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Spectrum of Side Effects of Anticonvulsants in Patients with Brain Tumours

Christa P Bénit, Charles J Vecht

Abstract: Seizures are a common manifestation in patients with brain tumours, and most patients need anticonvulsants. Apart from seizure control, the risk of side effects makes the proper choice of anticonvulsants a major concern. Toxicities not only exist as common side effects, but also appear as drug-drug interactions, neurotoxicities, and other organ dysfunctions.

One reason for interactions is the use of the classical anti-epileptic drugs (AED), phenobarbital (PB), phenytoin (PHT), and carbamazepine (CBZ). Large differences in dose regimens with concomitant chemotherapy reflect the potency of these effects. Although valproic acid (VPA) can be beneficial to prevent tumour growth, it may lead to bone marrow suppression and other toxicities because of its enzyme-inhibiting properties.

Another noteworthy side effect are skin reactions, like erythema multiforme, which occasionally develops during radiation. Although this side effect is rare, it can be life-threatening. Many anti-epileptic drugs can have extra toxic effects with existing organ dysfunction, like bone-marrow suppression or liver abnormalities, this applies particularly for PB, PHT, CBZ, and VPA.

Existing clinical or subclinical signs of brain damage secondary to space-occupying tumoural effects or the sequelae of previous neurosurgery, radio-, and chemotherapy enhance the chances of neurotoxicity. Besides, the intake of anticonvulsants itself and their total number strongly contribute to cognitive dysfunction. As neurocognitive decline interferes with quality of life, such changes may substantially affect daily activities of patients and their family members.

The multitude of co-therapies applied with brain tumours contributes to a myriad of side effects that are almost impossible to unravel, as drugs and other therapies used can have aggravating or counteracting effects on each other. Knowledge of individual anticonvulsants and anticipation of toxicity including the recognition of already existing co-morbidities all contribute to better selection and dosing of anticonvulsants, including the choice of agents that do not interact. Although this survey is not aimed at the proper drug choice, future studies need to show which anti-epileptic agents or combinations would be the best match to achieve effective seizure control together with good tolerability. **Eur Assoc Neurooncol Mag 2012; 2 (1): 15–24.**

Key words: brain tumour, seizure, anticonvulsant, drug interaction, toxicity, cognitive dysfunction

Introduction

Epilepsy is common in patients with brain tumours, and seizures constitute the presenting symptom in 30–50 % of patients with brain tumours [1]. Seizures can also affect patients with systemic cancer with brain or leptomeningeal metastases or by organ dysfunction or drug treatment, including chemotherapy causing metabolic or toxic encephalopathies [2]. For these reasons, patients with seizures and cancer often need anticonvulsants; ⅔ of patients with primary brain tumours use AEDs [3]. Unavoidably, this may lead to side effects either as general toxic effects, or more specifically related to the underlying condition, for example the occurrence of interactions with concomitantly administered chemotherapeutic agents. In this review, we will comment on the general side effects of anticonvulsants, followed by a more extensive discussion on side effects of anticonvulsants associated with brain tumours or systemic cancer.

Side effects of anticonvulsants are more common in patients with brain tumours (20–40 %) than in other types of epilepsy and lead in almost ¼ to a discontinuation of therapy [4]. These effects include cognitive changes, abnormalities related to organ function, interactions with other drugs, most notably chemotherapy, and other toxicities particularly associated with brain tumours.

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Seizures in patients with brain tumours can be classified as partial (simple or complex partial) or symptomatic, with or without secondary generalisation. Here we briefly mention the main characteristics of anticonvulsants, and Table 1 depicts an overview of the main mechanisms of action, the metabolic pathways involved, their pharmacokinetic properties and common toxicities, including idiosyncratic side effects occurring in cancer patients.

Phenobarbital (PB) is one of the oldest anticonvulsants and still in use in many parts of the world. Major drawbacks are its relatively strong sedating effect as well as its being a strong enzyme-inducer. Nevertheless, because of its action as a broad-spectrum anticonvulsant, it may still be applied in treatment-resistant seizures. In cancer patients, one should be aware of cognitive side effects, hepatic dysfunction, skin reactions including Stevens-Johnson syndrome (SJS), and drug interactions.

Phenytoin (PHT) is a first-generation anticonvulsant which is also employed in status epilepticus. It is a strong enzyme-inducer and has been implied in many reports on interactions with co-administered agents, including chemotherapeutic drugs (CTD). Besides, it shows non-linear pharmacokinetics and has a relatively small therapeutic window. Today, it is mainly applied by the intravenous route in status epilepticus, and is felt to be less suitable for oral maintenance therapy. Interaction with other drugs and side effects like encephalopathy, hepatitis, coagulation defects, and bone marrow hypoplasia are of concern in patients with brain tumours.

Carbamazepine (CBZ) is a still widely used first-generation anticonvulsant for partial seizures. It is a potent enzyme-inducer and can strongly accelerate the metabolism of many

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Table 1. Mechanisms of action of AEDs (in alphabetical order) and pharmacokinetic characteristics. Based on [5–8].

