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Comparison of Anti-Epileptic Drug Levels in Different Cases of Sudden Death*

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ABSTRACT: Sudden unexplained death syndrome (SUDS) in epilepsy is identified as death in an epileptic individual with no anatomic cause found at autopsy. SUDS appears to be associated with subtherapeutic levels of anticonvulsants. Sudden death with no demonstrable cause at autopsy accounts for 5% to 30% of deaths in epileptic individuals. In the majority of cases, however, the cause of death in epileptic individuals can be demonstrated at autopsy. We examined the anti-epileptic drug concentrations in decedents who died as a direct result of epilepsy and compared these findings with those from a control population of epileptic patients who died suddenly due to some unrelated cause. This retrospective study was conducted on all deaths involving patients with epilepsy examined at the Jefferson County Coroner/Medical Examiner office from 1986–95. Out of 115 total cases the underlying cause of death was epilepsy in 60 cases—52 cases of SUDS and 8 deaths caused by an accident precipitated by a seizure. In 44 cases death was unrelated to the decedent's epilepsy. In 11 cases the contribution of epilepsy to death could not be determined. Published articles on SUDS report subtherapeutic anti-epileptic medication levels in 63% to 94% of cases. We found subtherapeutic drug levels in 69% of the 52 cases of SUDS, in 75% of the 8 cases where a seizure precipitated an accident causing death, and in 34% of the control population. The incidence of subtherapeutic anticonvulsants is significantly greater in patients dying as a direct result of their epilepsy than in those dying of an unrelated cause.

KEYWORDS: forensic science, epilepsy, seizure, sudden death, anticonvulsants, forensic pathology

Sudden unexplained death syndrome (SUDS) in epilepsy is identified by Earnest et al. as death due to epilepsy with no anatomic cause found at autopsy (1). SUDS appears to be associated with subtherapeutic postmortem concentrations of anti-epileptic drugs. In a study conducted by Earnest et al. at the Denver General Hospital the postmortem serum anti-epileptic drug concentrations were below therapeutic levels in 35 of 38 patients who died of SUDS (1). According to a review of published studies, sudden death with no demonstrable cause at autopsy accounts for 5% to 30% of deaths in patients with epilepsy (2). Therefore, in 70% to 95% of sudden death among epileptics the cause of death *can* be demonstrated at autopsy. In some epileptic patients death is completely unrelated to their disease, as in a homicidal gunshot wound. Other patients die accidental deaths in which a seizure precipitated the accident. For example, an adult with epilepsy who has drowned in the bathtub and who is not intoxicated has drowned as a consequence of his epilepsy. Whether death was caused by an accident precipitated by a seizure or by SUDS, finding a subtherapeutic concentration of anti-epileptic medication helps to clarify the chain of events that ended in death. Several articles discuss the incidence of subtherapeutic concentrations of anti-epileptic medications in cases of SUDS among epileptics (1–3), but none records the medication levels found in epileptic patients who have died of some cause other than epilepsy. This study compares the incidence of subtherapeutic anti-epileptic drug concentrations in two distinct patient populations: (1) patients who died suddenly as a direct result of their epilepsy, and (2) patients who had epilepsy, but who died suddenly due to some unrelated cause.

Methods

We conducted a retrospective study of all death cases investigated by the Jefferson County Coroner/Medical Examiner Office during the ten years 1986–1995. Cases were identified by a computer search for all individuals in which the cause of death was listed as a seizure and for all cases in which toxicological analysis revealed the presence of an anti-epileptic medication (phenytoin, phenobarbital, carbamazepine, valproic acid, or felbamate). We found 197 cases by this search. We reviewed the investigative reports, autopsy findings, and, when available, hospital records with two criteria in mind: first, whether the decedent had a chronic history of epilepsy, and second, whether the circumstances surrounding death indicated that the decedent died as a direct result of epilepsy. Cases were excluded from further study if:

(1) the decedent received anti-epileptic medication in a hospital as a therapeutic precaution following an acute head injury that led to death in a matter of hours or days;
(2) the decedent took anti-epileptic medication as a prophylactic measure following a remote head injury, but never had a seizure between the time of injury and his death months to years after the injury;
(3) the decedent was an alcoholic whose seizures began after becoming an alcoholic or who most likely died as a result of alcoholic withdrawal seizures; or
(4) no definite history of seizures could be determined due to incomplete history or poor documentation.

