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Drug Effects on the Human EEG

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ABSTRACT: *The effects of drugs on the EEG have been of interest since Berger demonstrated in 1929 that electrical signals could be recorded from the scalp. Berger described changes in the EEG following a variety of medications and, based on these observations, hypothesized that there was a relationship between changes in alpha activity and mental processes. A large number of drugs have now been demonstrated to alter the EEG and many of these drug-induced changes may be clinically useful. Understanding the effects and significance of drug effects on the EEG requires an understanding of the physiological basis of electroencephalography. This paper reviews the physiological basis of the EEG and the effects of commonly used drugs on background rhythms and epileptiform activity. The effects of prenatal and postnatal drug exposure on the neonatal EEG are also reviewed.*

KEY WORDS. *Antiepileptic medications, EEG, newborn, psychotropic medications, seizures.*

INTRODUCTION

Hans Berger (1873–1941), the father of electroencephalography, was the first to describe the effects of drugs on the EEG (Gloor 1969, Gibbs 1970, Fink 1984, Van Wieringen 1990). In a paper in 1931, Berger reported that the amplitude of the alpha waves increased after the administration of cocaine, at a time when the pupils were dilated, pulse rate increased, and psychic processes enhanced (Fink 1984). Following an intramuscular injection of phenobarbital he noted "the alpha wave(s) showed an increased length, . . . became strikingly low in voltage . . . and tended to fuse with each other" (Gloor 1969). Berger also found that scopolamine increased the frequency of EEG beta activity during behavioral

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agitation or excitation and caused slowing of the alpha when the patient was drowsy. He observed desynchronization of the EEG following caffeine (Fink 1984).

Unfortunately, while Berger's theories regarding the relationship between EEG changes and behavior have been generally confirmed, EEG changes following drug administration vary considerably from patient to patient and have not been specific enough to allow prediction of drug effect in individual patients. Nevertheless, the effect of drugs on the EEG is an important concern in the day-to-day interpretation of records. A large percentage of patients sent to the clinical neurophysiology laboratory are taking medications and it is important that the technologist and physician performing and interpreting these studies be aware of the changes in the record and what drugs may be responsible for these changes. In this paper, selected, commonly used drugs that alter the EEG in neonates, children, and adults will be reviewed. Since space limitations prevent a discussion of all possible effects of drugs on the EEG, recent developments will be emphasized. This paper will serve to complement, but not replace, more extensive reviews by other authors (Miller 1985, Duncan 1987, Glaze 1990, Van Wieringen 1990). In order to understand the significance of drug-induced changes on the EEG, some basic principles of electroencephalography will be discussed initially.

PHYSIOLOGICAL EFFECTS OF DRUGS ON THE EEG

Fortunately, EEG patterns are not totally chaotic. Much of the resting EEG activity involves rhythmic activity such as alpha rhythm and sleep spindles. A variety of medications, particularly benzodiazepines and barbiturates, can also result in spindle-like fast waves. These rhythmic, reverberating EEG waves reflect the ability of the brain to generate collective oscillations, with a group of neurons discharging repetitively and synchronously. This rhythmic EEG activity might be related to local circuits or arise from pacemaker cells at a distance from the recording electrodes.

Some central nervous system neurons display spontaneous oscillations in vitro, even after blockage of synaptic transmission. The intrinsic electrophysiological properties of thalamic, neocortical, and allocortical neurons allow them to oscillate within different frequency spectra. In the intact brain, however, the intrinsic properties of single cells are subjected to controlling influences from synchronizing pacemakers. Steriade et al. (1990) noted that the synchronizing systems can be viewed as multiple neurons with equal properties of rhythmicity and mutual influences within a series of interconnected structures. The synchronization of large aggregates of neurons permits rhythmic activity to be recorded from the surface of the brain.

Two of the most rhythmic activities seen in the EEG are spindles and alpha

rhythm. Following work by Andersen and Andersson (1968, 1974), EEG rhythmicity of these two waveforms was thought to be secondary to thalamic pacemakers. These authors postulated that spindles originated in feedback inhibitory loops, disseminated in virtually all thalamic nuclei and involving thalamocortical neurons, their presumed local axonal collateral, and intrinsic inhibitory cells (or interneurons). Each thalamic nucleus was thought to have intrinsic oscillatory properties and no single nucleus was regarded as the central pacemaker. The spread and synchronization of oscillations were ascribed to "distributor" neurons linking various thalamic nuclei.

This theory of intrinsic oscillatory properties of thalamic nuclei being responsible for EEG rhythms has subsequently been disputed on several grounds, viz., intranuclear recurrent collateral of thalamocortical axons are absent and there is little "cross talk" between various thalamic nuclei. Thalamic nuclei have not been demonstrated to have an ability to generate spindles when the nuclei are isolated from the reticular thalamic nucleus. The reticular thalamic nucleus has now been implicated as a primary source of oscillatory EEG activity.

The reticular thalamic nucleus is a peripheral sheet of GABA-ergic neurons covering the rostral, lateral, and ventral surfaces of the thalamus. Intracellular recordings show spindle oscillations to be associated with slowly growing and decaying depolarization with superimposed spike barrages in reticular thalamic nuclei. The reverse image is seen in their target cells, the thalamocortical neurons. The thalamocortical neurons simultaneously display rhythmic long-lasting hyperpolarization that occasionally activates a spike burst (Figure 1). The burst, an intrinsic property of thalamic cells, is transferred along thalamocortical axons to neocortical neurons where it triggers EPSPs and spikes in the frequency range of spindles. Stimulation of mesopontine cholinergic fibers induces depolarization of the thalamocortical neurons and a hyperpolarization of the reticular thalamic neurons. Direct excitation of the thalamocortical neurons, however, results in excitation of reticular thalamic neurons and disrupts the synchronization of spindle oscillations (Figure 2).

Medications may have their effect on central nervous system physiology at any of several levels of the neuraxis. Medications may affect the oscillatory rhythms, leading, in some instances, to increased spindle-like activity and in other cases to a slowing of background rhythms. Drugs may affect neuronal function and EEG background activity by a variety of mechanisms. These include alteration of brain excitability by changing neuronal membranes or metabolism, or by modifying the synthesis, release, or uptake of neurotransmitters.