AED	Usual dosage (mg/day)	Therapeutic range (mg/l)	Common/important side effects	Main mechanism of action	Oral bio-availability (%)	Time to peak levels (h)	Metabolism and excretion	V_d (l/kg)	$T_{1/2}$ (h)	CL (l/kg/h)	Protein binding (%)
CBZ	400–1600	4–12	Leukopenia, aplastic anaemia, hepatotoxicity, hyponatraemia, SJS/TEN	Blocks voltage-dependent Na^+-channels	75–85	4–8	Hepatic epoxidation, conjugation	0.8–2	5–26	0.133	75
CZP	0.5–4	0.02–0.08	Sedation, cognitive effects, drowsiness	GABA receptor agonist	90	1–4	Hepatic reduction and acetylation	1.5–4.4	20–80	0.09	86
FBM	1200–3600	30–100	Hepatic disturbance, SJS aplastic anaemia, insomnia, weight loss	NMDA and Na^+-channel conductance	> 90	2–6	Hepatic hydroxylation and conjugation (60 %), renal excretion (40 %)	0.75	13–30	0.027–0.032	20–25
GBP	900–3600	2–20	Weight gain, worsening of seizures	Blocks Ca^+-channels, GABA receptor agonist	< 65	2–3	Renal excretion without metabolism	0.65–1.04	5–7	0.120–0.130	None
LCM	200–400	10–20	Dizziness, headache, nausea, diplopia, blurred vision, cognitive dysfunction, skin reactions	Slow inactivation of voltage-dependent Na^+-channels	> 95	2–4	Hepatic demethylation, unchanged renal excretion (40 %)	0.6	13		< 15
LTG	200–600	1–15	Rash, SJS, TEN, DRESS, headache, blood dyscrasia, ataxia	Blocks voltage-dependent Na^+-channels	> 95	1–3	Hepatic glucuronidation (without phase-1 reaction), renal excretion (10 %)	1.0–1.3	12–60	0.044–0.084	55
LEV	1000–3000	3–30	Somnolence, asthenia, irritabiity psychosis	Binding to synaptic vesicle protein 2 (SV2A)	> 95	0.6–1.3	Partially hydrolysed in the blood,	0.5–0.7	5–11	0.01	None
OXC	900–2400	10–35	Somnolence, headache, diplopia, SJS, bone marrow suppression, hyponatraemia	Blocks voltage-dependent Na^+-channels	> 95	4–6	Hydroxylation, glucuronidation	0.3–0.8	8–10		38
PB	30–180	15–40	Rash, hepatotoxicity, impaired cognition, ataxia, mood change, SJS/TEN	GABA receptor agonist, glutamate antagonist, blocks voltage-dependent Na^+-/Ca^+-channels	80–100	1–3	Hepatic oxidation, glucosidation, hydroxylation, conjugation	0.42–0.75	46–136	0.006–0.009	45–60
PHT	150–400	10–20	Blood dyscrasia, hepatitis, SJS, gum hyperplasia, lupus-like reactions, hirsutism	Blocks voltage-dependent Na^+-channels	95	4–12	Hepatic oxidation, hydroxylation, conjugation	0.5–0.8	24–72	0.003–0.02	85–95
PGB	150–600	2–8	Somnolence, dizziness, ataxia	Binds to Ca^+-channels	90	1	No metabolism, renal excretion		6.3		None
TPM	100–500	2–20	Impaired cognition, hepatotoxicity, weight loss, renal calculi	Blocks Na^+-channels, GABA receptor agonist, blocks NMDA receptors	81–95	2–4	No metabolism, mainly renal excretion	0.6–1.0	19–25	0.022–0.036	9–17
VGB	200–300	0.8–36	Visual field defects (33 %, often irreversible), fatigue, drowsiness	GABA transaminase inhibitor	80–90	1–2	No metabolism, renal excretion (70 %, unchanged)	0.8	6–8	Similar to GFR	None
VPA	500–2500	50–100	Hepatotoxicity, thrombo- and neutropenia, aplastic anaemia, tremor, weight gain, hair loss, ovarian cystic syndrome	Uncertain, may affect GABA glutaminergic activity	> 95	1–10	Hepatic glucuronidation, oxidation, conjugation	0.15	8–15	0.006–0.015	85–95
ZON	200–600	20–30	Somnolence, ataxia, dizziness, renal cuniculi	Blocks Na^+- and Ca^+-channels	> 95	2–6	Hepatic acetylation, glucuronidation (20 %), renal excretion (30 %)	1.2–1.8	60–70	0.015–0.019	40–50

AED: antiepileptic drug; V_d: volume of distribution; $T_{1/2}$: elimination half-life; Cl: clearance; DRESS: drug reactions with eosinophilia and systemic symptoms; Na^+: sodium; NMDA: N-Methyl-D-aspartate; Ca^+: calcium; K^+: potassium; GFR: glomerular filtration rate; CBZ: carbamazepine; CZP: clonazepam; FBM: felbamate; GBP: gabapentin; LCM: lacosamide; LTG: lamotrigine; LEV: levetiracetam; OXC: oxcarbazepine; PB: phenobarbitone; PHT: phenytoin; PGB: pregabalin; SJS: Stevens-Johnson syndrome; TEN: toxic epidermal necrolysis; TPM: topiramate; VGB: vigabatrin; VPA: valproic acid; ZON: zonisamide.

other drugs. Relevant side effects include drug interactions, hepatotoxicity, skin reactions including Stevens-Johnson syndrome (SJS), leukopenia, bone marrow dyscrasia, and hyponatraemia.

