

**BARBITURATES FOR TREATMENT OF EPILEPSY**

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Barbiturates in the brain. Barbiturates have their primary actions on the GABA_A receptor, but they also interact with glutamate receptors and voltage-gated ion channels. Because of the impressive recent advances in molecular biology techniques, our understanding of the GABA receptor and the actions of barbiturates on the central nervous system is likely to be significantly improved in the next decade. Barbiturates are a large class of drugs, consisting of many different brand name products with generic equivalents that are used primarily for mild sedation, general anaesthesia, and as a treatment for some types of epilepsy. From their introduction into clinical practice at the beginning of the 20th century until recent years,

Key words: barbiturates, epileptic seizures, bipolar disorder

INTRODUCTION:

Barbiturates have historically played an important role in the treatment of a variety of disorders, including anxiety disorders, sleep disorders, seizure disorders and muscle spasm, and they have proven useful in anaesthesia and in localizing brain dysfunction prior to neurosurgery. Although their use in clinical practice has mostly been replaced by the safer benzodiazepines, they are still used in certain clinical situations. Recently, major advances have been made in our understanding of the receptor mechanisms and molecular pharmacology underlying the actions of barbiturates in the brain. Barbiturates have their primary actions on the GABA_A receptor, but they also interact with glutamate receptors and voltage-gated ion channels. Because of the impressive recent advances in molecular biology techniques, our understanding of the GABA receptor and the actions of barbiturates on the central nervous system is likely to be significantly improved in the next decade. Barbiturates are a large class of drugs, consisting of many different brand name products with generic equivalents that are used primarily for mild sedation, general anaesthesia, and as a treatment for some types of epilepsy. From their introduction into clinical practice at the beginning of the 20th century until recent years, the barbiturates have enjoyed a central place in the pharmacopoeia of CNS drugs. Until the benzodiazepines were introduced in the 1960s, barbiturates were widely used clinically for a range of indications, including the treatment of anxiety, insomnia, seizure disorders and as muscle relaxants and anaesthetics agents. Benzodiazepines

and the newer non-benzodiazepine hypnotics are now preferred over barbiturates for most of these clinical uses because they have a wider therapeutic index, tolerance develops more slowly, and their liability for abuse is lower than that of the barbiturates. Nevertheless, barbiturates remain an important class of drugs from a scientific point of view, because they have played a central role in the characterization of the GABA_A receptor complex. This chapter will focus in particular on current knowledge and recent developments in our understanding of the receptor actions of barbiturates. We will also review the clinical pharmacology of this class of drugs, with particular attention to similarities and differences between barbiturates and benzodiazepines and their effects on sleep. One barbiturate, butalbital, exists only as a component of several headache preparations. The most common members of the barbiturate family are phenobarbital (Luminal), pentobarbital (Nembutal), amobarbital (Amytal), secobarbital (Seconal), thiopental (Pentothal), methohexital (Brevital), and butalbital (component of Fiorinal and Fioricet). They exist in numerous formulations and strengths.

Anticonvulsants: The anticonvulsants are a diverse group of pharmaceuticals which are used in the treatment of epileptic seizures. The use of anticonvulsants increased in the treatment of bipolar disorder, because many seem to act as mood stabilizers. The aim of an anticonvulsant is to abolish the accelerated and excessive activation of neurons that begin a seizure. Because of this, anticonvulsants also are proven to be effective in the

treatment of many types of dysfunctional anxiety. An effective anticonvulsant should prevent the spread of the seizure inside the brain and provide protection against possible excitotoxic effects that may cause brain damage. However, anticonvulsants have been associated to lower IQ in children. Anticonvulsants are also called antiepileptic drugs or antiseizure drugs. Anticonvulsant drugs include drugs such as phenobarbital, carbamazepine (Tegretol), phenytoin (Dilantin), and valproic acid (Depakote, Depakene). The drugs are only available with a prescription and come in tablet, capsule, liquid, and sprinkle forms. The recommended dose depends on the type of anticonvulsant, its strength, and the type of seizures for which it will be taken.