As would be expected, antiepileptic drugs (AEDs) have many effects on neuronal physiology and cause a change in EEG activity. For example, the barbiturates prolong GABA-mediated chloride-channel openings while the benzodiazepines increase the frequency of GABA-mediated chloride-channel open-

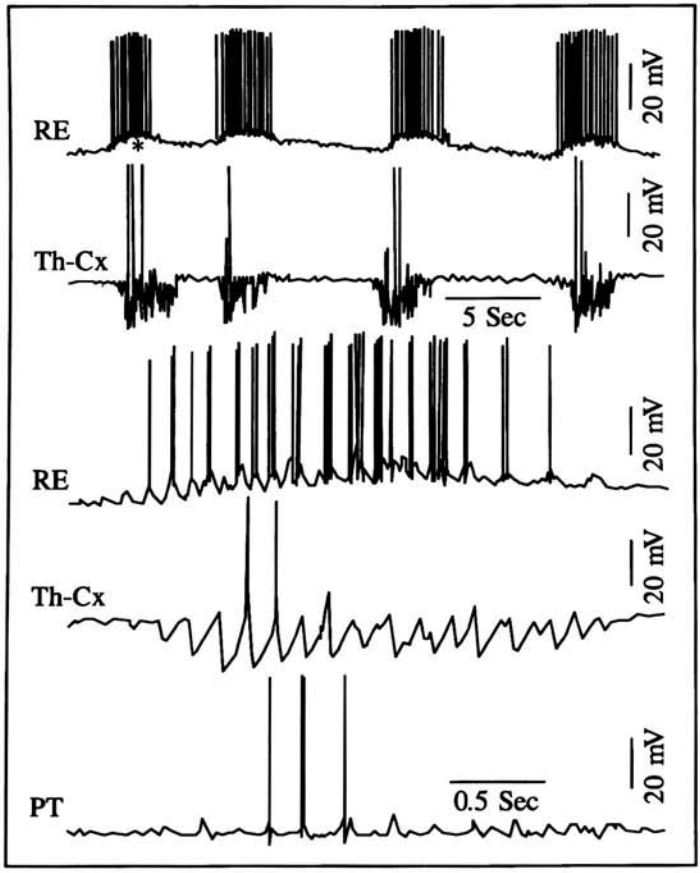

FIG. 1. Intracellular aspects of spindling oscillatory activities in reticular thalamic (RE), thalamocortical (Th-Cx; recorded from the ventrolateral nucleus), and pyramidal tract (PT; recorded from motor cortex) neurons of cats given barbiturate anesthesia. The spindle sequences marked by asterisks in top traces of RE and Th-Cx neurons are depicted below at higher speed. In the top traces, the slow rhythm of spindle sequences, recurring every 5–10 seconds. The spindle oscillations of GABA-ergic RE neurons are superimposed on a slowly growing and decaying depolarization, whereas spindles of Th-Cx cells are characterized by rhythmic hyperpolarizations that occasionally deactivate a low-threshold rebound spike. (Reprinted by permission from Steriade 1988.)

ings. Both drugs reduce CNS excitability and the barbiturates have been shown to reduce cellular metabolism (Brazier and Finesinger 1945). It is not known why these physiological changes result in an increase in beta activity at therapeutic levels, and slowing of background rhythms at higher serum levels. However, other conditions which decrease cellular metabolism, such as hypoglycemia,

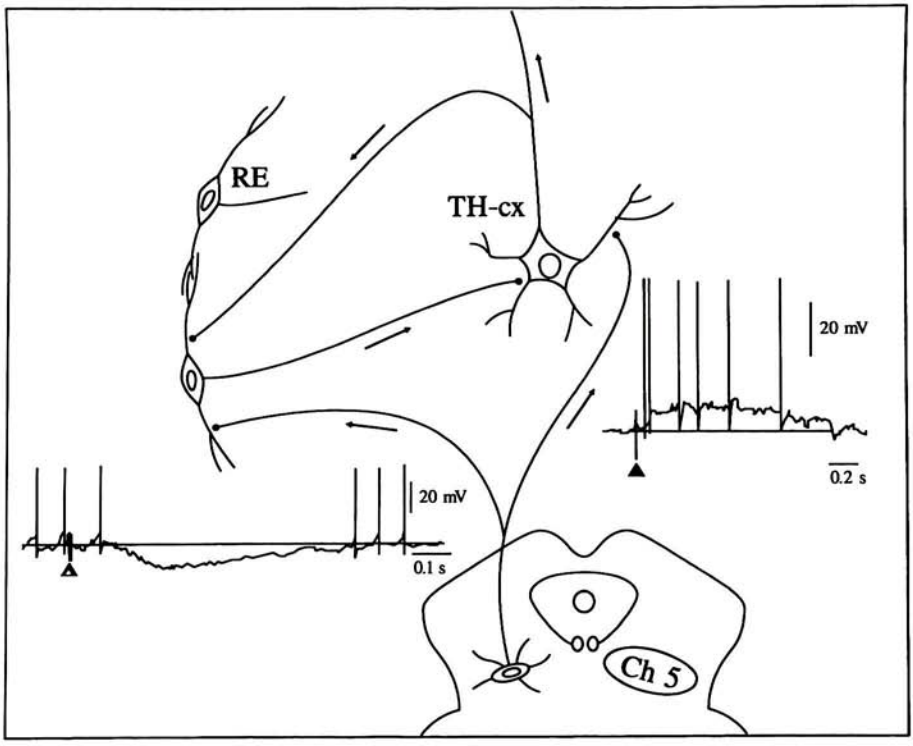

FIG. 2. Recurrent inhibitory loop of thalamocortical (TH-cx) and reticular thalamic (RE) neurons, and modulation of TH-cx and RE cells by mesopontine cholinergic afferents. (Ch 5 group of pedunculopontine tegmental neurons are depicted.) Ch 5 stimulation induces a depolarization of TH-cx neurons and a hyperpolarization of RE neurons. The direct excitation of TH-cx cells is accompanied by their disinhibition (through inhibition of GABA-ergic RE cells). These effects are effective in disrupting synchronized spindle oscillations in TH-cx systems, the thalamic part of the EEG desynchronization process. (Reprinted by permission from Steriade et al. 1990)

hypoxia, and hypothyroidism, are known to slow the frequency of the EEG whereas drugs such as thyroxin, which increases cellular metabolism, can accelerate EEG rhythms.

