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review

Clinical Pharmacology of Anti-epileptic Drugs: A Summary of Current Information

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This compendium represents what we believe to be the most current and reliable pharmacological data on anticonvulsant drugs. The information presented is derived from determinations of the drugs in plasma or serum by gas–liquid chromatography in studies of the efficacy of anti-epileptic agents. We present information on the limitations of therapeutic concentration ranges, half-lives, active and inactive metabolites, and structure/activity relationships of anticonvulsant drugs. This report provides answers to many of the questions clinicians direct to anticonvulsant-monitoring laboratories. Information on other pharmacological variables supplements this review in the interest of the clinical investigator.

Additional Keyphrases: *drug assay · monitoring therapy · treatment with anticonvulsants*

The evidence that anticonvulsants exert their therapeutic effects at biological sites in the brain still remains empirical. The plasma is a readily obtainable body fluid for use in the practical measurement of anticonvulsant concentrations at their active site(s). Since almost all of the anticonvulsant drugs listed here accumulate as parent or metabolite during chronic administration, the stable concentrations in plasma should be in equilibrium with the drug at its active site(s).

With the advent of gas–liquid chromatography in clinical studies of this group of drugs, a positive relationship between the concentrations of several anticonvulsants in the plasma and their efficacy in seizure control has been demonstrated. Consequently, many clinical laboratories now provide measurements of anticonvulsant drug concentrations in plasma (or serum), as evidenced in the Antiepileptic Drug Quality Control Program, a cooperative service of the Department of Neurology at the Columbia University College of Physicians and Surgeons and the Epilepsy Foundation of America, which listed 407 voluntary laboratories as of January 1, 1977. This program was instituted when a survey was made of clinical laboratories and it was concluded that interlaboratory variability of plasma anticonvulsant drug concentrations was unacceptable (*1*). Since this program was instituted it appears that laboratories are becoming more reliable in assaying this particular class of drugs and are therefore adding significantly to the treatment of epilepsy in man.

Success with anticonvulsants in the treatment of seizure disorders depends upon an understanding of their pharmacological properties and actions (*2*). With the increase in reliability of measuring anticonvulsant drugs in the blood and the important role of such measurements in the treatment of seizure disorders, we decided that a single reference to the most current and reliable pharmacologic parameters would prove valuable to laboratory and clinical investigators. We frequently receive calls in our laboratory in the Epilepsy Center from clinicians and clinical investigators requesting specific pharmacological data, the concentrations to be expected or sought in plasma, metabolites, etc., for this particular drug group. Several researchers in clinical and laboratory settings have presented reliable and reproducible data in independent assessments analyzing the efficacy of anti-epileptic medication and correlations with concentrations in plasma. Various reviews (*2–4*) of these clinical and pharmacological investigations have contributed information for this compendium. Gaps or omissions in the tables signify either unavailable data or results that are questionable or supported by too few observations. Select information on the more obscure drugs is presented in the interest of clinical investigators.

The information in Table 1 on ranges for therapeutic concentrations of drugs in plasma is derived primarily from analysis by gas–liquid chromatography. The use of therapeutic ranges has been extensively discussed (*5*), especially when physicians place more emphasis on the analytical values than on an individual patient's clinical status. Such ranges are no guarantee of seizure control but merely provide the best estimate as to an optimal range for a heterogeneous seizure population. Because seizures represent a graded phenomenon, individual variations will exist, and patients with high drug concentrations in their plasma may continue to have seizures while others improve with concentrations that are below what is currently considered to be the therapeutic range.

Drugs and their metabolites listed under the "Therapeutic plasma concentration range" heading of Table

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Table 1. Pharmacological Aspects of Anticonvulsant Drugs in Patients with Epilepsy

