Antiepileptic drug distribution in cerebral cortex, Ammon’s horn, and amygdala in man

VITTORIO A. SIRONI, M.D., GIANPIERO CABRINI, M.D., MARIA G. PORRO, Pharm.D., LUIGI RAVAGNATI, M.D., AND FRANCO MAROSSERO, M.D.
Institute of Neurosurgery, School of Medicine, University of Milan, and Mario Negri Pharmacological Research Institute, Milan, Italy

Significant correlations in the concentrations of phenobarbital, phenytoin, and carbamazepine in the brain, plasma, and cerebrospinal fluid were found in 12 surgically treated epileptic patients. These findings confirm the clinical reliability of monitoring anticonvulsant drug plasma levels as part of the routine management of epilepsy. Phenobarbital, phenytoin, and carbamazepine are uniformly distributed in the gray and white matter in different brain areas (except for a higher concentration of phenobarbital in the rhinencephalic structures in comparison with the corresponding temporal neocortex) and in normal and scar tissue. In these 12 patients, all of whom were medically resistant, molar cortex concentration of phenobarbital and phenytoin was at “therapeutic” levels or even higher. These data suggest that in therapy-resistant patients, despite cerebral drug concentrations of the same therapeutic level as, or higher than, those present in medically controlled patients, anticonvulsant drugs are pharmacologically ineffective.

KEY WORDS • epilepsy • anticonvulsant drug • brain drug concentration

MONITORING the level of antiepileptic drugs in plasma as part of the clinical management of epileptic patients implies a close correlation between plasma and brain drug concentration, since therapeutic activity of anticonvulsant drugs is presumably determined by their concentration at the receptor sites in the brain. In animals, antiepileptic activity has been correlated with the concentration of drugs or their active metabolites in the brain, and many studies have shown that anticonvulsant drug levels in plasma are related to their concentration in the brain by a constant ratio.

Neurosurgical procedures for treatment of intractable focal epilepsy offer the opportunity of measuring the brain concentrations of antiepileptic drugs in man. Constant brain:plasma ratios for phenobarbital (PB), phenytoin (DPH), primidone (PRI), and carbamazepine (CBZ) have been demonstrated in epileptic patients. A correlation between brain and plasma levels of CBZ and CBZ-epoxide was also found in nonepileptic patients. Sherwin, et al. have reported a significantly higher concentration of antiepileptic drugs in the brains of patients with low seizure frequency than in those with high seizure frequency.

Extending previously reported observations, this paper reports our preliminary data on PB, DPH, and CBZ concentrations in plasma, cerebrospinal fluid (CSF), and brain in a series of epileptic patients who had been surgically treated.

Clinical Material and Methods

This study involved 12 consecutive patients (nine males and three females), aged from 11 to 56 years, selected for surgical treatment for unresponsive epilepsy of nontumoral etiology. After undergoing clinical, electroencephalographic (EEG), and neuroradiological studies, the patients were submitted to preoperative depth electrode study by stereotaxic technique, as previously described, and to perioperative electrocorticograms.

They had received antiepileptic drugs at therapeutic plasma levels for periods of years before admission. The patients were given PB, in association with other antiepileptic drugs: DPH in seven cases, CBZ in one case, clonazepam (CNP) in one case, and CBZ combined with CNP in another case. Two patients were receiving CBZ alone (Table 1). Seven patients received their last dose at 8 p.m. on the night before morning surgery. Therapy was withdrawn from 36 to 96 hours before surgery in five cases to activate the electrocorticographic recordings. These cases have been considered separately.
At surgery, seven patients had a unilateral anterior temporal lobectomy, two had a parietal cortectomy, two a frontal lobectomy, and one a frontotemporal partial resection. In all cases, anesthesia was induced with hydroxyzine hydrochloride (Atarax, 1.5 to 2.5 mg/kg) and maintained with N₂O:O₂ (70:30) and d-tubocurarine (up to 0.3 to 0.5 mg/kg). Mechanical ventilation maintained PaCO₂ between 25 and 30 mm Hg and PaO₂ at about 120 mm Hg to avoid interference of possible acidosis with electroencephalographic recordings and with brain and plasma levels of anticonvulsant drugs.