USE OF MEDICATIONS TO LOCALIZE ABNORMALITIES

Barbiturates

Asymmetries of beta activity may have lateralizing or localizing value (Grabow 1990). Pampiglione (1952) administered either oral seconal sodium or in-

travenous sodium amytal to 40 patients with a variety of cerebral lesions. Beta activity, between 18 and 26 Hz, appeared first in the frontal regions, followed in the parietal, temporal, and eventually in the occipital regions; the beta activity disappeared in the reverse order. The author found decreased beta on the side of the lesion in patients with cerebral lesions (Pampiglione 1952).

Methohexital (Brevital) has been used as an activator of focal and generalized seizures (Musella et al. 1971). Wyler et al. (1987) used methohexital as an activating agent in 62 patients undergoing focal cortical resections of epileptogenic foci and in 6 patients undergoing chronic EEG and video monitoring with intracranial strip electrodes. In 87% of the patients, methohexital caused selective activation of the epileptogenic focus during acute electrocorticography. The authors did not find activation of epileptiform activity outside of the epileptogenic zone. In a study of 50 patients, Musella and colleagues (1971) found that intravenous methohexital resulted in activation of temporal lobe spikes in 18 of 25 patients (72%) with complex partial seizures but did not produce any epileptiform activity in control patients.

Amobarbital. Some epilepsy centers have used intracarotid amobarbital to localize EEG abnormalities. Amobarbital typically has been used in patients with generalized spike-and-wave activity in whom the investigator wishes to determine if there is a focal onset. In theory, if amobarbital is perfused through the hemisphere in which the spike-and-wave originates it would be expected that the discharges will cease. Conversely, if amobarbital is injected into the internal carotid that perfuses the side opposite the primary focus, the spike-and-wave activity will continue contralateral to the side of the injection and be reduced or eliminated on the side of injection. If there is no difference in the responses to injections of amobarbital into the left and right carotids, bilateral synchrony is suggested (Grabow 1990).

Benzodiazepines

Diazepam. Brazier and colleagues (1976) administered diazepam to 13 patients with intractable seizures in whom unequivocal lateralizing signs were not possible. The authors found that in areas of abnormal cortex diazepam did not result in as much beta activity as normal cortex. Niedermeyer (1970) demonstrated that diazepam is more effective in eliminating generalized discharges than focal discharges.

Pentylenetetrazol

Pentylenetetrazol (PTZ), an activator of epileptiform activity, has been used to localize seizure foci (Ambrosetto and Lugaresi 1977). Injections of a series of

small doses of PTZ through the internal carotid artery on the side of the focus would be expected to elicit epileptiform activity and seizures at lower doses than on the contralateral side. Unfortunately, due to blood flow across carotid circulations, both hemispheres may be affected by the injections. Since many patients have equivocal or nonreproducible responses, these tests are now infrequently used. Long-term monitoring, using either conventional electroencephalography or invasive monitoring (subdural or depth electrodes), has generally replaced this test for localization purposes.

Phenothiazines

The phenothiazines have been used to activate epileptiform activity in patients with suspected epilepsy (Itil 1982). Unfortunately, phenothiazines may activate abnormalities in patients without a previous history of seizures as well. Because of this, these drugs are rarely used to activate seizures in patients.

EFFECTS OF SPECIFIC DRUGS ON THE EEG

As will be discussed, the effect of the drug on the EEG is dependent on many factors including dosage and blood level, concurrent medications, presence or absence of cerebral damage, coexisting metabolic abnormalities, and age of the patient (Kovnar 1992). For example, phenobarbital may produce an increase in frontal beta when the blood level is in the therapeutic range or beta superimposed upon delta when the level is in the toxic range. Asymmetrical beta activity may be present if there is an underlying structural lesion. Phenobarbital administered to patients with metabolic derangements or patients taking other sedating medications may lead to increased amounts of slow activity. Phenobarbital may lead to increased beta activity in newborns, but is far more likely to do so in older children and adults.

Antiepileptic Drugs

Computerized axial tomography (CAT) and magnetic resonance imaging (MRI) have now replaced the EEG as tools used to evaluate central nervous system structural lesions, although the EEG is still the best tool for evaluating functional disorders. The primary use of the EEG is for the evaluation of patients with proven or suspected epilepsy. It is not surprising, therefore, that the most frequently encountered drug-induced changes on the EEG are secondary to AEDs.

As a general rule, the AEDs reduce epileptiform activity (Milligan and Richens 1981), although they can exacerbate EEG abnormalities and seizures

(Snead and Hosey 1985). In patients with generalized spike-and-wave activity on the EEG, there is a good correlation between AED levels of valproic acid (Bruni et al. 1980), ethosuximide, and clonazepam (Browne 1976) and the number of generalized spike-and-wave discharges. However, the relationship between the numbers of interictal focal EEG spikes and sharp waves and AED levels is less clear (Cereghino et al. 1974, Bielmann et al. 1978, Duncan 1987). Even when seizures are adequately controlled, epileptiform discharges frequently persist. This is particularly true in some of the benign seizure disorders such as benign rolandic epilepsy and occipital lobe epilepsy (Loiseau et al. 1983, Ambrosetto et al. 1987).

Barbiturates. The barbiturates are well known to cause increased amounts of beta on the EEG (Ambrosetto and Lugaresi 1977). Brazier and Finesinger (1945) administered sodium amytal (250–650 mg), sodium pentothal (125–500 grams), or sodium pentobarbital (300 mg) to adult patients. The initial effect was the appearance of high voltage fast activity, occurring at a frequency of 21–32 Hz with voltages between 25 and 100 μV. In patients who received larger doses, delta activity (3–4 Hz) developed. In all patients, the high voltage fast activity first appeared in the frontal leads, followed by the parietal, temporal, and finally occipital leads, and disappeared in the reverse order. The authors made the interesting observation that the beta activity occurred first in the areas that were of most recent ontogenetic and phylogenetic development. As noted above, asymmetries of beta activity are useful in localizing areas of abnormal tissue.

