A Neurophysiological and Pharmacological Approach to Correlation of Serum Drug Concentrations with Seizure Control

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Treatment of patients with epilepsy should: a) control seizures and all ictal-associated alterations in cerebral function; and b) prevent transient dose-related toxicity due to excessive levels of antiepileptic drugs (AEDs).

Attempts to find correlations between AED levels and degree of control of seizures in patients with epilepsy have, in general, been unsuccessful because of wide individual variations in AED levels and degree of control (12); such studies produced "desirable therapeutic ranges." Rowan and co-workers (13) have pointed out that, because of wide variations in AED levels in the course of a day, sampling at random times may provide misleading information. Such studies have also not addressed the question of the clinical state of the patient at the time when a single sample was obtained. The term "intensive monitoring" (IM) has been applied to the simultaneous performance of electroencephalograms (EEGs) and video recording of patients. Initially such studies were directed at systematic analysis of ictal behavior and concomitant alterations in EEG, but IM has now been extended to include multiple determinations of AED levels (13,14).

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Such studies have focused largely on types of epilepsy with known strongly coupled electroclinical events, for example, absence seizures. Few studies have addressed the more difficult problem of patients who suffer less frequent but disabling seizures, such as automatisms, and whose EEGs show only infrequent focal interictal spikes (4).

When IM studies have led to alterations in AED regimens, seizures have often been reduced in number and severity (11). At times improvement has been complicated by dose-related toxicity which has not been identified directly by IM. In patients receiving multiple AEDs, such studies have not clearly determined relative efficacy of AED. Indeed, the presence of multiple drugs may defy even statistical analysis of relative efficacy.

Pharmacokinetic models permit calculation of precise dose and interdose intervals to maintain plasma levels between any two arbitrary values (9). In testing patients with epilepsy we propose that the lowest effective level (LEL) be the minimum concentration of an AED which controls seizures and all ictal- associated alterations

of cerebral function, and that the highest tolerable level (HTL) be the maximum concentration of an AED which produces no transient dose-related toxicity. Quantitative behavioral measures are necessary to determine LEL and HTL. To study processing in the cortex, we have used computer-synthesized sparse acoustic stimuli (SAS), which contain certain acoustic features of speech sounds (6,7). In addition to those changes observed during seizures, we have found various, slowly fluctuating alterations in perception of SAS. Some appear to accompany declining or augmenting cortical inhibition (1,3); others appear to signal impaired vigilance (3,5). We have used these to establish HTL and LEL.

DETERMINATION OF DOSE AND INTERDOSE INTERVAL

By whatever route of administration, any drug appears in the plasma as though it were either injected directly or absorbed from some other organ of the body. We shall treat these two models as a) a bolus injection into a vein and b) an entry by absorption from another body compartment. Kinetic models may have more than one compartment represented in the equations. We shall use only the one-compartment model because what is to be illustrated is almost independent of the number of compartments.

Bolus Injection

After a sufficient number of equally spaced bolus injections the amount of drug in the body X, at time t (min, hr, etc.) after most recent injection is

$$X_t = \frac{X_0 e^{-kt}}{1 - e^{-k\tau}} \qquad [1]$$

wherein X_O = dose repeated every τ units of time, k = elimination or dissipation constant, τ = interdose interval, and e = 2.71828 ·

Here we assume LEL and HTL are known and set

$$X_M = \text{HTL} = \frac{X_0}{1 - e^{-k\tau}}$$

$$\qquad [2]$$

$$X_m = \text{LEL} = \frac{X_0 e^{-k\tau}}{1 - e^{-k\tau}}$$

Then interdose interval τ and dose X_O are, respectively,

$$\tau = \frac{\log \dfrac{X_M}{X_m}}{k} \qquad [3]$$

$$X_0 = (X_M)(1 - e^{-k\tau})$$

For this simplified model both are easily determined giving a mathematical guarantee that level of AED within the body is never less than LEL and never greater than HTL.

First-Order Absorption

Absorption prior to appearance in plasma is equivalent to placing a compartment preceding plasma compartment and introducing a bolus (pill) into that compartment. The amount within the body τ units of time after the most recent dose of a long sequence of equally spaced doses is now

$$X_t = \frac{k_a F X_0}{k_a - k} \cdot \left[\frac{e^{-kt}}{1 - e^{-k\tau}} - \frac{e^{-k_a t}}{1 - e^{-k_a \tau}} \right] \quad [4]$$

wherein the additional constants are

F = fraction of X_O absorbed and maintained in active state

k_a = absorption constant in the precursor compartment (sublingual, buccal, stomach, etc.),

and all other constants are the same.