Valproic acid (VPA) is a broad-spectrum anticonvulsant for both generalized and partial epilepsy with rather mild toxicity. Recent reports indicate that it may also have anti-tumour effects in glioblastoma multiforme and other types of cancer, possibly secondary to its action as a histone-deacetylase inhibitor [9–11]. In children and adults with high serum levels, one should be aware of a disturbed haemostasis; monitoring of liver functions, platelet counts, and coagulation parameters is advisable. The impact of these abnormalities is uncertain as clinical studies have not indicated enhanced bleeding tendencies following neurosurgery. Nevertheless, in patients with cancer, one should be aware of drug-drug interactions and side effects including hepatotoxicity, disturbed haemostasis, bone marrow suppression, and skin reactions, ie, rash, SJS, or toxic epidermal necrolysis (TEN).

Clonazepam (CZP) is a benzodiazepine, and a broad-spectrum and effective anticonvulsant. Because its use may easily lead to sedation and tolerance, its application is generally restricted to the abrogation of acute seizures, in status epilepticus, or as a last resort therapy when other antiepileptic drugs have failed.

Lamotrigine (LTG) represents a first-choice anticonvulsant for symptomatic partial epilepsy. However, although lamotrigine by itself has only weak inducing and inhibiting activities of the P-450 co-enzyme system of the liver, LTG is susceptible to induction by concomitantly given drugs. A drawback of lamotrigine is that the initiation of therapy requires a long time period of dose increments before therapeutic ranges are reached. One should be aware of side effects in cancer patients such as skin reactions (SJS, TEN), bone marrow toxicity, and drug interactions.

Oxcarbazepine (OXC) has a close structural similarity to CBZ but it is better tolerated and shows fewer drug interactions. In patients with cancer, one should be aware of hyponatraemia, skin reactions (SJS, TEN), and sometimes bone marrow suppression.

Topiramate (TPM) is a second-generation and effective broad-spectrum AED with no obvious drug interactions, although its tolerability is lower than for many of the other newer AEDs. In cancer patients, one should be aware of cognitive dysfunction, hepatic abnormalities, and blood dyscrasia (rare).

Gabapentin (GBP) is one of the second-generation anticonvulsants, it is generally well-tolerated and shows no interaction with other drugs. However, it has a limited efficacy and sometimes a worsening of seizures may happen. In patients with renal dysfunction, dose adjustment is necessary.

Felbamate (FBM) can lead to serious adverse events, like hepatic abnormalities or aplastic anaemia; its use is mainly restricted to intractable types of epilepsy.

Levetiracetam (LEV) has good anti-seizure efficacy, including in brain tumours [12–15]. Its major advantage is the absence of interactions with other agents. It is being excreted by the kidney, and in the presence of renal dysfunction, dose adjustment is necessary. Side effects include irritability and psychosis; blood dyscrasia is rare.

Pregabalin (PGB) is a third-generation anticonvulsant that does not show pharmacokinetic interactions with enzyme-inducing or -inhibiting drugs. To date, there is little experience with pregabaline as an anticonvulsant, including its application in brain tumour patients. In patients with renal dysfunction, dose adjustment is necessary.

Lacosamide (LCM) selectively enhances slow sodium channel inactivation. Because of the absence of drug interactions, lacosamide seems a promising AED in cancer. Presently, it is registered for use as an add-on AED. Side effects include cognitive dysfunction and skin reactions.

Zonisamide (ZON) is a broad-spectrum anticonvulsant and is metabolised by conjugation with glucuronic acid. It does not inhibit or induce hepatic co-enzymes, however, other enzyme-inducing drugs, like PHT and PHB, can enhance its metabolism. Side effects like weight loss and cognitive disturbances are of concern in patients with brain tumours.

Drug Interactions

Drug interactions are characterized as either pharmacokinetic (when uptake, distribution, metabolism, or excretion is affected) or pharmacodynamic (when target organs or receptor sites are affected). Pharmacokinetic drug-drug interaction _occurs when ≥ 2 drugs are administered simultaneously and one drug modifies the metabolism of the other. In this way, serum concentrations of co-administered drugs can become reduced or elevated, leading to either ineffective therapy or drug toxicity. The most common interactions between antiepileptic and cytostatic drugs are of a pharmacokinetic nature, and as a rule may occur when both are being metabolized by a corresponding co-enzyme of the P450 CYP system, by epoxide oxidation, or by glucuronidation in the liver [16, 17]. Although the CYP system consists of approximately 60 different iso-enzymes, 5 of them (CYPs 3A4, 2D6, 2C9, 2C19, and 1A2) are responsible for the metabolism of 95 % of all drugs, of which the CYPs 3A4, 2C9, and 2C19 (Table 2) are particularly important in relation to potential interactions of AEDs [19, 20]. An overview of the different groups of chemotherapeutic agents and the interactions they may have with anticonvulsants, most notably with enzyme-inducing AEDs, is given in Table 3.

Compromised Activity of CTDs by Enzyme-Inducing AEDs

Alkylating Agents

Cyclophosphamide is an alkylating agent and is commonly administered in the treatment of malignant lymphomas, leukaemias, neuroblastoma, retinoblastomas, and carcinomas of the ovary, breast, endometrium, and lung, usually in combination with other chemotherapeutic drugs [25]. By itself, cyclophosphamide is inactive and requires enzymatic bioactiv-

Table 2. Mechanisms of metabolism of AEDs and their effects on the P450 hepatic CYP system. Based on [16, 18].