Because beta activity is very common with barbiturates, the lack of beta may have prognostic significance. Niedermeyer et al. (1970) reported that the absence of barbiturate-induced beta activity in patients with seizures was associated with severe cerebral impairment.

There may be an increase in epileptiform activity during the withdrawal of barbiturates (Logar et al. 1986). Seizures may also occur with rapid withdrawal of the barbiturates, even in patients without a history of seizures (Wikler and Essig 1970).

Primidone. Primidone (Mysoline), which is metabolized to phenobarbital, can cause the same changes as phenobarbital, e.g., beta activity at therapeutic levels and diffuse slowing at high levels (Brillman et al. 1974).

Benzodiazepines. As with barbiturates, the benzodiazepines markedly increase beta activity (Brazier et al. 1976). With high blood levels, slowing of background activity can also occur. Figure 3 is from a seven year old patient taking clonazepam (Klonapin). Sudden withdrawal of benzodiazepines can lead to an increase in epileptiform activity and even seizures (Lund and Trolle 1973, Specht et al. 1989).

The combination of clonazepam and valproic acid (Depakene) has been

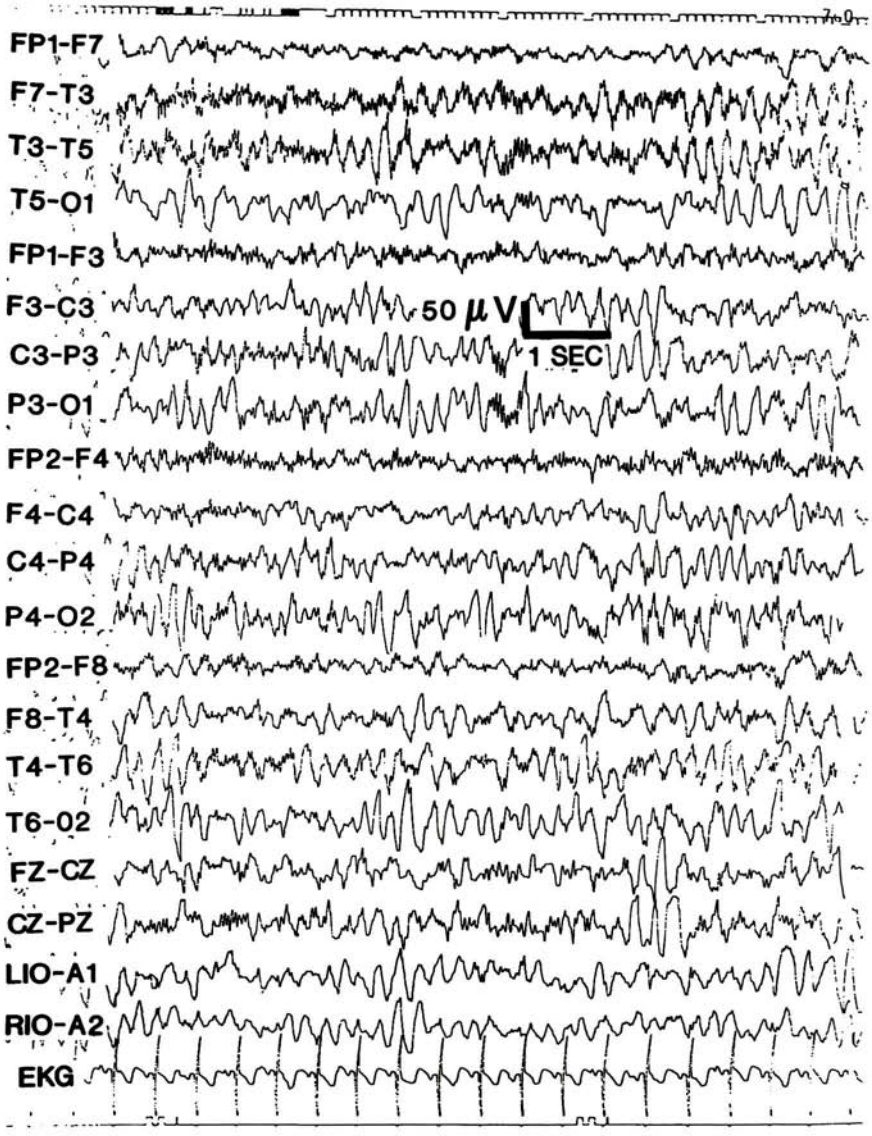

FIG. 3. Example of excessive beta in a 7-year-old patient on clonazepam.

reported to precipitate absence seizures, including the possibility of absence status (Jeavons et al. 1977). Unfortunately this fear of absence status limited the combination therapy of clonazepam and valproic acid. It is now known that this risk of absence status is low and in the vast majority of patients the drugs can be used together safely.

Phenytoin. Typically only toxic levels of phenytoin (Dilantin) affect the EEG. The alterations of the EEG vary from mild slowing of the alpha rhythm to diffuse delta and theta activity (Roseman 1961). However, Riehl and McIntyre (1968) found that, although intravenous administration of phenytoin to normal patients resulted in no change in the EEG, administration of the drug to patients with epilepsy produced a moderate degree of slowing and increase in amplitude of the EEG ten to fifteen minutes after the injection. The authors postulated that the effect of phenytoin might be secondary to existing alterations in the blood-brain barrier or due to a preferential effect of the drug on abnormal neurons. There have been several reports of increased seizures with toxic levels of phenytoin (Levy and Fenichel 1965, Troupin and Ojemann 1975).

Carbamazepine. Carbamazepine (Tegretol) may cause either no change in the EEG or bursts of theta activity (Monoca et al. 1980a, 1980b). Slowing of the EEG can be seen with toxic doses of the medication. It is becoming increasingly recognized, however, that carbamazepine may exacerbate seizures or epileptiform activity in some patients (Sachdeo and Chokroverty 1985). Snead and Hosey (1985) reported 15 children with seizures in whom one or more seizure types were exacerbated during treatment with carbamazepine. Generalized atypical absence (11 patients) was the most common seizure type to be exacerbated. Four patients had an increase in generalized tonic-clonic or tonic seizures. The authors reported that bilaterally synchronous spike-and-wave discharges of 2.5–3 cycles per second were predictive of increased atypical absence seizures with carbamazepine whereas generalized bursts of spikes and slow waves of 1–2 cycles per second placed the patient at risk for increased tonic-clonic seizures.

