Peer reviewed article

Appropriateness of serum level determinations of antiepileptic drugs

Nadia Affolter[a], *Stephan Krähenbühl*[b], *Raymond G. Schlienger*[a, b]

[a] Institute of Clinical Pharmacy, Department of Pharmacy, University of Basel, Basel, Switzerland
[b] Division of Clinical Pharmacology & Toxicology, Department of Internal Medicine, University Hospital Basel, Basel, Switzerland

Summary

Aim: To assess the appropriateness of the determination of the serum levels of the antiepileptic drugs (AEDs) phenytoin, valproic acid and carbamazepine in inpatients of a tertiary care institution.

Methods: We performed a retrospective analysis of 602 AED serum level determinations. Appropriateness criteria regarding indication and timing were defined a priori using existing criteria from the literature. The main outcome measure was the proportion of serum levels with an appropriate indication and sampling time.

Results: Of 602 levels assessed, 463 (77%; 95% confidence interval [95% CI], 74–80%) had an appropriate indication with a range of 68% to 84% for individual AEDs; overall, 65% (95% CI: 61–69%) met the criteria for appropriate timing. Combining the two criteria, 268 (48%; 95% CI: 44–52%) AED level measurements were assessed as appropriate. Of 139 (23%, 95% CI: 20–27%) levels assessed as having an inappropriate indication, the majority (77%) were performed for routine monitoring.

Conclusions: Less than half of all AED measurements met our criteria for appropriate AED level determinations. This creates 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

Introduction

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.

A recent study at our institution showed that the majority of digoxin plasma level determinations did not have an appropriate indication which was associated with unnecessary additional costs but no therapeutic benefit for the patients [9]. The present retrospective study was performed to assess the proportion of AED serum level determinations for phenytoin, carbamazepine and valproic acid fulfilling criteria for appropriate drug level monitoring in hospitalised patients. The main outcome measure was the proportion of measurements with an appropriate indication and sampling time.

The present study was not funded.

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.

The therapeutic range of phenytoin was defined as 10–20 mg/l [17–19], of valproic acid as 50–100 mg/l [7, 17], and of carbamazepine as 4–10 mg/l [7, 17].

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 asses 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.

	Phenytoin (n = 280)	Valproic acid (n = 183)	Carbamazepine (n = 139)	All (n = 602)
Age [years], median (range)	58 (16–92)	62 (17–91)	56 (16–88)	59 (16–92)
Male sex, n (%)	150 (53.6)	83 (45.4)	71 (51.1)	304 (50.5)
Length of hospital stay [days], median (range)	20 (2–82)	16 (2–101)	14 (2–111)	18 (2–111)
Hospital speciality, n (%)				
Internal medicine	80 (28.6)	80 (43.7)	54 (38.8)	214 (35.5)
Surgery	161 (57.5)	50 (27.3)	58 (41.7)	269 (44.7)
Neurology	31 (11.1)	44 (24.1)	25 (18.0)	100 (16.6)
Other	8 (2.8)	9 (4.9)	2 (1.5)	19 (3.2)
Estimated renal function, n (%)				
normal (≥50 ml/min)	249 (88.9)	152 (83.1)	120 (86.3)	521 (86.5)
decreased (i.e. <50 ml/min)	14 (5.0)	15 (8.2)	10 (7.2)	39 (6.5)
unclear	17 (6.1)	16 (8.7)	9 (6.5)	42 (7.0)
Liver function, n (%)				
normal	160 (57.1)	143 (78.2)	94 (67.7)	397 (65.9)
impaired *	64 (22.9)	22 (12.0)	18 (12.9)	104 (17.3)
unclear	56 (20.0)	18 (9.8)	27 (19.4)	101 (16.8)
Plasma albumin concentration (reference 35–52 g/l)				
≥35 g/l	134 (47.9)	117 (63.9)	54 (38.8)	305 (50.7)
<35 g/l	86 (30.7)	4 (24.6)	60 (43.2)	191 (31.7)
not available	60 (21.4)	21 (11.5)	25 (18.0)	106 (17.6)

* 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.