AED	Metabolism	Substrate (CYP)	Inducer (CYP)	Inhibitor (CYP)
CBZ	Cytochrome P450	1A2, 2C9, 2C19, 3A4	1A2 (s), 2B6 (s), 2C9 (s), 2C19 (s), 3A4 (s) 3A4 (s)	–
CZP	Cytochrome P450	3A4	–	–
FBM	Cytochrome P450	2E1	2C19, 3A4 (w)	2C19
GBP	Not metabolised	–	–	–
LCM	Partial cytochrome P450	2C19	–	–
LTG	UDPGT glucuronidation	–	UDGPT (w)	–
LEV	Non-hepatic hydrolysis	–	–	–
OXC	UDPGT glucuronidation, limited cytochrome P450 metabolism	–	2C19 (w), 3A4 (w)	2C19 (w)
PB	Cytochrome P450	2C9, 2C19, 2E1	1A2 (s), 2B6 (s), 2C8 (s), 2C9/C19 (s), 3A4 (s)	–
PHT	Cytochrome P450	2C8, 2C9, 2C19	1A2, 2B6 (s), 2C9/19 (s), 3A4 (s)	–
PGB	Not metabolised	–	–	–
TPM	Mainly renal excretion, limited cytochrome P450 metabolism, UDPGT glucuronidation	–	2C19 (w), 3A4 (w)	2C19 (w)
VGB	Not metabolised	–	–	–
VPA	Cytochrome P450, UDPGT glucuronidation, β-oxidation	2A6, 2B6, 2C9, 2C19	–	2C9, EH, UDPGT
ZON	Cytochrome P450	2C19, 3A4, 3A5	–	–

AEDs: see Table 1; s: strong; w: weak; CYP: cytochrome P450 enzyme; UDPGT: uridine diphosphate glucuronyltransferase

ation in the liver and various CYP iso-enzymes have been demonstrated to be involved, including 3A4/5 and 2C9/19 [25]. PB, PHT, and CBZ can induce the clearance of cyclophosphamide via its action on enzyme-inducing iso-enzymes [62]. As a faster metabolism may also lead to an increased exposure to active metabolites, this combination can also result in toxicity [22]. Lower plasma concentrations of ifosfamide have also been observed in combination with PHT, probably due to enhanced activity of CYP2B6 [24].

Busulphan is an alkylating agent that is applied with autologous bone marrow transplantation. Concomitant prescription of AEDs is recommended because busulphan gives rise to epileptic seizures. However, administration of PHT may result in reduced steady-state levels of busulphan [63].

Antimitotic Cytostatics

Vinca alkaloids, including vinblastine, vincristine, and vindesine, are largely metabolized by 3A4/5 iso-enzymes [64, 65]. Systemic clearance (Cl) of vincristine is 63 % higher, the elimination half-life ($T_{1/2}$) 35 % shorter, and the total area-under-the-plasma-concentration-time curve (AUC) 43 % smaller in patients receiving PTH or CBZ, probably as a result of an accelerated metabolism of vincristine [39].

Taxanes

Paclitaxel is widely used in different types of cancer, including lung, breast, and ovarian carcinoma and acts by stabilisation of tubulin polymerization. Its metabolism takes place through oxidative metabolism mediated by 3A4/5 and 2C8 [66]. In combination with enzyme-inducing AEDs, the maximum tolerated dose (MTD) of paclitaxel is 43–50 % higher and depends to some extent on the way of administration [34, 35].

Antimetabolites

Methotrexate is an antimetabolite that acts as a folate antagonist, it is widely applied in different types of cancer, including leukaemia, lymphomas, and breast cancer. Methotrexate inhibits dihydrofolate reductase, leading to reduced synthesis of DNA, RNA, and proteins [67]. Its elimination is mainly renal, and 80–90 % is unchanged excreted in urine [68]. In a retrospective study, 40 of 716 children with acute lymphoblastic leukaemia receiving PB, PHT, or CBZ had a lower plasma clearance of methotrexate and teniposide, together with a worse event-free survival, more haematological and CNS relapses, and a shorter survival [26]. In a small retrospective study, blood levels of methotrexate were lower in patients receiving EIAEDs as compared to either the non-EIAED topiramate or not receiving any anticonvulsant [27]. The exact mechanism of interaction between the AEDs methotrexate and EIAEDs is not known.

Topo-Isomerase Inhibitors

Etoposide and teniposide are used in non-small-cell lung carcinoma (NSCLC) and acute myeloid leukaemia, (non-) Hodgkin's lymphoma, acute lymphoblastic leukaemia, and in autologous bone marrow transplantation, and are mainly metabolized by CYP 3A4 [64]. The Cl of etiposide is about 77 % faster in patients on concomitantly administered EIAEDs [38]. Concomitant use of PB or PTH leads to a 2–3-fold increase of Cl of teniposide, which may thus compromise its efficacy [37].

The camptothecin analogue topotecan is mostly used in refractory small-cell lung cancer and ovarian cancer, and co-administration of PHT leads to a 47-% increase of Cl and fewer haematological side effects [69]. For 9-aminocamptotecin, plasma concentration levels are 3× lower with concomi-

