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Review On Drug Interactions in Neurosurgical Patients

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Abstract
A drug interaction is a change in the action or side effects of a drug caused by concomitant administration with a food, beverage, supplement, or another drug a cause of a drug interaction involves one drug which alters the pharmacokinetics of another medical drug. Alternatively, drug interactions result from competition for a single receptor or signaling pathway. Both synergy and antagonism occur during different phases of the interaction between a drug and an organism. For example, when synergy occurs at a cellular receptor level this is termed agonism, and the substances involved are termed agonists. On the other hand, in the case of antagonism, the substances involved are known as inverse agonists. The risk of a drug-drug interaction increases with the number of drugs used. Over a third (36%) of the elderly in the U.S. regularly uses five or more medications or supplements, and 15% are at risk of a significant drug-drug interaction. [1]

Keywords
Neurosurgical disorder, drug-drug interaction, thiopentone and suxamethonium

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INTRODUCTION:

Drug interactions in a clinical setting:

Prediction and Clinical Management of Drug Interactions in Vitro Screening

Clinical Trials

Case Reports

Transport and distribution interactions

The main interaction mechanism is competition for plasma protein transport. In these cases, the drug that arrives first binds with the plasma protein, leaving the other drug dissolved in the plasma, which modifies its concentration. The organism has mechanisms to counteract these situations (by, for example, increasing plasma clearance), which means that they are not usually clinically relevant. However, these situations should be taken into account if other associated problems are present such as when the method of excretion is affected.[15]

Metabolism interactions

Many drug interactions are due to alterations in drug metabolism.[16] Further, human drug-metabolizing enzymes are typically activated through the engagement of nuclear receptors.[16] One notable system involved in metabolic drug interactions is the enzyme system comprising the cytochrome P450 oxidases.

CYP450

Cytochrome P450 is a very large family of haemoproteins (hemoproteins) that are characterized by their enzymatic activity and their role in the metabolism of a large number of drugs.[17] Of the various families that are present in human beings the most interesting in this respect are

the 1, 2 and 3, and the most important enzymes are CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4.[18] The majority of the enzymes are also involved in the metabolism of endogenous substances, such as steroids or sex hormones, which is also important should there be interference with these substances. As a result of these interactions the function of the enzymes can either be stimulated (enzyme induction) or inhibited (enzyme inhibition).

Enzymatic inhibition

If drug A is metabolized by a cytochrome P450 enzyme and drug B inhibits or decreases the enzyme's activity, then drug A will remain with high levels in the plasma for longer as its inactivation is slower. As a result, enzymatic inhibition will cause an increase in the drug's effect. This can cause a wide range of adverse reactions.

It is possible that this can occasionally lead to a paradoxical situation, where the enzymatic inhibition causes a decrease in the drug's effect: if the metabolism of drug A gives rise to product A_2, which actually produces the effect of the drug. If the metabolism of drug A is inhibited by drug B the concentration of A_2 that is present in the blood will decrease, as will the final effect of the drug.

Enzymatic induction

If drug A is metabolized by a cytochrome P450 enzyme and drug B induces or increases the enzyme's activity, then blood plasma concentrations of drug A will quickly fall as its inactivation will take place more rapidly. As a result, enzymatic induction will cause a decrease in the drug's effect.

As in the previous case, it is possible to find paradoxical situations where an active metabolite causes the drug's effect. In this case, the increase in active metabolite A_2 (following the previous example) produces an increase in the drug's effect.

It can often occur that a patient is taking two drugs that are enzymatic inductors, one inductor and the other inhibitor or both inhibitors, which greatly complicates the control of an individual's medication and the avoidance of possible adverse reactions.

An example of this is shown in the following table for the CYP1A2 enzyme, which is the most common enzyme found in the human liver. The table shows the substrates (drugs metabolized by this enzyme) and the inductors and inhibitors of its activity: [18]

Table 1: Drugs related to CYP1A2

Drugs related to CYP1A2		
Substrates	**Inhibitors**	**Inductors**
• Caffeine	• Omeprazole	• Phenobarbital
• Theophylline	• Nicotine	• Fluvoxamine
• Phenacetin	• Cimetidine	• Venlafaxine
• Clomipramine	• Ciprofloxacin	• Ticlopidine
• Clozapine		
• Thioridazine		

Enzyme CYP3A4 is the enzyme that the greatest number of drugs uses as a substrate. Over 100 drugs depend on its metabolism for their activity and many others act on the enzyme as inductors or inhibitors [16, 17]

Types of drug interactions

There are several different types of drug interactions to be aware of. Let's explore each one a little further.

