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Premature Deaths in Persons with Seizure Disorders—Subtherapeutic Levels of Anticonvulsant Drugs in Postmortem Blood Specimens

The purpose of this paper is to point out the possibility of death occurring prematurely in epileptics from apparently inadequate anticonvulsant therapy. Moreover, the information may be useful to the forensic pathologist faced with the "difficult autopsy" [*1*] where no definite cause of death is found. Toxicology is most useful in demonstrating deaths resulting from overdoses. However, subtherapeutic or negative anticonvulsant drug levels in a known epileptic may have equal usefulness in establishing a probable cause of death. The potential problem for the pathologist may be emphasized if he realizes there are approximately 1.7 million epileptics living in the United States today [*2*]. Rarely does the death of an epileptic make headlines in a major newspaper.

Methods and Materials

Eleven cases of unattended, unexpected deaths in epileptics were taken from the El Paso County Coroner's Office in Colorado from January 1975 through December 1976. Toxicologic studies on bile, blood, urine, gastric contents, and vitreous humor augmented the postmortem examinations. A pathologist or deputy coroner, or both, visited the death scene in each case. Types of medications present at the scene were noted. Physicians who had prescribed the anticonvulsant drugs were contacted to confirm the diagnosis of epilepsy in each case. However, precise information concerning the amount of anticonvulsant drugs prescribed by the physician was not available.

Discussion

The four classes of anticonvulsant drugs and their clinical uses are presented in Table 1 [*3,4*]. Primidone is included with the barbiturates only because the parent compound metabolizes to phenobarbital and the metabolite exerts the principal anticonvulsant effect. Phenytoin and phenobarbital remain the most common anticonvulsants encountered in our toxicology laboratory. Diazepam, used more frequently for treatment of status epilepticus, is occasionally encountered [*3*].

To appreciate the significance of the anticonvulsant blood levels found at postmortem

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TABLE 1—Major anticonvulsant drugs and therapeutic use.

Drug	Use
Barbiturates	
Phenobarbital (Luminal®)	primarily for grand mal and focal cortical seizures; symptomatic seizures
Mephobarbital (Mebaral®)	
Primidone (Mysoline®)[a]	
Hydantoins	
Phenytoin (Dilantin®)	primarily in grand mal and psychomotor epilepsy; symptomatic seizures
Mephenytoin (Mesantoin®)	
Succinimides	
Phensuximide (Milontin®)	primarily petit mal; Celontin in psychomotor seizures
Methsuximide (Celontin®)	
Ethosuximide (Zarontin®)	
Iminostilbenes	
Carbamazepine (Tegretol®)	psychomotor epilepsy

[a] Metabolizes to phenobarbital.

in these cases, a list of half-life and steady state data is given in Table 2. Phenytoin half-life is dose-dependent. The low concentration has a half-life of only 7 to 42 h, but the high concentration of phenytoin has a half-life of 2 to 5 days. A steady state with uniform serum phenytoin levels is achieved in 2 to 5 days with the low dose and 10 to 15 days with the high dose. Children achieve a steady state with phenobarbital and ethosuximide faster than adults. However, the half-lives of these two drugs in children are only approximately 50% of the half-lives in adults. The need for monitoring serum levels in clinical practice with young epileptics is therefore very important. The published serum half-life values for diazepam are unusually long in our experience. The half-life for serum diazepam following intravenous administration is about 3 to 4 h.[2] Clinical effects of diazepam may persist for 12 to 24 h, however.

An example of a serum anticonvulsant drug report form is showed in Table 3. Phenytoin and phenobarbital have a fairly wide margin of safety. Therapeutic levels are readily available for each drug. The toxic levels are generally available only for phenytoin, phenobarbital, and diazepam.

Results

Table 4 summarizes the autopsy finding in the eleven cases of unexpected death in epileptics. The most common indicator of epilepsy was historical or death scene evidence of epilepsy. Scene findings suggested epilepsy in all cases. Gingival hyperplasia was found in two of the eleven cases (18%). Trauma to lips, tongue, and face was supportive evidence of seizures and was noted in nine of the eleven cases (82%). Brain abnormalities were noted in only three cases (27%). Two cases showed sclerosis of Ammon's horn and one case showed postoperative cystic infarct of the temporal lobe. The cause of death was acute pulmonary and cerebral edema secondary to terminal seizures in six of the eleven cases (55%). Cases 6, 7, and 11 drowned in freshwater pools or a bathtub. Cases 2 and 3 aspirated gastric contents.

Table 5 lists the drug levels of anticonvulsant drugs found at autopsy in this group of epileptics. Interestingly, 36% (four of the eleven cases) showed no anticonvulsant drugs at postmortem and 55% (six cases) showed subtherapeutic blood levels of one or both anticonvulsant drugs. One case showed a high blood level of ethanol (0.21% w/v). Only one case (Case 9) showed a therapeutic level of anticonvulsant medication, that is, primidone (0.4 mg/dl) and phenobarbital (2.7 mg/dl).

[2] Unpublished information, St. Francis Hospital Toxicology Laboratory, February 1977.

TABLE 2—*Half-lives and steady states of anticonvulsant drugs* [4].