Table 3. Interactions between AEDs and CTDs

Table 3a. *AED that reduce CTD efficacy*

Group CTD	Type of CTD	AED that reduces CTD	Effect	Reference
Alkylating agents	Busulphan	PHT	Cl 15 % ↑, AUC 16 % ↓, $T_{1/2}$ 23 % ↓	[21]**
	Cyclophos-phamide	PB, PHT	AUC 67 % ↓, biotransformation 200–300 % ↑	[22]* [23]*
	Ifosfamide	PHT	AUC ↓ (ns), Cl ↑ (ns)	[24]*
	Thiotepa	PHT	AUC 29 % ↓	[25]*
Antimetabolites	Methotrexate	PB, PHT, CBZ	Cl ↑ (ns), C_{pl} 90 % ↓	[26]*** [27]*
Antimitotic agents	9-Amino-camptotecin	PB, PHT, CBZ	C_{pl} 67 % ↓, MTD 109 % ↑, Cl 122 % ↑	[28]*** [29]**
	Irinotecan	PB, PHT, CBZ, PRM, OXC	MTD 160–250 % ↑, Cl 61 % ↑	[30]*** [31]*** [32]***
	Topotecan	PHT	Cl 47 % ↑	[33]***
	Paclitaxel	EIAEDs (ns)	MTD 43–57 % ↑, MTD 50 % ↑, C_{ss} 55 % ↓	[34]*** [35]*** [36]***
	Teniposide	PB, PHT	Cl 146 % ↑	[37]*
	Etoposide	AEDs (ns)	Cl 77 % ↑	[38]*
	Vincristine	PHT, CBZ	Cl 63 % ↑, AUC 43 % ↓	[39]**
Proteinkinase inhibitors	Bortezomib	EIAEDs (ns)	MTD 47 % ↑	[40]**
	Enzastaurin	EIAEDs (ns)	C_{pl} 80 % ↓	[41]**
	Erlotinib	EIAEDs (ns)	AUC 55 % ↓, MTD 150–333 % ↑	[42]*** [43]**
	Gefitinib	PB, PHT, CBZ, PRM, OXC	AUC 60 % ↓, MTD 300 % ↑	[44]**
	Imatinib	PHT, CBZ, PRM, OXC, TPM	C_{pl} 66–68 % ↓, MTD 50 % ↑	[45]*** [46]***
	Sorafenib	EIAEDs (ns)	C_{pl} ↓	[47]**
	Tipifarnib	PB, PHT, CBZ	AUC 83 % ↓, MTD 100 % ↑	[48]***
	Vatalinib	PB, PHT, CBZ, PRM, OXC	Cl 200 % ↑, C_{max} 67 % ↓	[49]**
	Temsirolimus	PB, PHT, CBZ, OXC	C_{max} 73 % ↓, MTD 47 % ↑, C_{pl} 33 % ↓	[50]*** [51]**
	Sirolimus	PB, PHT, CBZ, OXC	AUC 39 % ↓, MTD 100 % ↑	[52]*** [53]**
	Everolimus	EIAEDs (ns)	Lower C (ns)	[50]*** [51]**

Table 3b. *Increase of toxicity*

CTD	AED that increases toxicity of CTD	Result	Reference
CCNU (Lomustine)	VPA	Frequency of haematological toxicity 60 % ↑	[9]***
AED	**CTD that increase toxicity of AED**	**Effect**	**Reference**
PHT	5-Fluorouracil	C_{pl} (PHT) 170–225 % ↑	[54]* [55]*
	Capecitabine	C_{pl} (PHT) 168–171 % ↑	[55]* [56]*
	Doxifluridrine	C_{pl} (PHT) 400 %	[57]*
	Erlotinib	C_{pl} (PHT) 322–406 % ↑	[58]*
	Tamoxifen	C_{pl} (PHT) 44 %	[59]*
VPA	Fotemustine/Cisplatin	Frequency of haematological toxicity 300 % ↑	[60]****
PHT, PB, CBZ, VPA (as combination therapy)	Procarbazine	Frequency of skin hypersensitivity reactions 390 % ↑	[61]****

CTD: chemotherapeutic drug; AED: antiepileptic drug (abbreviations: see Table 1); Cl: clearance; AUC: area-under-the-concentration-time curve; $T_{1/2}$: elimination half-life; ns: not specified; C: concentration; EIAED: enzyme-inducing antiepileptic drug; C_{pl}: plasma concentration; MTD: maximum tolerated dose; PRM: primidone; TD: tolerated dose; C_{ss}: steady-state concentration; C_{max}: peak plasma concentration. case report (1–4 patients); ** small series (4–19 patients); *** large series (20–49 patients); **** large prospective series (> 50 patients)

tant EIAEDs [28]. Co-medication with EIAEDs results in an increase in clearance of 27–57 % and a decrease in bioavailability of 75 % of irinotecan [28].

Other Cytostatic Drugs

Ixabepilone is a novel microtubule-targeting agent with antitumour activity against ovarian, colon, cervical, gastric, breast, melanoma, NSCLC, and non-Hodgkin's lymphoma. Together with EIAEDs, the MTD is 41 % and the Cl 50 % higher, probably by induction of 3A4 [70].

Proteinkinase Inhibitors

Research into the development of gliomas and other carcinomas has improved the understanding of specific cellular, molecular, and genetic mechanisms that lead to cancer growth and progression. To date, many agents can target these pathways, including tyrosine-kinase inhibitors and angiogenic inhibitors. The metabolism of these drugs is often influenced by concomitant administration of anticonvulsants.

Erlotinib is an inhibitor of the epidermal growth factor receptor (EGFR) and is used in NSCLC, and mainly metabolized via the iso-enzymes 3A4, 3A5, and to a lesser extent by 1A2 [43]. The MTD for erlotinib is 200 mg/day without enzyme induction and more than 2–3× higher (450–650 mg/day) together with an EIAED [42, 43].