The dose function X_τ after each dose X_O, begins at a minimum X_m, which we take as LEL, and rises to a

maximum X_M, which we take as HTL, at

$$t_m = \frac{1}{k_a - k} \log\left(\frac{k_a(1 - e^{-k\tau})}{k(1 - e^{-k_a\tau})}\right) \qquad [5]$$

and returns to its starting value at $t = \tau$. From Eq. 5 and Eq. 4 we derive

$$X_M(e^{-k\tau} - e^{-k_a\tau}) = X_m[(1 - e^{-k_a\tau})R^{k/(k_a-k)}$$
$$- (1 - e^{-k\tau})R^{k_a/(k_a-k)}]$$
$$\text{where } R = \frac{k(1 - e^{-k_a\tau})}{k_a(1 - e^{-k\tau})} \qquad [6]$$

From Eq. 6 with the help of a computer program, the interdose interval is calculated on a case by case basis. Once r is obtained, however, the dose X_O is immediate from

$$X_0 = \left(X_m \frac{k_a - k}{k_a F}\right) \cdot \left(\frac{1 - e^{-k\tau}}{1 - e^{-k_a\tau}}\right) \qquad [7]$$
$$\times (e^{-k\tau} - e^{-k_a\tau})$$

Additional compartments add terms to the equation for X_t; although numerically cumbersome both t and X_a can still be calculated given X_m and X_m. However, even with single-compartment kinetics, addition of a second and perhaps a third AED introduces complexities that quickly pass from the level of being cumbersome to being practically intractable.

TWO OR MORE DRUGS

Nonreactive

The simplest one-compartment model allows two drugs, neither of which interacts chemically nor competes for binding sites. If such drugs produce similar therapeutic effects, effective quantities may be described formally through a constant multiplier called relative potency, ρ.

If each is injected as per the bolus injection, supra, then Equation 1 holds for each

with the effective dose X_t, being

$$X_t = X1_t + \rho X2_t \qquad [8]$$

wherein both $X1_t$ and $X2_t$ have identical functional forms as found in Eq. 1. They may differ only in elimination constants k_1 and k_2. Should these be known through separate kinetic studies, potency, p, remains to be determined.

Determining ρ requires measuring effects of both drugs and expressing those effects quantitatively so that for the same endpoint reaction $X2$ is equivalent to $pX2$ of $X1$. Equation 8 is then expressed in units *of X1* as a function of time.

However, having obtained ρ allows the clinician to choose between the two drugs, making it unnecessary in many instances to use them in combination. In combinations, AED can interact in unexpected ways; Sackellares and associates (15) have reported 4 cases of stupor induced by use of multiple AEDs.

Capacity-Limiting Doses

Drugs which bind strongly to a plasma protein follow first-order kinetics only if they are present in small concentrations. If concentrations approach or exceed capacity of the carrier system, we must use higher order (nonlinear) equations to characterize kinetics (9). In such cases, LEL and HTL may be close and in the region of "nonlinear" kinetics. This can cause situations in which small overdoses prolong duration of toxicity.

Interactions Between AEDs

Antiepileptic drugs may interact directly or may compete for binding sites and metabolic pathways. From a study involving simultaneous administration of phenytoin and valproic acid, Koch and co-workers (10) have suggested that increased levels of unbound phenytoin probably resulted from displacement from protein-binding sites and inhibition of

metabolism of phenytoin by valproic acid. Although both free and total plasma concentrations may be easily measured, plasma kinetics with multiple AEDs frequently resist even mathematical description.

Consider two drugs which are mutual antagonists and, except in the presence of the other, follow first-order kinetics. Governing equations are

$$dA/dt = -k_a A - k_{ab} AB \qquad [9]$$

$$dB/dt = -k_b B - k_{ba} AB \qquad [10]$$

wherein k_{ab} represents removal of A in the presence of B and likewise k_{ba} for the effect of A on B. If either drug, for example A, is concentrated enough to be near capacity, then the first part of Eq. 9 should be modified and might read

$$dA/dt = -k_a A - k_{ab} AB - VA/(K + A) \qquad [11]$$

As simple as Eqs. 9 through 11 may seem, numerical solutions become intractable. The LEL and HTL cannot be accurately determined with two or more drugs unless their combined kinetics/dynamics are understood. Thus, introduction of a second AED reduces determination of dose and interdose interval to an artistic guessing game.

AED LEVELS AND CORTICAL FUNCTION

We present 2 cases which illustrate HTL and LEL. The patients listen to sets of 12 computer-synthesized SAS which differ systematically along some acoustic dimension. The set consists of randomized sequences of at least 48 presentations. Patients indicate classification of each SAS by a motor act, e.g., pointing. Responses for each set are arranged in contingency tables and tested for departure from homogeneity. We use likelihood ratio chi-squares to measure: a) whether performance differed from chance, and if so, b) whether performance differed from normal (2,8).