Drug-drug

A drug-drug reaction is when there's an interaction between two or more prescription drugs.

One example is the interaction between warfarin (Coumadin),an anticoagulant (blood thinner), and fluconazole (Diflucan), an antifungal medication. Taking these two drugs together can lead to a potentially dangerous increase in bleeding.

Drug-nonprescription treatment

This is a reaction between a drug and a nonprescription treatment. These include over the counter (OTC) medications, herbs, vitamins, or supplements.

An example of this type of interaction can occur between a diuretic — a drug that attempts to rid the body of excess water and salt — and ibuprofen (Advil). The ibuprofen may reduce the diuretic's effectiveness because ibuprofen often causes the body to retain salt and fluid.

Drug-food

This happens when food or beverage intake alters a drug's effect.

For example, some statins (used to treat high cholesterol) can interact with grapefruit juice. If a person who takes one of these statins drinks a lot of grapefruit juice, too much of the drug may stay in their body, increasing their risk for liver damage or kidney failure.

Another potential outcome of the statin-grapefruit juice interaction is rhabdomyolysis. This is when skeletal muscle breaks down, releasing a protein

called myoglobin into the blood. Myoglobin can go on to damage the kidneys.

Drug-alcohol

Certain medications shouldn't be taken with alcohol. Often, combining these drugs with alcohol can cause tiredness and delayed reactions. It can also increase your risk for negative side effects.

Drug-disease

This interaction is when the use of a drug alters or worsens a condition or disease. Additionally, some medical conditions can increase the risk of side effects from specific drugs.

For example, some decongestants that people take for colds can increase blood pressure. This is a potentially dangerous interaction for people with high blood pressure (hypertension).

Another example is metformin (a diabetes drug) and kidney disease. People with kidney disease should use a lower dosage of metformin or not take it at all. This is because metformin can accumulate in the kidneys of people with this disease, increasing the risk of severe side effects

Drug-laboratory

Some medications can interfere with specific laboratory tests. This can result in inaccurate test results.

For instance, tricyclic antidepressants have been shown to interfere with skin prick tests used to determine whether someone has certain allergies.

Other factors in drug interactions

While it's important to educate yourself on your potential for drug interactions, understand that this information doesn't tell you everything you need to know. Just because a drug interaction can occur doesn't mean it will.

Personal traits can play a role in whether a drug interaction will happen and if it will be harmful. Specifics about your drugs, including dosage, formulation, and how you take them, can also make a difference.

The following factors of an individual's medical history influence possible drug interactions:

Genetics

Variations in individual genetic makeup can make the same drug work differently in different bodies.

As a result of their genetic code, some people process certain medications more quickly or more slowly than others.

This may cause the drug levels to go down or go up more than expected. Your doctor will know which drugs require genetic testing to find the correct dosage for you.

Weight

Some drugs are dosed according to how much a person weigh.

Weight changes could affect dosage and also increase or decrease the risk of drug interactions. So if you have a substantial change in your weight, you could need a different dosage of some medications.

Age

As we age, our bodies change in many ways, some of which may affect how we respond to medications. The kidneys, liver, and circulation system may slow down with age. This can slow the breakdown and removal of drugs from our bodies.

Neurosurgical Procedures

- Minimally Invasive Spine Surgery
- Microvascular Decompression
- Peripheral Nerve Surgery
- Base of Skull Surgery
- Pituitary Surgery
- Cervical Spine Surgery

Minimally Invasive Spine Surgery

Recent advances in surgical technology have meant that the focus of treatment for spinal conditions has progressed towards preservation of normal spinal motion and sparing of structures adjacent to problem areas. This has meant reductions in time spent in the operating room and hospital. The length of the surgical incisions is much less and the pain associated with surgery is minimal in most cases. In most minimally invasive spine cases the patient can walk on the day of surgery and is home within one to two days. Long term mechanical consequences of surgery are decreased compared to long segment operations and spinal fusions. The most common procedures are microdiscectomy, microforaminotomy, and rhizolysis. Endoscopic discectomy utilizes a circular retractor and endoscopic instruments. In general, minimally invasive spinal surgery is appropriate for pain, weakness, and numbness due to nerve compression and has little role to play in mechanical or arthritic back pain.

Microvascular Decompression

Microvascular decompression (MVD) is a surgical procedure for the treatment of cranial nerve compression syndromes. The commonest of these syndromes is Trigeminal Neuralgia (severe pain affecting one side of the face). Other syndromes include Hemifacial Spasm (severe involuntary twitching of one side of the face), and Glossopharyngeal Neuralgia (severe pain in one side of the throat associated with swallowing).

