a subtherapeutic anticonvulsant blood level (Glantz et al., 1996). A clinically significant decrease in the incidence of a first seizure was not seen in this group of individuals treated with valproic acid. Subtherapeutic anticonvulsant blood levels are regrettably a familiar occurrence even in established epilepsy patients and brain tumor patients with known cases of epilepsy (Glantz et al., 2000). Therefore, treating patients with prophylactic AEDs should be discouraged due to their unproven benefit of use.

Choosing an AED

Healthcare providers have several different anticonvulsant medications to choose from for the treatment of epilepsy. The older generation AEDs include phenobarbital (Luminal), phenytoin (Dilatin), carbamazepine (Tegretol), and valproic acid (Depakote). Nine newer AEDs have been approved by the Federal Drug Administration since the early 1990s. These medications include felbamate (Felbatol), gabapentin (Neurontin), lamotrigine (Lamictal), topiramate (Topamax), tiagabine (Gabitril), levetiracetam (Keppra), oxcarbazepine (Trileptal), zonisamide (Zonegran), and pregabalin (Lyrica; Stevens, 2006). At present, there is no single AED of choice (Sperling & Ko, 2006). Each patient should be treated individually by seeking the best available treatment option for his or her set of circumstances. Although no apparent agreement regarding the prophylactic use of AEDs exists, universal conformity is observed with the use of long-term AEDs in brain tumor patients who have experienced a seizure. Healthcare providers concur with this practice because of the 72% seizure recurrence rate (van Breemen & Vecht, 2005).

In 2004, a published report was complied by the Therapeutics and Technology Assessment Subcommittee and Quality Standards Subcommittee of the AAN and the American Epilepsy Society on the efficacy and tolerability of the new AEDs (French et al., 2004a, 2004b). This report recommends options for the treatment of new-onset epilepsy and refractory epilepsy. For new-onset epilepsy patients, initiation of first-generation AEDs carbamazepine, phenytoin, valproic acid, and phenobarbital as well as the newer AEDs lamotrigine, gabapentin, oxcarbazepine, and topiramate are all recommended for monotherapy (French et al., 2004a, 2004b). The choice of drug should be based on each individual's

set of circumstances including the type of seizures the patient is experiencing. This evidence is based on Level A recommendations. Level A recommendations must have at least one convincing Class I study or at least two consistent Class II studies (French et al., 2004a, 2004b). A Class I study must be a prospective, randomized controlled trial with masked outcome assessment in a representative population (French et al., 2004a, 2004b). These studies must have primary outcomes that are clearly recognized, inclusion–exclusion criteria that are evidently defined, a minimal potential for bias, and appropriate baseline characteristics between treatment groups (French et al., 2004a, 2004b). A Class II study is a prospective matched group cohort study in a representative population with masked outcome that meets the criteria for Class I evidence or a randomized control trial missing one of the criteria from the Class I requirements. Class III studies are all other controlled trials, and a Class IV rating is evidence from uncontrolled studies, expert opinion, case series, and case reports (French et al., 2004a, 2004b).

This same report also gave recommendations for the use of new AEDs in the treatment of refractory partial epilepsy. Gabapentin, lamotrigine, tiagabine, topiramate, oxcarbazepine, levetiracetam, and zonisamide are all recommended for add-on therapy in patients with refractory partial epilepsy (Level A; French et al., 2004a, 2004b). Oxcarbazepine and topiramate (Level A) and lamotrigine (Level B) are recommended for monotherapy in this epilepsy population. Because of the lack of clinical trials focusing solely on the treatment of epilepsy in brain tumor patients, healthcare providers are recommended to follow these standard guidelines for all epilepsy patients. The goal should be for total seizure control. Healthcare providers are advised to start treatment with monotherapy. If monotherapy at a starting dose is ineffective, titration to maximum dose of that drug should take place. If this first drug ultimately proves to be unsuccessful, initiating a new drug with monotherapy is warranted. If this second drug fails to be beneficial, the next step is to add an additional drug, but in consultation with an epileptologist (Amidei, 2005). More research and clinical trials are needed in the brain tumor population to distinguish which drugs are best for these patients.