Blood and lumbar CSF samples were taken immediately after the induction of anesthesia; brain specimens were obtained 2 hours later. Blocks of brain tissue, including the regions of maximum epileptogenic activity (recorded at depth EEG and/or electrocorticograms), and of scar tissue, when present, were taken just after excision. The pia and the superficial arteries and veins were removed, and with the use of razor blades and optical magnification, the cerebral tissue was clearly separated into gray, white, and gray plus white matter. In only two patients were the rhinencephalic specimens suitable for this study. The samples of plasma, CSF, and brain were kept at −20°C until analysis. The wet weight of brain samples ranged between 350 and 3400 mg. Determination of anticonvulsant drugs in plasma and CSF was performed by gas chromatography according to the analytical procedures described by McGee for PB and DPH, and by Morselli, et al., for CBZ. Determination of drug concentration in the brain was performed by gas chromatography as previously described in detail by Baruzzi, et al., for PB and DPH, and by Morselli, et al., for CBZ.

The follow-up period for these patients ranged from 2 to 4 years. The patients were divided into a “success group” (seizure-free patients or those with a marked reduction in seizure frequency), and a “failure group” (patients with no reduction in seizure frequency).

### Results

Table 2 shows the concentration of PB, DPH, and CBZ in plasma, CSF, and brain in all the patients in steady state. Mean plasma levels were from 18.5 to 42.2 μg/ml for PB, from 1.9 to 23.4 μg/ml for DPH, and from 2.2 to 5.1 μg/ml for CBZ. Concentration in the CSF ranged from 11.9 to 23 μg/ml for PB, from 0.5 to 2.3 μg/ml for DPH, and was 0.9 μg/ml for CBZ.

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Sex, Age (yrs)</th>
<th>Type &amp; Frequency of Seizures</th>
<th>Depth EEG Focus</th>
<th>Drug Therapy (mg/day)</th>
<th>Surgical Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F, 17</td>
<td>psychomotor &amp; cognitive, 8–10/wk</td>
<td>rt temporal</td>
<td>PB 200</td>
<td>rt temporal</td>
</tr>
<tr>
<td>2</td>
<td>M, 21</td>
<td>psychomotor, 6–8/wk</td>
<td>unilateral</td>
<td>DPH 300</td>
<td>lobectomy</td>
</tr>
<tr>
<td>3</td>
<td>M, 17</td>
<td>motor versive &amp; psychomotor, 8–10/wk</td>
<td>temporal foci</td>
<td>PB 200</td>
<td>lobectomy</td>
</tr>
<tr>
<td>4</td>
<td>M, 11</td>
<td>autonomic, motor, &amp; sec gen, 8–10/wk</td>
<td>multifocal (lt parietaltemporal)</td>
<td>DPH 200</td>
<td>lobectomy</td>
</tr>
<tr>
<td>5</td>
<td>M, 56</td>
<td>somatomotor &amp; sec gen with grand mal status, 1–2/wk</td>
<td>rt frontal</td>
<td>PB 200</td>
<td>lobectomy</td>
</tr>
<tr>
<td>6</td>
<td>M, 22</td>
<td>somatosensory &amp; motor, 4–6/wk</td>
<td>rt frontal</td>
<td>PB 300</td>
<td>lobectomy</td>
</tr>
<tr>
<td>7</td>
<td>M, 17</td>
<td>somatosensory, 30–50/wk</td>
<td>rt parietal</td>
<td>DPH 300</td>
<td>lobectomy</td>
</tr>
<tr>
<td>8</td>
<td>M, 21</td>
<td>somatomotor, 10–20/wk</td>
<td>rt parietal</td>
<td>CBZ 600</td>
<td>cortectomy</td>
</tr>
<tr>
<td>9</td>
<td>F, 25</td>
<td>psychomotor, 15–20/wk</td>
<td>lt temporal</td>
<td>PB 300</td>
<td>lobectomy</td>
</tr>
<tr>
<td>10</td>
<td>F, 37</td>
<td>psychomotor, 15–20/wk</td>
<td>bilateral</td>
<td>CNP 3</td>
<td>lobectomy</td>
</tr>
<tr>
<td>11</td>
<td>M, 22</td>
<td>autonomic &amp; affective, 100–200/wk</td>
<td>rt temporal</td>
<td>CBZ 1000</td>
<td>lobectomy</td>
</tr>
<tr>
<td>12</td>
<td>M, 21</td>
<td>psychomotor &amp; sec gen, 6–8/wk</td>
<td>rt temporal</td>
<td>CBZ 1800</td>
<td>lobectomy</td>
</tr>
</tbody>
</table>