Case 1

A 12-year-old boy was unable to remain alert while reading, studying, or watching television despite adequate night-time sleep. Mother and maternal grandfather were similarly afflicted. Patient had neither structural brain disease nor other neurologic defect; he was of above-average intelligence on psychometric testing.

Figure 1 shows the patient's performance over 20-min periods of SAS testing on six occasions. When untreated, the boy's ability to classify consistently set GY fluctuated with vigilance. Probability that performance differs from chance during each of four successive 5-min intervals changed 100-fold ("untreated", upper portion); performance remained within normal limits during only one interval. Classifications during entire period differed significantly from composite of 40 neurologically normal subjects (dotted line, "untreated", lower portion).

Treatment with methylphenidate (Ritalin®) restored and sustained vigilance on a regimen equivalent to 15-mg doses administered sub-lingually at $\tau = 2$ hr. Classifications remained well-defined $(p \leq 0.00005)$, and performance remained within normal limits (methylphenidate in Fig. 1).

In sufficiently high concentration, many compounds acutely impair vigilance or produce somnolence. In Case 1 both patient and mother have experienced recurrent depression. On one occasion the patient's pediatric neurologist treated this with the tricyclic anti-depressant, amitriptyline. Treatment was discontinued because the patient's vigilance became so impaired he could not function effectively.

Testing during 6 weeks of stepped withdrawal disclosed the extent of impaired vigilance to be dose dependent. With 7- fixed at 12 hr, on doses of 10 mg in the a.m. and 30 mg in the p.m., SAS were classified randomly (lower left in Fig. 1). Following
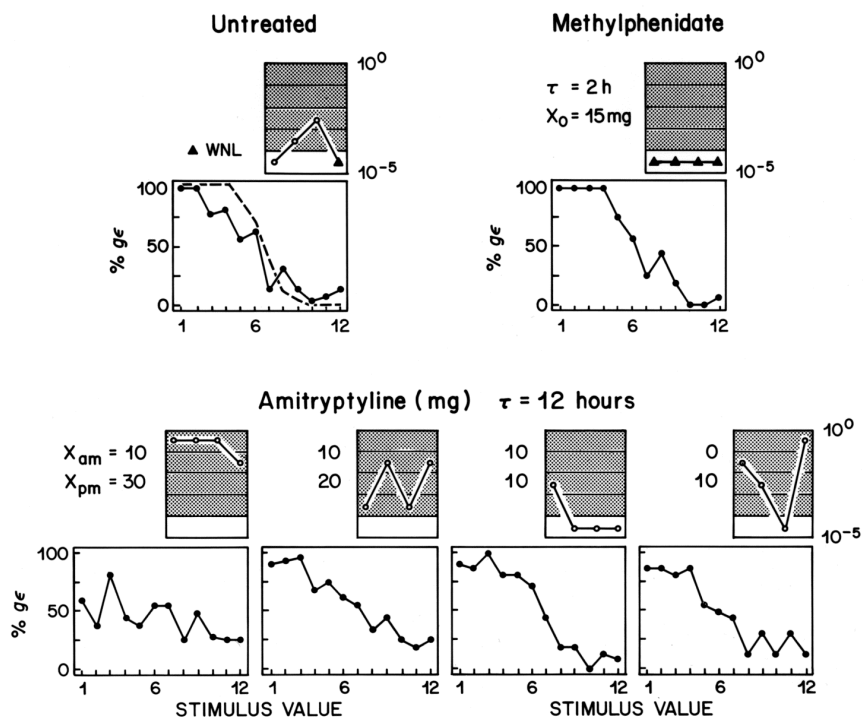
FIG. 1. Case 1: Results of monaural testing with set GY over 20-min periods. Untreated = following 2 months with no medication; methylphenidate = 1 hr following last dose of 20 mg methylphenidate sub-lingual; "amitriptyline" = following dose reduction indicated (a.m. = 0800 hr; p.m. = 2000 hr); $p(X^2 > G^2)$ probability that in each test interval, classification of 4 presentations of 12 stimulus values is at chance levels. %gϵ = percent of stimuli of each value identified as "geh"; ---- = composite performance of 40 normal subjects; WNL = within normal limits.

each 10-mg. reduction in p.m. dose, performance improved more than tenfold. On doses of 10 mg in the a.m. and $\geq$ 10 mg in the p.m. (even when classes were well-defined) performance remained aberrant, as with "untreated."