Another tyrosine-kinase receptor inhibitor is the small molecule gefitinib that is used in NSCLC and is metabolized by 3A4, 3A5 co-enzymes, and the non-inducible CYP2D6. For patients using an EIAED, the peak dose of gefitinib is –45 %, the AUC –60 % and the MTD 4× higher (1000 mg/d) as com-

pared to an MTD of 250 mg/day without EIAEDs [44]. Imatinib, another selective inhibitor of tyrosine-kinase, is administered in chronic myeloid leukaemia and with gastrointestinal stromal tumours, and largely metabolized by CYP3A4 [46]. Mean trough levels of imatinib are 2.9× lower with an MTD of 1200 mg/day for patients on EIAEDs as compared to 800 mg/day normally [45, 46]. For sorafenib, which is mostly used in advanced renal cell carcinoma and hepatocellular carcinoma, the peak concentration (Cmax) is –54 % and the AUC –63 % for patients on EIAEDs [47].

Tipifarnib is currently under investigation, mostly in blood and breast cancers. A phase-I trial of tipifarnib in patients with recurrent glioma using EIAEDs showed that the MTD is 2× higher, and the AUC approximately 2× lower than for patients not on EIAEDs. It is unclear to what extent either glucuronidation or oxidative metabolism by P450 co-enzymes is responsible for this decrease in systemic exposure [48].

Bortezomib is applied in multiple myeloma and in recurrent mantle-cell lymphoma. The use of EIAEDs can lead to an acceleration of metabolism requiring 2× higher doses of bortezomib [40].

In enzastaurin, a VEGFR inhibitor, which is investigated in B-cell lymphoma, chronic lymphatic leukaemia, and solid tumours including glioblastoma, simultaneous EIAED use leads to approximately –80 % AUC [41].

Temsirolimus is an ester of the immunosuppressive agent sirolimus and inhibits the mammalian target of rapamycin. It is mainly used in metastatic renal cell carcinoma and under investigation in glioblastoma multiforme. Sirolimus is an immunosuppressant agent mostly given to transplant patients, and may have anti-tumour activity against malignant gliomas [53]. Both temsirolimus and sirolimus constitute substrates of iso-enzymes 3A4/5. In one study, the peak concentration of temsirolimus was –73 % and of sirolimus –47 % and the AUC –50 % with EIAED co-therapy. Grade-3 haematological toxicity was more commonly seen (20 vs 3 %) in patients on non-EIAEDs [50, 53]. Also, everolimus concentrations are lower with concomitant 3A4-inducing AEDs [71].

Increased Toxicity by AEDs or CTDs

Increased toxicity of AEDs may occur when enzyme-inhibiting CTDs are concurrently prescribed. Toxicity of PHT has been observed when combined with 5-fluorouracil, tamoxifen, capecitabine, erlotinib, or doxifluridine [55, 57–59]. The underlying mechanism of these interactions is probably a competitive inhibition of PTH clearance by 2C9 and 2C19 iso-enzymes. The use of the alkylating agent procarbazine in combination with PB, PTH, CBZ, or VPA can lead to hypersensitivity reactions of the skin. In a fotemustine-cisplatin regimen, the use of VPA leads to a 4-fold increase of thrombopenia, neutropenia, or both [60].

Corticosteroids

Glucocorticosteroids are frequently used in patients with brain tumours and systemic cancer, their administration can cause drug-drug interactions because of enzyme-inducing effects on the 3A4 iso-enzyme [72]. Vice versa, they are susceptible to agents affecting 3A4; PB, PHT, and CBZ enhance the clearance of dexamethasone 2–4× [5, 73, 74]. Hydrocortisone is metabolized via the hepatic 11-B-hydroxysteroid dehydrogenase system, which is also susceptible to enzyme induction. PB, PHT, and CBZ induce the metabolism of prednisolone with enhanced clearances of 79 %, 41 % and 77 %, respectively, and the metabolism of methylprednisolone more than 3.4, 1.5, and 2×, respectively [75]. Vice versa, dexamethasone given together with PHT may lead to an increased clearance of PHT and therefore with a lesser anti-epileptic activity. Increased seizure frequency has indeed been observed with co-therapy of dexamethasone with 38–50 % lower serum PHT levels [76–78]. When dexamethasone is discontinued, PHT concentrations can easily rise to toxic levels [79].

These observations emphasize that it is equally important to apply dose adjustment not only at the time of initiating medication but also when interacting co-therapy is discontinued. However, also increased levels of PHT have been observed with co-medication of dexamethasone. Apparently, the use of dexamethasone can lead to unpredictable interactions with PHT, including either enzyme-inducing or -inhibiting effects.

From these observations, one may conclude that simultaneous use of enzyme-inducing anticonvulsants and corticosteroids should rather be avoided, or, when given simultaneously, that plasma concentrations of anticonvulsants should be monitored.

Idiosyncratic and Skin Reactions

Bone marrow suppression and liver dysfunction can occur as a side effect of a number of individual AEDs, and are more frequently seen in association with brain tumours than with other co-morbidities [4]. This can be explained by overlapping adverse events of CTDs, which are often more pronounced with the concomitant use of AEDs. For example, haematotoxicity can be the result of administration of PB, PHT, CBZ, or VPA, but is also common with use of temozolomide and other chemotherapeutic agents [80, 81].

