

NEUROPHARMACOLOGY

SEDATIVE-HYPNOTIC DRUGS

A sedative, or anxiolytic, agent should reduce anxiety and exert a calming effect. A hypnotic drug should produce drowsiness and encourage the onset and maintenance of sleep. Hypnotic effects involve more pronounced depression of the CNS than sedative effects. With such drugs, an increase in dose higher than that needed for sedation may cause anesthesia or respiratory arrest.

Benzodiazepines (Benzos)

Diazepam, Lorazepam, Alprazolam, Midazolam; not an all-inclusive list; these are the key players... Benzos (and Barbiturates, Zolpidem, Zaleplon, Eszopiclone) bind to GABA receptors in the CNS.

Barbiturates

Phenobarbital is the prototype. Barbiturates also facilitate the actions of GABA at multiple sites in the CNS

Non-benzodiazepines

Zolpidem, Zaleplon, and Eszopiclone

Antagonists

Flumazenil blocks the actions of benzodiazepines, eszopiclone, zaleplon, and zolpidem, but does not antagonize the actions of barbiturates or ethanol.

Sedation

Benzos, barbiturates, and most others exert calming effects with concomitant reduction of anxiety at relatively low doses. The anxiolytic actions are accompanied by some depressant effects on psychomotor and cognitive functions. Benzos also exert dose-dependant anterograde amnesia effects (causing the inability to remember events occurring during the drug's administration).

Hypnosis

All these drugs induce sleep if high enough doses are given.

Anesthesia (More to come...)

High doses of certain drugs depress the CNS to the point known as Stage III of general anesthesia. Benzos are used IV, usually in combo with other agents, in anesthesia. They are reversible with flumazenil.

Anti-convulsant effects (More to come...) Many of these drugs are capable of inhibiting the development and spread of epileptiform electrical activity in the CNS. Several benzos are used in the management of seizures.

Flumazenil

It has a high affinity for the benzodiazepine binding site on the GABA receptor and thus acts as a competitive antagonist to benzos. It does not block the actions of barbiturates, ethanol, opioids, or general anesthetics, but will block the actions of benzos, zolpidem,

zaleplon, and eszopiclone. It is used to reverse overdose and to hasten recovery following administration of benzos.

Clinical Pharmacology

Anxiety states: The psychic awareness of anxiety is accompanied by enhanced vigilance, motor tension, and autonomic hyperactivity. The benzos are used for acute anxiety attacks and for rapid control of panic attacks. They are also used in the long term treatment of general anxiety disorder (GAD) and panic disorders. Alprazolam (Xanax) is particularly effective in the treatment of panic disorders and agoraphobia. Be careful when mixing benzos with alcohol or over the counter medicines! Doses of these drugs should be such that they minimize adverse effects. Avoid combinations of anti-anxiety drugs.

Sleep problems: True primary insomnia is rare. Proper diet, exercise, avoidance of stimulating agents before bedtime, a comfortable sleeping environment, and a regular bedtime can all help.

Benzos can cause a dose dependent decrease in both REM and slow-wave sleep, although to a lesser extent than barbiturates. The newer hypnotics such as zolpidem (Ambien), zaleplon, and eszopiclone (Lunesta) are less likely than benzos to change sleep patterns. “Hangover” effects should be avoided. Tolerance can occur if benzos are used nightly, which may lead to the patient wanting a dose increase to produce the desired effect.

Short acting drugs are good for their sedative and possible amnestic effects while longer lasting drugs (such as chlordiazepoxide and diazepam {Valium} and even phenobarbital) are useful in weaning patients off their dependencies (like alcohol or other sedative-hypnotic drugs). Parental lorazepam (Ativan) is used to suppress the symptoms of delirium tremens.

Toxicology: Relatively low doses may lead to drowsiness, impaired judgment, and diminished motor skills. Benzos may cause a significant dose-related anterograde amnesia. This effect is used for uncomfortable clinical procedures. Benzos have been used criminally as “date rape” drugs.

ANTISEIZURE DRUGS

Causes of epilepsy are very diverse, encompassing genetic and developmental defects and infective, traumatic, neoplastic, and degenerative disease processes. Existing antiseizure meds provide adequate seizure control in about 2/3 of patients.

Seizure Classifications (see pgs 127 – 133 in Neurology)

Partial seizures are those in which a localized onset of the attack can be ascertained; i.e., the attack begins in a specific locus of the brain. There are three types of partial seizures: **Simple partial seizure:** characterized by minimal spread of the abnormal discharge such that normal consciousness and awareness are preserved. The patient is completely aware of the attack and can describe it in detail. The EEG may show an abnormal discharge highly localized to the involved part of the brain.

Complex partial seizure: has a localized onset, but the discharge becomes more widespread (usually bilateral) and almost always involves the limbic system. Most arise from the temporal lobes. Clinically, the patient may have a brief warning followed by an alteration of consciousness during which some patients stare and others stagger or even fall. Most demonstrate fragments of integrated motor behavior called **automatisms** for which the patient has no memory. These usually include lip smacking, swallowing, fumbling, scratching, or even walking about. After 30-120 seconds, the patient makes a gradual recovery to normal consciousness but may feel ill or tired for several hours after the attack.