Drug Interactions Between AEDs and Common Drugs Used in Brain Tumor Patients

Antiepileptic drugs have many known side effects. These include sedation, headache, nausea, dizziness, rash, and confusion (Thompson et al., 2006). Central nervous system toxicity and drug interactions are potential problems brain tumor patients can encounter while taking these drugs (Hildebrand, 2004). Problems can occur due to the combination of AEDs with antineoplastic agents. The cytochrome P-450 (CYP-450) system is a main pathway in the liver where many substances are metabolized. This is a vital enzyme system for the metabolism of several AEDs (Stevens, 2006). Unfortunately, many antineoplastic agents are degraded with this same system, and their simultaneous use can cause the potential for harmful side effects (Batchelor & Byrne, 2006). Certain AEDs can cause induction or inhibition of this system, which can lead to undesirable levels of concurrently used medications. Induction of hepatic enzymes takes place with the use of phenytoin, carbamazepine, phenobarbital, and oxcarbazepine. Consequently, these drugs increase the clearance of other drugs metabolized by this pathway, which can cause the occurrence of subtherapeutic blood levels of essential drugs. Valproate is a CYP-450 inhibitor, which can contribute to a decreased clearance of other drugs used by this same pathway. With this inhibition, toxic levels of concurrent medications may result (Sperling & Ko, 2006). Treatment with corticosteroids, chemotherapy, and radiation therapy all can cause potential hazardous side effects when combined with these AEDs. Careful review of all medications is essential to help prevent these reactions from occurring.

Cerebral edema is a probable complication seen in most brain tumor patients. This edema is caused by a local rise in water and sodium content. Disruption in the blood−brain barrier causes this edema to occur. With brain tumors growing beyond 1 to 2 mm, the newly formed blood vessels that supply the brain tumor lack the advantages of the blood−brain barrier. The disturbed barrier then is unable to eliminate the increased concentration of water-soluble substances. These substances are then forced into the surrounding brain tissue, consequently causing edema. The use of glucocorticoids is the treatment of choice for brain edema. These steroids are thought to reestablish normal vascular permeability. Dexamethasone is the steroid used most often in brain tumor patients because of its decreased rates of impaired cognition and infection (Batchelor & Byrne, 2006).

The use of steroids remains an important part of the treatment plan for brain tumor patients. However, dexamethasone can contribute to significant drug interactions with AEDs. When dexamethasone is combined with phenytoin, alterations in blood levels of both drugs can occur. Most often these two drugs will jointly decrease the efficacy of the other drug,

causing an increased dosage of each medication needed to reach the required therapeutic effect (Ruegg, 2002). Although the standard dose for phenytoin is 300 mg/day (Amidei, 2005), Ruegg (2002) reported that an increase in phenytoin of 600−1,000 mg/day is often needed with the combined use of dexamethasone. Dosing alterations require careful and frequent phenytoin level monitoring. With the tapering of dexamethasone, the requirements of phenytoin also decline. This shows the unpredictable disadvantages that the combination of these two drugs can produce. If dosing is not altered, serious phenytoin toxicity can occur that can produce somnolence, ataxia, diplopia, dizziness, nystagmus, and severe skin reactions (Batchelor & Byrne, 2006; Ruegg, 2002). Because of the many side effects seen with the combination of these drugs, avoidance of the use of phenytoin as an AED for long-term treatment in brain tumor patients should be considered. Although phenytoin should be discouraged for long-term use in this population, it is often the drug of choice for perioperative management. A review of the use of phenytoin in the perioperative course and for the first week after surgery revealed that this drug decreased the incidence of seizure by 40%−50% (Thompson et al., 2006).

Many AEDs may interact with chemotherapy agents by hastening their metabolism. This alteration in metabolism produces decreased plasma levels of chemotherapy drugs and ultimately causes lower antitumor activity (Vecht & Van Breemen, 2006). Phenytoin is known to interact with many chemotherapeutic agents including methotrexate, cisplatin, carboplatin, bleomycin, carmustine, and vinblastine. The combination of these drugs can cause CYP-450 enzyme induction and protein binding variations, which can contribute to the alteration of phenytoin absorption (Sperling & Ko, 2006). Once again, the use of these agents can cause a need to increase the dosing of phenytoin and other enzyme inducing AEDs.

