Appropriateness of serum level determinations of antiepileptic drugs

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Epileptic seizures are one of the most prevalent neurological disorders, affecting approximately 1% of the population in developed countries [1, 2]. Until recently, drug treatment of epilepsy has been empirical but in recent years due to improved understanding of seizure neurochemistry and of the mechanisms of action of antiepileptic drugs (AEDs), drug therapy has become more rational. Nevertheless, it is currently impossible to predict which patient will respond to a particular AED, and which patient will experience adverse drug effects. The only practical way to determine whether a drug will work in a specific patient, is to try it [2].

It is difficult to evaluate the therapeutic success of AED therapy due to the lack of a direct method to measure the effect. Therapeutic drug monitoring (TDM) – the measurement of drug concentrations in biological fluids combined with clinical pharmacology – may therefore be an important and helpful tool in guiding and optimising AED therapy, especially in those patients in whom epileptic seizures occur only rarely. Appropriate and rational utilisation of TDM may improve drug therapy by maximising seizure control and minimising the risk of adverse drug reactions and therefore, may also have a cost-saving effect [3–5].

However, several studies have shown that AED level measurements are often requested without an appropriate indication, that blood sampling is done at an incorrect time point or that the result is interpreted incorrectly [6–8]. This may lead to suboptimal AED therapy and result in additional unnecessary costs. Our data indicate the need for means to improve the rational use of AED serum level determination.

Key words: phenytoin; valproic acid; carbamazepine; therapeutic drug monitoring; hospital; inpatients
Methods

Setting

The study was conducted at the University Hospital of Basel, an 815 bed teaching hospital providing primary and tertiary care to an urban population of approximately 200,000 inhabitants. It also serves as a tertiary care referral centre for north west Switzerland with a catchment area of approximately 450,000 people. Resident physicians are the primary orderers of tests. Members of the division of clinical pharmacology provide routine pharmacokinetic consultations only for aminoglycosides. However, a variety of serum drug levels, including those of AEDs, are interpreted and a written comment (e.g. dose recommendations) is provided by the clinical pharmacology team for each drug level determined.

Appropriateness criteria

Criteria for appropriate AED level monitoring were defined a priori combining criteria previously described in the literature [8, 10–16]. The criteria were focused on the antiepileptic treatment of adult hospitalised patients.

The following two criteria had to be fulfilled in order to assess an AED drug level determination as appropriate (for explicit criteria see Appendix): (1) adequate indication for the measurement, and (2) correct sampling time (trough level [i.e. sampling just prior to the next dose] and steady state conditions).

Measurement of AED levels

Serum levels of phenytoin, valproic acid and carbamazepine were measured by the clinical medical laboratory using the AxSYM® II microparticle enzyme immunoassay (Abbott Laboratories, Abbott Park, IL). The laboratory results were interpreted by a member of the clinical pharmacology team. A written comment and, if necessary, information on dosage adjustment or other remarks were provided for each AED level determination requested.

Sampling and data collection

From January 1999 to June 2002, a total of 8'057 plasma levels of phenytoin, valproic acid, and carbamazepine were measured, of which 2'279 (28.3%) were done in inpatients of our hospital. A sample of 602 (26.4%) drug level determinations in inpatients for whom both the medical record and the TDM request form were available, were selected for further analysis. In patients for whom more than one AED level determination was performed during the same hospital stay, one was randomly selected for analysis. Drug level determinations in patients for whom AED therapy was prescribed for indications other than seizures (e.g. bipolar disorders, cluster headache, neuropathic pain) were not included in the analysis because of the lack of an established therapeutic range.

Medical records of adult inpatients (≥ 16 years of age) for whom an AED level was determined and who were included in the analysis, were abstracted together with the TDM request form to obtain the following information: age, sex, weight, seizure type, clinical condition, daily AED dose and dosing interval, indication for AED level determination, serum albumin level, levels of transaminases, alkaline phosphatase and bilirubin to assess the hepatic function, and serum creatinine level to estimate the creatinine clearance as a marker for renal function. We used the equation of Dettli (i.e. (150–age) × body weight [kg] × 0.9 [women] or 1.1 [men] / serum creatinine [μmol/l]) to estimate the renal function [20].

Statistical analysis

Data are presented as median with the corresponding range or as proportions with 95% confidence intervals (95% CI) calculated according to standard procedures [21].