Secondarily generalized attack: a partial seizure immediately precedes a generalized tonic-clonic (grand mal) seizure.

Generalized Seizures are those in which there is no evidence of localized onset. There are many different types.

Generalized tonic-clonic (grand mal) seizure: these are the most dramatic of all seizures and are characterized by tonic rigidity in all extremities, followed in 15-30 seconds by a tremor that is actually an interruption of the tonus by relaxation. As the relaxation phase becomes longer, the attack enters the clonic phase, with massive jerking of the body. The clonic jerking slows over 1 to 2 minutes, and the patient is usually left in a stuporous state. The tongue or cheek may be bitten, and urinary incontinence is common. Primary generalized tonic-clonic seizures begin without evidence of localized onset, whereas secondary generalized tonic-clonic seizures are preceded by another seizure type, usually a partial seizure. The medical treatment of both primary and secondary is the same and uses drugs appropriate for partial seizures.

The absence (or petit mal) seizure: characterized by both sudden onset and abrupt cessation. Its duration is usually less than 45 seconds. Consciousness is altered; the attack may also be associated with mild clonic jerking of the eyelids or extremities, with postural tone changes, autonomic phenomena, and automatisms. These begin in childhood or adolescence and can occur up to 100 times a day. The EEG shows a spike and wave pattern.

Myoclonic jerking: these are seen in a wide variety of seizures. Treatment of seizures with myoclonic jerking should be aimed at the primary seizure rather than the myoclonus.

Atonic seizures: the patient has a sudden loss of postural tone. If standing, the patient may fall to the floor and be injured. If seated, the patient's head and torso may suddenly drop forward. This is most often seen in children, but is not unusual in adults. Most of these patients wear helmets to prevent head injury. These are often refractory to all meds.

Infantile spasms: these are an epileptic syndrome and not a seizure type. The attacks are usually bilateral. They are characterized by brief, recurrent myoclonic jerks of the body with sudden flexion or extension of the body and limbs. The forms of infantile spasms are very heterogeneous. 90% of these patients have their first attack before age one. Most patients are mentally retarded, presumably from the same cause as the spasms. It is associated with tuberous sclerosis. Drugs used to treat infantile spasms are only effective in some cases. The MR associated with this disorder is usually not relieved, even if the spasms are. Corticosteroids, benzos, and vigabatrin may be effective.

Drugs used in Generalized Tonic-Clonic and Partial Seizures

Phenytoin (Dilantin): It is the oldest nonsedative antiseizure drug. Phenytoin blocks sustained high-frequency repetitive firing of APs. It has a use-dependent effect on sodium conductance. Phenytoin is effective against partial seizures and generalized tonic-clonic seizures.

Carbamazepine (Tegretol): This drug is a tricyclic compound effective in the treatment of bipolar depression. It blocks sodium channels at therapeutic concentrations and inhibits high-frequency repetitive firing in neurons. It also acts presynaptically to decrease synaptic transmission. This drug has been on the market for awhile for the treatment of partial seizures and generalized tonic-clonic seizures, but some of the newer drugs are beginning to replace it.

Oxcarbazepine (Trileptal): This drug is similar to carbamazepine and is useful in the same seizure types; however, it is an improved toxicity profile.

Phenobarbital: Its mechanism is unclear, but it involves enhancement of inhibitory processes and diminution of excitatory transmission. It is most useful against partial seizures and generalized tonic-clonic seizures. It can sometimes worsen absence seizures or infantile spasms.

Vigabatrin: This drug is an irreversible inhibitor of GABA-T, the enzyme responsible for the degradation of GABA. It acts by increasing the amounts of GABA released at synaptic sites, thereby enhancing its inhibitory effects. It is useful in the treatment of partial seizures.

Lamotrigine (Lamictal): This drug suppresses sustained rapid firing of neurons and produces a voltage and use-dependent inactivation of sodium channels. This action probably explains Lamotrigine's efficacy in focal epilepsy. This drug is also useful against absence seizures in children. It also decreases the synaptic release of glutamate. This drug is widely prescribed for partial seizures.

Gabapentin (Neurontin) and Pregabalin (Lyrica): Gabapentin is an analog of GABA that is effective against partial seizures. Both of these drugs modify the synaptic or nonsynaptic release of GABA. They both also act presynaptically to decrease the release of glutamate. Gabapentin is effective against partial seizures and generalized tonic-clonic seizures. It is also effective in treating neuropathic pain and is now indicated for postherpetic neuralgia. The most common adverse effects include somnolence, dizziness, ataxia, headache, and tremor.

Pregabalin is approved for the treatment of partial seizures, with or without secondary generalization. It is also used for neuropathic pain, including painful diabetic neuropathy and postherpetic neuralgia.

Drugs Used in Generalized Seizures

Ethosuximide: It is a first line drug against absence seizures. It has an important effect on calcium currents, reducing the low-threshold current. These calcium currents are thought to be a pacemaker current in thalamic neurons responsible for generating the rhythmic cortical discharge of an absence attack.