Dosage: The typical dose of phenobarbital for use as an anticonvulsant in adults is 50–100 mg given two to three times per day. When a series of serious seizures known as status epilepticus occurs, adults are usually first given 300–800 mg intravenously (directly into the vein) followed by 120–240 mg every 20 minutes up to a maximum of 1000–2000 mg. For sedation, adults are given 30–120 mg per day divided into two or three doses. For sedation before surgery, 100–200 mg are given in an intramuscular injection (a shot) about one hour before the surgery. The

usual dosage of Phenobarbital is 3-6 mg per kilogram of body weight per day. The typical dose for an anticonvulsant effect in newborns is 2 mg to 4 mg of phenobarbital per kilogram of body weight per day. In infants, this dose is 5 mg to 8 mg per kilogram of body weight per day. In children one to five years of age, the dose is 6 mg to 8 mg per kilogram of body weight per day. In children aged five to 12 years, the dose is 4 mg to 6 mg per kilogram of body weight per day. All of these doses are given in one to two divided doses per day. In newborns with status epilepticus, phenobarbital 15 mg to 20 mg per kilogram of body weight is given in a single or divided dose. Infants and children are given 10 mg to 20 mg per kilogram of body weight in a single or divided dose. They may also receive 5 mg per kilogram of body weight every 15 to 30 minutes up to a maximum of 40 mg per kilogram body weight. For anesthesia before surgery, 1 mg to 3 mg per kilogram of body weight is given about one hour before the surgery. The typical dose of butalbital, as a component of headache preparations such as Fiorinal or Fioricet, is 50-100 mg administered every four to six hours as needed. Examples of Anticonvulsant Barbiturates in the Market are those given in the table below-

Name	Chemical name	Chemical formula	CAS No	Control status 1971 UN Convention Schedule	Medical use	Pharmaceutical name
Allobarbital	5,5-diallylbarbituric acid	C ₁₀ H ₁₂ N ₂ O ₃	52-43-7	IV	insomnia	Dialog®
Amobarbital	5-ethyl-5-isopentylbarbituric acid	C ₁₁ H ₁₈ N ₂ O ₃	57-43-2	III	insomnia, sedation, seizures	Amytal® Tuinal®
Barbital	5,5-diethylbarbituric acid	C ₈ H ₁₂ N ₂ O ₃	57-44-3	IV	insomnia	Malonal Veronal
Butalbital	5-allyl-5-isobutylbarbituric acid	C ₁₁ H ₁₆ N ₂ O ₃	77-26-9	III		Lanorinal
Butobarbital	5-butyl-5-ethylbarbituric acid	C ₁₀ H ₁₆ N ₂ O ₃	77-28-1	IV	insomnia, sedation	Soneryl®
Cyclobarbital	5-(1-cyclohexen-1-yl)-5-ethylbarbituric acid	C ₁₂ H ₁₆ N ₂ O ₃	52-31-3	III		Cyclodorm®
Methylphenobarbital	5-ethyl-1-methyl-5-phenylbarbituric acid	C ₁₃ H ₁₄ N ₂ O ₃	115-38-8	IV	epilepsy, daytime sedation	Prominal®

Name	Chemical name	Chemical formula	CAS No	Control status 1971 UN Convention Schedule	Medical use	Pharmaceutical name
Pentobarbital	5-ethyl-5-(1-methylbutyl)barbituric acid	C ₁₁ H ₁₈ N ₂ O ₃	76-74-4	III	insomnia, sedation, seizures	Nembutal®
Phenobarbital	5-ethyl-5-phenylbarbituric acid	C ₁₂ H ₁₂ N ₂ O ₃	50-06-6	IV	epilepsy	Luminal® Gardenal®
Secbutabarbital	5-sec-butyl-5-ethylbarbituric acid	C ₁₀ H ₁₆ N ₂ O ₃	125-40-6	IV		Butabarb®
Secobarbital	5-allyl-5-(1-methylbutyl)barbituric acid	C ₁₂ H ₁₈ N ₂ O ₃	76-75-3	II	insomnia, sedation, seizures	Quinalbarbitone Seconal® Tuinal®
Vinylbital	5-(1-methylbutyl)-5-vinylbarbituric acid	C ₁₁ H ₁₆ N ₂ O ₃	2430-49-1	IV		Optanox®

MECHANISM OF ACTION:

No drug has a single action. Perhaps no class of drugs better illustrates this most important of axioms in pharmacology than the barbiturates. The barbiturates have sedative-hypnotic, anticonvulsant, anaesthetics and respiratory depressant effects that are mediated by their actions at various target sites in the body. Despite the different mechanisms, however, there is considerable overlap between the therapeutic/toxic dose-response curves with these drugs. For example, the anticonvulsant effects of phenobarbital are associated with significant sedation, and the anaesthetics effects of pentobarbital with respiratory depression. Researchers have attempted to identify the actions of barbiturates in the CNS since the discovery of this class of drugs. Early attempts to identify the basis of their CNS actions related to the hydrophobic nature of the drugs and their possible interactions with membrane phospholipids, interference with cellular energy metabolism and intracellular free ionized calcium levels. All of these concepts eventually fell victim to a second important pharmacological principle: drug mechanisms in vitro are only important if they occur over a concentration range relevant to the therapeutic/toxic effects under consideration. For example, the fluidizing actions of barbiturates on membrane phospholipids are rather small until suprathreshold concentrations are reached. More recently, neurophysiologists have pursued the idea that the site of general anaesthesia/CNS depression could be a protein. This idea originated with researchers studying neurotransmitter receptors and ion channels involved in the control of CNS excitability. Several neuronal targets are

affected by pharmacologically relevant concentrations of barbiturates, including ligand-gated and voltage-gated ion channels. The role of these different potential targets in synaptic transmission is summarized.

Barbiturate Interactions with Phenyl-Aminobutyric Acid (GABA):

Postsynaptic inhibition in the brain, is usually mediated by GABA. Action potentials generated in the inhibitory interneuron trigger release of GABA, which binds to postsynaptic receptors and causes the opening of chloride ion channels in the postsynaptic membrane. A transient change in postsynaptic membrane potential and a fall in input resistance results, stabilizing the postsynaptic membrane potential below threshold. Presynaptic inhibition also occurs in the CNS, in which case the output of excitatory neurotransmitter is reduced by the action of an inhibitory transmitter acting at a presynaptic receptor on the excitatory nerve terminal. As a result of research, GABA-mediated presynaptic inhibition of cat motoneurons was prolonged by barbiturates. Later it was shown that hippocampal postsynaptic inhibition is also prolonged by pentobarbital. Such increases in pre- and postsynaptic inhibition are invariably associated with decreased neuronal firing and network activity. These findings led naturally to a focus on interactions of barbiturates with the GABA_A receptor. This 'classical' GABA receptor is blocked competitively by bicuculline and non-competitively by picrotoxin. It also possesses a number of important allosteric modulatory sites at which various drugs act. There is a distinct site for non-competitive GABA

antagonists, such as picrotoxin, and a relatively well-characterized binding site for anxiolytic and hypnotic benzodiazepines (BZ). In addition, the GABA_A receptor is modulated at unknown sites by barbiturates. The imidazodiazepine flumazenil antagonizes all of the actions of the BZs, but fails to influence those of the barbiturates, demonstrating that BZs and barbiturates act at distinct allosteric sites on the GABA_A receptor macromolecule. The effects of barbiturates on the GABA_A receptor have been extensively studied using electrophysiological techniques *in vivo* and in isolated or tissue-cultured neurons, in which barbiturates enhance the actions of submaximal GABA concentrations, by prolonging the openings of individual GABA-operated chloride channels. The potency of various barbiturates as modulators of the GABA_A receptor correlated well with their hydrophobicity and with their potency as hypnotics and anaesthetics. Radioligand binding studies also revealed allosteric interactions of the barbiturates at the GABA_A receptor, with barbiturates causing an increase in the binding of labeled GABA and benzodiazepines to the receptor. Barbiturate effects on GABA_A receptor function have been studied at the single-channel level in cultured mouse spinal neurons. Openings of the GABA-activated chloride channels occur in 'bursts', interrupted by frequent brief closures. The channel kinetics are best described by a complex model involving three open states, having open time constants of 1, 4 and 11 msec. As the concentration of GABA is increased, the channels open more frequently and exhibit longer open times, entering the longest-lived open states more frequently. In the presence of 50 M pentobarbital, the main conductance state, opening frequency, and individual open time constants are not altered, but the frequency of occurrence of the longest open state increases, as does the occurrence of long bursts generated by that long open state. Barbiturates therefore promote entry of GABA-activated channels into a long-lived open state, whereas BZs increase only the frequency of channel opening into the initial open state. These mechanistic studies reveal interesting details of the changes in channel gating caused by barbiturates but as yet have yielded no insights into the molecular sites of action. An additional interesting effect of barbiturates is direct gating of the channels, i.e., the barbiturates may open the channel even in the absence of GABA. This usually occurs at significantly higher concentrations than those which potentiate the actions of GABA, these concentrations also are generally higher than those required for clinically effective anaesthesia.