Deep vein thrombosis (DVT) is especially common in brain tumor patients. The release of plasmin-inhibitory substances produced by tumor cells is hypothesized to aid in the production of DVTs (Batchelor & Byrne, 2006). Mobility, sequential compression devices, and subcutaneous heparin are commonly recommended during the postoperative period. With the development of a DVT, the use of warfarin and low-molecular weight heparinoids is recommended with caution during the use of AEDs. These combined drugs may cause unpredictable coagulation control and may alter serum AED levels (Batchelor & Byrne, 2006).

Skin reactions may also develop with the use of certain AEDs and is something all healthcare providers need to be familiar with. The use of phenytoin, carbamazepine, and lamotrigine has been linked to serious hypersensitivity reactions including Stevens-Johnson Syndrome (SJS; Sirven et al., 2004). SJS is a multisystemic reaction, which can include fever, lymphadenopathy, eosinophilia, and a mucocutaneous rash. This syndrome can be life threatening. In a study of SJS related to AEDs, researchers suggested that over 90% of cases contracted this syndrome within the first 60 days of starting a new AED (Mockenhaupt, Messenheimer, Tennis, & Schlingmann, 2005). This should alert providers to educate their patients to do thorough skin assessments, especially when starting a new AED. Although not all rashes lead to this fatal syndrome, it is important to question individuals on the occurrence of any skin changes. One study of individuals with malignant gliomas reported that 25% of those using phenytoin and 26% of those taking carbamazepine reported a rash. This was an especially common occurrence in individuals also receiving radiation therapy (Sirven et al., 2004).

Immunosuppression is regrettably a complication of chemotherapy, radiation therapy, and corticosteroid use. As a result, patients with brain tumors, like all patients with cancerous tumors, have an increased risk for developing infections. The use of steroids along with radiation treatments in brain tumor patients can significantly affect the immune system. Twenty-four percent of brain tumor patients in one study exhibited a CD4 cell count of less than 200 cells/mm during concurrent treatment with radiation and steroids. Careful monitoring of opportunistic infections is therefore important when CD4 counts decrease (Batchelor & Byrne, 2006). The use of antibiotics must also be used with caution in these individuals due to their ability to interact with AEDs.

According to the Office for Alternative Medicine, 70% of patients taking complimentary or alternative medicines did not report their use to healthcare providers (Stevens, 2006). The Glioma Outcomes Project again reviewed the use of alternative therapies among brain tumor patients. Results indicated that 49% of patients were using at least one alternative treatment during their initial 3-month postoperative period. The alternative therapies used in this group of patients showed meditation and prayer at 28%, high dose vitamins at 23%, and herbs at 18% (Hariharan, Landolfi, & More, 2000). Unfortunately, some of these alternative therapies can interrupt the metabolism of AEDs and therefore contribute to their inactivation or cause toxicity. In another study focusing on alternative therapies in this population, 19% of 187 participants were using therapies that could alter the metabolism of AEDs. Some of these therapies included St. John's Wort, Echinacea, and garlic. Even

more frightening, 14% of these patients were using therapies that were actually known to be epileptogenic such as ephedra, ginseng, evening primrose, and ginkgo (Plunkett, Klein, & Alldredge, 2004). It is essential to ask all patients about their use of alternative therapies, as they may severely interact with AEDs.

Healthcare providers need to be especially careful when prescribing AEDs in the elderly brain tumor patient. Increased concern must be initiated in this population due to the possibility of increased drug interactions that can occur due to decreased hepatic and renal function, a reduction in serum albumin concentration, atrophy of the gastric mucosal, and an increase in ratio of fat to lean body mass (van Breemen & Vecht, 2005). Recently, AEDs have been linked to possibly aiding in the process of osteoporosis. One study found that in a population of women older than 65 years who were taking AEDs, there was a 1.8-fold greater rate of bone loss seen during a 6-year period. Osteoporosis is thought to occur because of altered metabolism of vitamin D with concurrent use of several AEDs. With altered vitamin D metabolism, calcium is therefore unable to be absorbed properly, leading to decreased calcium levels. As mentioned, brain tumor patients are likely to be on concurrent therapy with steroids, which are also known to be linked to osteoporosis. Although there are yet-to-be-published reports suggesting that brain tumor patients should take calcium supplements, unless patients have a specific contraindication, calcium 1,000−1,500 mg/day and vitamin D 400 IU/day are often recommended (Stevens, 2006).