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TABLE 1—*Therapeutic concentrations of six anti-epileptic drugs (4).*

Drug	Therapeutic Level (mg/L)
Carbamazepine	4–12
Primidone	5–15
Phenytoin	10–20
Phenobarbital	10–40
Valproate	50–100
Felbamate	not yet available

Based on these criteria we excluded 82 cases from further study, leaving 115 cases of sudden death in patients with epilepsy. The determination of whether an anticonvulsant was within or below the therapeutic range was made using the following therapeutic ranges: carbamazepine 4 to 12 mg/L; primidone 5 to 15 mg/L; phenytoin 10 to 20 mg/L; phenobarbital 10 to 40 mg/L; and valproate 50 to 100 mg/L (listed in Table 1) (4). A therapeutic range for felbamate is not yet available. In cases of combination drug therapy the decedent was considered to have a therapeutic level if any drug was within the therapeutic range.

We next assigned each decedent to one of four categories based on the case history and the autopsy findings: (1) sudden, unexpected death due to the decedent's epilepsy, (2) death due to an accident or injury occurring as a result of a seizure, (3) death unrelated to epilepsy, or (4) unable to determine degree to which epilepsy contributed to death. These categories are in keeping with those listed by Prahlow et al. (5). In order to be assigned to the category of death due to epilepsy, the decedent had to die suddenly and unexpectedly, and epilepsy had to be the most likely cause of death following investigation and examination. We included in the category of death due to epilepsy six decedents who had external examinations only. These six comprised four females (ages 12, 32, 45, and 49 years) and two males (ages 19 and 41 years). All six had had epilepsy for years, and all were found dead in bed or by their bed. The 12-year-old female had therapeutic concentrations of phenobarbital and phenytoin; the other five had subtherapeutic concentrations of anticonvulsants. The eight decedents included in the category of death due to accident as a result of a seizure were either witnessed to have a seizure at the time of the accident or were swimmers who were not intoxicated and who had been alone around water at the time of death. The 44 decedents for whom we considered death unrelated to their epilepsy had died either of demonstrable natural causes unrelated to epilepsy or due to nonnatural means in which epilepsy played no part. Table 2 shows the most common causes of death in the category of death unrelated to epilepsy. Finally, decedents were placed in the undetermined category when the role of epilepsy in causing death was unclear.

TABLE 3—*Comparison of concentration of anti-epileptic medications to underlying cause of death. (Note: The sum of cases in which a seizure did not cause death is one fewer than the 44 cases mentioned above because in one case phenobarbital was detected but not quantified.)*

Underlying Cause of Death	Epilepsy	Other	Undetermined	Total
Therapeutic [AED]*	18	28	4	50
Subtherapeutic [AED]	42	15	7	64
Total	60	43	11	114

*[AED] = concentration of anti-epileptic drug.

In this category were cases where the cause and manner of death remained undetermined after examination. Also included were unwitnessed accidents, such as automobile accidents, where the role of a seizure in causing the driver to have a wreck was unclear.

Statistical analysis was performed with the chi-square test using values stated in Table 3. The ''Epilepsy'' category was compared with the ''Other'' category, which served as the control. The events in the ''Undetermined'' category were excluded from analysis. In order to reject the null hypothesis that there is no relationship between sudden death and anticonvulsant medication levels, we required a probability of less than 5% ($p < 0.05$).

Results

Our search revealed 115 cases in which the decedent had a history of seizure disorder. The ages ranged from 2 months to 83 years with an average age of 38 years. The ratio of males to females was 81:34, and the ratio of white to black was 59:56. The manner of death was reported as natural in 71 cases, accident in 28 cases, suicide in 8 cases, and homicide in 5 cases; in 3 cases the manner remains undetermined. Epilepsy was the underlying cause of death in 60 of the 115 cases. The remaining 55 cases comprised 44 in which the decedents had a history of epilepsy but died by some other means, and 11 in which epilepsy was present but the degree to which it contributed to death was unclear. Table 2 shows the categories into which we divided our cases, with information on the number of autopsy versus external examinations in each category and the most common causes of death.