Valproic Acid and Sodium Valproate: Valproate blocks sustained high-frequency repetitive firing of neurons. Its actions against partial seizures may be a consequence of this effect on sodium current. Valproate is very effective against absence seizures. It is the drug of choice for patients who suffer from both absence seizures and generalized tonic-clonic seizures. It is also used to treat bipolar disorder and for migraine prophylaxis.

Oxazolinediones: Trimethadione is the prototype. They raise the threshold for seizure discharges following repetitive thalamic stimulation. It has the same effect on calcium currents as ethosuximide.

Other Drugs in the Management of Epilepsy

Benzodiazepines: Six benzos play prominent roles in epilepsy. Diazepam is highly effective against continuous seizure activity, specifically generalized tonic-clonic status epilepticus. Lorazepam is thought to be even more effective against status epilepticus than diazepam. Clonazepam has documented efficacy against absence attacks. Clorazepate dipotassium is used to treat complex partial seizures in adults. The sedative effects of benzos limit their usefulness, as does the tolerance issue associated with benzos.

Status Epilepticus: The most common form of status epilepticus is generalized tonic-clonic. It is a life-threatening emergency requiring immediate cardiac and respiratory care. It usually always requires IV administration of antiseizure meds. Diazepam is the most effective drug in this situation. IV administration of diazepam can cause severe respiratory sedation and resuscitation equipment must be immediately at hand. Diazepam is not a permanent fix, but does allow a 30-40 minute seizure free interval in which to give more definitive therapy. Some physicians prefer lorazepam, which is slightly longer acting than diazepam.

Fosphenytoin is the mainstay of continuing therapy in status epilepticus. It is safely given by IV push, but it can also be diluted with saline. Careful monitoring is necessary, especially in the elderly. If the patient does not respond to fosphenytoin, Phenobarbital is given next. Respiratory depression is a common side effect, especially if a benzo has already been given.

Teratogenicity: Children born to mothers taking antiseizure drugs have a two-fold risk for congenital malformations. Phenytoin causes fetal hydantoin syndrome. Valproate can cause spina bifida. Although these risks are here and should be considered and carefully avoided, maternal seizures should not be allowed to continue unchecked.

Withdrawal: Withdrawal from antiseizure drugs can increase seizure frequency and severity. Barbiturates and benzos are the most difficult to discontinue. If a patient is seizure free for 3 to 4 years, a trial of gradual discontinuance is often warranted.

Overdose: Antiseizure drugs are central nervous system depressants but are rarely lethal. The most dangerous effects of these drugs are respiratory depression, which may be potentiated by other agents, such as alcohol. Treatment of overdose of antiseizure meds is generally supportive.

GENERAL ANESTHETICS

Types of Anesthetics:

IV: barbiturates, benzos, propofol, ketamine, opioids, and sedative-hypnotics

Inhaled: Isoflurane, Desflurane, and Sevoflurane... Nitrous oxide is an adjuvant

Stages of Anesthesia

Stage I (Analgesia): analgesia without amnesia initially... eventually amnesia is elicited

Stage II (Excitement): patient is delirious, but with amnesia... respiration is irregular, and vomiting may occur if stimulated... this stage must be limited

Stage III (Surgical anesthesia): extends from regular respiration to cessation of spontaneous respiration

The most reliable indication that this stage has been reached is loss of responsiveness to noxious stimuli (trapezius squeeze) and reestablishment of regular breathing pattern

Stage IV (Medullary depression): severe depression of the vasomotor center in the medulla, as well as the respiratory center... death rapidly ensues without circulatory and respiratory support

The administration of other drugs on top of anesthetics can alter their effects.

Malignant hyperthermia is an autosomal dominant genetic disorder of skeletal muscle that occurs in susceptible individuals undergoing anesthesia with volatile agents and muscle relaxants. Symptoms include the rapid onset of tachycardia, hypertension, severe muscle rigidity, hyperthermia, hyperkalemia, and acid-base imbalance. It is rare, but very dangerous. The specific biochemical abnormality is an increase in free calcium concentration in skeletal muscle cells. Treatment includes administration of dantrolene (to reduce calcium release from the sarcoplasmic reticulum) and appropriate measures to reduce body temperature and restore electrolyte and acid-base imbalance.

Inhaled Anesthetics: Isoflurane, Desflurane, and Sevoflurane

Clinical Use of Inhaled (volatile) Anesthetics: Volatile anesthetics are rarely used as the sole agents for both induction and maintenance of anesthesia. Nitrous oxide, desflurane, sevoflurane, and isoflurane are the most commonly used in the U.S.

IV Anesthetics: IV Anesthetics do not require specialized vaporizer equipment for their delivery. IV drugs also have a faster onset of action; thus, they are commonly used for the induction of general anesthesia.

Barbiturates: Thiopental is a barbiturate commonly used for induction of anesthesia. After an IV bolus injection, rapid loss of consciousness is produced in one circulation time.

Benzodiazepines: Diazepam, Lorazepam, and Midazolam are used in anesthetic procedures. Flumazenil can be used to accelerate recovery in patients given benzos (especially in elderly patients). However, reversal of benzo-induced respiratory depression is not as easily predictable. Due to its short duration of action, multiple doses of flumazenil may be needed.

