Abstract

Objective—To determine the efficacy, tolerability, and impact on quality of life and cognitive functioning of anticonvulsant prophylaxis with phenytoin or sodium valproate in patients after craniotomy.

Methods—A prospective, stratified, randomised, double blind single centre clinical trial was performed, comparing two groups of 50 patients each, who underwent craniotomy for different pathological conditions and who were treated for 1 year after surgery with either 300 mg phenytoin/day or 1500 mg sodium valproate/day. During the study period patients were seen in the outpatient clinic at 1.5, 3, 6, and 12 months, when medical history, adverse events, and drug plasma concentrations were evaluated. Neuropsychological functioning and quality of life were assessed on the last three visits. In cases of a seizure an EEG was performed, drug plasma concentration assessed, and medication subsequently increased.

Results—Of the 100 included patients 14 (seven in each group) experienced one or more postoperative seizures. Severity of the seizures was comparable in the two groups. In all patients, drug plasma concentrations were in the low or subtherapeutic ranges at the time of the first postoperative seizure. Five patients in the phenytoin group and two in the valproate group had to stop their treatment due to drug related adverse events. Sixty patients completed the 12 month period. Analysis of neuropsychological and quality of life data showed no significant differences.

Conclusion—For efficacy, tolerability, impact on cognitive functioning, and quality of life, no major differences were found between phenytoin and valproate prophylaxis. Valproate is an alternative for anticonvulsant prophylaxis in patients after craniotomy.

Keywords: craniotomy; sodium valproate; phenytoin; seizures; quality of life; cognitive functioning

Neurosurgical procedures invading the anterior or middle cranial fossa carry the risk of postoperative epilepsy.1 2 The incidence of epilepsy primarily depends on the underlying pathology; the overall incidence is estimated to be 17%.3 Some neurosurgical diseases are related to a relatively high incidence of postoperative seizures—for example, cerebral abscess and head trauma with intracerebral haematoma.4 7 Other specific high risk patient categories are: aneurysmal subarachnoid haemorrhage,8 9 arteriovenous malformation,10 11 meningioma,12 14 and glioma.11 16 In brain tumours the incidence is roughly inversely related to the degree of malignancy.1 16 Another important determinant of postoperative epilepsy is the location of the lesion: falk and parasagittal meningiomas have a higher incidence than meningiomas located elsewhere,4 14 17 and aneurysms of the middle cerebral artery carry a higher risk of epilepsy than other aneurysms.18 Other known factors of influence for postoperative epilepsy are complications (infection, ischaemia) and the surgical approach to the lesion.9

The untoward effects of epilepsy are found in transient or permanent neurological disability and complications in the direct postoperative period.1 19 20 Socioeconomic consequences of epilepsy can be severe—for example, occurrence of a seizure may result in the loss of a person’s driving licence,21 underscoring the importance of preventing seizures when possible.

As prophylaxis after a craniotomy, anticonvulsant drugs should ideally be easy to use, provide adequate control, and generate no major side effects. Especially in postoperative patients sedative effects are unwanted because of interference with adequate diagnosis of postoperative complications such as haemorrhage. Intravenous preparations are necessary during recovery from anaesthesia. In postcraniotomy prophylaxis the most widely used drug today is phenytoin. Until now, reports on the use of sodium valproate for this indication are limited. Price found a control rate of nearly 90% in 70 neurosurgical patients who previously had at least five seizures/month.22 Most required daily doses of less than 2 g/day of sodium valproate; three patients had to stop treatment due to drug intolerance.

Treatment of epilepsy with sodium valproate in therapeutic doses is thought to produce relatively few cognitive side effects.23 24 Although its superiority in this respect over older drugs such as phenobarbital is well established, the advantage of valproate over phenytoin is less clear. Results of direct comparisons on
cognitive function between the last two have been equivocal or slightly in favour of valproate.\textsuperscript{25-28} Possibly a differential effect is clearer in patients with lesions, in whom anticonvulsant medication seems to have more impact on cognition than in patients with idiopathic epilepsy.\textsuperscript{29} However, this may not be easy to assess, as the study of such patients introduces numerous potential confounding factors, such as lesion size and rate of recovery. Nevertheless, the presence of brain damage may interact with type of medication to cause observable differences with respect to neuropsychological test performance or subjective wellbeing.