Valproic Acid. Bruni et al. (1980) did not observe consistent changes in the EEG following valproate (Depakote) nor find the valproate-induced changes in the spectral EEG in children that have been reported (Benninger et al. 1985). As with other AEDs, toxic levels of valproic acid may lead to slowing of background activity. Pedersen and Juul-Jensen (1984) described a series of EEGs from a patient who ingested 75 grams of sodium valproate. The first EEG, at the time of a sodium valproate level of 1500 μg/ml (usual therapeutic range is 50–150 μg/ml), showed diffuse slowing. Eight hours later, when the serum level was 1800 μg/ml the record consisted of low voltage delta activity. The following day, the EEG was "almost without activity." Six days later, the patient's clinical condition was normal and the EEG had returned to normal.

Table 1 summarizes the side effects from the commonly used AEDs.

TABLE 1. *Effects of antiepileptic drugs on the EEG.*

Antiepileptic drugs	Low serum levels	High serum levels
Benzodiazepines	Increased beta	Increased beta Reduction in alpha frequency Increased theta
Phenytoin	No changes	Reduction in alpha frequency Increased theta Increased delta
Carbamazepine	Usually no changes May reduce alpha frequency and increase theta and delta activity	Reduction in alpha frequency Increased theta Increased delta
Barbiturates	Increased beta	Increased beta Reduction in alpha frequency Increased theta Increased delta
Valproate	Usually no changes May be associated with increased theta activity	Reduction in alpha frequency Increased theta Increased delta
Ethosuximide	No changes	Reduction in alpha frequency Increased theta Increased delta

Psychotropic Medications

The phenothiazines, butyrophenones, tricyclic antidepressants, and lithium may all induce epileptiform discharges on the EEG and in some patients seizures can be precipitated by these drugs. According to Itil and Soldatos (1980), chlorpromazine and lithium markedly potentiate epileptiform discharges; thioxanthenes, butyrophenones, and amitriptyline are moderately potentiating; and imipramine, monoamine oxidase inhibitors, thioridazine, meprobamate, chlordiazepoxide, and methylphenidate have slight or no potentiating tendencies. In patients with a history of seizures, increased numbers of epileptiform discharges have been found following intravenous administration of imipramine (Kiloh et al. 1961) and amitriptyline (Davidson 1965). However, these drugs rarely cause seizures in patients without a history of seizures.

Epileptiform activity is more likely to be precipitated during the first weeks of treatment and during withdrawal (Itil and Soldatos 1980, Logar et al. 1986) than thereafter, and is more commonly observed in children than in adults (Itil 1982). Logar and colleagues (1986) evaluated the EEGs in 31 patients undergoing withdrawal from tranquilizers and found that 35% of the patients had generalized spike activity. Patients who combined tranquilizers with alcohol or barbiturates had an even higher rate of abnormal EEGs during withdrawal.

The tricyclic antidepressants generally have few effects on EEG background activity. There may be increased amounts of theta and beta activity (Florio et al. 1977). The major tranquilizers usually result in few changes but may increase the amount of theta and decrease alpha frequency. Methylphenidate (Ritalin), caffeine, and nicotine typically result in a mild increase in the frequency of alpha.

Investigators have attempted to correlate changes in the EEG following treatment with psychotropic medication with clinical efficacy of the drugs. For example, Shagass (1956) claimed that while patients with psychopathology exhibit resting EEG patterns which are indistinguishable from those of normal subjects, they differ in their response to chemical stimulation. Roth (1951) reported that patients who showed a large degree of EEG delta slowing after the first treatment achieved better outcomes than those who failed to show such slowing. Unfortunately, the predictive value of the EEG following treatment with psychotropic medications has not been verified by other authors.

There are times when patients under psychiatric treatment may show a dramatic change in behavior. This may result from drug toxicity, and serial EEG records can reflect this development and its resolution (Fink 1984).

Lithium. Lithium can produce significant changes of the EEG (Struve 1987, Ulrich et al. 1987). Significant EEG abnormalities can occur even at therapeutic serum concentrations of lithium. Reported changes include epileptiform discharges and alteration of the background rhythms (Schou et al. 1968, Small 1986, Helmchen and Kanowski 1971). Slow activity can occur diffusely, focally, or in generalized bursts (Johnson 1969, Platman and Fieve 1969, Helmchen and Kanowski 1971). Small (1986) observed that although EEG abnormalities tend to increase with higher plasma levels, no correlation is noted between EEG changes and plasma levels within the therapeutic range.

Struve (1987) compared the generalized or paroxysmal delta activity in EEGs from patients treated with lithium carbonate (either alone or in combination with other agents) with that seen in records from medication-free patients and patients on other psychotropic medications. The author found abnormal EEG changes in 30–39% of lithium-treated patients but in only 2–5% of medication-free controls. The prevalence of abnormal EEGs was also significantly higher for lithium-treated patients than for patients treated with other psychotropic agents. Triphasic waves (Small 1986, Glaze 1990) and periodic complexes similar to those in Jakob-Creutzfeldt have been reported (Smith and Kocen 1988). Small (1986) has reported that lithium may suppress EEG epileptiform activity.

EEG changes associated with lithium occur in both children and adults. Bennett and colleagues (1983) compared baseline EEGs with those repeated after treatment of aggressive behavior with haloperidol (Haldol), lithium, or placebo in 48 children between 5 and 12 years of age. During the baseline placebo period, 58% of the children had abnormal EEGs. Children receiving haloperidol or

lithium had a significant probability that their EEGs on optimal dose would worsen, and would be more likely to show paroxysmal or focal abnormalities, than those children treated with placebo. The combination of haloperidol and lithium has also been associated with increased neurotoxicity. This combination of treatment may result in photomyoclonic and photoparoxysmal responses (Addy et al. 1986).

