Pharmacotherapy of neurologic diseases

Stroke

is a heterogeneous group of disorders involving sudden, focal interruption of cerebral blood flow that causes neurologic deficit.

Stroke symptoms lasting < 1 h are termed a transient ischemic attack (TIA). Strokes can be ischemic (80%), typically resulting from thrombosis or embolism, or hemorrhagic (20%), resulting from vascular rupture (eg, subarachnoid or intracerebral hemorrhage). Today we will talk about ischemic stroke.

**Etiology.** Ischemic strokes result from events that limit or stop blood flow, such as extracranial or intracranial thrombosis, embolism, thrombosis in situ, nonthrombotic occlusion of small, deep cortical arteries (lacunar infarction) or relative hypoperfusion.

**Risk factors** for ischemic stroke include modifiable and nonmodifiable etiologies. Nonmodifiable risk factors are age, race, sex, ethnicity, heredity. Modifiable risk factors include the following: hypertension (the most important), diabetes mellitus, cardiac disease, hypercholesterolemia, carotid stenosis, lifestyle (excessive alcohol intake, tobacco use, illicit drug use, obesity, physical inactivity), oral contraceptive use.

**Epidemiology.** Stroke is the leading cause of disability and the third leading cause of death. Men are at higher risk for stroke than women. Risk of stroke increases with age, especially in patients older than 64 years, in whom 75% of all strokes occur. The prognosis after acute ischemic stroke varies greatly, depending on the stroke severity and on the patient’s premorbid condition, age, and poststroke complications.

**Pathophysiology.** Mechanisms of ischemic injury include edema, microvascular thrombosis, programmed cell death (apoptosis), and infarction with cell necrosis.

**Symptoms and signs.** Stroke should be considered in any patient presenting with an acute neurologic deficit (focal or global) or altered level of consciousness. Initial symptoms (numbness, weakness, headache) occur suddenly. Common
symptoms of stroke include paralysis of the contralateral limbs and the face, hemisensory deficits, monocular or binocular visual disturbances (visual field deficits, diplopia), dysarthria, dizziness or loss of balance and coordination (ataxia), vertigo, aphasia, sudden decrease in the level of consciousness. Although such symptoms can occur alone, they are more likely to occur in combination and depend on the part of the brain affected.

**Treatment**

- Acute antihypertensive therapy only in certain circumstances
- Antiplatelet therapy
- Occasionally for acute treatment, tPA or thrombolysis-in-situ
- Sometimes anticoagulation
- Long-term control of risk factors
- Sometimes carotid endarterectomy

Patients with acute ischemic strokes are usually hospitalized. Perfusion of an ischemic brain area may require a high BP because autoregulation is lost; thus, BP should not be decreased except in the following situations:

1. BP is > 220/120 mm Hg on 2 successive readings > 15 min apart.
2. There are signs of other end-organ damage (eg, aortic dissection, acute MI, pulmonary edema, hypertensive encephalopathy, retinal hemorrhages, acute renal failure).
3. Use of recombinant tissue plasminogen activator (tPA) is likely.

If indicated, nicardipine 5 mg/h IV is given initially; dose is increased by 2.5 mg/h q 5 min to a maximum of 15 mg/h as needed to decrease systolic BP by 10 to 15%. Alternatively, IV labetalol can be used.

Most patients are not candidates for thrombolytic therapy; they should be given an antplatelet drug usually aspirin 325 mg po when they are admitted to the hospital. Contraindications to antplatelet drugs include aspirin- or NSAID-induced asthma or urticaria, other hypersensitivity to aspirin or to tartrazine, acute GI bleeding, G6PD deficiency, and use of warfarin.
Recombinant tPA is used for patients with acute ischemic stroke of < 3 h duration and no contraindications to tPA. **tPA (alteplase)** must be given within 3 h of symptom onset. Before treatment with tPA, brain hemorrhage must be excluded by CT, and systolic BP must be < 185 mm/110 mm Hg; antihypertensive drugs may be given as above. Dose of tPA is 0.9 mg/kg IV (maximum dose 90 mg); 10% is given by rapid IV injection, and the remainder by constant infusion over 60 min. Any bleeding complications are aggressively managed. Anticoagulants and antiplatelet drugs are not used within 24 h of treatment with tPA.