*PB = phenobarbital, DPH = phenytoin, CBZ = carbamazepine, CNP = clonazepam, EEG = electroencephalogram, sec gen = secondary generalized seizure.
†Posttraumatic etiology.
‡Prevalent left temporal focus with rare asynchronous contralateral interictal abnormalities.
§Therapy withdrawn 36–96 hours before surgery.
||Prevalent left temporal focus with only rare contralateral electroclinical seizures recorded during withdrawal of therapy.

---

**Table 1**

**Summary of seizure activity and drug therapy in 12 patients***
FIG. 1. Relationship between brain and plasma concentrations of phenytoin (DPH) ($r^2 = 0.74, r = 0.86, p < 0.01$) and phenobarbital (PB) ($r^2 = 0.76, r = 0.87, p < 0.01$).

CBZ. The CSF:plasma ratio was $0.51 \pm 0.11$ for PB, $0.12 \pm 0.02$ for DPH, and $0.17$ for CBZ.

In the brain tissue, PB concentration ranged from 12.3 to 32.2 μg/gm, DPH concentrations were from 1.8 to 27.2 μg/gm, and CBZ ranged from 3.0 to 8.4 μg/gm. No significant differences have been found between concentrations of PB in the white and gray matter; DPH and CBZ concentrations were slightly higher in white matter. The relationship between PB and DPH brain and plasma concentration is shown in Fig. 1.

The brain:plasma ratio for PB was $0.71 \pm 0.21$ in gray matter, $0.76 \pm 0.14$ in white matter, and $0.75 \pm 0.19$ in white plus gray matter. The brain:plasma ratio for DPH was $1.13 \pm 0.24$ in gray matter, $1.33 \pm 0.48$ in white, and $1.18 \pm 0.35$ in white plus gray matter. In the two patients receiving CBZ, the brain:plasma ratio was $1.36$ and $1.25$ in the gray, $1.59$ and $1.64$ in the white, and $1.64$ and $1.33$ in the white and gray matter.

The regional distribution of antiepileptic drugs in the normal cerebral cortex is shown in Fig. 2. The frontal lobes showed slightly higher PB levels than the parietal and temporal lobes (Fig. 2 left). The DPH concentration in the temporal lobes was twice as high as that found in the frontal lobe; the parietal lobe level was also higher than the frontal lobe in one patient (Fig. 2 center). The CBZ concentration in the temporal and parietal lobes (Fig. 2 right) is not comparable because the two patients were in different pharmacokinetic situations (one was in steady state, and the other had been withdrawn from antiepileptic therapy for 48 hours).

Table 3 compares PB and CBZ concentrations in the hippocampal formation (Ammon’s horn and amygdala) and in the corresponding temporal...
Distribution of antiepileptic drugs in brain

**TABLE 2**

*Drug concentrations in plasma, cerebrospinal fluid (CSF), and brain in 12 patients in steady state*