Opioid Analgesics (More to come...): Large doses of opioids have been used in conjunction with large doses of benzos to achieve a general anesthetic state. Even with these high doses of opioids, awareness during anesthesia and unpleasant postoperative recall can occur. **Fentanyl** and **Sufentanil** are the two most commonly used. Opioids can be given by the epidural and subarachnoid route to produce excellent postoperative analgesia.

Propofol: Propofol has become the most popular IV anesthetic. Compared to barbiturates, its duration is just as long, but its recovery is more rapid, and patients are able to ambulate earlier after general anesthesia. It also causes a reduction in postoperative nausea and vomiting, so patients feel better. The drug is also useful to provide prolonged sedation in patients in the critical care setting. It can produce dose-related depression of central ventilatory drive and apnea.

Ketamine: This drug produces a dissociative anesthetic state characterized by catatonia, amnesia, and analgesia, with or without loss of consciousness. It has a high abuse potential owing to its psychoactive properties. Its mechanism involves blockade of glutamate.

LOCAL ANESTHETICS

Lidocaine and Bupivacaine are the most commonly used, although there are many others.

Clinical Pharmacology

Local anesthetics can provide highly effective analgesia in well-defined areas of the body. Usual routes of administration include topical injection, injection in the vicinity of peripheral nerve endings and major nerve trunks, and injection into the epidural or subarachnoid spaces surrounding the spinal cord. IV regional anesthesia is used for short surgical procedures involving the upper and lower extremities (less than 60 minutes).

The choice of local anesthetic for infiltration, peripheral nerve blocks, and central neuraxis blockade is usually based on the duration of action required. Procaine and chlorprocaine are short-acting; lidocaine, mepivacaine, and prilocaine are intermediate-acting; tetracaine, bupivacaine, levobupivacaine, and ropivacaine are longer-acting.

The anesthetic effect of the shorter-acting agents can be prolonged by increasing the dose or by adding a vasoconstrictor agent (such as epinephrine or phenylephrine). The vasoconstrictor agents slow the removal of the local anesthetic from the injection site. Local anesthetic is used topically for eye, ear, nose, and throat procedures, and for cosmetic surgery. Cocaine, because of its excellent penetration and local vasoconstrictor effects, has been used extensively for ENT procedures. Cocaine is somewhat irritating

and is used less frequently for ophthalmic procedures. Recent concern about its cardiotoxicity when combined with epinephrine has made most ENT doctors switch to a combination of lidocaine and epinephrine.

Topical local anesthetics are also used to treat patients with neuropathic pain syndromes, especially in combination with tricyclic antidepressants. These neuropathic pain syndromes are thought to be due to excessive neuronal firing.

SKELETAL MUSCLE RELAXANTS

Two groups: **Neuromuscular Blockers** (used in surgical procedures and in ICU settings to produce muscle paralysis for patients requiring ventilatory assistance) and **Spasmolytics** (those used to reduce spasticity)

Neuromuscular Blocking Drugs (Nondepolarizing)

Rocuronium is the prototype; Tubocurarine is also very important

Mechanism : When small doses of nondepolarizing muscle relaxants are given, they act predominantly at the nicotinic receptor by competing with ACh (acetylcholine). These drugs can also block prejunctional sodium channels. As a result of this action, muscle relaxants interfere with mobilization of ACh at the nerve ending.

Clinical Pharmacology of Neuromuscular Blockers: During anesthesia, administration of IV tubocurarine initially causes motor weakness, followed by the skeletal muscles becoming flaccid and inexcitable to electrical stimulation. Larger muscles (abdominal, diaphragm, paraspinal, trunk) are more resistant to blockade and recover more rapidly than smaller muscles (facial, foot, hand). The diaphragm is usually the last muscle paralyzed. No adverse effects occur, assuming that ventilation is maintained. When these drugs are discontinued, recovery of muscles usually occurs in reverse order, with the diaphragm regaining function first.

Reversal of Nondepolarizing Neuromuscular Blockade: The cholinesterase inhibitors effectively antagonize the neuromuscular blockade caused by nondepolarizing drugs.

Neostigmine and pyridostigmine antagonize nondepolarizing neuromuscular blockade by increasing the availability of ACh at the motor end plate, mainly by inhibition of AChE (acetylcholinesterase).

Uses of Neuromuscular Blockers: The most important application of the neuromuscular blockers is in facilitating intracavitary surgery (especially intra-abdominal and intrathoracic procedures).

Depolarizing Relaxant Drugs

Succinylcholine is the only clinically significant depolarizing blocking drug. Its neuromuscular effects are like those of ACh except that succinylcholine produces a longer effect at the myoneural junction. Succinylcholine reacts with the nicotinic receptor to open the channel and cause depolarization at the motor end plate, and this in turn spreads to the adjacent membranes, causing contractions of the muscle motor units. Because succinylcholine is not metabolized effectively at the synapse, the depolarized membranes remain depolarized and unresponsive to subsequent impulses. A flaccid paralysis results, because the membrane cannot repolarize and re-fire.

Clinical Pharmacology of Depolarizing Relaxant Drugs

Following administration of IV succinylcholine, transient muscle fasciculations occur over the chest and abdomen within 30 seconds. As paralysis develops rapidly, the arm, leg, and neck muscles are initially relaxed followed by the respiratory muscles. The whole effect lasts less than ten minutes due to succinylcholine's rapid hydrolysis by cholinesterase in the plasma.