Women on birth control pills need to be aware that the AEDs involved with induction of the CYP-450 system, including phenytoin, phenobarbital, carbamazepine, oxcarbazepine, and also topiramate, may increase the metabolism of these hormones. This increased metabolism raises the possibility of contraceptive failure. Therefore, women on these medications need to be prescribed a higher dose of contraceptive and also instructed to use a barrier method due to the unpredictability of the metabolism of these drugs. Women, as well as men, who are especially concerned with their weight should consider which drugs can aid in weight gain or loss. Valproate, gabapentin, and pregabalin may contribute to weight gain, whereas topiramate and zonisamide may aid in weight loss (Sperling & Ko, 2006). This may be an important issue in brain tumor patients on chemotherapy and radiation. Significant weight loss is regularly seen in these individuals, and selecting an AED that may contribute to weight gain may be an important option in several patients.

Use of Second-Generation AEDs for Seizures

Realizing that an estimated 60% of patients will fail first-line treatment with AEDs has stimulated researchers to determine the effectiveness of second-generation AEDs as adjunctive therapy or monotherapy in the brain tumor population (Vecht & Van Breemen, 2006). In a recent consensus analysis of epilepsy experts, their recommendations for the treatment of epilepsy in patients with other comorbidities were either levetiracetam or lamotrigine (Vecht & Van Breemen, 2006). There is limited research on the study of second-generation AEDs in brain tumor patients, but levetiracetam has been shown to have efficacy as either an adjunctive treatment or as monotherapy.

Several studies have shown that add-on treatment with levetiracetam have been successful in controlling seizures in the brain tumor population. Levetiracetam is a second-generation AED that is fortunately not hepatically metabolized, therefore limiting its side effect profile. It is, however, cleared renally so dosing should be altered in patients with renal insufficiency or failure (Stevens, 2006). In a study by Wagner, Wilms, Van Donselaar, and Vecht (2003), of 28 participants, 65% of individuals had a 50% reduction in seizure frequency, and many of which were started on monotherapy with levetiracetam. Similar results were found in a retrospective analysis of the efficacy of levetiracetam in metastatic brain tumor patients. This study evaluated 13 patients with metastatic brain tumors who also suffered from epilepsy. Their results showed a reduction in seizure frequency by 50% in 100% of their patients, and 10 of the 13 participants had total seizure control (Newton, Dalton, Goldlust, & Pearl, 2007).

Although these results are promising, the small number of individuals in these studies has reduced their generalizability. However, a recent abstract submitted to the American Epilepsy Society in December 2007 has offered more hopeful results on the use of levetiracetam in brain tumor patients. Connely, Malkin, Krouwer, and Mushtaq (2007) confirmed the results of these earlier studies in a retrospective analysis of over 200 patients with brain tumors. They discovered that 80.5% of individuals had complete seizure control while being treated with levetiracetam, and 73% of these individuals received levetiracetam as monotherapy. This evidence has shown that levetiracetam used as monotherapy can be effective and therefore can be suggested for treatment in the brain tumor population. Data collection was still ongoing at the time the abstract was submitted, but these results are very promising. This review also showed that there was no statistically significant difference in the rates of seizure control among different

tumor types, meaning that seizure control was the same whether the patient had a low-grade or high-grade tumor (Connely et al., 2007). However promising, prospective randomized studies are still needed to confirm these findings with the use of levetiracetam and with other second-generation AEDs.