Results

Of 602 AED level determinations selected for analysis, 280 (46.5%) were for phenytoin, 183 (30.4%) for valproic acid, and 139 (23.1%) for carbamazepine. Demographic and clinical information on the 602 patients for whom an AED level measurement was performed are displayed in Table 1.

Overall, the majority of AED level determinations were done in patients with known seizure disorders, approximately one third in patients after neurosurgery (Table 2). Almost 90% of the patients received oral AED formulations at the time of drug level measurement, with a high percentage of slow release formulations in patients with carbamazepine or valproic acid therapy. Half of all AED level determinations were within the therapeutic range, with the highest proportion in patients with carbamazepine therapy.

The indication was assessed as appropriate in 463 (77%; 95% CI: 73% to 80%) of 602 AED level determinations. Details of appropriate indications are displayed in Table 3. The proportion of appropriate indications for individual AEDs was 84% (95% CI: 79% to 88%) for phenytoin, 74% (95% CI: 67% to 80%) for valproic acid, and 68% (95% CI: 59% to 76%) for carbamazepine. Of 139 (23%; 95% CI: 20% to 27%) level determinations assessed as having an inappropriate indication, the majority (77%) involved routine monitoring (i.e. repeat measurement without change of dose, comedication or clinical status), and the remaining 23% were measurements after dose changes of carbamazepine or valproic acid or measurements in patients with adverse drug reactions that were not concentration dependent.

Overall, 418 (69.4%) measurements were done after steady state conditions had been reached, and 506 (84.1%) of all determinations measured a trough level. Combining the two aspects showed that 391 (65%; 95% CI: 61% to 69%) measurements fulfilled the criteria for appropriate timing. With regard to individual AEDs, appropriate timing was highest for valproic acid (80%), while the proportion for carba-
Table 1
Characteristics of 602 inpatients for whom a drug level determination of phenytoin, carbamazepine or valproic acid was done.

<table>
<thead>
<tr>
<th></th>
<th>Phenytoin (n = 280)</th>
<th>Valproic acid (n = 183)</th>
<th>Carbamazepine (n = 139)</th>
<th>All (n = 602)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age [years], median (range)</td>
<td>58 (16–92)</td>
<td>62 (17–91)</td>
<td>56 (16–88)</td>
<td>59 (16–92)</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>150 (53.6)</td>
<td>83 (45.4)</td>
<td>71 (51.1)</td>
<td>304 (50.5)</td>
</tr>
<tr>
<td>Length of hospital stay [days], median (range)</td>
<td>20 (2–82)</td>
<td>16 (2–101)</td>
<td>14 (2–111)</td>
<td>18 (2–111)</td>
</tr>
</tbody>
</table>

Hospital speciality, n (%)

<table>
<thead>
<tr>
<th></th>
<th>Internal medicine</th>
<th>Surgery</th>
<th>Neurology</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>80 (28.6)</td>
<td>161 (57.5)</td>
<td>31 (11.1)</td>
<td>8 (2.8)</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>80 (43.7)</td>
<td>50 (27.3)</td>
<td>44 (24.1)</td>
<td>9 (4.9)</td>
</tr>
<tr>
<td>Length of stay [days], median (range)</td>
<td>54 (38.8)</td>
<td>58 (41.7)</td>
<td>25 (18.0)</td>
<td>2 (1.5)</td>
</tr>
</tbody>
</table>

 Estimated renal function, n (%)

<table>
<thead>
<tr>
<th></th>
<th>normal (≥50 ml/min)</th>
<th>decreased (&lt;50 ml/min)</th>
<th>unclear</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>249 (88.9)</td>
<td>14 (5.0)</td>
<td>17 (6.1)</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>152 (81.3)</td>
<td>15 (8.2)</td>
<td>16 (8.7)</td>
</tr>
<tr>
<td>Length of stay [days], median (range)</td>
<td>120 (86.3)</td>
<td>10 (7.2)</td>
<td>9 (6.5)</td>
</tr>
</tbody>
</table>

Liver function, n (%)