SPASMOLYTIC DRUGS

Spasticity is characterized by an increase in tonic stretch reflexes and flexor muscle spasms (i.e. increased basal muscle tone) together with muscle weakness. It is often associated with cerebral palsy, MS, and stroke. These conditions often involve abnormal function of the bowel and bladder as well as skeletal muscle. Drugs that modify these conditions may modulate excitatory or inhibitory synapses.

Baclofen: Baclofen was designed to be an orally active GABA-mimetic agent. It exerts its spasmolytic activity at GABA receptors. Actions of these receptors by baclofen result in hyperpolarization, probably by increased potassium conductance. Baclofen may also reduce pain in patients with spasticity, perhaps by inhibiting the release of substance P in the spinal cord.

Gabapentin (Neurontin): Gabapentine is an antiepileptic drug that has shown considerable promise as a spasmolytic agent in patients with MS. Pregabalin is a new analog of gabapentin that may also be useful.

Dantrolene: Dantrolene is related to phenytoin. It has a unique mechanism of spasmolytic activity. Dantrolene reduces skeletal muscle strength by interfering with excitation-conduction coupling in the muscle fibers. Calcium is released from the sarcoplasmic reticulum, causing a contractile response, via the ryanodine receptor. Dantrolene interferes with the release of activator calcium by binding to the ryanodine receptor and blocking it. Motor units that contract rapidly are more sensitive to this drug's effects.

Dantrolene is used in the treatment of malignant hyperthermia. Patients at risk for this disease have a hereditary impairment in the ability of the SR to sequester calcium. After administration of one of the triggering agents (volatile anesthetics or neuromuscular blockers), there is a sudden and prolonged release of calcium, and body temperature skyrockets. Prompt treatment is essential to control acidosis and body temp and to reduce calcium release. IV Dantrolene will reduce the calcium levels.

Botulinum Toxin (Botox): This drug is used for ophthalmic purposes and for local muscle spasm as discussed earlier. Local facial injections are widely used for short term treatment of wrinkles around the eyes and mouth. It has also been used locally for treatment of cerebral palsy.

PARKINSONISM and other Movement Disorders

Parkinsonism is characterized by a combination of rigidity, bradykinesia, tremor, and postural instability that can occur for a variety of reasons, but is usually idiopathic. The normally high concentration of dopamine in the brain is reduced in parkinsonism, and

pharmacologic attempts to restore dopamine activity have been successful. Antimuscarinic drugs can also be used to treat this disease.

Levodopa (L-dopa): Dopamine does not cross the blood-brain barrier; thus, if it is given through the peripheral circulation, it cannot treat parkinsonism. However, the immediate precursor of dopamine does enter the brain. Therefore, Levodopa is a drug given for Parkinsonism; This drug is most effective in relieving bradykinesia and its associated disabilities. However, it treats all symptoms of Parkinsonism.

DOPAMINE RECEPTOR AGONISTS

Bromocriptine: Bromocriptine is a D-2 agonist. This drug treats Parkinsonism and hyperprolactinemia (at lower doses than for Parkinsonism).

MONOAMINE OXIDASE INHIBITORS (MAOIs)

Monoamine oxidase A metabolizes norepinephrine and serotonin. Monoamine oxidase B metabolizes dopamine. Selegiline, a reversible inhibitor of monoamine oxidase B at normal doses and A at higher doses, retards the breakdown of dopamine. Therefore, it enhances and prolongs the antiparkinsonism effects of levodopa and may reduce mild “on-off phenomena.” It has only very mild antiparkinsonism effects when given alone. Rasagiline, another monoamine oxidase B inhibitor, is more potent than selegiline in preventing parkinsonism and is being used as a neuroprotective agent and for early symptomatic treatment. The combined administration of levodopa and both forms of monoamine oxidase inhibitors must be avoided, as it may lead to hypertensive crises due to the peripheral accumulation of norepinephrine.

Restless Legs Syndrome: This disorder is characterized by an unpleasant creeping discomfort that seems to arise deep within the legs and occasionally the arms. Dopaminergic treatment is the first line, such as dopamine agonists, levodopa, clonazepam, and even opiates. Ropinirole (Requip) has recently been approved for this use.

Wilson’s Disease: A recessively inherited disorder of copper metabolism, Wilson’s Disease is characterized by reduced serum copper and ceruloplasmin concentrations, increased concentration of copper in the brain and viscera, and by clinical signs of hepatic and neurologic dysfunction. Tremor, choreiform movements, rigidity, hypokinesia, dysarthria, and dysphagia can also occur. Penicillamine, a chelating agent that forms a ring around copper, is given for patients with Wilson’s Disease.

ANTIPSYCHOTIC AGENTS AND LITHIUM

The terms antipsychotic and neuroleptic are used interchangeably to refer to a group of drugs that treat schizophrenia and other psychoses.

BASIC PHARMACOLOGY OF ANTIPSYCHOTICS

Phenothiazines: These drugs were once the most widely prescribed antipsychotics. This group includes chlorpromazine and thioridazine.

Thioxanthene Derivatives: In general, these are less potent than phenothiazines.