Use of Second-Generation AEDs for Psychosocial Manifestations

Depression is often an overlooked variable in brain tumor patients. In another report citing the Glioma Outcomes Project, investigation into the prevalence of depression in brain tumor patients was examined. This investigation suggested that, although over 93% of brain tumor patients reported symptoms of depression in the early postoperative period, physicians only recognized depression in 15% of these individuals. This report also suggests that if providers increase the awareness of treating these depressive symptoms significant improvement in quality of life may occur. Much more investigation needs to take place to identify those patients in need of antidepressant therapy (Litofsky et al., 2004). Possible drug interactions with AEDs may be the reason for resistance. Counseling and antidepressant therapy may be considered; however, some antidepressants may actually increase the seizure risk and must be used with caution (Amidei, 2005). Antidepressants that have been shown to have the highest overall incidence of contributing to seizure development are clomipramine, bupropion, and maprotiline (Koppel, 2004). It is important to make sure that brain tumor patients on AEDs also avoid taking St. John's Wort for the treatment of their depression, as this is another inducer of the CYP-450 enzymes (Stevens, 2006). Treating these depressive symptoms with AEDs has been shown to be just as effective as antidepressant drugs and should be considered for brain tumor patients. In one study topiramate and bupropion were evaluated and shown to be comparable with decreased depressive symptoms after 8 weeks of use. Zonisamide has shown great benefit for individuals in need of mood stabilization, and tiagabine has demonstrated beneficial outcomes for the use with major depression (Thompson et al., 2006). With these new findings, healthcare providers can look to newer generation AEDs to treat two underlying conditions with one medication.

Pain can often be a significant burden to brain tumor patients. Headaches are especially common. It is estimated that 35% of those with brain tumors report having a headache at the time of diagnosis, and up to 70% experience headaches at some point in the course of their disease (Amidei, 2005). Although headaches are quite common in this population of patients, headaches in combination with nausea, vomiting, changes in consciousness, blurry vision, and change in headache severity all require prompt evaluation. These symptoms can be signs of a neurological emergency. Several second-generation AEDs are also approved for use in chronic headaches such as gabapentin and topiramate. These AEDs have a low side effect profile and may be considered as adjunct therapy for these patients. Anxiety is another issue that these individuals face. Loss of appetite, insomnia, and fatigue can all result from anxiety. Gabapentin and pregabalin are two second-generation AEDs with proven anxiolytic qualities and their use may be beneficial (Thompson et al., 2006). Therefore it is important to observe for signs and symptoms of depression, pain, and anxiety when choosing a second-generation AED for brain tumor patients as these symptoms can be controlled by their use.

Nursing Implications and Discussion

As healthcare providers, it is important to educate epilepsy patients on known inducing and triggering factors that may provoke seizures. Inducing factors consist of environmental causes that can actually reduce the seizure threshold, and triggering factors activate chemical or physiological stimulation, which in turn can produce a seizure (Nakken et al., 2004). Nakken et al. (2004) performed a study to discover seizure-precipitating factors in a group of epilepsy patients and to determine which factors were most reported by its participants. Of the 1,677 participants in this study, 53% stated that they had at least one precipitating seizure factor. The top three factors reported were emotional stress, sleep deprivation, and tiredness. Other common factors reported were alcohol consumption, menstruation, inconsistent diet, and flickering lights. Although it may be extremely hard to determine the actual precipitating factors for patients, careful consideration must take place to educate patients on possible variables that may provoke their seizures.

The unpredictability of seizure occurrence causes an increased stress to patients who already have a dismal diagnosis. Not only do many of these individuals have a poor prognosis, but the available treatments offered may severely reduce their quality of life. These patients usually suffer from side effects of antineoplastic agents treating their underlying brain tumor, thus finding the proper AED becomes imperative. Determining the right drug combination can help to increase independence and dignity.

It is essential to provide comprehensive and updated care to these individuals. A thorough history and physical examination is required to assess for any possible contraindications or reactions. Psychosocial

assessments are also needed to screen for anxiety, depression, and overall quality of life. Cognitive and social constraints can play a major role in a person's overall outlook on life and must be addressed. Providers should consider using the Karnofsky Performance Status Index for assessing quality of life and the Mini-Mental Status Examination for gauging cognition. An Adverse Effects Profile should also be completed on every brain tumor patient who is taking AEDs. These assessments can help evaluate what side effects or degree of disease progression the patient may already be experiencing, which can therefore help in the selection of the most appropriate AED for the particular patient.