Drug	Half-Life[a]	Steady State Achieved by
Phenytoin (Dilantin)	dose-dependent: low concentration 7-42 h; high concentration 2-3 days	dose-dependent: low concentration 2-5 days; high concentration 10-15 days
Methsuximide (Celontin)	2-4 h	not available
Ethosuximide (Zarontin)	48-72 h (A) 24-48 h (P)	10-15 days (A) 5-10 days (P)
Primidone (Mysoline)	3-19 h (A)	4-7 days (A)
Phenobarbital (Luminal)	2-6 days (A) 1.5-3 days (P)	2-3 weeks (A) children less than adults
Carbamazepine (Tegretol)	12-17 h	2-4 days
Diazepam (Valium)	2-3 h	not available

[a]A = adult and P = pediatric.

TABLE 3—*Anticonvulsant report.*

Drug Level	Amounted Noted	Therapeutic Level	Toxic Level
Phenytoin (Dilantin)	_____mg/dl	0.6-1.7	2-5
Methsuximide (Celontin), as *N*-desmethylmethsuximide	_____mg/dl	1.0-4.0	...
Primidone (Mysoline)	_____mg/dl	0.2-1.2	...
Phenobarbital (Luminal)	_____mg/dl	1.5-4.0	4-6
Carbamazepine (Tegretol)	_____mg/dl	0.2-1.0	
Diazepam (Valium)	_____mg/dl	0.05-0.25	0.5-2.0
Ethosuximide (Zarontin)	_____mg/dl	4-6	...
Other	_____mg/dl	...	...
Other	_____mg/dl	...	...

TABLE 4—*Autopsy data in eleven cases of unexpected death in epileptics.*

Observations	Number	Percentage
History- or scene-indicated epilepsy	11/11	100
Gingival hyperplasia	2/11	18
Injuries involving lips, tongue, head	9/11	82
Central nervous system abnormalities	3/11	27
Cause of death		
Acute cerebral and pulmonary edema, secondary to terminal seizure	6/11	55
Asphyxia, secondary to drowning	3/11	27
Asphyxia, secondary to aspiration of gastric contents	2/11	18

The group of epileptics investigated for this report had a fairly broad age range of 44 years, extending from age 10 to 54 years, with a median age of 31 years. The ratio of men to women in this series is approximately equal (6:5). Most cases were in the second, third, and fourth decades (eight cases). The data are outlined in Table 6.

TABLE 5—*Postmortem toxicological data in eleven cases of epilepsy; blood levels in mg/dl.*[a]

Case	Dilantin	Phenobarbital	Others	Blood Alcohol
1	0	0	negative	0
2	0.4	0.1	negative	219
3	0.6	0.9	negative	0
4	9	trace	negative	0
5	0.2[b]	0.6	negative	0
6	0.3	0.7	negative	0
7	0.3	1.5	negative	0
8	0	0	...	0
9	0.0	2.7	0.4 (mysoline)	0
10	0	0	negative	0
11	0	0	negative	0

[a] Note: 4/11 or 36%—no anticonvulsant drugs; 6/11 or 55%—subtherapeutic levels.
[b] Dilantin detected in gastric contents also.

TABLE 6—*Age and sex data for eleven epilepsy cases.*

Age range, years	10-54
Median age, years	31
Male/female ratio	6:5
By decade	8 of 11 cases in second, third, or fourth decade

It is difficult to explain these premature deaths and low anticonvulsant drug concentrations in epileptics. Some of the reasons for individual differences in drug responses are described in Table 7. Noncompliance or failure of the patient to follow physicians' orders concerning anticonvulsant medications is probably the most common reason. Personality changes, drowsiness, fatigue, and lack of mental acuity resulting from anticonvulsant medications are common complaints of epileptic patients. Certainly the bioavailability and formulation of the drug as it is taken by the epileptic affects the serum levels. Underlying diseases and variations in absorption, distribution, metabolism, and excretion because of heredity may also influence an individual's response to anticonvulsant drugs.

Summary

Eleven autopsy cases from a Colorado coroner's service are presented in which postmortem levels of anticonvulsant drugs were subtherapeutic. Scene investigation or medical history, or both, revealed evidence of epilepsy in all eleven cases. Five of the deaths (three drowning and two with aspiration of gastric contents) occurred during a suspected seizure. The six remaining deaths were attributed to asphyxia associated with terminal

TABLE 7—*Individual differences in drug response.*

A. Secondary to inherited or acquired variations in drug disposition, that is, absorption, distribution, metabolism, and excretion
B. Secondary to underlying disease with low renal clearance, hepatic failure, congestive heart failure, and so forth
C. noncompliance with physician's instructions
D. varying bioavailability of the drug as administered

seizures. Because anatomic evidence of epilepsy is often minimal and nonspecific, the authors think that levels of anticonvulsant drugs should be determined in cases of sudden unexpected death with a history of epilepsy. It is probable that these eleven deaths were preventable with better patient motivation and compliance with the physicians' orders. Many epileptic patients fail to take their medications as directed because of the undesired side effects. Lower doses of anticonvulsant drugs could reduce the degree and number of unwanted side effects and encourage patient compliance. Therefore, careful monitoring of serum anticonvulsant levels during the life of the patient might permit lower but still adequate drug levels with fewer adverse effects and hence encourage the epileptic to comply with the doctor's orders, take his medication, and live.

References

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