Butyrophenone Derivatives: This group includes haloperidol. They are more potent and have less autonomic effects, but more extrapyramidal effects.

Miscellaneous: This group includes pimozide, molindone, loxapine, clozapine, olanzapine, quetiapine, risperidone (Risperdal), ziprasidone (Geodon), and aripiprazole.

PHARMACOLOGIC EFFECTS

The first phenothiazine antipsychotics, with chlorpromazine as the prototype, proved to have wide effects on the CNS, autonomic nervous system, and endocrine system. These actions were traced to the drugs' ability to block dopamine, alpha-adrenoceptor, muscarinic, H-1, and serotonin receptors.

Dopamine Receptors: To date, five dopamine receptors have been described. Excessive dopamine release is theorized to be a possible cause of schizophrenia. Thus, any drug that stimulates the release of dopamine can exacerbate schizophrenia. Therefore, antagonism of dopamine is theorized to somewhat alleviate the effects of schizophrenia.

Psychological Effects: Most antipsychotic drugs cause unpleasant subjective effect in nonpsychotic individuals; the combination of sleepiness, restlessness, and autonomic effects creates experiences unlike those associated with other sedatives or hypnotics. Nonpsychotic individuals also experience impaired performance as judged by a number of motor and psychometric tests. Psychotic individuals, however, may actually show improvement in their performance as the psychosis is alleviated.

Electroencephalographic (EEG) Effects: Antipsychotics produce shifts in the pattern of EEG frequencies, usually slowing them and increasing their synchronization. The slowing is sometimes focal or unilateral, which may lead to erroneous diagnostic interpretations. Some of the neuroleptic agents lower the seizure threshold and induce EEG patterns typical of seizure disorder. However, with careful titration, most can be used safely in epileptic patients.

CLINICAL PHARMACOLOGY

Schizophrenia is the primary indication for antipsychotic agents, which remain the mainstay of treatment for this condition. Antipsychotics are also indicated for schizoaffective disorders, which share characteristics of schizophrenia and affective disorders. Antidepressants, lithium, or valproic acid, plus antipsychotics, are used to treat these diseases.

The manic phase of bipolar disorder can also be treated with antipsychotics, lithium, or valproic acid and supplemented with benzodiazepines. Other indications for antipsychotics include Tourette's syndrome, disturbed behavior in Alzheimer patients, and psychotic depression (along with antidepressants). Antipsychotics are NOT indicated for patients in withdrawal syndrome. Many of these drugs cause "pseudodepression."

Extrapyramidal side effects caused by these drugs include Parkinson's syndrome, akathisia (uncontrollable restlessness), and acute dystonic reactions (like spastic retrocollis and torticollis). The parkinsonism can be treated with antimuscarinics (NEVER with levopopa). Benadryl (diphenhydramine) can be used to treated the akathisia and acute dystonic reactions. These EPS are caused less frequently by the newer antipsychotics (those listed in the miscellaneous category).

Tardive dyskinesia is a late occurring syndrome of abnormal choreathetoid movements. It is the most important unwanted effect of the antipsychotics. Early recognition of this side effect is very important, as it occurs in 20 – 40% of patients on chronic therapy. Advanced cases of tardive dyskinesia are difficult to reverse.

Neuroleptic Malignant Syndrome: This life-threatening disorder occurs in patients who are extremely sensitive to the EPS of antipsychotics. The initial symptom is marked muscle rigidity. If sweating is impaired (due to side effects), fever may ensue, often reaching dangerous levels. The stress leukocytosis and high fever may erroneously suggest an infectious process. Autonomic instability, with altered blood pressure and heart rate, is often present. Creatine kinase enzymes are usually elevated, reflecting muscle damage. This syndrome is believed to be caused by excessively rapid blockade of postsynaptic dopamine receptors. A severe form of EPS follows. Vigorous early treatment with antiparkinsonism drugs is worthwhile. Muscle relaxants are also useful, as are dopamine agonists. If fever is present, cooling procedures should be done.

Overdoses: Poisonings with antipsychotics are rarely fatal, unlike TCAs (more to come...).

LITHIUM: Lithium is often referred to as an “antimanic” drug. Its primary action is to prevent mood swings in patients with bipolar affective (manic-depressive) disorder.

Bipolar affective disorder is characterized by cyclic attacks of mania, but many also have symptoms of paranoid schizophrenia (grandiosity, bellicosity, paranoid thoughts, and overactivity). The cause of the mood swings involved in bipolar affective disorder is unknown. Drugs that increase catecholamines tend to exacerbate the mania, while those that reduce the activity of dopamine or norepinephrine relieve mania. Bipolar disorder has a very strong genetic component.

Effects on Neurotransmitters: Lithium appears to enhance some of the activity of serotonin. It may also decrease epinephrine/norepinephrine turnover. It also blocks the development of dopamine receptor supersensitivity that accompanies chronic therapy of antipsychotics. It also may augment the synthesis of acetylcholine.

Clinical Pharmacology of Lithium

Valproate, Olanzapine, and other newer psychotics have now joined lithium in the fight against bipolar disorder. Lithium has a very slow onset, so other drugs can be given in conjunction. The depressive phase of bipolar disorder often requires the concurrent use of

antidepressants. TCAs have been linked to the precipitation of mania. SSRIs are less likely to induce mania, but are less effective overall.