**Anticoagulation** with heparin or low molecular weight heparin is used for stroke caused by cerebral venous thrombosis, emboli due to atrial fibrillation. Before anticoagulation, hemorrhage must be excluded by CT. Heparin give bolus of 80 units/kg, than infuse 18 units/kg/h, and 6 h after bolus chek PTT and adjust dose according to PTT. Adverse effects of all heparins include the following: bleeding, thrombocytopenia, urticaria, thrombosis or anaphylaxis (rarely). **Low Molecular Weight:** dalteparin give 100 units/kg sc q 12 h or 200 units/kg once/day, prophylactic dose is 2500–5000 units once/day, enoxaparin give 1 mg/kg sc q 12 h or 1.5 mg/kg sc once/day, tinzaparin give 175 units/kg sc once/day. Low molecular weight heparins are usually given by sc injection in the abdominal area while the patient is supine. Warfarin is begun simultaneously with heparin.

**Thrombolysis-in-situ** (angiographically directed intra-arterial thrombolysis) can sometimes be used for major strokes if symptoms have begun > 3 h but < 6 h.

**Secondary prevention.** Oral antiplatelet drugs are used to prevent subsequent strokes. Aspirin 81 or 325 mg once/day, clopidogrel 75 mg once/day, or the combination product aspirin 25 mg/extended-release dipyridamole 200 mg bid may be used. In patients taking warfarin, antiplatelet drugs additively increase risk of bleeding and are thus usually avoided.

**MIGRAINE**

Migraine is an episodic, often debilitating disorder characterized by attacks of severe headache in association with combinations of neurologic and gastrointestinal
symptoms.

**Epidemiology.** Migraine most commonly begins during puberty or young adulthood, waxing and waning in frequency and severity over the ensuing years; it often diminishes after age 50. Studies show familial aggregation of migraine.

**Etiology.** Many potential migraine triggers have been identified; they include the following: drinking red wine, skipping meals, excessive afferent stimuli (eg, flashing lights, strong odors), weather changes, sleep deprivation, stress, hormonal factors, head trauma, neck pain, or temporomandibular joint dysfunction sometimes triggers or exacerbates migraine.

**Pathophysiology.** Migraine is thought to be a neurovascular pain syndrome with altered central neuronal processing and involvement of the trigeminovascular system (triggering neuropeptide release, which causes painful inflammation in cranial vessels).

**Symptoms and Signs.** Often, attacks are heralded by a prodrome (a sensation that a migraine is beginning), which may include mood changes, loss of appetite, nausea, or a combination. Auras are temporary neurologic disturbances that can affect sensation, balance, muscle coordination, speech, or vision; they last minutes to an hour. Headache varies from moderate to severe, and attacks last from 4 hours to several days, typically resolving with sleep. The pain is often unilateral but may be bilateral, most often in a frontotemporal distribution, and is typically described as pulsating or throbbing. Migraine is more than a headache. Associated symptoms such as nausea (and occasionally vomiting), photophobia, sonophobia, and osmophobia are prominent. Patients report difficulty concentrating during attacks. Attacks vary significantly in frequency and severity.

**Pharmacotherapy.** Pharmacologic agents used for the treatment of migraine can be classified as abortive (ie, for alleviating the acute phase) or prophylactic (ie, preventive). Abortive medications include the following: Selective serotonin receptor (5-HT$_1$) agonists (triptans), Ergot alkaloids, Analgesics, Nonsteroidal anti-inflammatory drugs (NSAIDs), Combination products, Antiemetics. Prophylactic medications include the following: Antiepileptic drugs, Beta-blockers, Tricyclic
antidepressants, Calcium channel blockers, Selective serotonin reuptake inhibitors (SSRIs), Serotonin antagonists, Botulinum toxin.

**Selective Serotonin Receptor (5-HT1) Agonists.** Triptans are selective serotonin agonists, specifically acting at 5-hydroxytryptamine 1B/1D/1F (5-HT1B/1D/1F) receptors on intracranial blood vessels and sensory nerve endings. Triptans are used as abortive medications for moderately severe to severe migraine headaches. *Sumatriptan* 50–100 mg po, 5–20 mg nasal spray, or 6 mg sc. *Naratriptan.* 2.5 mg po. It is useful for patients with slow onset, prolonged migraine, such as menstrual migraine. *Zolmitriptan* 2.5–5 mg po or 5 mg nasal spray. *Rizatriptan* 10 mg po. *Almotriptan.* 12.5 mg po. *Frovatriptan* 2.5 mg po. *Eletriptan.* 20–40 mg po.