Alcohol. With low levels of ethanol there is an increase in the amount of alpha (Lukas et al. 1989). With higher levels of alcohol there is a mild shift in the EEG to slower frequencies (Bergleiter and Platz 1972, Ehlers et al. 1989). Krauss and Niedermeyer (1991) reported that 56% of 136 patients with chronic alcoholism and normal EEGs had voltages below 25 μV compared to 13.9% of 1167 patients without a history of alcoholism ($p < 0.001$). However, as noted by the authors, a low voltage EEG is not specific for alcoholism.

There is some controversy regarding the effects of alcohol withdrawal on the EEG (Wickler et al. 1956, Victor and Brausch 1967, Reilly et al. 1979, Logar et al. 1986, Fisch et al. 1989). Victor and Brausch (1967) observed that during alcohol withdrawal in unmedicated patients, photic stimulation may produce a photomyogenic response, representing a nonspecific state of neuromuscular irritability. These same authors also reported photoparoxysmal responses during the acute withdrawal phase. These responses developed within 24 hours after the last alcohol intake, peaked during the second day, and disappeared after the fifth day following withdrawal. Hauser et al. (1982), however, studied 117 patients with presumed alcohol withdrawal seizures. Only one patient demonstrated a photoparoxysmal pattern. Vossler and Browne (1988) recorded EEGs from 40 patients who had stopped drinking within the preceding 96 hours. They found no photomyoclonic or photoparoxysmal responses. However, since the patients were on benzodiazepines at the time of the recording, the paroxysmal responses may have been suppressed. Fisch et al. (1989) analyzed EEG findings in 49 patients with clinical withdrawal symptoms not treated with benzodiazepines. Two patients had a photomyoclonic response, but none showed photoparoxysmal responses. Spontaneous epileptiform discharges are seldom seen in alcohol withdrawal.

Table 2 lists the effects on EEG background activity of some of the commonly used psychotropic medications.

Chemotherapy

As noted by Kovnar and Ward (1992), effective chemotherapy requires a delicate balance between cytotoxicity toward neoplastic cells and clinical toxicity. It is not surprising, therefore, that chemotherapeutic compounds can lead to alteration in cerebral electrical activity. Vanionpää et al. (1988) performed EEGs

TABLE 2. *Effects of psychotropic medications on the EEG.*

Drug	Non-toxic levels	Toxic levels
Tricyclic antidepressants		
Amitriptyline Desipramine Imipramine Nortriptyline Protriptyline	Increased theta and beta Sometimes decreased alpha frequency	Slowing with increased beta
Major tranquilizers		
Phenothiazines Butyrophenones Thioxanthenes Indoles	Few changes; increased theta Decreased alpha frequency Decreased beta Rarely paroxysmal patterns	Decreased alpha Increased theta and delta
CNS stimulants		
Methylphenidate Caffeine Nicotine	Mild increase in alpha frequency and increased amounts of beta	Slowing with theta and delta
Lithium	Mild reduction in alpha frequency and amount	Decreased alpha with increased delta and theta Sharp waves Rarely periodic complexes
Alcohol	Little or no change	Slowing with theta and delta

on 66 children with acute lymphoblastic leukemia and compared the results to age and sex-matched controls. The children with leukemia had significantly more background abnormalities and increased slowing in the occipital and temporal regions than the controls. Patients who had chemotherapy administered before the EEG recordings had more severe abnormalities than children who had not yet started on chemotherapy.

Methotrexate may cause generalized slow activity as well as focal polymorphic delta activity (Kovnar and Ward 1992). The EEG changes usually are seen in patients who have an encephalopathy characterized by somnolence, confusion, headache, seizures, and transient focal neurologic deficits (Bleyer 1981, Packer et al. 1983, Jaffe et al. 1985).

L-asparaginase administration may result in an increase of theta and delta activity (Land et al. 1972).

Ifosfamide has also been reported to show slowing of the alpha rhythm, followed by increases in slow activity within the delta frequency range as well as high voltage rhythmic delta activity (Pratt et al. 1986, Kovnar and Ward 1992).

Cyclosporin A, an antilymphocytic polypeptide, may produce diffuse slow-

ing, focal slowing, or epileptiform discharges (Joss et al. 1982, Rubin and Kang 1987).

Interferon has been associated with the following EEG changes: slowing of the dominant alpha rhythm, diffuse arrhythmic delta activity, and frontally dominant intermittent rhythmic delta activity (Suter et al. 1984).

Lichter-Konecki et al. (1987) found that children with acute lymphoblastic leukemia (ALL) treated with a combination of vincristine, daunorubicin or adriblastine, prednisone, and L-asparaginase had slowing on their EEG. Vincristine and L-asparaginase were felt to be the drugs responsible for the EEG changes.

General Anesthetics

In general, anesthetic agents such as cyclopropane, nitrous oxide, and enflurane, produce predictable EEG changes which are dependent on the depth of anesthesia (Clark and Rosner 1973, Kovnar and Ward 1992). Initially the alpha rhythm disappears while beta activity increases in voltage and distribution. As the anesthesia becomes deeper, slow activity in the delta and theta range becomes prominent. This slow activity then gradually increases in voltage and decreases in frequency until a burst suppression pattern appears. With increasing levels of the anesthetic agent, the bursts of activity become lower in voltage and further apart until the EEG becomes isoelectric. As the anesthetic level declines, the EEG background activity returns in a manner similar to the way it disappeared. Bursts of low voltage activity gradually increase in voltage and duration until continuous, slow activity is present.

EEG slowing following enflurane anesthesia may last for weeks (Burchiel et al. 1977, Kovnar and Ward 1992). Enflurane may also include spikes and spike-and-wave activity in normal subjects as well as in patients with a history of seizures (Neigh et al. 1971, Burchiel et al. 1977, Flemming et al. 1980). Ito and colleagues (1988) compared the effect of isoflurane and enflurane on the electrocorticogram of patients with intractable epilepsy undergoing temporal lobectomy. The mean frequency of epileptiform spikes decreased during the use of isoflurane but not enflurane. When compared to nitrous oxide anesthesia, isoflurane decreased the mean number of electrodes detecting spike activity whereas enflurane increased the mean number of electrodes demonstrating epileptiform activity.

Both phenobarbital and pentobarbital (Osorio and Reed 1989) have been used to induce burst-suppression in patients with status epilepticus. As with the general anesthetics noted above, there is a progression in the EEG from slowing to complete electrical inactivity as the dosage of the barbiturates is increased.