A review of investigative reports and police reports revealed that approximately 52% of victims who died of epilepsy were found dead in bed. The incidence in our study of recent bite marks or contusions of the tongue suggesting a seizure was 20%. We found grossly evident brain lesions in 38% of our autopsy cases,

TABLE 2—*Summary of categories into which seizure deaths placed. External examinations performed on motor vehicle accident cases, suicidal gunshot wound cases, and burn cases.*

Category	Autopsy/External	Total	Causes and Manners of Death*
Death due to epilepsy	46/6	52	All dead of seizures
Death due to accident due to seizure	7/1	8	5 drowning, 2 MVA, 1 fall from roof
Death unrelated to epilepsy	34/10	44	19 natural (4 cardiomyopathy, 10 ischemic heart disease); 12 accident (2 BFT, 2 drowning while intoxicated, 2 drug overdose, 2 smoke inhalation and burns); 8 suicide (5 GSW, 2 overdose, 1 drowning); 5 homicide (3 GSW, 1 BFT, 1 poisoning)
Contribution of epilepsy to death	4/7	11	5 natural (all undetermined cause); 4 accident (2 BFT, 1 overdose, 1 hypothermia); 2 undetermined manner and cause
undetermined			
Total	91/24	115	

*MVA = motor vehicle accident, BFT = blunt force trauma, GSW = gunshot wound.

the most common of which were old traumatic lesions (11 cases). A variety of other structural lesions were found, including infarcts (6 cases), tumors (5 cases), malformations (4 cases), hypoxic birth injuries (2 cases), and atrophy (2 cases). We found one case each of disarray of cortical lamination, telangiectasia, hippocampal scarring, and encephalomalacia.

Toxicological analysis for anticonvulsant medications was performed in all 115 cases (see Table 3). [Anticonvulsants are sought in blood whenever investigation has revealed that the decedent had a history of seizures. Our toxicologist routinely performs alkaline and acid drug screens by thin-layer chromatography on all cases where urine is available. When these screens reveal a compound, it is confirmed and quantified by gas chromatography/mass spectrometry (GC/MS). When urine is unavailable an enzyme multiplied immunoassay screen for drugs of abuse is performed on bile or blood. When no anatomic cause of death is found, acid and alkaline extracts of blood are subjected to GC/MS as indicated by the case history.] A therapeutic level of at least one anticonvulsant was detected in 64 cases and subtherapeutic levels in 50 cases. In one case phenobarbital was detected but was not quantified; this case was excluded from chi-square analysis. No drugs were detected in 14 cases. In three of the 14 cases the decedent's physician had terminated therapy after a period of no seizures. In 8 of the 14 cases the decedents were noncompliant with recommended therapy. In one case the decedent had never been treated by a physician and was taking no medication for his seizures. It is unknown why the other two decedents were not taking medication to prevent seizures. More than one anti-epileptic medication was detected in 38 cases, 34 cases in which two anti-epileptic medications were detected and 4 cases in which three different medications were detected. In 25 of the combination drug therapy cases we found a subtherapeutic level of at least one of the drugs, and in 11 of the cases all anti-epileptic medications were below the therapeutic level. Chi-square analysis of the 103 cases with toxicological analysis yielded $\chi^2 = 12.5$, which corresponds to $p < 0.005$.

Discussion

In 1964 Freytag and Lindenberg reported a series of 294 medicolegal autopsies on patients with epilepsy (6). The authors found an anatomic lesion that could serve as an epileptogenic focus in 63% of their cases. Hirsch and Martin found anatomic lesions in the brain in 21% of their cases (7). Leestma et al. report finding grossly evident structural lesions in the brain in 60% of their cases (8), and Terrence et al. found structural lesions in 14% of their cases (3). We found grossly evident lesions in 38% of our autopsy cases.

Sometimes the tongue is bitten during the tonic-clonic phase of a seizure. The injury that results may be the only anatomical evidence of a seizure (9). DiMaio and DiMaio report finding bite marks of the tongue in approximately 25% of cases in which death was caused by a seizure (10). Leestma et al. found acute tongue lacerations in 12% of their cases (2). We found tongue lacerations or contusions in 20% of our autopsies on individuals who died as a result of epilepsy in the absence of any other blunt force injury. The diagnosis of sudden unexplained death in those with epilepsy depends upon sound history and appropriate scene findings. Tongue injuries are noteworthy when present, but their scarcity hampers their routine usefulness.

As mentioned in the introduction, Leestma et al. report that SUDS accounts for 5% to 30% of deaths in patients with epilepsy (2). We had an incidence in our medical examiner population of 44%. The greater incidence in our study may reflect a bias in our medical examiner population toward sudden, unexpected death. Because all sudden and unexpected deaths in our county fall under our jurisdiction, we should receive all cases that will eventually fit the description of SUDS. We have no jurisdiction over, and therefore would not see, any epileptic patient who, for example, contracted pneumonia and died of that pneumonia while under a physician's care.