In view of this possibility it was considered worthwhile to compare cognitive function in neurosurgical patients who were prophylactically treated with either valproate or phenytoin (intravenously and orally), using neuropsychological tests focused on attention, memory, and speed of information processing as well as perceived quality of life. Our aim was to compare the efficacy and tolerability of sodium valproate with phenytoin.

**Patients and methods**

**DESIGN**

A single centre, stratified, randomised, double blind, comparative clinical trial was performed. The procedures followed were approved by the institutional ethics committee, and were in accordance with the Helsinki Declaration of 1975, as revised in 1983. Randomisation started in August 1993 and was stopped after reaching the preset inclusion of 100 patients—50 patients in each group—in August 1995. Patients were stratified depending on the type of their intracranial pathology: brain tumour, trauma, or vascular lesions. Random allocation was carried out with sealed envelopes for each stratum, each patient receiving a separate treatment number determining whether the patient was treated with phenytoin or valproate. Sanofi Winthrop Recherche, Montpellier, France provided all pre-coded packaged material.

**CRITERIA FOR INCLUSION**

Patients could be included if they would undergo supratentorial surgery for one of the above mentioned pathological conditions, were aged between 18 and 80 years, and had given written informed consent. Exclusion criteria were: a life expectancy of less than 6 months, preoperative use of anticonvulsant drugs for more than 3 months, a history of epileptic seizures apart from seizures caused by the presenting disease (this was the case in 23 patients, most of whom had a glioma), chronic use of psychopharmaceuticals, alcohol or drug misuse, severe psychiatric illness, and participation in an experimental drug trial. The demographic data of the included patients are presented in table 1. In view of the few trauma cases, the strata were collapsed to two categories (tumour v other).

**Table 1 Baseline characteristics of study groups**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Phenytoin</th>
<th>Valproate</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of cases</td>
<td>50</td>
<td>50</td>
<td>100</td>
</tr>
<tr>
<td>Men/women</td>
<td>26/24</td>
<td>21/29</td>
<td>47/53</td>
</tr>
<tr>
<td>Mean age/ range (y)</td>
<td>55/21–78</td>
<td>51/21–77</td>
<td>53/21–78</td>
</tr>
<tr>
<td>Completed 12 months</td>
<td>29 (27)</td>
<td>31 (28)</td>
<td>60 (55)</td>
</tr>
<tr>
<td>Pathology:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malignant glioma</td>
<td>7 (0)</td>
<td>11 (2)</td>
<td>18 (2)</td>
</tr>
<tr>
<td>Low grade glioma</td>
<td>2 (1)</td>
<td>1 (0)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Metastasis</td>
<td>9 (2)</td>
<td>4 (1)</td>
<td>13 (3)</td>
</tr>
<tr>
<td>Meningioma</td>
<td>7 (6)</td>
<td>8 (7)</td>
<td>15 (13)</td>
</tr>
<tr>
<td>Other tumours*</td>
<td>4 (4)</td>
<td>4 (4)</td>
<td>8 (8)</td>
</tr>
<tr>
<td>Traumatic head injury</td>
<td>2 (1)</td>
<td>2 (1)</td>
<td>4 (2)</td>
</tr>
<tr>
<td>Chronic subdural haematoma</td>
<td>1 (0)</td>
<td>2 (2)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Intracranial haemorrhage</td>
<td>3 (2)</td>
<td>1 (1)</td>
<td>4 (3)</td>
</tr>
<tr>
<td>Aneurysmal SAH</td>
<td>15 (11)</td>
<td>13 (5)</td>
<td>28 (16)</td>
</tr>
<tr>
<td>Cavernoma</td>
<td>0 (0)</td>
<td>4 (4)</td>
<td>4 (4)</td>
</tr>
</tbody>
</table>

* Other brain tumors were a pituitary adenoma, neurocytoma, schwannoma, and a haemangio-blastoma in the phenytoin group, and two colloid cysts, a pituitary adenoma, and a hamartoma in the valproate group. SAH=Subarachnoid haemorrhage. The number of patients with complete cognitive assessment are shown in parentheses.

**DRUG TREATMENT**

Intravenous administration of 100 mg phenytoin thrice daily or 500 mg valproate thrice daily was started immediately postoperatively in the recovery room. We did not use loading doses. As soon as possible, patients switched to the same regimen in oral formulation of phenytoin or valproate (Depakine chrono®). In selected cases of critically ill patients with a long stay in the intensive care unit, medication was administered as syrup via a nasogastric tube. No other maintenance anticonvulsant medication, including barbiturates, hypnotics, and benzodiazepines, was acceptable during the study. Otherwise, the patient was withdrawn from the study and considered a treatment failure.