This patient suffers hereditary impairment of vigilance (narcolepsy). Treatment with amytriptyline, which frequently produces side-effects of somnolence, exacerbated his underlying impaired vigilance in a dose-dependent fashion; treatment with methylphenidate has restored and sustained vigilance in dose-dependent fashion but left depression unaltered.

Case 2

This patient was in apparent good health until age 14, when she suffered a spontaneous subarachnoid hemorrhage. A large left posterior mediofrontal arteriovenous malformation was discovered and subsequently resected. Her first seizure occurred at age 17 and consisted of a sensation of unsteadiness, followed by conscious deviation of head to the right and loss of contact; she was then briefly unable to speak. The patient has since experienced partial seizures with brief arrest of speech, inability to respond if spoken to, or "forgetting" what she

wanted to say. During these episodes her face flushes and her eyelids half close. Electroencephalography has demonstrated primary left-sided 2/sec spike and slow wave discharges, or bilateral multiple spike and slow wave discharges involving frontotemporal regions. Independent right-sided discharges occur occasionally.

Seizures remained refractory on combinations of AED. To determine relative efficacy of AED in her regimen, the patient underwent prolonged monitoring using concurrent cable-telemetered EEG, SAS testing, video monitoring, and periodic sampling for AED levels.

During the 8-hr monitoring study, plasma concentrations of sodium valproate (VPA) and phenytoin (PHT) fluctuated independently (Fig. 2). From an initial value of 64.5 μg/ml, VPA decreased to 37.6 μg/ml at 1100 hr and remained near that level until 1320 hr. The level increased abruptly, reaching

a maximum of 80μg/ml at 1520 hr, then decreased during the remainder of the study. In contrast, PHT increased from an initial value of 13.6 μg/ml to 17.4 μg/ml at 1320 hr. The level decreased to a minimum of 12.3 μg/ml at 1420 hr and remained at that level for the duration of the study.

Figure 2, parts A-E illustrate results of continuous SAS testing with GY over 10-min intervals. With continuing low levels of VPA, despite increasing levels of PHT, performance became increasingly aberrant (Fig. 2, A-C).

With VPA levels > 70 μg/ml, performance became less aberrant, even with minimum PHT level (Fig. 2, D). Despite slightly increased PHT levels, performance deteriorated with lower VPA levels (Fig. 2, E). The nature of changes from A to C and D to E is consonant with diminishing inhibitory functioning. Only with higher levels of VPA did episodes of fixed perception occur.
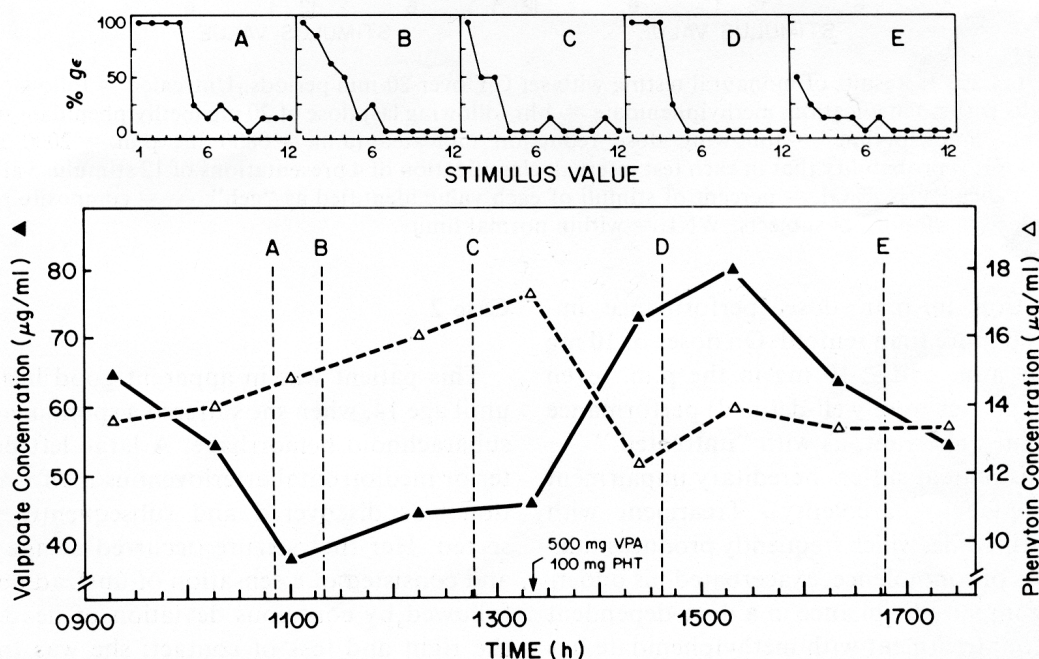

FIG 2. Case 2: Results of monaural testing with set GY over approximately 10-min periods from 8¾ hr prolonged monitoring study. Graphs A through E correspond with center of intervals shown over plasma level determinations: —— sodium valproate; ---- phenytoin concentration (μg/ml); time in hours; 500 mg VPA, 100 mg PHT given at time indicated (before lunch).