	Phenytoin (n = 280)	Valproic acid (n = 183)	Carbamazepine (n = 139)	All (n = 602)
Indication for antiepileptic therapy, n (%)				
focal seizures	62 (22.1)	68 (37.2)	58 (41.7)	188 (31.2)
generalised seizures	64 (22.9)	55 (30.1)	28 (20.1)	147 (24.4)
status epilepticus	7 (2.5)	6 (3.3)	–	13 (2.2)
seizure prophylaxis after neurosurgery	131 (46.8)	29 (15.8)	33 (23.8)	193 (32.1)
unclear	16 (5.7)	25 (13.7)	20 (14.4)	61 (10.1)
Daily dose [mg], median (range)	300 (100–750)	1000 (200–2600)	800 (100–3000)	–
Route of administration, n (%)				
orally, instant release	246 (87.9)	62 (33.9)	36 (25.8)	344 (57.1)
orally, slow release	–	97 (53.0)	98 (70.5)	195 (32.4)
intravenously	33 (11.8)	21 (11.5)	–	54 (9.0)
rectally	–	1 (0.5)	1 (0.7)	2 (0.3)
unclear	1 (0.4)	2 (1.1)	4 (2.9)	7 (1.2)
AED level, n (%)				
below the usual therapeutic range	145 (51.8)	97 (53.0)	27 (19.4)	269 (44.7)
within usual therapeutic range*	115 (41.1)	81 (44.3)	101 (72.7)	297 (49.3)
above the usual therapeutic range	20 (7.1)	5 (2.7)	11 (7.9)	36 (6.0)

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

mazepine and phenytoin was 68%, and 53%, respectively.

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).

Table 3

Reasons for plasma level determinations of 463 measurements of antiepileptic drugs assessed as having an appropriate indication.

	Phenytoin (n = 234)	Valproic acid (n = 135)	Carbamazepine (n = 94)	Total (n = 463)
Newly initiated or reinitiated therapy	106 (45.3%)	45 (33.3%)	22 (23.4%)	173 (37.3%)
Insufficient clinical effect	28 (12.0%)	26 (19.3%)	25 (26.6%)	79 (17.1%)
Suspected change of pharmacokinetics	27 (11.5%)	32 (23.7%)	15 (16.9%)	74 (16.0%)
Calculation of individual pharmacokinetics	2 (0.9%)	–	–	2 (0.4%)
Suspected toxicity or concentration-dependent adverse drug reaction	19 (8.1%)	13 (9.6%)	17 (18.1%)	49 (10.6%)
Potential drug-drug interaction	17 (7.3%)	13 (9.6%)	12 (12.8%)	42 (9.1%)
Dosage adjustment of phenytoin	30 (12.8%)	–	–	30 (6.5%)
Level measurement after epileptic seizure (within 6 h)	5 (2.1%)	6 (4.4%)	3 (3.2%)	14 (3.0%)

Table 4

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.

	Indication n (%)	Timing n (%)	Both criteria fulfilled n (%)
Phenytoin (n = 280)	234 (83.6%)	149 (53.2%)	114 (40.7%)
Carbamazepine (n = 139)	94 (67.6%)	95 (68.3%)	67 (48.2%)
Valproic acid (n = 183)	135 (73.8%)	147 (80.3%)	108 (59.0%)
All (n = 602)	463 (76.9%)	391 (65.0%)	289 (48.0%)

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.

Correspondence
Dr. Raymond Schlienger
Division of Clinical Pharmacology & Toxicology
University Hospital of Basel
Petersgraben 4
CH-4031 Basel
E-Mail: schliengerr@uhbs.ch