**Ergot Alkaloids.** *Dihydroergotamine* is an alpha-adrenergic blocking agent with a direct stimulating effect on smooth muscle of peripheral and cranial blood vessels. It depresses central vasomotor centers. A dose of 1 mg intravenously every 8 hours with or without metoclopramide is safe and effective for treatment of status migrainosus. Also can use 0.5–1 mg sc or 4 mg/mL nasal spray.

**Analgesics.** *Oxycodone, morphine, meperidine, hydromorphone, butorphanol.* These agents are used as initial abortive therapy for patients with infrequent migraines.

There are **Combination Analgesics.** Combination of *sumatriptan* 85 mg and *naproxen sodium* 500 mg. It is indicated for acute migraine. *Butalbital, aspirin, and caffeine* (Fiorinal). This combination drug is effective for mild to moderately severe migraine headache. The barbiturate component has generalized depressant effect on CNS. Caffeine is used to increase GI absorption. *Isometheptene, dichloralphenazone, and acetaminophen.* This combination drug has sympathomimetic properties. It dilates cranial and cerebral arterioles, causing a reduction in the stimuli that lead to vascular headaches. *Butalbital, acetaminophen, and caffeine.* *Acetaminophen and codeine.* Thise drug combination are indicated for treatment of mild to moderately severe headache.

**Nonsteroidal Anti-inflammatory Drugs** (NSAIDs) are generally used as
abortive therapy in mild to moderately severe migraine headaches. NSAIDs are also used as prophylactic agents, but they are associated with a higher risk of adverse effects, particularly gastropathy or nephropathy, than when used as abortive medications. Aspirin is a mild analgesic that can be used to treat infrequent migraine episodes. Ketorolac is indicated for short-term (up to 5 d) management of moderate to moderately severe pain. Ibuprofen, naproxen, ketoprofen are used for relief of mild to moderately severe headaches and inflammation.

**Antiemetics.** As dopamine antagonists, these agents are effective if nausea and vomiting are prominent features. They also may act as prokinetics to increase gastric motility and enhance absorption. Chlorpromazine, Droperidol, Prochlorperazine. Promethazine

**Antiepileptics.** These drugs are effective in prophylaxis of migraine headache. Divalproex sodium/valproate is now considered first-line preventive medication for migraine. Gabapentin and Topiramate are used for migraine headache prophylaxis.

**Beta-blockers.** Significant to their activity as migraine prophylactic agents is the lack of partial agonistic activity. Latency from initial treatment to therapeutic results may be as long as 2 months. Metoprolol, Propranolol, Timolol, Nadolol are effective in prophylaxis of migraine headache.

**Tricyclic Antidepressants.** Amitriptyline, nortriptyline, doxepin, and protriptyline have been used for migraine prophylaxis, but only amitriptyline has proven efficacy and appears to exert its antimigraine effect independent of its effect on depression.

**Calcium Channel Blockers.** Flunarizine and verapamil are commonly used as prophylactic medication. This group is particularly useful in patients with comorbid hypertension and in those with contraindications to beta-blockers. This group may have particular advantage in patients with prolonged aura, vertebrobasilar migraine, or hemiplegic migraine.

**Selective Serotonin Reuptake Inhibitors.** Paroxetine, Fluoxetine, Sertraline is may be considered first-line drugs, but they have low efficacy.

**Histamine H_{1} Antagonists.** Cyproheptadine acts primarily as antagonist of
cerebral vascular 5-HT2 receptors and has been used traditionally for pediatric migraine prevention despite minimal objective evidence of its efficacy.

**Neuromuscular Blocker Agents, Toxin.** Botulinum toxin A may be beneficial in patients with intractable migraine headaches that fail to respond to at least 3 conventional preventive medications. *Onabotulinumtoxin A* (BOTOX). This is one of several toxins produced by Clostridium botulinum. It blocks neuromuscular transmission through a 3-step process. The injections are administered to the scalp and temple. They may reduce the frequency and severity of migraine attacks after 2-3 months of injections.

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**Epilepsy**

(also called epileptic seizure disorder) is a chronic brain disorder characterized by recurrent (≥ 2), unprovoked seizures (ie, not related to reversible stressors). Epilepsy is often idiopathic, but various brain disorders, such as malformations, strokes, and tumors, can cause symptomatic epilepsy.