In cases of adverse events, intoxication or toxic drug plasma concentrations (>200 mg/l valproate and 50 mg/l phenytoin) the medication regimen was adjusted at the judgement of the unblinded investigator (DGAK), who was not otherwise involved in the data collection. Subsequent control plasma concentrations were taken. In case of a seizure a detailed description of the event was obtained to classify it according to the ILAE international classification and elaborate its severity according to the national hospital seizure severity score NHSS.\textsuperscript{30, 31} If possible, a drug plasma concentration was taken, an EEG was performed, and medication was adjusted.

**PHARMACOKINETIC CALCULATIONS**

Average individual steady state serum concentrations were calculated using the population pharmacokinetic software programme MW/Pharm with general population models for phenytoin and valproic acid.\textsuperscript{32} Models were fit to the patient data (weight, height, age) and serum concentration data using Bayesian regression to obtain the individual pharmacokinetic parameters (phenytoin: volume of distribution and elimination rate constant). These individualised pharmacokinetic parameters were used to calculate individual steady state serum concentrations.

**ASSESSMENTS**

During the recovery period, vital signs, adverse events, and a drug plasma concentration on the third postoperative day were assessed. Patients were followed up for 1 year, during which...
period they were controlled by the study coor-
dinator (LFMB) at the outpatient clinic at 1, 3,
3, 6, and 12 months for: medical history
including possible seizures and adverse effects
of the anticonvulsant, physical examination,
Karnofsky performance status, and laboratory
tests including drug plasma concentration. At
3, 6, and 12 months neuropsychological and
quality of life tests were administered.

NEUROPSYCHOLOGICAL TESTS
Neuropsychological tests consisted of two
standard clinical tasks and three computerised
tasks; the last were derived from a battery
designed for the testing of epileptic patients
and have been shown to be useful in the study
of anticonvulsant drugs.35–37

(1) Serial word learning36
The learning of a list of 15 orally presented
words is measured by immediate recall (sum of
5 trials), delayed recall after an interval of 20
minutes, and recognition (yes/no choice in a list
of 30 words).

(2) Categoric word fluency, derived from a Dutch
intelligence test37
The patient is required to name as many
animals and professions as possible, one
minute each.

(3) Simple auditory reaction time
The space bar must be pressed as fast as possible
with the preferred hand in response to an
auditory stimulus. Performance is measured as
the median reaction time in 30 trials.

(4) Binary choice task
The patient must press a left or right key in
response to respectively a green square on the
left side and a red square on the right side of
the screen, appearing in random alternation.
Each response is immediately followed by a
new stimulus. Performance is measured by the
average reaction time in 60 trials.

(5) Visual searching task
A non-verbal design in the centre of the screen
must be matched to one out of 24 surrounding
patterns. Performance is measured by the aver-
age search time in 24 trials.

The Dutch version of the National adult
reading test,38 a measure of vocabulary insensi-
tive to brain dysfunction,39 was administered
on the visit at 3 months to estimate premorbid
intelligence.

QUALITY OF LIFE MEASURES
Emotional status was measured with a short-
ened Dutch version of the profile of mood
states (POMS),40,41 which yields five subscales:
depression, anger, fatigue, vigour, and tension.
Fatigue was additionally assessed with the
more extensive fatigue severity scale (FSS).42
Furthermore, a self developed questionnaire
was administered, previously employed in a
study in patients with low grade glioma,43
referring to perceived dependency in activities
of daily living (six three point items), physical
complaints (seven three point items), cognitive
restrictions (five five point items), sense of
restriction in daily functioning (one five point
item), satisfaction with health (one five point
item), and general wellbeing (one five point
item).

ANALYSIS
At the end of the study, recorded variables for
each individual patient were elaborated and
analysed. Outcome measurements for the
study were: efficacy as determined by the
occurrence of seizures and their severity score
following the national hospital seizure severity
score, clinical tolerability, cognitive functioning
evaluated by neuropsychological tests, and
quality of life. For efficacy, seizure severity, and
tolerability, group differences were tested with
t tests and non-parametric tests ($\chi^2$ or Fisher's
exact, Mann-Whitney $U$ test) as appropriate.
Neuropsychological and quality of life data
were analysed with repeated measurements
analysis of variance (ANOVA), using poly-
momial contrasts. Independent variables were
group (phenytoin vs valproate) and stratum
(tumour vs other). The outcomes considered—
reflecting possible differential medication
effects—were the overall group difference
(phenytoin vs valproate) and the linear or quad-
ratic group by visit interaction. This analysis
was restricted to 55 patients who could be fully
tested on all three occasions (table 1), which
excluded 11 patients who were tested partially
and 24 who could not be tested at all. Due to a
high mortality, the excluded group contained
most patients with high grade gliomas or meta-
static tumours. A power analysis indicated that,
given the design and group size, the statistical
power to show significance for a difference of
0.5 SD at the two tailed 5% level was 0.87.
Significance was accepted at the two tailed 5%
level.