Barbiturate Interactions with Glutamate Receptors: L-

Glutamate is now known to be the universal fast excitatory neurotransmitter of the mammalian central nervous system. There are multiple receptor subtypes for

L-glutamate, and these can be broadly subdivided pharmacologically into AMPA- (or quisqualate), N-methyl D-aspartate (NMDA) and kainate receptors, according to their preferred selective agonists among amino acid analogs of L-glutamate. As the major central excitatory transmitter, glutamatergic synapses are an obvious target for the actions of CNS depressant drugs such as the barbiturates. Richards first noted the depression of EPSPs by pentobarbital in slices of olfactory cortex and subsequently demonstrated that pentobarbital also depressed the excitation of neurons in the prepyriform cortex by L-glutamate. Similar effects were noted in tissue cultured neurons. In sodium flux measurements, barbiturates depressed flux induced by quisqualate but not by NMDA. A study in cortical slices showed that pentobarbital depressed responses to quisqualate and kainate but not those elicited by NMDA, indicating a receptor-subtype-selective action of the barbiturate. Studies in cultured neurons confirmed these findings. The block of the channels associated with the AMPA receptor appears to be both voltage- and use-dependent, indicating penetration of the barbiturate deep into the ion conducting pore. Cloning of the glutamate receptor subunit cDNAs has enabled investigators to explore this problem at the molecular level, where it was noted that the potency of pentobarbital as a glutamate antagonist is critically dependent upon the result of editing of the crucial Gln/Arg site in the pore-forming loop of the Glu-R subunits. A specific RNA editing enzyme can interconvert a glutamine or arginine codon at a position which is also crucial to the ion selectivity and permeation of the glutamate-operated ion channel.

Barbiturate Interactions with Voltage-gated Ion Channels: Voltage-dependent Sodium Channels:

Voltage-dependent sodium channels allow sodium to enter the cell in response to membrane depolarization. These channels are thus crucial in the generation and conduction of the action potential. Although undoubtedly the primary site of action of local anaesthetics, the voltage-gated sodium channel has not been thought to be of primary importance in the CNS depressant actions of the barbiturates. Axonal conduction in peripheral nerves is quite unaffected by anaesthetics concentrations of the barbiturates, for example. However, various anticonvulsant drugs, including phenobarbitone, have been shown to limit extremely high-frequency firing of neurons, and these effects are likely to involve voltage-gated Na⁺ channels. Some interesting alterations in the voltage-dependent gating of sodium channels have been reported. Although these effects generally occur at concentrations beyond the therapeutic range, the concentration-dependence of barbiturates may vary with sodium channel subtypes.

Novel brain sodium channels have been revealed by cloning techniques, and these may have higher sensitivity to the barbiturates than those channels studied to date.

Voltage-dependent Potassium Channels:

Voltage-dependent potassium channels allow potassium to exit the cell, often in response to membrane depolarization. These channels are therefore usually involved in repolarization following excitation or in regulating and controlling the resting membrane potential. Researchers have identified and cloned a seemingly infinite number of potassium channels. Barbiturates inhibit some voltage-gated potassium channels, notably the large conductance calcium-activated K⁺ channels, and some inwardly rectifying K⁺ channels. However, the concentrations of barbiturates responsible for inhibiting K⁺ channel function tend to be relatively high, and in general such actions would lead to increases in neuronal excitability, thus opposing the general trend toward CNS depression by these drugs. It is possible that the paradoxical effects of certain barbiturates (e.g., methohexital [Brevital]) can precipitate epileptiform discharges in the EEG of sedated epileptic patients) might result from interference with K⁺ channel function. In fact, some barbiturates are potent convulsants, and yet these compounds are known to share the potentiating actions of pentobarbital at GABA_A receptors, rather than to act as GABA antagonists, as do certain other convulsants. Clearly, the convulsant barbiturates must possess potent actions at CNS targets which override their effects on GABA_A receptors. K⁺ channel mechanisms might bear closer inspection in this context, since the mechanisms of the convulsant barbiturates remain quite unexplained.