Generic (and U. S. trade) name	Daily dose adult, mg	Form	Therapeutic plasma concn range, mg/liter	Plasma half-life[a] adult, h	Peak time, h	References
Phenytoin Dilantin®	200–600	30-, 100-mg capsules; 30-, 125-mg/5 ml suspension; 50-mg Infatabs	10–20 (30)	24 ± 12	4–8	*2, 3, 4, 8*
Mephenytoin Mesantoin®	300–700	100-mg tablets	mephenytoin metabolite: Nirvanol®: 15–40 (total = mephenytoin + Nirvanol®)	mephenytoin: 34 Nirvanol®: 72		*8, 9*
Ethotoin Peganone®	2000–3000	250-, 500-mg tablets	15–50	3–9	1–2	*8, 10, 11, 12, 13*
Phenobarbital Luminal®	60–300	16-, 32-mg tablets	10–30	96 ± 12	6–18	*3, 8, 14*
Mephobarbital Mebaral®	120–600	32-, 50-, 100-, 200-mg tablets	mephobarbital metabolite: phenobarbital: 10–25 (30)	mephobarbital: 24–45 phenobarbital: 48–144		*2, 4, 8*
Metharbital Gemonil®	200–300	100-mg tablets	metharbital metabolite: barbital			*8, 14*
Primidone Mysoline®	500–1500	50-, 250-mg tablets; 250-mg/5 ml suspension	primidone: 5–15 metabolite: phenobarbital: 10–30 phenylethylmalonamide	primidone: 12 ± 6 phenobarbital: 48–144 PEMA: 20–40	3.2 ± 1.0	*2, 3, 8, 14*
Carbamazepine Tegretol®	600–1800	200-mg tablets	carbamazepine: 6–12 metabolite: 10, 11-epoxycarbamazepine	12 ± 3 (chronic) 36 ± 15 (initial)	2–6	*2, 3, 4, 8*
Phenacemide Phenurone®	1500–5000	500-mg tablets				*8*
Methsuximide Celontin®	600–1800	150-, 300-mg capsules	metabolite: desmethyl-methsuximide: 10–40	methsuximide: 2.6 desmethyl-: 36–45	<3	*4, 8, 14*
Ethosuximide Zarontin®	500–2000	250-mg capsules; 250-mg/5 ml syrup	40–100	24–72	2–3	*2, 3, 4, 8*
Phensuximide Milontin®	2000–4000	250-, 500-mg capsules; 300-mg/5 ml suspension	phensuximide	4	1–4	*8, 14*
Clonazepam Clonopin®	1.5–20	0.5-, 1-, 2-mg tablets	0.005–0.050	22–33	1–2	*4, 15*
Diazepam Valium®	6–30	2-, 5-, 10-mg tablets	diazepam: >0.6 metabolite: desmethyl-diazepam: >1.0	diazepam: 24–48 desmethyl-: 24–48	diazepam: 1–2 desmethyl-: 24–48	*2, 8, 16*

(Continued)

Table 1. *(Continued)*

Generic (and U. S. trade) name	Daily dose adult, mg	Form	Therapeutic plasma concn range, mg/liter	Plasma half-life[a] adult, h	Peak time, h	References
Clorazepate Tranxene®	15–60	3.75-, 7.5-, 15-mg capsules; 22.5-mg tablets	metabolite: desmethyldiazepam: >1.0	desmethyl-: 24	desmethyl-: 1	*17*
Chlordiazepoxide Librium®	20–60	5-, 10-, 25-mg capsules; 5-, 10-, 25-mg tablets	metabolite: desmethyldiazepam			*8*
Trimethadione Tridione®	600–1800	300-mg capsules; 150-mg dulcet tablets; 40-mg/ml solution	trimethadione metabolite: dimethadione: >700	trimethadione: 12–24 dimethadione: 144–312	trimethadi-one: 0.5–2 dimethadione: 120–240	*2, 4, 8*
Paramethadione Paradione®	600–1800	150-, 300-mg capsules; 300-mg/ml solution	paramethadione metabolite: ethyl-methyl-oxazolidinedione			*8*
Acetazolamide Diamox®	500–1000	125-, 250-mg tablets; 500-mg capsules	10–14	4–10	2–3	*8, 14*
Sodium valproate Depakine®,[b]	1000–1600	200-mg tablets; 200-mg/5 ml syrup	50–100	7–9	1–4	*18*
Diazepam Valium®,[c]	5–10 (i.v.) (can be repeated)	5-mg/ml ampuls vials	1.0 at peak 0.1 — 0.5 at 15–20 min after injection	0.25		*8, 16*

[a] Elapsed time for the plasma concentration to plateau (steady state) is five half-lives for most drugs (*19*).
[b] Not presently available in the United States.
[c] Drug of choice in status epilepticus (*20*).
Note: Values in parentheses represent differences of opinion.