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>PB</td>
<td>6</td>
<td>± 31.38 ± 8.45</td>
<td>± 15.56 ± 4.08</td>
<td>± 0.51 ± 0.11</td>
<td>± 22.17 ± 7.22</td>
<td>± 0.71 ± 0.21</td>
<td>± 23.25 ± 5.29</td>
<td>± 0.76 ± 0.14</td>
<td>± 22.78 ± 5.58</td>
<td>± 0.75 ± 0.19</td>
</tr>
<tr>
<td>± S.D.)</td>
<td></td>
<td>-4-8.45</td>
<td>-4-4.08</td>
<td>+0.11</td>
<td>-4-7.22</td>
<td>+0.21</td>
<td>-4-5.29</td>
<td>+0.14</td>
<td>-4-5.58</td>
<td>+0.19</td>
</tr>
<tr>
<td>DPH</td>
<td>5</td>
<td>± 12.86 ± 9.63</td>
<td>± 1.50 ± 0.75</td>
<td>± 0.12 ± 0.02</td>
<td>± 15.27 ± 8.63</td>
<td>± 1.13 ± 0.24</td>
<td>± 15.92 ± 11.58</td>
<td>± 1.33 ± 0.48</td>
<td>± 14.16 ± 9.25</td>
<td>± 1.18 ± 0.35</td>
</tr>
<tr>
<td>± S.D.)</td>
<td></td>
<td>-t-9.63</td>
<td>+0.75</td>
<td>-0.02</td>
<td>+8.63</td>
<td>+0.24</td>
<td>+11.58</td>
<td>+0.48</td>
<td>+9.25</td>
<td>+0.35</td>
</tr>
<tr>
<td>CBZ</td>
<td>Case 10</td>
<td>± 2.20 ± 5.10</td>
<td>± 0.90 ± 0.17</td>
<td>± 0.17</td>
<td>± 3.00 ± 6.40</td>
<td>± 1.36 ± 1.25</td>
<td>± 3.50 ± 8.40</td>
<td>± 1.59 ± 1.64</td>
<td>± 3.80 ± 6.80</td>
<td>± 1.64 ± 1.33</td>
</tr>
<tr>
<td></td>
<td>Case 11</td>
<td>± 5.10 ± 4.10</td>
<td>± 0.90 ± 0.17</td>
<td>± 0.17</td>
<td>± 6.40 ± 8.40</td>
<td>± 1.25 ± 1.64</td>
<td>± 8.40 ± 1.64</td>
<td>± 1.64 ± 1.33</td>
<td>± 6.80 ± 1.64</td>
<td>± 1.33 ± 1.33</td>
</tr>
</tbody>
</table>

*PB = phenobarbital, DPH = phenytoin, CBZ = carbamazepine.

**TABLE 3**

*Comparison of PB and CBZ concentrations in two patients*

<table>
<thead>
<tr>
<th>Electrical Activity</th>
<th>Structures</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>PB</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Level (µg/gm)</td>
</tr>
<tr>
<td>Amygdala</td>
<td></td>
<td>22.2</td>
</tr>
<tr>
<td>Ammon's horn</td>
<td></td>
<td>17.2</td>
</tr>
<tr>
<td>Neocortex</td>
<td></td>
<td>12.3</td>
</tr>
</tbody>
</table>

*Interictal depth electroencephalogram, and phenobarbital (PB) and carbamazepine (CBZ) concentrations in the rhinencephalic structures (Ammon's horn and amygdala) and in the neocortex in two patients. PUT = putamen; GP = globus pallidus; M = mammillary body; FORN = fornix.*
horn (17.2 µg/gm) and in the neocortex (12.3 µg/gm) in one patient. Ammon's horn showed no differences in CBZ concentration from the corresponding neocortex in the two cases studied.

The concentration of PB and DPH in scar tissue and in normal tissue was studied in two patients, and no significant difference was found (Table 4). The patients not in steady state condition showed a CSF:plasma ratio for PB, DPH, and CBZ of the same order as those of patients in steady state; the brain:plasma ratio remained the same for PB, but not for DPH and CBZ, where the ratio was 1.3-fold less than the ratio for steady state after 36 hours. The molar cortical concentration of PB and DPH was compared in patients with different surgical outcome. It was found to be higher (144.7 ± 31.6 µM/kg) in patients in whom surgery was unsuccessful, compared to those (108.8 ± 8.4 µM/kg) who became seizure-free after surgery.

**Discussion**

Our data suggest the existence of a significantly (p < 0.01) constant correlation between plasma and brain concentrations of PB and DPH. These findings confirm the brain:plasma ratio values previously reported in humans and animals. The brain:plasma ratio for CBZ in our patients is in agreement with that of Morselli, et al., in non-epileptic patients, and of Friis, et al., in epileptic patients. Our observations on mean CSF:plasma ratios for PB, DPH, and CBZ are in agreement with those reported previously by other authors.

Concentrations of antiepileptic drugs in gray and in white matter have been investigated in several animal species in chronic and acute studies and in epileptic patients. In our cases, evaluation of the drug concentration in gray and in white matter shows a rather uniform distribution, with only a slight trend toward higher concentrations in white matter for DPH and CBZ, as reported by Sherwin, et al.