Voltage-dependent Calcium Channels:

Voltage-dependent calcium channels allow calcium ions to pass into cells in response to membrane depolarization. Many calcium channel subtypes have been identified, with L-type channels predominant in heart and skeletal muscle, but a complex array of N, T, P, Q and R types identified in neurons. Barbiturates inhibit the flow of calcium through several types of voltage-gated calcium channels, and blockade of L-type Ca²⁺ channels is likely to explain in part their sometimes profound cardiac depressant actions. Neuronal N-type calcium channels are also barbiturate-sensitive, and inhibition of these channels may be relevant to the presynaptic effects of barbiturates to decrease the output of excitatory transmitter at certain synapses. An explosion of activity in cloning calcium channel subtypes has taken place since these studies on neuronal calcium currents, and so a re-examination of the effects of barbiturates on various cloned channel subtypes is to be anticipated.

Effects on Sleep:

The barbiturates were the most widely used sedative/hypnotics from the early part of this century until the early 1970s, when flurazepam (the first benzodiazepine specifically recommended for sleep) entered the US market. The agents most commonly used as hypnotics are the short- to intermediate-acting compounds such as amobarbital, pentobarbital and secobarbital, which have half-lives of 10-15 hours to 40-50 hours. Efficacy studies of barbiturates on sleep are reviewed by Mendelson. Barbiturates produce the classical (indeed, they define the classical) effects of hypnotics, which include shortened sleep latency, increases in total sleep, and often a decrease in waking time during the night. Whereas the barbiturates have inconsistent effects on slow-wave sleep, they consistently and potently depress rapid eye movement (REM) sleep. Benzodiazepines, in contrast, are potent suppressors of slow-wave sleep but have relatively mild REM-suppressing effects. The lesser effect of benzodiazepines on REM suppression was at one time viewed as advantageous. However, later researchers have questioned the degree to which REM suppression is harmful, or whether it is harmful at all and indeed REM deprivation studies have indicated that in some situations it may even be therapeutic (i.e., as a treatment for depression). Moreover, since the functions of the various sleep stages remain uncertain, at this time it is not clear whether there are advantages to relative reductions in one specific stage, relative to another. Abrupt cessation of recommended doses of hypnotic barbiturates, as with shorter-acting hypnotics, leads to transient sleep disturbance. This is often accompanied by temporary increases in the amount of REM sleep. Once again, it is not clear whether the elevated duration of REM sleep specifically translates into the subjective experiences of distressed sleep. During sleep, barbiturates reduce neurogenic respiratory drive; doses approximately three times those used therapeutically virtually eliminate neurogenic drive and greatly reduce hypoxic drive. Protective respiratory reflexes such as coughing are only mildly affected until very high doses are administered. For these reasons, patients with pre-existing respiratory compromise (e.g., sleep apnea) may be at increased risk when given hypnotic barbiturates. Cardiovascular effects of oral hypnotic barbiturates are minimal and usually confined to mild reductions in blood pressure during sleep. Orally administered hypnotic doses do not affect the rate of gastric emptying. Hepatic effects include induction of microsomal enzymes responsible for the metabolism of many other drugs as well as endogenous compounds such as steroids, cholesterol and some vitamins. Mitochondrial and cytoplasmic enzymes may also be affected. Oral

hypnotic doses have virtually no analgesic properties, suggesting that they are not helpful (at least when given alone) in patients for whom sleep disturbance is secondary to pain.