Schizoaffective disorder, characteristics of symptoms of schizophrenia and depression, is treated with antipsychotics alone or in combination with lithium. Various antidepressants can also be added.

Lithium alone is rarely effective against schizophrenia, but is quite effective against this disease in combination with other antipsychotics.

Serum lithium concentrations must be continually monitored for patients taking lithium, usually taken ten to twelve hours after the last dose.

ANTIDEPRESSANTS

Major depression is one of the most common psychiatric disorders. About 10% of the population will be depressed at some point in their lives. Depression is a heterogeneous disorder that has been classified in a variety of ways. Major depressive disorder, dysthymia, bipolar disorder, and cyclothymic disorder are all labels for different kinds of depression. Bipolar disorder and cyclothymic disorder are both characterized by the presence of mania while dysthymia and major depressive disorder are purely depressive in nature.

Pathogenesis of Depression: After the introduction of the drug Reserpine, it was realized that the drug could induce depression. It worked by depleting stores of amine neurotransmitters. Therefore, drugs that increase amine function can relieve depression. However, even though drugs such as TCAs and MAOIs have prompt pharmacologic function, their physiologic function takes weeks to manifest.

BASIC PHARMACOLOGY

First Generation Agents: TCAs (Tricyclic Antidepressants): These drugs somewhat resemble phenothiazines. Imipramine and amitriptyline are the prototypical drugs of this class. These two are mixed norepinephrine and serotonin uptake inhibitors. The first generation agents demonstrate varying degrees of selectivity for the reuptake pumps for norepinephrine and serotonin; overall, selectivity is much lower than for the SSRIs. They also have numerous autonomic side effects.

Second Generation Agents: Second generation antidepressants include Amoxapine, Maprotiline, Trazodone and Bupropion. These agents cause dopamine antagonism, thus can lead to parkinsonism-like symptoms.

Third Generation Agents: These drugs include Venlafaxine, Mirtazapine, Nefazodone, and Duloxetine. These drugs inhibit serotonin and norepinephrine transport to varying degrees.

SSRIs (Selective Serotonin Reuptake Inhibitors): Fluoxetine is the prototype SSRI. Others include Paroxetine, Sertraline, Fluvoxamine, and Citalopram. These drugs have fewer side effects than the TCAs.

MAOIs (Monoamine Oxidase Inhibitors): Phenelzine and Tranylcypromine are included in this group. Both of these are nonselective MAOIs. However, Selegiline, is an MAO-B Inhibitor used to treat Parkinson's Disease.

CLINICAL PHARMACOLOGY

Depression: Major depressive episodes are diagnosed on the basis of the persistent degree and quality of depressed mood or loss of interest and pleasure in most activities, usually accompanied by disturbances of sleep, appetite, sexual drive, activity, or ability to concentrate. The depressed phase of bipolar disorder definitely demands treatment due to the high rate of suicide among these individuals. Standard antidepressants are usually added to lithium to treat this portion of bipolar disorder. SSRIs are less likely to induce mania than the older TCAs.

Anxiety Disorders: Panic, Generalized Anxiety, and Social Phobia

Imipramine (a TCA) has beneficial effects against the acute episodes of anxiety known as panic attacks. SSRIs, Venlafaxine, and Duloxetine are also effective against GAD and social phobia, but they require six to eight weeks to work.

Obsessive-Compulsive Disorder: Potent SSRIs are helpful in this disease. Fluoxetine and Clomipramine are most beneficial. Fluvoxamine is marketed specifically for this disorder.

Enuresis: Bed wetting is an established indication for TCAs. Drug therapy is not the preferred approach, however, because of the risk of overdoses and cardiovascular side effects.

Chronic Pain: TCAs are useful in this situation. SSRIs are not effective against chronic pain.

Miscellaneous: Fluoxetine is useful against bulimia. Fluoxetine is useful against PMDD (premenstrual dysphoric disorder). Imipramine and Desipramine are helpful against attention deficient hyperkinetic disorder. Atomoxetine (Strattera) will treat ADHD.

DRUG CHOICE: Patients depressed enough to be hospitalized benefit more from TCAs than from SSRIs. However, SSRIs have much favorable tolerability. The newer antidepressants and the SSRIs have the greatest benefit in their lack of side effects, not in their efficacy. MAOIs are reserved for patients who have failed two courses of therapy due to their side effects. Lithium added to an antidepressant can give a favorable response when the antidepressant does not work alone. Only the older antidepressants increase the suicide risk.

Review of Different Classes of Antidepressants:

TCAs: Amitriptyline (Elavil), Clomipramine, Desipramine, Doxepin, Imipramine, Nortriptyline, Protriptyline, Trimipramine

2nd and 3rd generation agents: Amoxapine, Bupropion (Wellbutrin), Duloxetine (Cymbalta), Maprotiline, Mirtazapine (Remeron), Nefazodone, Trazodone (Desyrel), Venlafaxine (Effexor)

MAOIs: Phenelzine, Tranylcypromine

SSRIs: Citalopram (Celexa), Fluoxetine (Prozac), Fluvoxamine, Paroxetine (Paxil), Sertraline (Zoloft), Escitalopram (Lexapro)

OVERDOSES

TCAs: these are especially dangerous when taken in large quantities.