1 are found in plasma and have anticonvulsant properties (*2*). In some cases only the parent drug is assayed, as with phenytoin and phenobarbital; in other cases, only the metabolite is of clinical significance, as is the case for methsuximide, trimethadione, and clorazepate. A combination of parent drug and metabolite concentrations is measured in the case of mephenytoin. Concentrations in plasma are listed for parent drug or metabolites, or both (*2*) if they are known, and if clinical evaluation has suggested a therapeutic range. Some drugs or their metabolites for which there is no information on ranges are listed; this is because of their apparent anticonvulsant activity and their possible role in the composite anticonvulsant properties of a particular drug. Drugs or metabolites that have been determined not to be clinically significant are not listed—for example, methsuximide or oxazepam, a metabolite of diazepam and clorazepate.

The biological half-life data in Table 1 was accumulated from studies in epileptic patients on chronic, single-drug regimens. Drug interactions during combination therapy that result in deviations from the stated half-lives and concentrations in serum have been documented (*6*) but are too numerous and complex to include in these tables. Differences existing between half-lives after single vs. chronic dosing have been documented with carbamazepine (*7*), but remain speculative for others. Common to almost all of the anticonvulsants listed here is their long biological half-life. This makes it possible to attain stable concentrations in plasma in chronic dosing and contributes to the effectiveness of these drugs in seizure control.

Table 2 summarizes the metabolites derived from the major anti-epileptic drugs in human volunteers or patients. Although many of the metabolites have no anticonvulsant effect, measurement of some has been useful in assessing reliability of drug intake, completeness of absorption, or abnormalities in metabolism, as with *p*-hydroxydiphenylhydantoin, a metabolite of phenytoin that appears in the urine.

The similarity of the heterocyclic ring structure in most of the anti-epileptic drugs is apparent in Figure 1. In attempts to correlate chemical structure with anticonvulsant selectivity, it appears that aromatic sub-