TABLE 3. *Effects of street drugs on the EEG.*

Drug	Nontoxic levels	Toxic levels
Lysergic acid diethylamide (LSD)	Little or no change Occasionally increased beta	Continuous rhythmic theta activity with periodic slow-wave complexes
Cocaine	Mild increase in alpha frequency Increased amounts of beta	Slowing with theta and delta
Marijuana	Little or no change	Slowing with theta and delta
Phencyclidine	Rhythmic theta and delta activity Increased voltage of beta activity	Slowing with theta and delta
Psilocybin	Increased voltage of beta activity	Slowing with theta and delta

Street Drugs

Cocaine is one of 14 alkaloids found in the leaves of the erythroxylon coca plant (Conway et al. 1990). The most devastating form of the drug is crack, a free-base cocaine that is a mixture of cocaine, water, and baking soda that is heated to eliminate adulterants. Because of the widespread abuse of cocaine, the effect of the drug on central nervous system physiology has been extensively evaluated (Castellani et al. 1983; Herning et al. 1985a, 1987; Lukas et al. 1989; O'Connor et al. 1989; Alper et al. 1990; Livezey and Sparber 1990; Pickworth et al. 1990). Herning et al. (1985a) studied the effects of cocaine on EEGs from awake adults. Fifty subjects were given 1 to 3 intravenous cocaine doses (0.2, 0.4, and 0.6 mg/kg) while 33 volunteers received 1 to 3 oral doses of cocaine (2, 3, and 4 mg/kg). The EEGs were analyzed for spectral power of delta, theta, alpha, and beta bands. At each dose, and for each route of administration, cocaine increased the power of beta. The authors postulated that the increase in beta power was a consequence of a direct stimulation of the central noradrenergic arousal system. The amount of alpha activity has been reported in increase over the occipital and parietal areas during the euphoric phase that occurs with cocaine (Lukas et al. 1989, Alper et al. 1990).

Herning and colleagues (1985b) also found that cocaine altered long-latency evoked potentials. Administration of cocaine either orally or intravenously reduced the amplitude of the P200 and P300 components of the auditory evoked potential during an oddball task. There was a decrease in the P200 latency and a reduction in the N100 amplitude only after intravenous administration of cocaine.

Cocaine is known to increase brain excitability and epileptiform activity on the EEG and can lead to seizures in both children and adults (Merriam et al. 1988; Conway et al. 1990; Kramer et al. 1990a, 1990b; Pascual-Leone et al. 1990). Bateman and Heagarty (1989) described four pediatric patients who had

TABLE 4. *Effects of narcotics and other drugs on the EEG.*

Drug	Nontoxic levels	Toxic levels
Narcotics		
Morphine Heroin Methadone Codeine	Minimal changes May cause slowing of the background	Slowing with theta and delta
Antihistamines		
Diphenhydramine	Minimal changes May increase beta	Slowing with theta and delta
Chloral hydrate	Increased beta activity	Slowing with theta and delta

passively inhaled the smoke of crack used by their "caretakers." Two of the children had seizures. Chronic administration of cocaine has been used to produce kindling, an animal model of epilepsy (Post 1977, Kilbey et al. 1979, Livezey and Sparber 1990).

Marijuana. Cannabis is one of the oldest drugs known to man. Derived from the plants *Cannabis sativa* and *Cannabis indica*, it varies in potency from hashish (strongest) to marijuana (weakest). There are conflicting findings regarding EEG changes with marijuana (Verdeaux and Longo 1977, Glaze 1990). Volavka et al. (1971) reported that delta-9 tetrahydrocannabinol, the active component of marijuana, produced an increase in the amount of alpha activity and decrease in beta and theta activity whereas other authors report minimal or no changes with inhalation of the street drug (Deliyannaki et al. 1970; Rodin and Domino 1970; Fink 1974, 1984).

Morphine/Heroin. As with marijuana, morphine and heroin have variable effects on the EEG (Glaze 1990). Berger found slowing of the alpha rhythm without significant change in voltage with morphine while other studies have found an increase in voltage of fast frequencies and decreased voltage of alpha frequencies (Gloor 1969, Fink 1974). Heroin, shortly after administration, increases alpha voltage but decreases the frequency of the alpha rhythm. This is later followed by decreased amounts of alpha rhythm and increased theta and delta activity (Lewis et al. 1970, Volavka et al. 1971). Methadone, morphine, and heroin have also been reported to decrease the percentage of REM sleep (Lewis et al. 1970, Kay et al. 1979).

Phencyclidine. Phencyclidine, a drug originally introduced as an intravenous general anesthetic, is a potent and dangerous hallucinogenic drug. The drug is known on the streets as angel dust, angel mist, or PCP. Acute phencyclidine intoxication has been reported to produce widespread, sinusoidal theta rhythms interrupted every few seconds by periodic slow-wave complexes (Stockard et al.

1976, Fariello and Black 1978). Other hallucinogenic drugs such as lysergic acid diethylamide (LSD), mescaline, and psilocybin reduce the voltage and amount of alpha, theta, and delta waves (Browne 1968, Fink 1969). Interestingly, in studies done by Browne (1968), activation of the EEG with LSD, as measured by response to photic stimulation, was related to whether subjects demonstrated visual imagery with the medication.

Chloral hydrate. Chloral hydrate continues to be widely used as a sedative in clinical neurophysiology laboratories. While beta activity may be enhanced, chloral hydrate rarely leads to the degree of beta seen with the benzodiazepines and barbiturates.

Tables 3 and 4 list the effects of the common street drugs and chloral hydrate on the EEG.

EEG CHANGES IN ACUTE DRUG POISONING

Toxic levels of a number of drugs can produce severe EEG suppression, even to the point of electrocerebral inactivity (Kubicki et al. 1970, Haider et al. 1971). Haider et al. (1971) performed continuous EEG monitoring in 127 cases of acute drug poisoning. The drugs included the barbiturates, benzodiazepines, and tricyclic antidepressants as well as an assortment of others. The EEGs were classified as in Table 5. As can be seen, the authors found a significant correlation between the EEG grade of coma and the clinical assessment.