Effects on Mood and Psychomotor Performance:

The acute effects of barbiturates and benzodiazepines on mood and subjective state have been well documented both in healthy volunteers and in individuals with histories of drug abuse. Acute doses of barbiturates decrease anxiety and increase feelings of fatigue, dizziness, lightheadedness and lethargy. In individuals with a history of drug abuse, they also increase self-reported feelings of being "high." Some of these subjective experiences may be therapeutically desirable, such as the anxiolytic effect when the drug is used as a preoperative medication, or they may be undesirable, as in the case of the sedative effect when the drug is used as an anticonvulsant. The subjective states produced by sedative drugs are also closely associated with their abuse or non-medical use. Interestingly, sedative effects of barbiturates and benzodiazepines are considered pleasurable by individuals who have a history of drug abuse, while the same or similar effects are considered unpleasant by most individuals who lack an extensive history of drug use. The subjective effects of acute drug administration, especially ratings of 'liking' of the effects, are thought to be a good indicator of a drug's abuse liability. Laboratory studies have also been conducted to assess behavioral preference for barbiturates over a placebo, using double-blind choice tests. In these studies, healthy volunteers typically prefer an inactive placebo over a barbiturate, whereas individuals with a history of drug abuse typically prefer barbiturates over both placebo and comparable doses of benzodiazepines. Barbiturates, like benzodiazepines, impair performance in a dose-dependent manner on a wide range of psychomotor tasks. The psychomotor tasks typically used in laboratory studies represent components of the skills that are required for complex, coordinated activities such as driving a car. Barbiturates impair performance on standard tests of eye-hand coordination such as circular lights and the digit symbol substitution tests, and they decrease the number of items recalled in memory recognition tests. In most respects, the psychomotor effects of barbiturates resemble those of the benzodiazepines. Interestingly, however, benzodiazepines have more pronounced effects on memory than barbiturates, at doses that produced comparable subjective feelings of sedation. In addition, subjects under the influence of benzodiazepines underestimate their level of impairment on psychomotor tasks, compared with subjects under the influence of barbiturates. This relative lack of awareness of the motor impairment is likely to

increase the risks of performing tasks requiring concentration or dexterity (e.g., driving) under the influence of benzodiazepines.

Precautions:

Children who are hyperactive should not receive phenobarbital or other barbiturates. Some children paradoxically become stimulated and hyperactive after receiving barbiturates. The use of barbiturates in the elderly (over age 65) should be watched closely. Elderly patients must be carefully monitored for confusion, agitation, **delirium**, and excitement if they take barbiturates. Barbiturates should be avoided in elderly patients who are receiving drugs for other mental disorders such as **schizophrenia** or depression. Women should not use barbiturates during pregnancy unless they are necessary to control seizures. In these cases, they should take the minimum amount to control the seizures. Barbiturate use by pregnant women has been associated with increased risk of fetal damage and bleeding during childbirth. Women who are breast-feeding should not take barbiturates because these drugs enter the breast milk and may cause serious side effects in the nursing baby. Long-term barbiturate use should be avoided unless there is a strong medical need, as in the case of epilepsy, because of the potential addiction, dependence, tolerance, and withdrawal. People should not drive, operate heavy equipment, or perform other hazardous activities requiring mental alertness while taking barbiturates.

Side effects:

The most common side effect of barbiturate use is drowsiness. Less common side effects include agitation, confusion, breathing difficulties, abnormally low blood pressure, nausea, vomiting, constipation, lower body temperature, decreased heart rate, movement difficulty, nightmares, anxiety, nervousness, mental depression, and dizziness. Rare but reported side effects include fever, headache, anaemia, allergic reactions, and liver damage.

Interactions:

Patients should always tell their doctor and dentist when they are taking barbiturates. Barbiturates should generally not be taken with other drugs used to treat mental disorders. There are a number of drugs that barbiturates should not be combined with because the barbiturates may increase the metabolism of these drugs and thus, reduce the amount of these drugs available to be of benefit. These drugs include oral corticosteroids such as prednisolone, methylprednisolone, prednisone, or dexamethasone, estrogen and oral contraceptives, blood-thinning medications such as warfarin (Coumadin), the antibiotic doxycycline (Vibramycin), and anticonvulsants such as phenytoin (Dilantin). Barbiturates should not be

combined with alcohol because the combination produces additive depressant effects in the central nervous system. Barbiturates may lower the amount of absorption of the vitamins D and K.