<table>
<thead>
<tr>
<th></th>
<th>normal</th>
<th>impaired</th>
<th>unclear</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex, n (%)</td>
<td>140 (78.2)</td>
<td>22 (12.0)</td>
<td>18 (9.8)</td>
</tr>
<tr>
<td>Length of stay [days], median (range)</td>
<td>94 (67.7)</td>
<td>18 (12.9)</td>
<td>27 (19.4)</td>
</tr>
</tbody>
</table>

Plasma albumin concentration (reference 35–52 g/l)

<table>
<thead>
<tr>
<th></th>
<th>≥35 g/l</th>
<th>&lt;35 g/l</th>
<th>not available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex, n (%)</td>
<td>134 (47.9)</td>
<td>4 (24.6)</td>
<td>60 (43.2)</td>
</tr>
<tr>
<td>Length of stay [days], median (range)</td>
<td>117 (63.9)</td>
<td>21 (11.5)</td>
<td>25 (18.0)</td>
</tr>
</tbody>
</table>

* ALAT, ASAT, alkaline phosphatase or conjugated bilirubin above twice the upper limit of the reference value

Table 2
Characteristics of 602 drug level measurements of phenytoin, carbamazepine or valproic acid.

<table>
<thead>
<tr>
<th></th>
<th>Phenytoin (n = 280)</th>
<th>Valproic acid (n = 183)</th>
<th>Carbamazepine (n = 139)</th>
<th>All (n = 602)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indication for antiepileptic therapy, n (%)</td>
<td>focal seizures</td>
<td>generalised seizures</td>
<td>status epilepticus</td>
<td>seizure prophylaxis after neurosurgery</td>
</tr>
<tr>
<td></td>
<td>62 (22.1)</td>
<td>64 (22.9)</td>
<td>7 (2.5)</td>
<td>131 (46.8)</td>
</tr>
<tr>
<td></td>
<td>68 (37.2)</td>
<td>55 (30.1)</td>
<td>6 (3.3)</td>
<td>29 (15.8)</td>
</tr>
<tr>
<td></td>
<td>58 (41.7)</td>
<td>28 (20.1)</td>
<td>–</td>
<td>33 (21.8)</td>
</tr>
<tr>
<td></td>
<td>188 (31.2)</td>
<td>147 (24.4)</td>
<td>13 (2.2)</td>
<td>193 (32.1)</td>
</tr>
<tr>
<td>Daily dose [mg], median (range)</td>
<td>300 (100–750)</td>
<td>1000 (200–2600)</td>
<td>800 (100–3000)</td>
<td>–</td>
</tr>
<tr>
<td>Route of administration, n (%)</td>
<td>orally, instant release</td>
<td>orally, slow release</td>
<td>intravenous admission</td>
<td>rectally</td>
</tr>
<tr>
<td></td>
<td>246 (87.9)</td>
<td>97 (53.0)</td>
<td>33 (11.8)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td></td>
<td>62 (33.9)</td>
<td>98 (70.5)</td>
<td>21 (11.5)</td>
<td>2 (1.1)</td>
</tr>
<tr>
<td></td>
<td>36 (25.8)</td>
<td>195 (32.4)</td>
<td>–</td>
<td>4 (2.9)</td>
</tr>
<tr>
<td></td>
<td>344 (57.1)</td>
<td>195 (32.4)</td>
<td>54 (9.0)</td>
<td>7 (1.2)</td>
</tr>
<tr>
<td>AED level, n (%)</td>
<td>below the usual therapeutic range</td>
<td>within usual therapeutic range</td>
<td>above the usual therapeutic range</td>
<td></td>
</tr>
<tr>
<td></td>
<td>145 (51.8)</td>
<td>115 (41.1)</td>
<td>20 (7.1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>97 (53.0)</td>
<td>81 (44.3)</td>
<td>5 (2.7)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>27 (19.4)</td>
<td>101 (72.7)</td>
<td>11 (7.9)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>269 (44.7)</td>
<td>297 (49.3)</td>
<td>36 (6.0)</td>
<td></td>
</tr>
</tbody>
</table>