Results
DEMOGRAPHY
No significant differences were found in
baseline characteristics (sex, age, pathology,
and history of preoperative seizures) of the
medicine groups, either in the total sample or
in the subgroups with complete neuropsy-
chological and quality of life data. The estimated
premorbid IQ was distributed equally (pheny-
toin: 101 (SD 14), valproate: 100 (SD 14) in
the last two. Causes of drop out are listed in
table 2. The mortality rate tended to be higher
in tumour patients with phenytoin than in
those with valproate (43% v 18%), but the dif-
ference did not reach significance ($\chi^2=3.04$,
$p<0.10$). In other patients there was a non-
significant opposite tendency (phenytoin 5%
mortality, valproate 23%; $p=0.19$, Fisher's
exact test).

EFFICACY
Postoperative seizures occurred in both the
phenytoin group and the valproate group in
seven patients (table 3). The time of occur-
rence of the first seizure is shown in the figure.
In both groups two patients had their first sei-
zure on the day of operation. No difference was
Postoperative anticonvulsant prophylaxis

Table 2  Attrition by medicine group and stratum

<table>
<thead>
<tr>
<th></th>
<th>Phenytoin</th>
<th>Valproate</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tumour</td>
<td>Other</td>
<td>Tumour</td>
</tr>
<tr>
<td>Completed trial</td>
<td>13</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>Died in week 1</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>2–6</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>7–12</td>
<td>2</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>13–26</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>27–52</td>
<td>4</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Intercurrent illness</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Adverse drug reaction</td>
<td>1</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Needed concomitant medication</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Withdrew informed consent</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Lost to follow up</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 3  Cases with seizures

<table>
<thead>
<tr>
<th></th>
<th>Phenytoin</th>
<th>Valproate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperative</td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td>Simple partial</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Generalised</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Simple partial and generalised</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Postoperative</td>
<td>7 (2)</td>
<td>7 (3)</td>
</tr>
<tr>
<td>Simple partial</td>
<td>3 (1)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Generalised</td>
<td>2 (1)</td>
<td>4 (2)</td>
</tr>
<tr>
<td>Simple partial and generalised</td>
<td>2 (0)</td>
<td>1 (0)</td>
</tr>
</tbody>
</table>

Pathology associated with postoperative seizures:
- Malignant glioma: 2 (1) Tumour, 3 (0) Other
- Metastasis: 2 (1) Tumour, 0 (0) Other
- Low grade glioma: 1 (0) Tumour, 1 (1) Other
- Meningioma: 0 (0) Tumour, 1 (1) Other
- Neurocytoma: 1 (0) Tumour, 0 (0) Other
- Cavernoma: 0 (0) Tumour, 1 (1) Other
- Traumatic head injury: 1 (0) Tumour, 0 (0) Other
- Aneurysm ant comm artery: 0 (0) Tumour, 1 (0) Other

The number of patients with postoperative seizures who also had preoperative seizures are shown in parentheses.

Time (after operation) of first seizure.

SEIZURE ASSOCIATIONS
In nine of the 14 patients who experienced postoperative seizures, a primary or secondary brain malignancy was the underlying pathology. In four cases (two in each group), a recurrent tumour (after 11, 17, 23, and 29 weeks respectively) was concurrent with seizure presentation. Seizures were associated with a complicated postoperative course in four patients (two ischaemia, one oedema, one haemorrhage). In six of the 14 patients with postoperative seizures the occurrence of seizures was not related to either perioperative complications or radiological recurrence.