Alpha coma, which consists of the presence of a predominate alpha frequency rhythm in the EEG of a clinically comatose patient, can be seen following drug ingestion. Guterman et al. (1981) reported a patient who had alpha coma following ingestion of a large amount of lorazepam. Despite the presence of an EEG demonstrating nonreactive 9–10 Hz alpha frequency over the entire head, the patient recovered fully. The authors emphasize that drug-induced alpha coma has a far better prognosis than alpha coma following anoxic insults or brainstem infarction.

EFFECT OF DRUGS ON THE NEONATAL EEG

Although studies on the effects of drugs on the neonatal EEG are few, most authors agree that certain drugs, especially in the toxic range, can alter background activity (Lombroso 1985, Rung et al. 1991). The acute administration of AEDs has also been noted to depress cerebral electrical activity (Radvanyi-Bouvet et al. 1982). Unfortunately AEDs, particularly barbiturates, are often administered to infants with seizures prior to their first EEG, raising the question of the prognostic value of the recording. To study this problem, Staudt et al. (1982) reviewed EEG records from a total of 26 neonates who had an EEG while

TABLE 5. *Alteration of EEG background and level of consciousness with toxic levels of drugs (Reprinted by permission from Haider et al. 1971.)*

Grade	Description	Number of patients	Clinical condition
I	Alpha rhythm or predominant alpha rhythm with beta or some rare theta waves	20	Conscious or drowsy
II	Predominantly theta rhythm with some alpha, beta, or low voltage delta activity	17	Conscious or drowsy
III	Predominantly low/high voltage delta rhythm mixed with some theta waves	24	Unconscious, responded to painful stimulation
IV	Delta waves with or without brief isoelectric intervals	19	Unconscious, responded to painful stimulation
V	Suppression burst activity	19	Deep coma
VI	Near silence but with isolated and low voltage, 3–7 Hz occurring singly or in bursts of half a second duration	12	Deep coma
VII	An isoelectric record, totally unresponsive to all stimuli	10	Deep coma

on phenobarbital treatment. In five infants, an EEG was available prior to treatment with barbiturates. In one infant, mild background suppression improved to normal in spite of a high barbiturate level. In a second infant, viral encephalitis was felt to be responsible for changing the EEG from excessive slowing and frequent central sharp waves to moderate suppression with multifocal spike activity. In two infants, no change in background activity occurred, even though barbiturates reduced the number of interictal discharges. In the fifth infant, the EEG improved from a mild suppression with focal seizures to normal. The authors also compared EEG background activity with phenobarbital blood levels. The phenobarbital plasma levels in the group with severe or moderate suppression were not statistically different from those showing mild suppression or normal background activity. The authors concluded that background suppression does not occur with phenobarbital plasma levels of 1.3 to 5.9 mg/dl. Supporting this observation, Benda et al. (1989), in a study of 46 premature infants, reported that mean phenobarbital levels at the time of the EEG failed to show a significant relationship with the duration of the inactive phase of discontinuous sleep.

However, Ashwal (1989) and Ashwal and Schneider (1989) reported that, in sick or young neonates, phenobarbital levels greater than 25 μg/ml may suppress EEG activity. These authors found a discordance between EEG activity and radionucleotide uptake in infants with levels of 25–35 μg/ml. The lack of EEG activity in the presence of cerebral blood flow suggested that the pheno-

barbital suppressed EEG activity. One infant, who met the clinical criteria for brain death, had absent cerebral activity with a level of 30 μg/ml but had some cerebral electrical activity when the level fell to zero. Pezzani et al. (1986) reported two patients with high AED levels that were probably the cause of those patients' severely abnormal EEGs. In the first child, an isoelectric record was obtained from a day-old infant whose mother was taking 35 mg/day of diazepam. Four hours after the first recording, the record was only moderately abnormal. The other infant had a permanently discontinuous record and a high level of phenobarbital (serum level 68 μg/ml). A repeat study, on day two of life, demonstrated an only moderately abnormal EEG although the blood level of phenobarbital was unchanged. The outcome in this child was favorable.

The question of how much AEDs alter the neonatal EEG remains open to question and needs further study. It is wise therefore to be cautious in making prognostic statements about infants with high levels of AEDs or infants who have been acutely loaded with AEDs.

Medications other than AEDs may also alter the neonatal EEG. We have made unpublished observations that opiates may depress background activity, increase the amount of discontinuity, and alter sleep cycles. In addition, drugs consumed during pregnancy may alter the neonatal EEG. An excess of spikes and sharp waves were seen in 17 of 38 (45%) neonates born to mothers abusing cocaine during pregnancy (Doberczak et al. 1988). The abnormalities were multifocal in 14 of 17 of the tracings. On follow-up, 9 of 17 infants with abnormal EEGs continued to show abnormal EEGs during the second week of life. By 3–12 months of age, however, 9 of 10 infants with previously abnormal tracings had normal records. None of the infants had clinical seizures.

Alcohol consumption during the first trimester of pregnancy has been associated with disturbances in sleep and arousal; marijuana affects sleep and motility, regardless of when it was used (Scher et al. 1988). Ioffe et al. (1984, 1988) reported that newborn infants of mothers who abused alcohol during pregnancy had hypersynchronous EEGs with higher total power of spectral analysis in quiet, indeterminate, and rapid eye movement sleep (REM) than control infants. The authors found that the power of the EEG, using linear regression analysis, was significantly higher in infants of mothers who were binge drinkers than in those of mothers who were alcoholics. It was concluded that exposure to high quantities of alcohol was even more harmful to the fetal brain than continuous chronic exposure (Ioffe and Chernick 1988).

Infants born to drug-dependent mothers are at risk for behavioral and developmental abnormalities (van Baar et al. 1989a, 1989b). Van Baar and colleagues (1989a) compared neurobehavioral development and EEGs in 35 infants of drug-dependent mothers with 37 control infants. The drug-dependent mothers had abused a variety of drugs including methadone, heroin, cocaine, tranquil-

izers, amphetamines, typically in combination. EEGs and behavioral rating skills were abnormal more frequently in the first month of life in the infants of the drug-abusing mothers. However, by one year of age there were no differences between the two groups (van Baar et al. 1989b).

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