Results of the study demonstrated VPA to be the effective drug, and PHT was eliminated from patient's regimen. Following appropriate adjustment of VPA dose and inter-dose interval, the patient's seizures have been controlled. She has remained free of seizures for over 2 years on this regimen.

DISCUSSION

Case 1 demonstrates spontaneous fluctuations in vigilance which alter performance on SAS testing. Administration of a drug which impairs vigilance exacerbates aberrant performance in proportion to dose. Administration of a different drug which alleviates impaired vigilance increases stability of performance in proportion to dose.

Case 2 illustrates behavioral manifestations of changes in cortical inhibitory state which can be used in determining LEL of particular AED or relative efficacy of different AED. This patient's seizures, which had remained refractory despite compound regimens of up to 4 AED, have been controlled effectively for over 2 years using one AED with appropriate dose and interdose intervals. Effective treatment in this case has not required accurate determination of HTL.

We have found that changes in perception of SAS are more pervasive and enduring than interictal electrographic discharges. In Case 2, interictal spikes did not herald consistent behavioral changes nor were they sufficient to account for the more pervasive and enduring alterations in perception of SAS. Surprisingly, however, certain changes in stimulus response latency consistently predicted absence of interictal spikes.

CONCLUSION

Prolonged monitoring using video recording of patient and EEG, continuous testing with SAS and frequent determinations of AED levels permits accurate determination of LEL and HTL. With appropriate quantitative pharmacokinetic models, we believe that effective treatment regimens can be prescribed for individual patients.

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APPENDIX

Dose and interdose interval may be approximated without behavioral testing given: a) LEL and the ratio of HTL to LEL, b) biologic half-life, TD50, and its ratio to the absorption half-life, TA50, and c) Table 1. Within Table 1 the constants C1, C2, and C3 are to be used as follows:

I. Dose by bolus injection:
  Dose   = HTL-LEL
  Interdose interval   = C3 * TD50
II. Dose through absorption:
  Dose   = C1 * LEL
  Interdose interval   = C2 * TD50

For example, consider an AED requiring an LEL of 100 μg, and HTL of 150 μg, with TA50 = 0.5 hr and TD50 = 3 hr.   HTL / LEL = 1.5, and TD50 / TA50 = 6.   Interpolating between TD50 / TA50 = 5.0 and 10 with column HTL / LEL = 1.5, we calculate C1 = 1.10, C2 = 1.21, and C3 = 0.585. Thus, a drug-free patient who received an initial injection of 150 μg, and (0.585)-(3) = 1.76 hr (1 hr 45 min) later begins taking capsules of (1.21)-(100) = 110 μg every 1.21 hr (1 hr 12 min) should remain between an LEL of 100 and an HTL of 150. Such an approach would require, of course, appropriate estimates of HTL, LEL, TA50, and TD50 and careful frequent monitoring of AED levels during treatment.

TABLE 1. *Estimation of dose and interdose interval*

Ratio TD50/TA50		Ratio HTL to LEL				
		1.1	**1.3**	**1.5**	**2.00**	**3.00**
	C1	1.33	2.50	3.46	5.66	9.80
	C2	1.80	3.02	3.80	5.09	6.61
0.5	C3	0.138	0.375	0.585	1.00	1.58
	C1	0.935	1.76	1.43	3.94	6.78
1.0	C2	1.27	2.12	2.66	3.53	4.54
	C1	0.66	1.25	1.73	2.83	4.90
2.0	C2	0.90	1.51	1.90	2.54	3.31
	C1	0.43	0.82	1.15	1.94	3.46
5.0	C2	0.58	0.99	1.27	1.77	2.41
	C1	0.31	0.62	0.89	1.56	2.86
10.0	C2	0.42	0.75	0.99	1.45	2.06

*C1 * LEL is the dose by absorption to be given every C2 * TD50 units of time. C3 * TD50 is the interdose interval of bolus injections of size HTL-LEL, wherein TD50 / TA50 should be ignored, as TA50 = 0, and the ratio is infinite. TD50 is the elimination half-life; TA50 is the absorption half-life; LEL is the lowest effective level (dose); and HTL is the highest tolerable level (dose).*