DRUG PLASMA CONCENTRATIONS AND EFFICACY
Drug plasma concentrations taken after the first postoperative seizure were below the usual therapeutic range (<8 mg/l phenytoin, <50 mg/l valproate) in all seven patients of the phenytoin group and four out of the seven patients in the valproate group; in the other three valproate patients drug concentrations were below 62 mg/l. In the 10 patients whose first seizure occurred more than 1 day after the operation, the mean drug plasma concentrations were 5.1 (SD 2.3) mg/l for those on phenytoin (n=5) and 56.8 (SD 10.0) mg/l for those on valproate (n=5). In patients without postoperative seizures these values were 11.7 (SD 6.7) (phenytoin, n=43) and 70 (SD 13) (valproate, n=43), both significantly higher (p<0.05, t test). For the total sample, excluding patients with a change in medication, the steady state concentrations of phenytoin and valproate were 10.9 (SD 6.6) mg/l (range 4–28) and 68 (SD 13) mg/l (range 44–100) respectively.

DOSAGE REGIMEN CHANGES
The initial therapy regimen of tablets thrice daily remained unchanged in 81 patients, 38 of them receiving phenytoin, 43 of them taking valproate. Significantly more patients on phenytoin had to reduce their drug regimen to twice daily because of toxic drug plasma concentrations, seven out of 50 patients on phenytoin compared with no patients out of 50 on valproate (p=0.012, Fisher’s exact test). In five patients receiving phenytoin and in seven patients receiving valproate dosages had to be increased after seizures.

One patient in the phenytoin group and two in the valproate group experienced a single seizure (with seizure freedom after change of dosage). The other 11 patients had multiple seizures despite increased dosages. Subtherapeutic dosages were in themselves no reason to increase the dosage, whereas toxic dosages were.

ADVERSE EFFECTS
Seven patients had to stop treatment because of drug related side effects, five patients in the phenytoin group versus two in the valproate group (not significant). Four patients treated with phenytoin showed a hypersensitivity skin reaction, occurring between 6 days and 4 weeks after the start of treatment. After cessation of the therapy recovery of the patients was without sequelae within 1–2 weeks. In both study groups patients had transient gastrointestinal complaints. In one patient treated with phenytoin the nausea was persistent despite treatment with several antiemetics, and caused withdrawal from the trial. Also in both groups equal numbers of liver function disturbances were found (total number of patients six). In one patient treated with valproate there was a marked rise in liver enzymes which necessitated withdrawal from the trial. A contributing factor could have been the pre-existing minor disturbance of liver function associated with the use of amiodarone. In all patients liver enzymes returned to normal values, without lasting consequences to the patients. In one patient receiving valproate a thrombopenia necessitated discontinuation of treatment. Other known adverse effects of the

![Graph](https://example.com/graph.png)

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anticonvulsant drugs—for example, weight gain with valproate and anaemia with phenytoin—were minor and did not necessitate cessation of trial medication.

NEUROPSYCHOLOGICAL TESTS AND QUALITY OF LIFE
In a preliminary analysis, patients who were available for psychological assessment after 3 months but not after 12 months (n=11) were compared with patients who were assessed on all three occasions (n=55). The first had a higher mean age (p=0.03, t-test) and scored on average lower on immediate recall (p=0.007) and word fluency (p=0.009) on the first assessment; their rating of general wellbeing was also lower (p=0.050) but other differences on quality of life measures were not significant.

In patients with complete data, the analysis of neuropsychological test results disclosed no significant differences between the phenytoin and valproate groups. As table 4 shows, the averages generally favoured the valproate group, but the differences failed to reach significance because the SDs were large. Moreover, the interpretation of the learning test results is complicated by significant group by stratum interactions on all three measures, immediate recall (p=0.006), delayed recall (p=0.015) and recognition (p=0.005). In the phenytoin group tumour patients tended to score higher than other patients, but in the valproate group lower. For quality of life, valproate patients tended to rate themselves as less vigorous and more tired and tense than phenytoin patients, especially at the 6 month assessment; their rating of general wellbeing was also lower (p=0.050) but other differences on quality of life measures were not significant.

In this study, a randomised clinical trial evaluating the clinical impact of two widely used anticonvulsants as prophylaxis after craniotomy, we found no significant differences in efficacy and tolerability between the two treatment groups: both in the phenytoin group and the sodium valproate group the same number of patients had seizures. In both groups the seizures also had the same severity impact on patients.

Our data are comparable with the data from the double blind randomised trial carried out by North et al44 who had a similar study population and follow up of 1 year. In 281 postcraniotomy patients they compared 100 mg phenytoin thrice daily with placebo. Phenytoin significantly reduced seizure incidence.