We found a lower concentration of PB in the temporal lobe than in the frontoparietal areas. Distribution of DPH was twice as high in the temporal lobe than in the frontal and parietal lobes. On the contrary, Houghton, et al., and Sherwin, et al., found a higher DPH concentration in the frontal and parietal lobes. Our data on CBZ are limited, but the brain:plasma ratios in the temporal lobes of our two patients were higher than those reported by Morselli, et al., and similar to those of the parieto-occipital areas.

Rhinencephalic structures seem to have the same concentrations of PB and CBZ as those found in the gray matter of the temporal neocortex. In one patient with a primary rhinencephalic focus, we observed a PB concentration in the amygdala about twice as high as in Ammon's horn and the temporal neocortex.

The higher concentration of antiepileptic drugs in one structure as compared to another raises the problem of drug specificity. Studies with experimental animal models suggest that the zones with higher drug concentration should not be interpreted as "targets" or correlated with the specific therapeutic effect of drugs. The drug distribution in normal and pathological tissue may also be important. Rapport, et al., found a very remarkable decrease of DPH concentration in tissue with maximum epileptogenic activity and astrogliosis as compared to the normal tissue of four controls in humans.

In our two posttraumatic patients, no difference in PB and DPH concentrations was found between normal brain tissue and scar tissue, in which microscopic studies showed reactive astrogliosis. The areas of histologically normal tissue were characterized at the depth EEG or electrocorticogram by the presence of epileptogenic interictal activity, while scar tissue exhibited low-voltage slow activity and sporadic spikes. Differences in regional vascular supply might be responsible for differences in regional cortical concentration of the antiepileptic drug acutely given, as suggested by studies in animal models and in human epileptogenic tumors. In chronically treated patients, on the other hand, a combination of factors, such as vascular supply and pathological changes at cellular and subcellular levels, can be responsible for differences in drug distribution.

Considering the relationship between brain molar concentration and the clinical picture, Sherwin, et

**TABLE 4**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Case No.</th>
<th>Brain Area</th>
<th>Normal Tissue</th>
<th>Scar Tissue</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Level (µg/gm)</td>
<td>Brain:Plasma Ratio</td>
</tr>
<tr>
<td>PB</td>
<td>4</td>
<td>frontal lobe</td>
<td>25.9</td>
<td>0.75</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>parietal lobe</td>
<td>31.3</td>
<td>0.71</td>
</tr>
<tr>
<td>DPH</td>
<td>4</td>
<td>frontal lobe</td>
<td>17.0</td>
<td>0.72</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>parietal lobe</td>
<td>27.2</td>
<td>1.20</td>
</tr>
</tbody>
</table>

*PB = phenobarbital, DPH = phenytoin. Normal tissue includes white and gray matter.*

J. Neurosurg. / Volume 52 / May, 1980
Distribution of antiepileptic drugs in brain

al. in a study of patients with localized epilepsy, stressed the significantly higher total molar concentrations of PB and DPH (160.1 ± 20.4 μM/kg) in better controlled patients than in less well controlled patients (108.6 ± 5.4 μM/kg). In our cases, molar cortex concentration of PB and DPH was found to be higher in surgical failures than in patients with a good outcome.

Summary

In this series of 12 patients, a significant correlation between brain, plasma, and CSF concentration for higher in surgical failures than in patients with a good clinical reliability of monitoring antiepileptic plasma levels in epileptic patients.

The distribution of PB, DPH, and CBZ was similar in gray and white matter, in different brain areas (except for a higher concentration of PB in rhinencephalic structures in comparison with the corresponding temporal neocortex), and in normal and scar tissue. Differences in regional vascular supply and pathological cellular and subcellular changes could be responsible for different cerebral drug concentrations.

In our patients, all of whom were medically resistant and surgically treated, molar cortex concentration of PB and DPH was at "therapeutic" levels or even higher. These data suggest that in therapy-resistant patients, despite attained therapeutic cerebral drug concentrations of the same level as, or higher than, those present in medically controlled patients, anticonvulsant drugs are pharmacologically ineffective.

References


J. Neurosurg. / Volume 52 / May, 1980