Therapeutic Uses:

Barbiturates are used to sedate patients prior to surgery as well as to produce general anesthesia, to treat some forms of epilepsy, and to treat simple and migraine headache. These drugs are highly addictive and are often abused as recreational drugs. Although still commercially available, barbiturates such as secobarbital, pentobarbital, and amobarbital are no longer routinely recommended for the treatment of [insomnia](#) because of their ability to cause dependence, tolerance, and withdrawal. These drugs also have significant side effects when taken in large doses and can cause respiratory failure and death. Barbiturates still have certain therapeutic and diagnostic uses. Phenobarbital continues to be used in the treatment of seizure disorders, and the shorter-acting barbiturates are a useful adjunct, or occasionally even the primary agent, for anaesthesia. In addition, barbiturates are used as a diagnostic procedure prior to neurosurgery. This may involve administration of methohexital to localize epileptic foci, or it may involve intracarotid administration of sodium amobarbital. The sodium amytal procedure produces a transient unilateral suppression of hemispheric function, and it is the definitive diagnostic procedure to determine hemispheric dominance for speech and language. It is used to localize critical language and memory functions that should be spared in neurosurgical procedures. It has been used effectively for almost 50 years, and continues to be used by many centers today. Anticonvulsant peripheral neuropathy: a clinical and electrophysiological study of patients on single drug treatment with phenytoin, carbamazepine or barbiturates. Previous studies of phenytoin neuropathy in selected groups of chronic epileptic patients on polytherapy have indicated a widely varying incidence of clinical or electrophysiological abnormalities. In 51 previously untreated epileptic patients followed prospectively on phenytoin or carbamazepine monotherapy, assisted by blood level monitoring, for 1-5 years we found no clinical evidence of neuropathy. Eighteen per cent of the phenytoin group and none of the carbamazepine group had mild electrophysiological changes (abnormalities of sensory action potentials or sensory conduction). In the former group the occurrence of the electrophysiological abnormalities was possibly related to previous exposure to high phenytoin or low folate levels or both. In 10 chronic epileptic patients we demonstrated reversible slowing of sensory nerve conduction during phenytoin intoxication. In six selected epileptic patients on chronic barbiturate monotherapy we found clinical

evidence of neuropathy in two and electrophysiological abnormalities in five, including reversible slowing of sensory conduction during intoxication in one. This suggests that barbiturate drugs may, like phenytoin, also contribute to anticonvulsant neuropathy. Careful monitoring of single drug therapy with avoidance of acute toxicity may reduce the risk of chronic anticonvulsant neuropathy.

Convulsions in Non-Epileptic Patients on Withdrawal of Barbiturates and Alcohol:

Convulsions in nonepileptic persons after sudden withdrawal of hypnotic drugs are relatively unknown. Experience with 7 patients observed almost simultaneously has the value of an experiment and gives the starting point for a more systematic discussion of "withdrawal seizures." The 7 patients whose cases are described here belonged to a group of 50 or 60 very disturbed patients in Pilgrim State Hospital who had been kept under continuous sedation with soluble barbital U. S. P. for months or years, as reported by Polatin.¹ Treatment of chronically disturbed patients with mental disease by prolonged use of sedatives, such as bromides and barbiturates, has been recommended by various authors; no narcotic but merely a sedative effect is desired in such treatment. To these patients soluble barbital (sodium barbital, or sodium diethylbarbiturate) was given in aqueous solution, the average dose being 20 to 30 grains (1.3 to 1.95 Gm.) daily.

Increased Risk of Brain Tumors in Children Exposed to Barbiturates:

The possible etiologic role of barbiturates in the development of brain tumors in children was examined. Interviews were conducted with mothers of children with brain tumors and results compared with those from interviews with mothers of normal children and mothers of children with other cancers. Mothers of children with brain tumors more frequently reported having used barbiturates during their pregnancy with the index child than did mothers of normal children or mothers of children with other cancers. In addition, more children with brain tumors were reported to have used barbiturates than were normal children or children with other malignant diseases, with most of such uses appearing to be unrelated to symptoms resulting from the brain tumor itself. The results suggested that barbiturates may play an etiologic role, and it is estimated that as many as 8% of brain tumors in children may be attributable to use of barbiturates either by the child or prenatally by the mother.

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