* phenytoin: 10–20 mg/l, carbamazepine: 4–10 mg/l, valproic acid: 50–100 mg/l

When both, appropriateness of indication and correct timing were taken into account, 289 AED measurements (48%; 95% CI: 44% to 52%) met both criteria. The proportion of appropriate measurements was highest for valproic acid and lowest for phenytoin (Table 4).
Using a priori defined and reliable criteria we found that overall, approximately 77% of all AED level measurements had an appropriate indication with a range of 68% to 84% for individual AEDs. In other studies this proportion was highly variable ranging from 27% to 72% [8, 11, 15, 22, 23]. However, several of these studies used slightly different criteria from those used in our study, had only small sample sizes or the study was done in specialised settings (e.g., epilepsy clinics) which may at least partly explain some discrepancies. The most striking result is the big difference between our results and those of Schoenenberger et al. [8], who assessed 855 AED levels (including phenobarbital) in 330 patients in a tertiary care centre in the USA using very similar appropriateness criteria. Overall, the proportion of AEDs level measurements with appropriate indication in their study was 27%, ranging from 25% to 29%, for the individual AEDs assessed. Although in both studies phenytoin was the drug with the highest proportion of appropriate indications, in our study, this proportion was higher by a factor of approximately three (i.e. 84% versus 29%). While the difference between the individual AEDs was rather small in the study by Schoenenberger (e.g. 25% for carbamazepine versus 29% for phenytoin), it is more distinct in our study, with the lowest proportion seen with carbamazepine and the highest associated with phenytoin (i.e. 68% and 84%, respectively). Moreover, even though the proportion of measurements with an inappropriate indication was very different (73% versus 23%), the proportion of measurements with an inappropriate indication due to repeat measurements was very similar in both studies (73% in the study by Schoenenberger et al., 77% in the present study).

In our study as well as that of Schoenenberger et al. [8] and as in most of the other studies cited above, most inappropriate indications were identified in patients with routine monitoring (i.e. drug level measurement in a patient with good clinical response to AED therapy, no change of dose, clinical condition, or comedication, and no signs of adverse or toxic effects). Another common reason for inappropriate AED level measurement was drug level determination after dose adjustment (criterion 1.B.4). Even though carbamazepine shows dose-dependent induction of its own metabolism (autoinduction) [24–26], the clearance remains constant after reaching the maximal autoinduction which occurs approximately 1–2 weeks after initiating carbamazepine therapy. On the other hand protein binding of valproic acid is concentration-dependent and decreases with increasing dose. However, the variation in the free fraction of valproic acid begins to become significant only at a total drug concentration above 100 mg/l [27, 28]. Therefore, assuming linear kinetics and bearing in mind the above cited limitations, drug levels can easily be estimated. It is therefore generally not necessary to do an additional drug level measurement after dosage adjustment unless there are signs of adverse effects, or the comedication or the liver function have changed. This is different for phenytoin, since this drug shows non-linear phar-

### Table 3

<table>
<thead>
<tr>
<th>Reason for plasma level determinations of 463 measurements of antiepileptic drugs assessed as having an appropriate indication.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Phenytoin</strong> (n = 234)</td>
</tr>
<tr>
<td>Newly initiated or reinitiated therapy</td>
</tr>
<tr>
<td>Insufficient clinical effect</td>
</tr>
<tr>
<td>Suspected change of pharmacokinetics</td>
</tr>
<tr>
<td>Calculation of individual pharmacokinetics</td>
</tr>
<tr>
<td>Suspected toxicity or concentration-dependent adverse drug reaction</td>
</tr>
<tr>
<td>Potential drug-drug interaction</td>
</tr>
<tr>
<td>Dosage adjustment of phenytoin</td>
</tr>
<tr>
<td>Level measurement after epileptic seizure (within 6 h)</td>
</tr>
</tbody>
</table>

### Table 4

<table>
<thead>
<tr>
<th>Overview on appropriateness of 602 drug level measurements for phenytoin, carbamazepine or valproic acid with regard to indication and timing and the combination of both criteria.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Phenytoin</strong> (n = 280)</td>
</tr>
<tr>
<td><strong>Indication n (%)</strong></td>
</tr>
<tr>
<td>234 (83.6%)</td>
</tr>
<tr>
<td>94 (67.6%)</td>
</tr>
<tr>
<td>135 (73.8%)</td>
</tr>
<tr>
<td>463 (76.9%)</td>
</tr>
</tbody>
</table>