References

1 Browne TR, Holmes GL. Epilepsy. N Engl J Med 2001;344: 1145–51.
2 Patsalos PN. Antiepileptic drug pharmacogenetics. Ther Drug Monit 2000;22:127–30.
3 Glauser TA, Pippenger CE. Controversies in blood-level monitoring: reexamining its role in the treatment of epilepsy. Epilepsia 2000;41:S6–15.
4 Destache CJ. Use of therapeutic drug monitoring in pharmacoeconomics. Ther Drug Monit 1993;15:608–10.
5 Vozeh S. Cost-effectiveness of therapeutic drug monitoring. Clin Pharmacokinet 1987;13:131–40.
6 D'Angio RG, Stevenson JG, Lively BT, Morgan JE. Therapeutic drug monitoring: improved performance through educational intervention. Ther Drug Monit 1990;12:173–81.
7 McKee PJ, Larkin JG, Brodie AF, Percy-Robb IW, Brodie MJ. Five years of anticonvulsant monitoring on site at the epilepsy clinic. Ther Drug Monit 1993;15:83–90.
8 Schoenenberger RA, Tanasijevic MJ, Jha A, Bates DW. Appropriateness of antiepileptic drug level monitoring. JAMA 1995; 274:1622–6.
9 Mordasini MR, Krähenbühl S, Schlienger RG. Appropriateness of digoxin level monitoring. Swiss Med Wkly 2002;132:506–12.
10 Mattson RH. Antiepileptic drug monitoring: a reappraisal. Epilepsia 1995;36:S22–9.
11 Wing D, Duff HJ. The impact of a therapeutic drug monitoring program for phenytoin. Ther Drug Monit 1989;11:32–7.
12 Bussey HI, Hoffman EW. A prospective evaluation of therapeutic drug monitoring. Ther Drug Monit 1983;5:245–8.
13 Levine M, Chang T. Therapeutic drug monitoring of phenytoin. Rationale and current status. Clin Pharmacokinet 1990; 19:341–58.
14 Commission on Antiepileptic Drugs. Guidelines for therapeutic monitoring on antiepileptic drugs. Epilepsia 1993;34:585–7.
15 Levin B, Cohen SS, Birmingham PH. Effect of pharmacist intervention on the use of serum drug assays. Am J Hosp Pharm 1981;38:845–51.
16 Eadie MJ. Indications for plasma drug monitoring in patients with epilepsy. Implications for reducing costs. Pharmacoeconomics 1997;11:343–9.
17 Eadie MJ. Therapeutic drug monitoring – antiepileptic drugs. Br J Clin Pharmacol 2001;52:11S–20S.
18 Kilpatrick CJ, Wanwimolruk S, Wing LM. Plasma concentrations of unbound phenytoin in the management of epilepsy. Br J Clin Pharmacol 1984;17:539–46.
19 Winkler SR, Luer MS. Antiepileptic drug review: part 1. Surg Neurol 1998;49:449–52.
20 Dettli L. The kidney in pre-clinical and clinical pharmacokinetics. Jpn J Clin Pharmacol Ther 1984;15:241–54.
21 Altman D, Machin D, Bryant T, Gardner M. Statistics with confidence. 2nd edition ed. London: BMJ Books; 2000.
22 Levine M, McCollom R, Chang T, Orr J. Evaluation of serum phenytoin monitoring in an acute care setting. Ther Drug Monit 1988;10:50–7.
23 Pearce GA, Day RO. Compliance with criteria necessary for effective therapeutic drug monitoring. Ther Drug Monitor 1990; 12:250–7.
24 Kudriakova TB, Sirota LA, Rozova GI, Gorkov VA. Autoinduction and steady-state pharmacokinetics of carbamazepine and its major metabolites. Br J Clin Pharmacol 1992;33:611–5.
25 Bernus I, Dickinson RG, Hooper WD, Eadie MJ. Early stage autoinduction of carbamazepine metabolism in humans. Eur J Clin Pharmacol 1994;47:355–60.
26 Mikati MA, Browne TR, Collins JF. Time course of carbamazepine autoinduction. The VA Cooperative Study No.118 Group. Neurology 1989;39:592–4.
27 Gomez Bellver MJ, Garcia Sanchez MJ, Alonso Gonzalez AC, Santos Buelga D, Dominguez-Gil A. Plasma protein binding kinetics of valproic acid over a broad dosage range: therapeutic implications. J Clin Pharm Ther 1993;18:191–7.
28 Bowdle AT, Patel IH, Levy RH, Wilensky AJ. Valproic acid dosage and plasma protein binding and clearance. Clin Pharmacol Ther 1980;28:486–92.
29 Vozeh S, Follath F. Nomographic estimation of time to reach steady-state serum concentration during phenytoin therapy. Eur J Clin Pharmacol 1980;17:33–5.
30 Kildoo CW, Bolger PB, Ambrose PJ, Smith WE. Use of serum drug concentrations in a private outpatient clinic. Am J Hosp Pharm 1987;44:1410–1.
31 Elenbaas RM, Payne VW, Bauman JL. Influence of clinical pharmacist consultations on the use of drug blood levels tests. Am J Hosp Pharm 1980;37:61–4.
32 Chen P, Tanasijevic MJ, Schoenenberger RA, Fiskio J, Kuperman GJ, Bates DW. A computer-based intervention for improving the appropriateness of antiepileptic drug level monitoring. Am J Clin Pathol 2003;119:432–8.
33 Bourgeois BFD. Pharmacokinetic properties of current antiepileptic drugs. What improvements are needed? Neurology 2000; 55(Suppl. 3):S11–6.