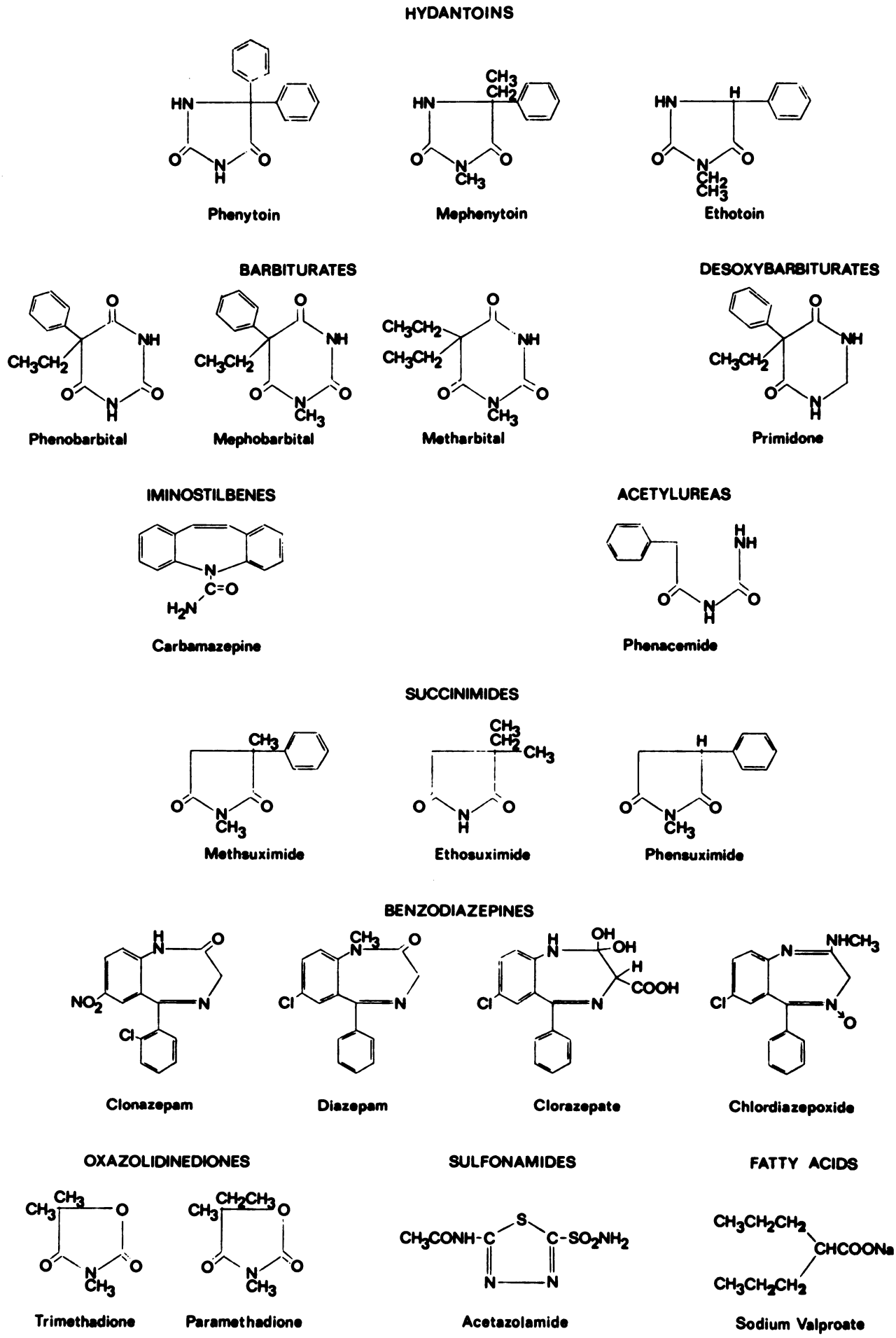

Fig. 1. Chemical structures of the anti-epileptic drugs

Table 2. Pharmaco-chemical Classification of Anticonvulsants and Their Metabolites

Parent drug	Metabolites
Hydantoins	
Phenytoin	*p*-OH-phenylphenylhydantoin[a]
	m-OH-phenylphenylhydantoin[a]
	dihydrodiol
	hydantoic acid
Mephenytoin	5-ethyl-5-phenylhydantoin (Nirvanol)[b]
	p-OH-phenylethylhydantoin[a]
Ethotoin	5-phenylhydantoin
	5-(*p*-hydroxyphenyl)hydantoin
	3-ethyl-5-(*p*-hydroxyphenyl)hydantoin
	2-phenylhydantoic acid
Barbiturates	
Phenobarbital	*p*-OH-phenobarbital[a]
Mephobarbital	phenobarbital[b]
	p-OH-phenobarbital[a]
Metharbital	barbital[b]
Desoxybarbiturates	
Primidone	phenobarbital[b]
	phenylethylmalonamide[b]
	p-OH-phenobarbital[a]
Iminostilbenes	
Carbamazepine	10,11-epoxycarbamazepine[b]
	others unidentified
Acetylureas	
Phenacemide	*p*-OH-phenacemide[a]
Succinimides	
Methsuximide	*N*-desmethylmethsuximide[b]
Ethosuximide	OH-ethosuximide
	others unidentified
Phensuximide	3-methyl-*p*-OH-phenylsuccimide
	others unidentified
Benzodiazepines	
Clonazepam	7-amino derivative
	7-acetyl amino derivative
	3-OH-clonazepam
Diazepam	*N*-desmethyldiazepam[b]
	Oxazepam[b]
	3-OH-diazepam
Clorazepate	*N*-desmethyldiazepam[b]
	Oxazepam[b]
Chlordiazepoxide	*N*-desmethylchlordiazepoxide[b]
	Demoxepam[b]
	N-desmethyldiazepam[b]
Oxazolidinediones	
Trimethadione	dimethadione[b]
Paramethadione	5-ethyl-5-methyl oxazolidinedione[b]
Sulfonamides	
Acetazolamide	none
Fatty acid salt	
Sodium valporate	

[a] Metabolite demonstrated to have no or negligible anticonvulsant activity. OH: hydroxy.

[b] Metabolite known to have significant anticonvulsant activity.

stitution is essential for anti-epileptic effects in certain seizure types. Many of the active metabolites in the plasma arise by *N*-demethylation and are found in much higher concentrations than are the parent drugs after chronic administration. The hydantoins and most of the barbiturates are inactivated by hydroxylation on the aromatic ring and subsequent complete or parital conjugation.

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