The surgery involves making a hole in the skull behind the ear, opening the lining of the brain (dura) and inspecting the origin of the affected cranial

nerve using the microscope for magnification and illumination. In most cases a blood vessel, usually an artery, sometimes a vein, is found to be compressing the origin of the nerve. The vessel is carefully moved away from the nerve. It is held away with one or more small pieces of woven fabric (Teflon), which remains in place and cushions the nerve from the vessel.

The surgery is successful in more than 85% of cases and allows the patient with severe Trigeminal Neuralgia to wean off the anticonvulsant medication which has been the mainstay of their medical treatment.

Peripheral Nerve Surgery

The brain and spinal cord make up the Central Nervous System (CNS). Surgery involving nerves outside the CNS is referred to as Peripheral nerve surgery. Nerves originating in the spinal cord in the neck leave the spinal cord and form a network of nerves called the Brachial plexus before dividing into specific nerves of the arm. Similarly, nerves originating in the lumbar spine form the Lumbosacral plexus before dividing into specific nerves of the leg. The commonest indications for peripheral nerve surgery include trauma to nerves, tumors in nerves and entrapment syndromes involving nerves. Carpal tunnel syndrome (CTS) is the commonest entrapment syndrome and Carpal tunnel release (CTR) is the most common procedure performed worldwide. Symptoms of CTS include pain and numbness in the hands and sometimes up the arm, typically occurring at night or when driving the car. Other common entrapment syndromes involve the ulnar nerve at the elbow, common peroneal nerve at the knee, and posterior tibial nerve at the ankle, to name just a few.

Many types of Tumors occur within nerves, but the most common are benign tumors called Schwannomas or Neurofibromas. Mostly these are one off sporadic case, but rarely are part of an inherited syndrome such as Familial Schwannomatosis or Hereditary Neurofibromatosis.

Trauma to nerves may take the form of sharp or blunt (stretch) injuries. Generally sharp injuries are surgically repaired early, while blunt injuries are observed for a short time to see if spontaneous recovery occurs.

Base of Skull Surgery

Tumors and vascular abnormalities such as aneurysms frequently occur at the base or floor of the skull. These abnormalities provide a significant surgical challenge because most of the major blood vessels to and from the brain, as well as most of the cranial nerves traverse this space.

In recent times neurosurgeons have developed specific skills and equipment to allow surgery to be done safely in this domain which was previously thought to be inoperable. Advances in magnification and illumination with state-of-the-art operating microscopes, computer generated neuronavigation equipment, laser technology, flexible and rigid endoscopes allowing minimally invasive keyhole surgery, rigid fixation retractor systems and intraoperative stimulation and monitoring machines, have all made this type of surgery more feasible.

Combined approaches with Ear, Nose and Throat Surgeons and Head and Neck Surgeons have allowed North Shore Neurosurgeons to remove difficult tumors at the Base of Skull via trans-nasal and cranio-facial approaches. Advances in endoscopes and specific drills allow this delicate surgery of the brain to be done through the nose.

Pituitary Surgery

Surgery in and around the Pituitary gland is a relatively common neurosurgical procedure which is often done through the nose (endonasal transsphenoidal). Pituitary tumors represent about 15% of all brain tumors, however, behave very differently to intrinsic brain tumors. The indications for surgical treatment are hormonal imbalance, due to over production of hormone, or pressure on surrounding structures (most commonly the eye nerves). Untreated they may lead to progressive health decline or loss of vision and blindness. Some abnormalities within the area of the pituitary gland may be treated non-surgically or simply followed with scans. Malignant pituitary tumors are rare. With more recent minimally invasive operative techniques, including the use of endoscopes, the operation has become safer and more effective at treating these conditions. Very large tumours may sometimes need to be treated with craniotomy (window of bone in the skull) and approach under the brain similar to other brain tumors.

Cervical Spine Surgery

There is a wide range of conditions that require cervical spine (neck) surgery, from nerve and spinal cord pinching to instability and pain. The most common surgical problem is brachialgia (arm pain from a pinched nerve). This condition in the majority of cases will improve without surgery; however, it may be required in those with weakness or severe unrelenting pain. Surgery is often done through a minimally invasive approach using microdiscectomy and microforaminotomy. Occasionally brachialgia may need to be treated by a complete discectomy and then either fusion or arthroplasty (artificial disc). Spinal cord pinching is rarely resolved with a minimally invasive approach due to the nature of the

condition, however, may require surgery from the back or front of the neck. Surgery for conditions such as whiplash and arthritic neck pain is rarely indicated.

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