Also, severe systemic allergic reactions can occur with the use of a number of AEDs, mainly at the time of initiation of therapy with PB, PHT, CBZ, OXC, VPA, or LTG [82]. The most common type of hypersensitivity is skin rash as a side effect of AEDs, which can be accompanied by fever, lymphadenopathy, and, occasionally, by multi-organ abnormalities [83]. Its frequency seems higher in patients carrying a brain tumour than in non-tumoural patients with epilepsy [84, 85]. More severe allergic reactions are erythema multiforme or the Stevens-Johnson syndrome and toxic epidermal necrolysis with necrosis and blistering of skin and mucosal membranes, which may lead to a potential mortality of up to 40 % [86]. A number of observations strongly suggests an increased appearance of SJS in patients undergoing cranial irradiation and receiving anticonvulsants, particularly with PB, PHT, or CBZ, often together with co-therapy with glucocorticosteroids [87, 88]. Nevertheless, the appearance of this severe dermatological complication is relatively rare. In one retrospective review of 289 patients receiving radiotherapy and anticonvul-

sants, only 1 patient developed SJS [85]. Recently, the human leukocyte antigen (HLA) class 1 allele B*1502 was associated with 100 % of patients with CBZ-induced SJS, and only in 3 % of CBZ-tolerant and in 8.6 % of controls in an Asian population [89]. PHT and OXZ have been associated with severe skin reactions in HLA-B*1502 carriers [90]. In Europe, one has observed that the HLA-A*3101 allele increases the risk of developing a CBZ-induced hypersensitivity from 5 % to 26 % [91]. By screening patients on specific HLA alleles before prescribing anticonvulsants these sometimes life-threatening skin reactions can possibly be prevented [92].

Cognition

Besides pharmacokinetic effects, antiepileptic drugs can also influence cognitive functioning. The conventional anticonvulsants PB, PHT, CBZ, and VPA are all associated with cognitive side effects showing impairments in memory, mental speed, and attention with a less favourable cognitive profile of PB as compared to other anticonvulsants [93–95]. Although these side effects are mild or moderate [93], their impact can be substantial if patients already suffer from cognitive dysfunction due to space-occupying effects of the tumour or by the sequelae of neurosurgery, radio-, and chemotherapy [96]. As neurocognitive decline interferes with quality of life, such changes may have great impact on the daily life of patients and family members [97].

In a group of 156 long-time survivors of low-grade gliomas, a higher seizure frequency was associated with mental deterioration. The use of one of the conventional anticonvulsants led to a worse performance in 6 out of 7 cognitive domains [98]. Particularly, an inverse relationship was observed between anti-epileptic polytherapy with AEDs, ie, the number of anticonvulsants taken simultaneously had an unfavourable effect on executive and psychomotor functioning in patients with low-grade gliomas and hypothalamic hamartomas [98–100].

In general, the newer AEDs like GBP, LTG, OXC, PGB, and LEV confer less pronounced cognitive side effects, with the exception of TPM (Table 4) [105–107]. A retrospective study comparing TPM (n = 429), LTG (n = 336), and LEV (n = 301) in non-brain tumour-related epilepsy showed that almost half the patients using TPM discontinued its use because of mental slowing in 27.8 % and dysphasia in 15 % [101, 108]. At the same time, almost 10 % of patients on LTG experienced positive cognitive effects like improved alertness, better emotional stability, or less irritability [108, 109]. In a study on 70 patients with gliomas, patients on one of the conventional AEDs suffered from more adverse events than those on OXC (42.9 % vs 11.4 %) and psychomotor slowness was only seen with the traditional AEDs (21.7 %) [102]. In another study on 40 patients with seizures and gliomas, switching to levetiracetam monotherapy showed no negative effects on 6 domains of cognition. LEV might even have positive effects as there were no signs of cognitive decline despite the presence of a brain tumour or administration of ancillary anti-tumour therapy [104]. Two smaller observational studies (including 11 and 29 patients, respectively) showed mild cognitive impairment, it is unclear whether this is caused by the disease (ie, tumour progression) or by the use of LEV [14, 103].

Conclusion

Today, patients with brain tumours undergo intensive therapy, including neurosurgery, radiation therapy, and chemotherapy, at various stages of the disease. Besides, the majority of patients needs anticonvulsants to control epileptic seizures, and often glucocorticosteroids or other ancillary therapies to control symptoms secondary to tumoural effects or to anti-tumour therapy. For these reasons, this multitude of co-treatments easily leads to a myriad of side effects in patients with brain tumours, drugs used simultaneously may either aggravate or counteract each other. The use of anticonvulsant drugs illustrates each of these situations, thus – apart from seizure control – a lot of attention is needed for avoiding or neutralizing these side effects in patients with brain tumours. Obviously, the first issue in prescribing anticonvulsants is to take into account pharmacokinetic properties and common side effects (Table 1). Another point of attention is the issue of recognition of interactions with chemotherapy due to the enzyme-inducing or -inhibiting effects of conventional AEDs (Table 2). The substantial effect that enzyme-inducing AEDS can have on the treatment of brain tumours is reflected by the large differences of dose regimens of chemotherapeutic agents, depending on whether or not patients receive an enzyme-inducing AED. Prospective phase-I/II trials on CTDs divided in strata with or without EIAEDs have produced corresponding data on drug clearance, area-under-the-curve values, and median or maximum tolerated doses of new cancer agents, and illustrate the strong enzyme-inducing capabilities of phenobarbital, phenytoin, and carbamazepine (Table 3).

Nevertheless, these effects are not so easily detected as they are mainly manifested by a potential inefficacy of chemotherapeutic or targeted drugs on the underlying tumour. As many types of brain tumours including low- and high-grade gliomas or systemic cancers often become resistant to anti-tumour-directed therapy, a poor response to therapy is easily accounted for by ineffective therapy rather than by co-treatment with an enzyme-inducing agent. Likewise, chemotherapeutic agents themselves often have enzyme-inducing or -inhibiting properties leading to either potential inefficacy or toxicity of antiepileptic drugs.