Because of the altered metabolism of anticonvulsant medications in brain tumor patients, serum concentrations of AEDs are often altered. Treatment should be determined by the amount of seizure control and the degree of unwanted side effects. Although frequent monitoring of AED levels is necessary, once a patient is stabilized and seizure-free, a baseline blood level is definitely recommended for future reference. Complete blood counts are also necessary to assess bone marrow function due to concurrent use of chemotherapy and radiation, which may all ultimately contribute to immunosuppression. Liver enzymes must also be monitored due to the increased clearance of drugs through this system.

Conclusion

The management of seizures in brain tumor patients is complex. Controversy still exists among healthcare providers regarding AED prophylaxis in brain tumor patients with no history of seizures. The guidelines from the AAN are still valid: Prophylactic use of AEDs is not necessary or needed. Postoperative AEDs should be tapered and discontinued 1 week after surgery as long as no seizures have occurred. There is a high risk for potential drug interactions with many of the first-generation AEDs, especially in combination with corticosteroids and chemotherapy agents. Second-generation AEDs are showing efficacy and tolerability in brain tumor patients and should be considered for use. Although these second-generation medications are showing promising results in this population, prospective randomized controlled trials are still needed to prove their reliability. The treatment of seizures in brain tumor patients should aim at decreasing morbidity and increasing quality of life.

References

Amidei, C. S. (2005). Managing symptoms and side effects during brain tumor illness. *Expert Review of Neurotherapeutics*, *5*(6), 71–75.

Batchelor, T. T., & Byrne, T. N. (2006). Supportive care of brain tumor patients. *Hematology/Oncology Clinics of North America*, *20*, 1337–1361.

Blumenfeld, H. (2002). *Neuroanatomy through clinical cases*. Sunderland, MA: Sinauer Associates.

Bromfield, E. B. (2004). Epilepsy in patients with brain tumors and other cancers. *Reviews in Neurological Diseases*, *1*(1), 27–33.

Central Brain Tumor Registry of the United States. (2005). *Statistical report: Primary brain tumors in the United States*, 1998–2002, 1–55. Retrieved from http://www.cbtrus.org/

Chang, S. M., Parney, I. F., Huang, W., Anderson, F. A., Asher, A. L., & Bernstein, M., et al. (2005). Patterns of care for adults with newly diagnosed malignant glioma. *Journal of the American Medical Association*, *293*(5), 557–564.

Claus, E. B., & Black, P. M. (2006). Survival rates and patterns of care for patients diagnosed with supratentorial low-grade gliomas: Data from the SEER program 1973–2001. *Cancer*, *106*(6), 1358–63.

Connely, J., Malkin, M. G., Krouwer, H., & Mushtaq, R. (2007). Seizure freedom with levetiracetam therapy in brain tumor patients; a retrospective study [Abstract]. *Epilepsia3*, *239*.

Demonte, F., Gilbert, M. R., Mahajan, A., & McCutcheon, I. E. (2007). *Tumors of the brain and spine: MD Anderson Cancer Care Series*. New York: Springer.

French, J. A., Kanner, A. M., Bautista, J., Abou-Khailil, B., Browne, T., Harden, C. L., et al. (2004a). Efficacy and tolerability of the new antiepileptic drugs I: Treatment of new onset epilepsy: Report of the Therapeutics and Technology Assessment Subcommittee and Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Neurology*, *62*(8), 1252–1260.

French, J. A., Kanner, A. M., Bautista, J., Abou-Khailil, B., Browne, T., Harden, C. L., et al. (2004b). Efficacy and tolerability of the new antiepileptic drugs II: Treatment of refractory epilepsy: Report of the Therapeutics and Technology Assessment Subcommittee and Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Neurology*, *62*(8), 1261–1273.

Giovagnoli, R. A., Silvani, A., Colombo, E., & Boiardi, A. (2005). Facets and determinants of quality of life in patients with recurrent high grade glioma. *Journal of Neurology, Neurosurgery and Psychiatry*, *76*(4), 562–568.