**Discussion**
Despite the frequent occurrence of seizures after a craniotomy the routine use of anticonvulsant drugs as prophylaxis is controversial. Anticonvulsant prophylaxis for the prevention of seizures is recommended in general if the risk of seizures exceeds 10%-15%, which is the anticipated incidence of serious adverse drug effects.1 Prophylaxis is also advised when a single seizure may have disastrous consequences or when seizures are a major impediment to a patient’s return to normal activity.

The choice of anticonvulsant prophylaxis should be determined on one hand by the risks and consequences of seizures during the immediate postoperative period and during the later course, and on the other hand by the efficacy and tolerability of each anticonvulsant drug. Furthermore, it should still be determined when to start and withdraw prophylactic medication and what dosages should be prescribed.

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Postoperative anticonvulsant prophylaxis

In our study, nine (64%) of the 14 patients who experienced seizures had their first seizure within 3 months after the operation. Of the 76 patients at risk at 3 months, five (7%) had their seizure presentation within 6 months. These findings are in line with the data from North et al., in which three quarters of all seizures occurred within 3 months. With a longer follow-up, the incidence in postoperative seizures increases depending on the underlying pathology: in cerebral abscess, first year incidence was 30%, rising to 72% after a median follow up of 11 years. Although some authors advocate prophylaxis during one to several years, in the long term, the benefits of seizure prevention may not outweigh the risks of chronic anticonvulsant use. Our study supports the idea of stopping prophylaxis after a 6 month period. Further elucidation on this matter should be obtained by a prospective study.

In conclusion, we compared two regularly used anticonvulsant drugs with both oral and intravenous formulation at standard dosages. In our study, nine (64%) of the 14 patients who experienced seizures had their first seizure within 3 months after the operation. Of the 76 patients at risk at 3 months, five (7%) had their seizure presentation within 6 months. These findings are in line with the data from North et al., in which three quarters of all seizures occurred within 3 months. With a longer follow-up, the incidence in postoperative seizures increases depending on the underlying pathology: in cerebral abscess, first year incidence was 30%, rising to 72% after a median follow up of 11 years. Although some authors advocate prophylaxis during one to several years, in the long term, the benefits of seizure prevention may not outweigh the risks of chronic anticonvulsant use. Our study supports the idea of stopping prophylaxis after a 6 month period. Further elucidation on this matter should be obtained by a prospective study.

For toxicity and adverse effects, in our study more patients were removed from the study treatment due to toxicity in the phenytoin group than in the valproate group (five phenytoin v two valproate). The 8% incidence of hypersensitive skin reactions associated with phenytoin use we found is well comparable with the literature. Other known adverse effects of both anticonvulsant drugs—for example, gastrointestinal complaints, liver function disturbances, anaemia (phenytoin), and weight gain (valproate)—were comparable with data reported in the literature and were in most cases of minor impact. Only in two patients (one in each group) did it necessitate cessation of trial medication.

With respect to the psychological evaluation, patients with valproate showed a slight but consistent advantage on cognitive measures, whereas they tended to complain more of tension and fatigue. Whether larger group sizes would have led to significant differences is doubtful. It must be taken into account that the patients had varied and often severe brain disease, and it is unlikely that the severity of the cognitive effects was entirely equated by the randomisation procedure. In this respect an increase in group sizes might well lead to smaller differences. At any rate the differential effect of phenytoin and valproate on cognition and quality of life seems negligible in comparison with the impact of disease and its treatment.

In conclusion, we compared two regularly used anticonvulsant drugs with both oral and intravenous formulation at standard dosages. No difference in either efficacy or impact on cognitive functioning and quality of life was found between the two drugs. In favour of valproate was the lower number of patients showing toxic serum drug concentrations. Both drugs can be recommended for the use of postoperative prophylaxis. For protection of
immediate postoperative seizures it is advised to start treatment 1 week before surgery, or if that is not possible to start treatment with a loading dose at least 20 minutes before wound closure.

A timely detection and adjustment of subtherapeutic concentrations is important; this requires frequent monitoring of blood concentrations, starting in the first postoperative week. The anticonvulsant prophylaxis can be stopped after 6 months.

Part of this study was presented at the 11th International Congress of Neurological Surgery, held 4–11 July 1997 in Amsterdam, The Netherlands. Drugs and an unrestricted educational grant were supplied by Sanofi Winthrop of, Govert van Wijnkade 48, 3144 RG Maassluis, The Netherlands.


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*J Neurol Neurosurg Psychiatry* 1999 67: 474-480
doi: 10.1136/jnnp.67.4.474

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