By making use of pharmacokinetic data on drug interactions (Tables 2, 3), one may argue that potential adverse interactions can be prevented by a timely dose adjustment according to the anticipated effect of these interactions. To do so reliably, this will require therapeutic drug monitoring of the applied chemotherapy as well as anticipating and accounting for a dose amendment at each change of the AED regimen. To what extent this approach is indeed feasible in daily practise is uncertain, as medical oncologists taking care of cancer treatment not seldom work in other hospitals than neurologists prescribing and monitoring anticonvulsants. In practice, this, makes proper adjustment of medication difficult to pursue or even elusive. Probably, the risks of harmful interactions take place on a much larger scale than we assume, as physicians probably often do not realise or are unaware of the possibility of interactions.

Obviously, the use of anticonvulsants may lead to interactions not only with chemotherapeutic agents, but also with many

Table 4. Cognitive side effects of AEDs in patients with brain tumours

	AED	Number of patients	Type of study	Methods	Method of cognitive function assessment	Mean follow-up (months)	Tumour diagnosis	Cognitive side effects	Main drawbacks of study
Maschio et al, 2008 [101]	TMP	33 TPM monotherapy, 14 TPM as add-on (also treated with PB, CBZ, PHT, LTG, VPA, LEV, OXC)	Observational, retrospective, and prospective	TPM monotherapy or as add-on Information on side effects was collected retrospectively	Clinical notes	Retrospective: 4.5; prospective: 16.5	LGG, AA, GBM, MEN, MBT	Two out of 47 treated with TMP monotherapy experienced cognitive side effects in comparison to 2/33 patients treated with other AEDs prior to entering the study	Retrospective assessment of baseline cognitive functioning
Maschio et al. 2009 [102]	OXC	35 on OXC vs 35 controls on PB, CBZ, PHT, VPA	Observational, retrospective	OXC monotherapy vs traditional AEDs	Clinical notes and hospital charts	13.7	LGO, LGA, AA, AO, GBM, MEN, MBT	Psychomotor slowness (21.7 %, 4 patients on PB and 1 on VPA) was seen only with traditional AEDs, no cognitive side effects with OXC	Retrospective assessment of cognitive functioning
Maschio et al, 2010 [14]	LEV	29	Prospective follow-up	LEV monotherapy, patients served as their own controls	MMSE	8.1	LGO, LGA, AO, AA, GBM, MEN, hemangiopericytoma, lymphoma	Significant worsening on MMSE	MMSE provides only partial insight into cognitive functioning
Usery et al, 2010 [103]	LEV	11	Prospective	LEV monotherapy, patients served as their own controls	Patients were weekly interviewed by telephone	1	LGO, AA, GBM, MEN, MBT, lymphoma	Two patients (18.2 %) were cognitively impaired	Unknown measurement tools for cognitive functioning, short follow-up
De Groot et al, 2011 [104]	LEV	40	Prospective follow-up	LEV monotherapy, patients served as their own controls	Neuropsychological assessment of 6 cognitive domains at baseline, 3, 6, and 12 months	12	LGG, HGG	No differences in neuropsychological assessment between baseline and subsequent follow-up measurements	So far, only published as an abstract

AED: antiepileptic drug (abbreviations see Table 1); AA: anaplastic astrocytoma; AO: anaplastic oligodendroglioma; GBM: glioblastoma multiforme; HGG: high-grade glioma; LGA: low-grade astrocytoma; LGO: low-grade oligodendroglioma; MEN: meningioma; MBT: metastatic brain tumour; MMSE: Mini Mental State Examination; TICS: Telephone Interview for Cognitive Status.

other kinds of drugs, for many other conditions or co-morbidities, which may accompany patients with brain tumours. One noteworthy side effect is the occurrence of severe dermatological complications, which is the result of an intricate interaction between anticonvulsants and the administration of cranial radiotherapy, possibly related to co-medication with steroids and expression of certain HLA alleles.

Apart from interactions, many anticonvulsants have side effects that can be extra damaging in patients already at risk for organ dysfunction like bone marrow suppression or liver dysfunction. Compared to the second- and third-generation anticonvulsants, the use of conventional anticonvulsants PB, PHT, and CBZ more often leads to hepatic dysfunction and, to a lesser extent, also to bone marrow suppression.

Lastly, also the risk on neurotoxicity is of major importance in patients with brain tumours and seizures, as both the need for anticonvulsants and the number of anticonvulsants used are each stronger contributing factors to the severity of cognitive dysfunction than having gone through earlier neurosurgical excision or radiation therapy (Table 4). Although reviewing satisfactory seizure control is beyond the scope of this paper, the risk of ineffective cancer treatment, organ dysfunction, and neurotoxicity illustrates the importance of effective and well-tolerated anticonvulsants that do not interfere with cancer treatment. Fortunately, there is a number of anticonvulsants that possess these properties. Oxcarbazepine, lamotrigine, and topiramate have only weak enzyme-inducing or -inhibiting properties. Although valproic acid can have enzyme-inhibiting activity and can lead to hepatic dysfunction and thrombopenia, its histone-deacetylase-inhibiting activity may help to control tumour progression. Lastly, gabapentin, levetiracetam, pregabalin, and lacosami-

de do all show no drug interactions. Future studies need to show which of these agents or combinations would be the best match to achieve effective seizure control together with good tolerability.

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