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

Swiss
Medical Weekly

Official journal of
the Swiss Society of Infectious disease
the Swiss Society of Internal Medicine
the Swiss Respiratory Society

The many reasons why you should choose SMW to publish your research

What Swiss Medical Weekly has to offer:

- SMW's impact factor has been steadily rising, to the current 1.537
- Open access to the publication via the Internet, therefore wide audience and impact
- Rapid listing in Medline
- LinkOut-button from PubMed with link to the full text website http://www.smw.ch (direct link from each SMW record in PubMed)

- No-nonsense submission – you submit a single copy of your manuscript by e-mail attachment
- Peer review based on a broad spectrum of international academic referees
- Assistance of our professional statistician for every article with statistical analyses

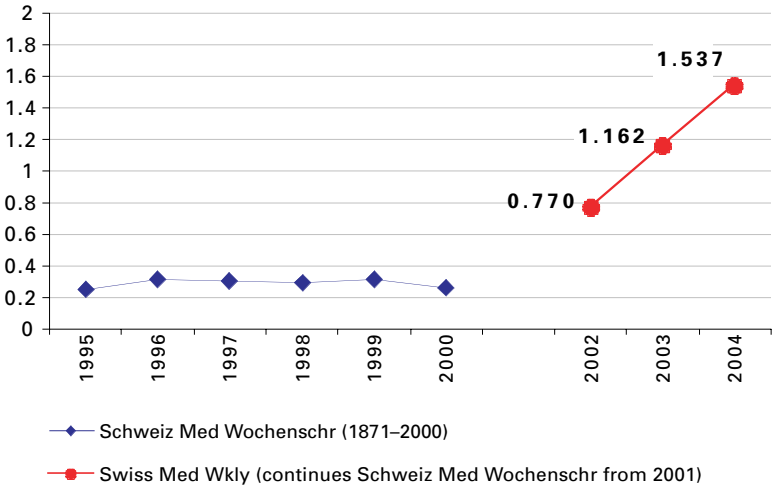
- Fast peer review, by e-mail exchange with the referees
- Prompt decisions based on weekly conferences of the Editorial Board
- Prompt notification on the status of your manuscript by e-mail
- Professional English copy editing
- No page charges and attractive colour offprints at no extra cost

We evaluate manuscripts of broad clinical interest from all specialities, including experimental medicine and clinical investigation.

We look forward to receiving your paper!

Guidelines for authors:
http://www.smw.ch/set_authors.html

Impact factor Swiss Medical Weekly



EMH FMH Schwabe
Editores Medicorum Helveticorum

All manuscripts should be sent in electronic form, to:

EMH Swiss Medical Publishers Ltd.
SMW Editorial Secretariat
Farnsburgerstrasse 8
CH-4132 Muttenz

Manuscripts: submission@smw.ch
Letters to the editor: letters@smw.ch
Editorial Board: red@smw.ch
Internet: http://www.smw.ch