### Discussion

Using a priori defined and reliable criteria we found that overall, approximately 77% of all AED level measurements had an appropriate indication with a range of 68% to 84% for individual AEDs. In other studies this proportion was highly variable ranging from 27% to 72% [8, 11, 15, 22, 23]. However, several of these studies used slightly different criteria from those used in our study, had only small sample sizes or the study was done in specialised settings (e.g., epilepsy clinics) which may at least partly explain some discrepancies. The most striking result is the big difference between our results and those of Schoenenberger et al. [8], who assessed 855 AED levels (including phenobarbital) in 330 patients in a tertiary care centre in the USA using very similar appropriateness criteria. Overall, the proportion of AEDs level measurements with appropriate indication in their study was 27%, ranging from 25% to 29%, for the individual AEDs assessed. Although in both studies phenytoin was the drug with the highest proportion of appropriate indications, in our study, this proportion was higher by a factor of approximately three (i.e. 84% versus 29%). While the difference between the individual AEDs was rather small in the study by Schoenenberger (e.g. 25% for carbamazepine versus 29% for phenytoin), it is more distinct in our study, with the lowest proportion seen with carbamazepine and the highest associated with phenytoin (i.e. 68% and 84%, respectively). Moreover, even though the proportion of measurements with an inappropriate indication was very different (73% versus 23%), the proportion of measurements with an inappropriate indication due to repeat measurements was very similar in both studies (73% in the study by Schoenenberger et al., 77% in the present study).

In our study as well as that of Schoenenberger et al. [8] and as in most of the other studies cited above, most inappropriate indications were identified in patients with routine monitoring (i.e. drug level measurement in a patient with good clinical response to AED therapy, no change of dose, clinical condition, or comedication, and no signs of adverse or toxic effects). Another common reason for inappropriate AED level measurement was drug level determination after dose adjustment (criterion 1.B.4). Even though carbamazepine shows dose-dependent induction of its own metabolism (autoinduction) [24–26], the clearance remains constant after reaching the maximal autoinduction which occurs approximately 1–2 weeks after initiating carbamazepine therapy. On the other hand protein binding of valproic acid is concentration-dependent and decreases with increasing dose. However, the variation in the free fraction of valproic acid begins to become significant only at a total drug concentration above 100 mg/l [27, 28]. Therefore, assuming linear kinetics and bearing in mind the above cited limitations, drug levels can easily be estimated. It is therefore generally not necessary to do an additional drug level measurement after dosage adjustment unless there are signs of adverse effects, or the comedication or the liver function have changed. This is different for phenytoin, since this drug shows non-linear phar-
macokinetics which makes it very difficult to estimate the drug concentration without computer programs or nomograms which help to calculate phenytoin drug concentrations after dose adjustment [29].

In the present study the sampling time was assessed as appropriate in 65% of all AEDs combined, ranging from 53% for phenytoin to 80% for valproic acid. Again, this proportion is higher in comparison with other studies where it was found to range from 26% to 57% [8, 12, 30]. This again, may be partly explained by the different definitions used in other studies. While, for instance, we defined the time to reach steady state conditions with phenytoin therapy rather conservatively as 10 days, most other studies defined it as a range of 5 to 7 days [8, 12, 15, 30]. In comparison with the results of Schoenenberger et al. [8] we found a notable difference in the results for valproic acid in the two studies. While we considered 80% of AED levels as appropriate in terms of the timing criterion, this was only 35% in the Schoenenberger study. The results for phenytoin are identical (53% in both studies), while the proportion for carbamazepine was again higher in our study (68% and 45%, respectively).

Correct interpretation of an AED serum level determination very much depends on information on sampling time and duration of AED therapy. It is important to ensure that after initiating AED therapy or after dose adjustment, steady state conditions have been attained. Additionally, trough levels are in general the standard samples that should be obtained (unless the indication is suspected toxicity) due to the minimal impact of absorption or elimination on plasma concentration at that time point.

The present study has several limitations. The assessment of the indication of an individual requested AED measurement was mainly based on information retrieved from the TDM request form which may contain incomplete or incorrect information. If the indication for the measurement was not explicitly stated on the request form, we tried to retrieve it from information available from the patient chart. Whether this always reflected the true indication is unclear and may therefore be the source of some misclassification. Some important information such as suspected adverse effects associated with AED therapy or seizure recurrence may not have always been adequately noted in the charts as a reason for ordering a drug level. Moreover, it was often not possible to retrieve information on the exact timing of blood sampling directly from the TDM request form. Instead, we used the time when the sample arrived in the clinical chemistry laboratory as a surrogate marker assuming that blood sampling usually occurred within approximately one hour before arrival there. Moreover, in patients receiving the AED intravenously and who had supratherapeutic AED concentrations we could not exclude with certainty that the possibility that the blood sample was taken from the same infusion line that was used for administering the AED.