Schwade and Otto report that accidental deaths occurring as a consequence of a seizure account for 17% of deaths in patients with epilepsy (11). Our study found that 7% of our 115 cases of epilepsy patients died an accidental death as a result of a seizure. The most common accident was drowning (5 cases). We inferred that a seizure led to drowning when an adult with epilepsy was found drowned, and toxicological analysis of the decedent's blood failed to detect intoxicants. Two deaths were caused by motor vehicle accidents, and in a single case the decedent fell from a house while working on the roof. In the cases of the motor vehicle accidents, witnesses saw the decedent ''slumped over'' or ''blacked out'' in the driver's seat. The man on the roof was seen to be shaking before he pitched forward off the roof. The time that any one human spends swimming, bathing, driving, or even working on a roof, is only a small fraction of that person's life. If an individual gets 7 hours of sleep per night and spends a total of 1 hour commuting to and from work 5 days per week, then he is nearly 10 times more likely to have a seizure while sleeping than he is while driving, based purely on time involved. This temporal disparity explains why accidental deaths precipitated by seizures are relatively rare.

All 5 epileptic individuals who drowned were alone and in the vicinity of water at the time of their death. Two were taking a bath, two were in a swimming pool, and one was fishing by a lake. The individuals in the swimming pools and the man in the lake all knew how to swim. As has been mentioned by others (12), such deaths could be prevented by always taking a shower rather than a bath and by never being alone around bodies of water. However good such advice may be, it is not always acceptable to some people, so accidental deaths precipitated by seizures, particularly drownings, will continue to occur.

Published articles on SUDS have called attention to the frequent finding of subtherapeutic concentrations of an anti-epileptic medication in patients who die suddenly and unexpectedly as a result of their epilepsy (1–3,7,8,13,14). The incidence of subtherapeutic medication concentrations in these studies ranges from 63% to 94%. In this study the incidence of subtherapeutic drug levels was 69% of 52 cases that fit the criteria for SUDS. The distribution of deaths according to anticonvulsant blood concentration is made clear in Fig. 1. Similarly, 6 of the 8 patients with epilepsy who died accidentally as a consequence of a seizure had a subtherapeutic concentration of anti-epileptic medication. In the control population of epileptic patients who died of a cause unrelated to epilepsy, the incidence of subtherapeutic drug levels was 34%. Comparisons of the SUDS cases to the control population are shown in Figs. 2 and 3 and in Table 4. The concentrations of phenobarbital and phenytoin shown in Figs. 1–3 are noteworthy. Although the lower end of the therapeutic range for both drugs is 10 mg/L, it seems clear that a level of 9.8 mg/L is more likely to be of some medical benefit than a level of 1.2 mg/L. In order to indicate this difference we divided the subtherapeutic range in Figs. 1–3 into those blood levels less than 5 mg/L and those from 5.0 to 9.9 mg/L. For both phenobarbital and phenytoin the number of deaths in those with very low subtherapeutic levels is far greater than for any other range of drug levels, primarily owing to those decedents in whom

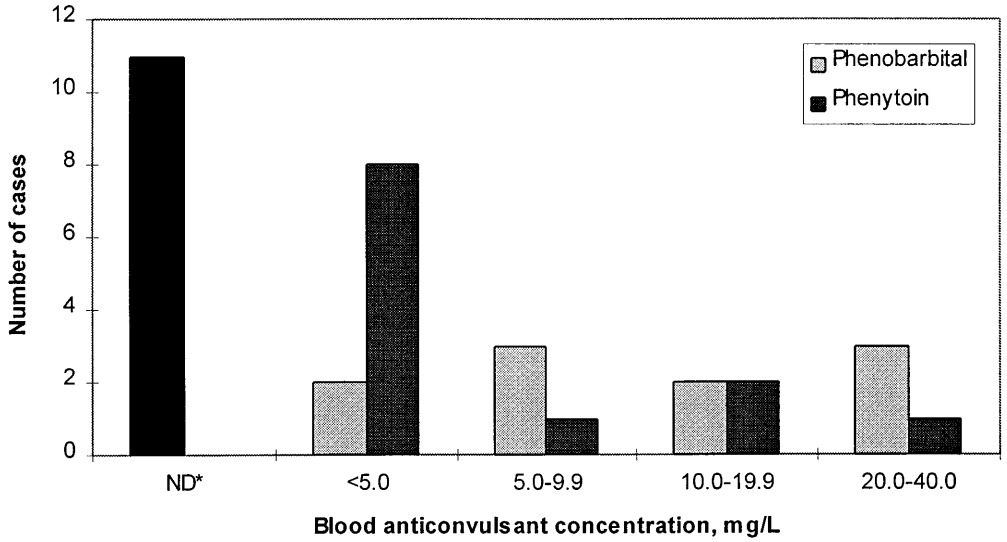

FIG. 1—*Comparison of SUDS deaths according to drug levels in cases of anticonvulsant monotherapy. *ND = not detected.*