MAOIs: Fatal OD on these is unusual

SSRIs: OD on these is rare (resulting in fatality that is); only supportive treatment can be offered

OPIOID ANALGESICS AND ANTAGONISTS

Morphine, the prototypical opioid agonist, has been around for hundreds of years.

BASIC PHARMACOLOGY: Opium, the source of morphine, is obtained from the poppy plant. Codeine is synthesized commercially from morphine. Opioid drugs include full agonists, partial agonists, and antagonists.

Endogenous Opioid Peptides

Opioid alkaloids produce analgesia (pain control) through actions at regions in the CNS that contain peptides with opioid-like properties. There are three families of these peptides: **endorphins, enkephalins, and dynorphins**. There are 3 receptor subtypes at which opioid peptides act: mu, delta, and kappa. All 3 of these are found in the dorsal horn of the spinal cord. Mu receptors are involved in supraspinal and spinal analgesia, sedation, inhibition of respiration, slowed GI transit, and modulation of hormone and NT release. Delta receptors are involved in supraspinal and spinal analgesia and modulation of hormone and NT release. Kappa receptors are involved in supraspinal and spinal analgesia, psychotomimetic effects, and slowed GI transit.

MECHANISM OF ACTION: Opioid agonists produce analgesia by binding to specific G protein-coupled receptors that are located in the brain and spinal cord regions involved in the transmission and modulation of pain. Opioid agonists close voltage-gated calcium channels on presynaptic nerve terminals and thereby reduce NT release. They also hyperpolarize and thus inhibit postsynaptic neurons by opening potassium channels.

The majority of currently available opioid analgesics act primarily at the mu opioid receptor. Analgesia, as well as euphoriant, respiratory depressant, and physical dependence properties of morphine result primarily from actions at the mu receptor. However, delta and kappa receptors are still involved. Opioids are usually given systemically, and thus act at several sites at once. Thus, they inhibit pain transmission on both ascending and descending levels.

Tolerance and Physical Dependence: With frequently related therapeutic doses of morphine or its surrogates, this is a gradual loss of effectiveness (**tolerance**). To reproduce the original response, a larger dose must be administered. Along with tolerance, **physical dependence** (characterized by a withdrawal or abstinence syndrome when a drug is stopped or an antagonist is administered) develops.

CNS effects of Opioids:

Analgesia: pain consists of sensory and emotional components; opioids can reduce both aspects of this, especially the emotional component

Euphoria: a pleasant floating sensation with lessened anxiety and distress; dysphoria (characterized by restlessness and malaise) can sometimes occur; IV morphine can induce euphoria or dysphoria

Sedation: drowsiness and clouding of mentation are common concomitants of opioid action. There is little or no amnesia.

Respiratory depression: all of the opioid analgesics can produce significant respiratory depression by inhibiting brainstem respiratory mechanisms.

Cough suppression: opioids cause cough suppression. Codeine, in particular, is not for this effect. However, this can lead to accumulation of secretions and thus airway obstruction and atelectasis.

Miosis: constriction of the pupils is seen with all opioid agonists. No tolerance develops to miosis.

Common opioids include Morphine, Hydromorphone (Dilaudid), Oxymorphone (Numorphan), Methadone, Meperidine (Demerol), Fentanyl, Sufentanyl, Alfentanil, Remifentanyl, Levorphanol (Levo-Dromoran), Codeine, Hydrocodone, Oxycodone (Percodan), Propoxyphene (Darvon), Pentazocine, Nalbuphine, Buprenorphine, and Butorphanol.

CLINICAL PHARMACOLOGY (As pertains to neuroanatomy)

Analgesia: Researchers in the hospice setting have noticed that fixed-interval administration of opioids is more effective than just giving them on demand.

Cough: Several synthetic compounds are now used in preference to opioids for cough suppression.

Shivering: Meperidine has the most anti-shivering effects, although all opioids do to some extent.

Anesthesia Applications: Opioids are frequently used as a premedicant before anesthesia and surgery, due to their sedative, anxiolytic, and analgesic properties. They are also used intraoperatively. Opioids can also be used as regional anesthetics in the epidural or subarachnoid spaces. Respiratory depression may require use of naloxone.

Treatment of Overdose: IV injection of naloxone dramatically reverses coma due to opioid overdose but not that due to other CNS depressants.

SPECIFIC AGENTS

Strong agonists: Morphine, hydromorphone, and oxymorphone are all similar... heroin is illegal in the US, but it is also in this group.

Methadone: It is used as an analgesic and also for withdrawal symptoms (especially for heroin addicts).

Fentanyl (the most widely used drug in this group), sufentanil, alfentanil, and remifentanil are all similar... Meperidine is also in this group. Fentanyl is often used for anesthetic purposes.

Mild to moderate agonists: Codeine, oxycodone, dihydrocodeine, and hydrocodone (all are somewhat less efficacious than morphine or have worse adverse effects)

OPIOID ANTAGONISTS: Naloxone and naltrexone: These can be used to reverse the effects of opioid agonists.