It is generally accepted that knowledge of the AED serum concentration is useful only when it is considered in the context of a patient’s clinical state and symptoms. Therefore, it is crucial that ordering a drug level determination should be done only when a specific clinical question can be answered by the measurement [8]. Due to the high proportion of determinations without appropriate indication or incorrect sampling found in previous studies, several interventions have been evaluated to decrease the use of inappropriate or irrational AED level monitoring. Programs focusing on physician education or on interventions using clinical pharmacists to run TDM services showed some effectiveness in improving the appropriate use of AED level monitoring and in decreasing the proportion of inappropriate level measurements [6, 11, 15, 23, 31]. Interestingly, a recent study showed that computerised screens at the time of electronic AED order entry may substantially decrease the total AED testing volume by reducing redundant orders [32]. While the effects of education measures generally disappear rapidly after discontinuation [11], computerised screening may durably affect physician behaviour [32] and may have a very favourable cost-benefit ratio.

In conclusion, less than half of all AED measurements met our criteria of appropriate AED serum level determinations which is associated with considerable, unnecessary costs. While these figures are better than those in other studies, they still indicate the need for means of improving the rational use of AED level determination.

We strongly suggest that laboratories and clinical pharmacologists engaged in TDM should have a mission in educating the prescribing physicians on appropriate criteria for requesting a drug level determination and how to supply sufficient information for a meaningful interpretation of plasma drug concentrations.

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University Hospital of Basel
Petersgraben 4
CH-4031 Basel
E-Mail: sbliengerr@uhbs.ch
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Appendix

Explicit criteria used to assess the appropriateness of drug level determinations of phenytoin, carbamazepine, and valproic acid

1. Criterion: indication
1.A Appropriate indications for antiepileptic drug (AED) level monitoring
1.A.1 Newly initiated or reinitiated therapy with an AED (including change to another generic drug)
1.A.2 Insufficient clinical response despite adequate dose due to
- suspected non-compliance
- suspected absorption problem
- concomitant interacting drug
1.A.3 Suspected change of the pharmacokinetics
- impaired renal function (i.e. estimated creatinine clearance < 50 ml/min) or impaired hepatic function (increase of transaminases, alkaline phosphatase or conjugated bilirubin above twice the upper reference value) *
- advanced age (> 80 years) and/or low body weight (i.e. < 40 kg)
- hypoalbuminaemia (i.e., albumin < 35 g/l) *
1.A.4 Calculation of individual pharmacokinetics of phenytoin
1.A.5 Suspected toxicity or concentration-dependent adverse drug reaction
1.A.6 Clarification of relevant potential drug drug interactions
Start or stop of potentially interacting drug
Dose change in potentially interacting drug
1.A.7 After every dosage adjustment of phenytoin
1.A.8 Plasma level measurement within 6 hours after an epileptic seizure
* if free concentrations of phenytoin or valproic acid can be measured
1.B. Inappropriate indications for antiepileptic drug (AED) level monitoring

1.B.1 Repeat measurement in patients with satisfactory therapeutic effect, without change of dose, comedication or clinical status, and without signs of adverse or toxic effects

1.B.2 Suspected adverse reaction independent of plasma concentration

1.B.3 Determination of individual pharmacokinetics of carbamazepine or valproic acid in patients with unchanged clinical state

1.B.4 After dose change in patients with chronic carbamazepine (i.e. >4 weeks of therapy) or valproic acid therapy (due to linear pharmacokinetics)

2. Criterion: timing

2.1 AED level measurement after reaching steady state conditions (i.e. after 4-5 half-lives of a drug) defined as 3 days for valproic acid [3], 28 days after newly initiated carbamazepine therapy due to autoinduction of the metabolism and 3 days in chronic users [3, 33], and 10 days for phenytoin

2.2 AED trough level measurement (i.e. prior to the next dose) except in case of an epileptic seizure or suspected toxic or concentration-dependent adverse effect
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