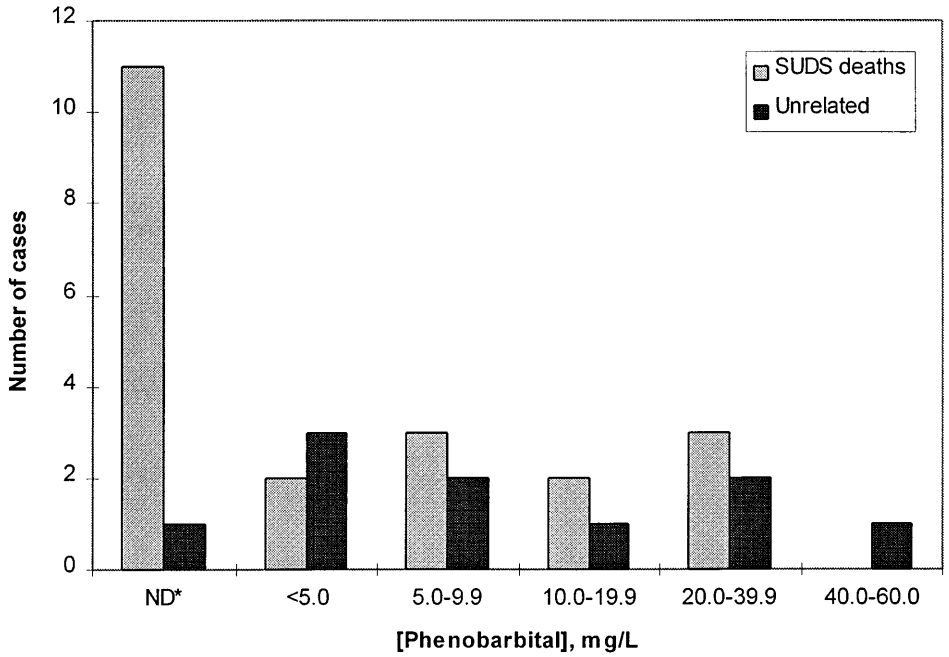

FIG. 2—*Incidence of various phenobarbital concentrations (monotherapy) in cases of sudden unexplained death syndrome and in deaths unrelated to an epileptic seizure. Note that the same 12 cases appear in the ND* = not detected column in Tables 2 and 3.*

no anticonvulsant was detected. It is interesting that the number of deaths in those decedents with very low subtherapeutic levels who died of unrelated causes is neither appreciably greater nor smaller than the number with any other range of drug levels. The existence of decedents with very low subtherapeutic drug levels whose deaths are unrelated to epilepsy suggests that some factor other than drug level is involved in causing sudden death.

Schwender and Troncoso report that phenobarbital appears ineffective at preventing sudden death in epileptics (13). These authors found that 8 of 15 decedents taking phenobarbital for seizure control died suddenly despite having a therapeutic level of phenobarbital. In contrast, Schwender and Troncoso found that only 2 of 11 decedents whose seizures were controlled by phenytoin died suddenly despite a therapeutic level of phenytoin. We did not find such a striking difference in our population. Nine of 22 decedents taking phenobarbital died despite a therapeutic level of drug, compared with 10 of 30 taking phenytoin.

The diagnosis of sudden, unexpected death due to epilepsy is a diagnosis of exclusion. As in the sudden infant death syndrome, any anatomical, toxicological, or scene finding that accounts for death precludes a diagnosis of SUDS. Conversely, when an otherwise healthy epileptic is found dead in the absence of any other cause of death, the death might properly be considered SUDS even if a therapeutic concentration of anti-epileptic medication is present. The justification for a diagnosis of SUDS in a patient with a therapeutic concentration of anti-epileptic medication is that a seizure can break through the chemical restraint at any time. But what is a therapeutic concentration of a medication? Porter, in a 1992