**Etiology.** Adults: Cerebral trauma, alcohol withdrawal, tumors, strokes, and unknown cause (in 50%). The elderly: Tumors and strokes.

**Classification.** Seizures are classified as generalized or partial. *Generalized seizures* include the following: Infantile spasms, Absence seizures, Tonic-clonic seizures, Atonic seizures, Myoclonic seizures. Partial seizures may be Simple (no impairment of consciousness), Complex (reduced but not complete loss of consciousness).

**Symptoms and Signs.** Seizures may be preceded by an aura. Auras may consist of sensory, autonomic, or psychic sensations (eg, paresthesias, a rising epigastric sensation, abnormal smells, a sensation of fear, a déjà vu sensation). Most seizures end spontaneously in 1 to 2 min. Generalized seizures are often followed by a postictal state, characterized by deep sleep, headache, confusion, and muscle soreness; this state lasts from minutes to hours. Most patients appear neurologically normal between seizures.
Treatment

- Elimination of the cause if possible
- Avoidance of or precautions during situations when loss of consciousness could be life threatening
- Drugs to control seizures
- Surgery if ≥ 2 drugs do not control seizures

Optimal treatment is to eliminate the causes whenever possible. If the cause cannot be corrected or identified, anticonvulsants are often required. During a generalized tonic-clonic seizure, injury should be prevented by loosening clothing around the neck and placing a pillow under the head. Attempting to protect the tongue is futile and likely to damage the patient's teeth or the rescuer's fingers. Patients should be rolled onto their left side to prevent aspiration. These measures should be taught to the patient's family members and coworkers.

Some general principles apply:

- A single drug, usually the 1st or 2nd one tried, controls epileptic seizures in about 60% of patients.
- If seizures are difficult to control from the outset (in 30 to 40% of patients), ≥ 2 drugs may eventually be required.
- If seizures are intractable (refractory to an adequate trial of ≥ 2 drugs), patients should be referred to an epilepsy center to determine whether they are candidates for surgery.

Some drugs (eg, phenytoin, valproate), given IV or orally, reach the targeted therapeutic range very rapidly. Others (eg, lamotrigine, topiramate) must be started at a relatively low dose and gradually increased over several weeks to the standard therapeutic dose, based on the patient's lean body mass. Dose should be tailored to the patient's tolerance of the drug.

Drug choice for long-term treatment: The drugs preferred vary according to type of seizure. For Primary generalized tonic-clonic seizures First-line monotherapy: Carbamazepine, Phenytoin, Valproate, Topiramate. 2nd-line monotherapy or adjunctive therapy: Lamotrigine, Levetiracetam; Adjunctive therapy
Zonisamide. Phenobarbital although effective, often considered 2nd-line monotherapy because it is sedating and can cause behavioral and learning problems in children.

Partial seizures with or without secondary generalization First-line monotherapy Carbamazepine, Lamotrigine, Oxcarbazepine, Phenytoin, Topiramate, Levetiracetam. 2nd-line monotherapy or adjunctive therapy Gabapentin, Pregabalin, Valproate, Zonisamide; 3rd-line monotherapy or adjunctive therapy Felbamate Tiagabine, Vigabatrin;

Typical absence seizures First-line monotherapy Ethosuximide, Lamotrigine, Valproate. Also effective Levetiracetam, Topiramate, Zonisamide.

Atypical absence seizures and Absence seizures associated with other seizure types First-line monotherapy Valproate, Lamotrigine, Topiramate, Felbamate. Clonazepam also effective, but often development of tolerance.

Infantile spasms, Atonic seizures, Myoclonic seizures First-line monotherapy; risk of irreversible visual field defects Valproate, Vigabatrin. 2nd-line Clonazepam

Tonic and atonic seizures First-line monotherapy Lamotrigine. Felbamate sometimes use for alternative or adjunctive therapy for atonic seizures.

Juvenile myoclonic epilepsy First-line monotherapy Valproate; 2nd-line monotherapy or adjunctive therapy Lamotrigine, Levetiracetam, Zonisamide.

Unclassifiable seizures First-line monotherapy Valproate; 2nd-line monotherapy Lamotrigine; 3rd-line monotherapy or adjunctive therapy Levetiracetam, Topiramate, Zonisamide.

For partial seizures and generalized tonic-clonic seizures, the newer anticonvulsants (eg, clonazepam, felbamate, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, zonisamide) are no more effective than the established drugs. However, the newer drugs tend to have fewer adverse effects and to be better tolerated.