Glantz, M. J., Cole, B. F., Forsyth, P. A., Recht, L. D., Wen, P. Y., & Chamerlain, M. C., et al. (2000). Practice parameter: Anticonvulsant prophylaxis in patients with newly diagnosed brain tumors: Report of the quality standards subcommittee of the American Academy of Neurology. *Neurology*, *54*(10), 1886–1893.

Glantz, M. J., Cole, B. F., Friedberg, M. H., Lathi, E., Choy, H., & Furie, K., et al. (1996). A randomized, blinded, placebo-controlled trial of divalproex sodium prophylaxis in adults with newly diagnosed brain tumors. *Neurology*, *46*, 985–991.

Hariharan, S., Landolfi, J., & More, J. (2000). Alternative therapy use by malignant glioma patients: Data from the glioma outcomes project. *Neuro-oncology*, *2*, 268.

Hildebrand, J. (2004). Management of epileptic seizures. *Current Opinion in Oncology*, *16*(4), 314–317.

Koppel, B. S. (2004). *Antidepressants*. Retrieved June 1, 2008, from http://professionals.epilepsy.com/page/drugs_antidepress.html

Litofsky, N. S., Farace, E., Anderson, F., Meyers, C., Huang, W., & Laws, E. R., et al. (2004). Depression in patients with high-grade glioma: Results of the Glioma Outcomes Project. *Neurosurgery*, *54*(3), 358–367.

Mockenhaupt, M., Messenheimer, J., Tennis, P., & Schlingmann, J. (2005). Risk of Stevens-Johnson Syndrome and toxic epidermal necrolysis in new users of antiepileptics. *Neurology*, *64*(7), 1134–1138.

Nakken, K. O., Solaas, M. H., Kjeldsen, M. J., Friis, M. L., Pellock, J. M., & Corey, L. A. (2004). Which seizure-precipitating factors do patients with epilepsy most frequently report? *Epilepsy and Behavior*, *6*, 85–89.

Newton, H. B., Dalton, J., Goldlust, S., & Pearl, D. (2007). Retrospective analysis of the efficacy and tolerability of levetiracetam in patients with metastatic brain tumors. *Journal of Neuro-oncology*, *84*(3), 293–296.

Plunkett, M., Klein, F., & Alldredge, B. (2004). Use of complementary and alternative medicine products by patients with epilepsy: How common is it? *Epilepsia*, *45*(7), 149.

Ruegg, S. (2002). Dexamethasone/Phenytoin interactions: Neurooncological concerns. *Swiss Medical Weekly*, *132*, 425–426.

Siomin, V., Angelov, L., & Li, L. (2005). Results of a survey of neurosurgical practice patterns regarding the prophylactic use of anti-epilepsy drugs in patients with brain tumors. *Journal of Neuro-oncology*, *74*(2), 211–215.

Sirven, J. I., Wingerchuk, D. M., Drazkowski, J. F., Lyons, M. K., & Zimmerman, R. S. (2004). Seizure prophylaxis in patients with brain tumors: A meta-analysis. *Mayo Clinic Proceedings*, *79*(12), 1489–1494.

Sperling, M. R., & Ko, J. (2006). Seizures and brain tumors. *Seminars in Oncology*, *33*, 333–341.

Stevens, G. H. (2006). Antiepileptic therapy in patients with central nervous system malignancies. *Current Neurology and Neuroscience Reports*, *6*, 311–318.

Thompson, D., Takeshita, J., Thompson, T., & Mulligan, M. (2006). Selecting antiepileptic drugs for symptomatic patients with brain tumors. *Journal of Supportive Oncology*, *4*(8), 411–416.

Van Breemen, M., & Vecht, C. J. (2005). Optimal seizure management in brain tumor patients. *Current Neurology and Neuroscience Reports*, *5*, 207–213.

Vecht, C. J., & Van Breemen, M. (2006). Optimizing therapy of seizures in patients with brain tumors. *Neurology*, *67*(4), S10–S13.

Wagner, G. L., Wilms, E. B., Van Donselaar, C. A., & Vecht, C. J. (2003). Levetiracetam: The preliminary experience in patients with primary brain tumors. *Seizure*, *12*, 585–586.

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