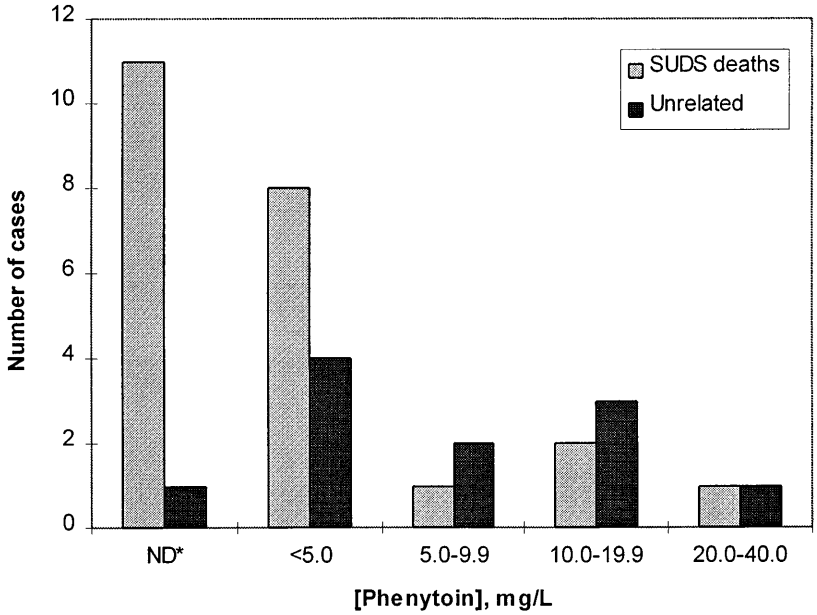

FIG. 3—*Incidence of various phenytoin concentrations (monotherapy) in cases of sudden unexplained death syndrome and in deaths unrelated to an epileptic seizure. Note that the same 12 cases appear in the *ND = not detected column in Tables 2 and 3.*

TABLE 4—*Drug concentrations in cases of dual therapy with phenobarbital and phenytoin.*

No.	Category	[Phenobarbital], mg/L	[Phenytoin], mg/L
1	Death due to epilepsy	2.7	0.8
2	Death due to epilepsy	4	6
3	Death due to epilepsy	4.9	<2.5
4	Death due to epilepsy	6.2	2.5
5	Death due to epilepsy	10	<5
6	Death due to epilepsy	10	5.7
7	Death due to epilepsy	10	15
8	Death due to epilepsy	17.5	5
9	Death due to epilepsy	19	1.9
10	Death unrelated to epilepsy	<5	12.9
11	Death unrelated to epilepsy	5.2	5.7
12	Death unrelated to epilepsy	7.6	2.7
13	Death unrelated to epilepsy	8	1
14	Death unrelated to epilepsy	12	4.3
15	Death unrelated to epilepsy	12	28
16	Death unrelated to epilepsy	12.6	4.4
17	Death unrelated to epilepsy	16.5	<5
18	Death unrelated to epilepsy	25	18
19	Death unrelated to epilepsy	29	7
20	Death unrelated to epilepsy	34	trace
21	Death unrelated to epilepsy	46	16
22	Death unrelated to epilepsy	49.4	17
23	Death unrelated to epilepsy	50	6.3

review of current medical therapy of epilepsy, makes several pertinent points (4). He says that blood levels of anticonvulsants should serve clinicians as a guide. One must always treat the patient and not the levels. Each patient has his own optimal concentration of anti-epileptic medication. It is possible that a given patient's seizures will be controlled with a drug concentration that is below the stated therapeutic range. Increasing the dose of anti-epileptic medication to bring such a patient into the published therapeutic range serves only to increase the chance of dose-related toxicity. On the other hand, another patient may require an anti-epileptic medication concentration greater than the upper limit of the published therapeutic range in order to achieve seizure control. Porter's discussion is addressed to clinicians, but his points are apropos for forensic pathologists. Even in the face of a subtherapeutic drug concentration, we do not make a diagnosis of SUDS when an alternative explanation for death is present. Likewise, in the presence of an appropriate history and setting for SUDS, we should not be deterred from the diagnosis by finding a therapeutic concentration of anticonvulsant in the blood.

Conclusions

We found that the incidence of subtherapeutic concentrations of anti-epileptic medications is significantly greater in patients dying as a direct result of epilepsy than in a control population of patients with epilepsy who died of unrelated causes. Nevertheless, both groups contain some individuals with therapeutic drug levels and others with subtherapeutic drug levels. The diagnosis of sudden, unexpected death due to epilepsy is a diagnosis of exclusion. Like the sudden infant death syndrome, any anatomical, toxicological, or scene finding that accounts for death precludes a diagnosis of SUDS. In a given case, the concentration of an anti-epileptic medication must be interpreted by using clinical judgment while weighing the other facts concerning the case.

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