Evaluation of the effect of placebo

Dr. Raz Mohammed

Lab. 6
Definition

• Placebo is defined as a substance that has no known specific pharmacological activity against the condition being treated. Placebos can be therapeutically beneficial to some patients when they give rise to the placebo effect.
• Placebo medication is a dosage form of material which is similar in appearance to an actual medication but contains only substances without pharmacological activity.

• Placebo Effects:
A remarkable phenomenon in which a placebo, an inactive substance like sugar, distilled water, or saline solution, can sometimes improve a patient's condition because the person has the expectations, belief, or hope that it will be helpful.
Factors that influence the response to placebos:

- Type of the patient
- The doctor’s attitude
- Doctor-patient relationship
- Type and even the color of the drug preparation
Symptoms and conditions that respond to placebo

Occasionally placebos are given to patients who are continuously complaining of some symptoms who are thought to be exaggerating and pain is usually involved.

1. Pain (severe pain)
2. Depression and anxiety
3. Gastric and duodenal ulcers
4. Chronic fatigue syndrome
Pain

• The placebo administration may prove to be a useful treatment in some specific cases where recommended drugs cannot be used. For example, burn patients who are experiencing respiratory problems cannot often be prescribed opioid (morphine), as it can cause further respiratory depression. In such cases placebo injections (normal saline) are useful in providing real pain relief to burn patients if those are conscious, are told they are being given a powerful dose of painkiller.
Mechanism of action of Placebo

• The mechanism in which placebos produce symptomatic relief is not known.
• Research on the placebo effect has focused on the relationship of mind and body.
• One of the most common theories is that the placebo effect is due to a person's expectations. If a person expects a pill to do something, then it's possible that the body's own chemistry can cause effects similar to what a medication might have caused.
• But some researchers believe that when a placebo is given to a patient, the brain releases endorphins, which are natural pain killers the brain produces.
• Placebos are also used in clinical trials (research).
• For determination of placebo effect, there are two ways:
  1. Single blind trials; only the researcher knows which medication the patient receives.
  2. Double-blind trials; neither the researcher nor the patient knows which medication the patient receives.
• The purpose of such a design is to eliminate or minimize the bias (unfair judgment) of the observer in evaluation of the responses of the patient.
Procedure

• The students should be divided into three groups. A volunteer in each group takes one of the following:
  • Cyproheptadine
  • placebo
Cyproheptadine

• Is a first-generation antihistamine used to treat allergic reactions, stimulate the appetite and may lead to weight gain, which is helpful for underweight people. Also used to treat sneezing, itching, watery eyes, runny nose, and other symptoms of allergies.

• **Side effects:**
  1. Dizziness
  2. Blurred vision
  3. Constipation
  4. Dry mouth, throat, or nose
  5. Nausea
  6. Nervousness
  7. Restlessness
Cyproheptadine

- Onset: 15-60 min
- Peak: 1-2 hr
- Duration: 8 hr
• Then the observer should fill the following sheet:
• The observer score sheet:
  • Time: .................................
  • Date: ....................................
  • Observer: ..............................
  • Environment:
  • ............... hours since medication.
  • ............... time of the last meal.
Condition of the student at the start of interview.

A. .......awake                              B. ......drowsy
A. .......Normal appetite  B. .....Increased appetite
A. .......standing               B. .......... sitting
A. .........restless            B. ..........lethargic
A. ............ Normal oral mucosa  B.......... Dry mouth
A............Normal vision         B.......... Blurred vision
• Response to the initial greeting by observer (e.g. response to good morning or other greeting)
  • A. ............ answers greeting
  • B.............. ignores greeting
• A. ............... looks at observer
  • B. ............ ignores observer
• Response of patient to the question “how do you feel?”
  • A. ............... smiles                      B. ............... frowns
  • A. ............. Answers                      B. ............... Doesn’t answer
• **Collection of data**

• Refer to sample sheets for method of scoring. Observer scoring sheet:

• A score of 10 is assigned to the scoring sheet at the start and indicates no changes. Add 1 point to those for each A box checked and subtract 1 point for each B box checked.

• The maximum score is therefore 20 and the minimum is zero.

• Compare drug scores with placebo scores. Placebo increases scores and cyproheptadine decreases scores.
Drug antagonism

Lab 7
Dr. Raz Mohammed
Opioid analgesics

• Opioids are obtained from the juice of the opium poppy.
• Opioids act by binding to specific opioid receptors in the CNS.
• Their primary use is to relieve intense pain and the anxiety that accompanies it, whether that pain is from surgery or a result of injury or disease, such as cancer.
Opioid analgesic classification

- **Strong agonist**: Morphine, Heroin, Fentanyl, Methadone, Meperidine (pethidine), oxycodone

- **Moderate agonist**: Codeine, Propoxyphene

- **Antagonist**: Naloxone, Naltrexone

- **Mixed agonist-antagonist**: pentazocin
Types of opioid receptors

• mu receptors (μ)
• kappa receptors (κ)
• delta receptors (δ)
Morphine

• Morphine is the major analgesic drug contained in crude opium and is the prototype strong agonist.

• Morphine shows a high affinity for mu receptors and varying affinities for kappa and delta receptors.
Mechanism of action of opioids

Opioids exert their effects by interacting with opioid receptors. Opioids cause:

1. Post synaptic: Activation of the opioid receptor increases K+ efflux and decreases the response of the post-synaptic neuron to excitatory neurotransmitters.

2. Presynaptic inhibition of transmitter release, it decreases the release of substance P, which modulates pain perception in the spinal cord.

Morphine also appears to inhibit the release of many excitatory Transmitters (glutamate) from nerve terminals carrying nociceptive (painful) stimuli.
Actions of morphine

1. Analgesia
2. Euphoria
3. Respiration: Morphine causes respiratory depression by reduction of the sensitivity of respiratory center neurons to carbon dioxide.
   - This occurs with ordinary doses of morphine and is increased as the dose increases until, ultimately, respiration stops.
   - Respiratory depression is the most common cause of death in acute opioid overdose.
4. Depression of cough reflex
5. Miosis
6. Emesis
7. Gastrointestinal tract
Anti-dote

- Opioid antagonists are not pain medications.

- but they block the effects of opioid agonists and are used to reverse adverse drug reactions, such as respiratory and CNS depression, produced by those drugs.
Opioid antagonists

• Naloxone
• Naltrexone
• Nalorphine: partial agonist
Binding of naloxone does not activate the receptor; therefore, naloxone reverses the effects of opioid agonists, such as morphine and heroin.
• Naloxone is used to reverse the coma & respiratory depression of opioid overdose.
• It rapidly displaces all receptor-bound molecule.
• It is competitive antagonist at three types receptors, with a 10-fold higher affinity for Mu and kappa receptors.
• Has a half-life of 60-100 min.
Procedure:

1. Record the animal’s normal respiratory rate as control.

2. Administer 10mg /kg of morphine, record the respiratory rate every 5 min over 30min.

3. When respiration depresses, inject naloxone (0.4mg - 0.8 mg) and record the respiratory rate.
CNS Stimulants

Dr. Raz Mohammed
Lab 8
Definition

• Stimulants are psychoactive drugs that induce temporary improvements in either mental or physical functions or both.
• Signs and symptoms:
• 1- Elevate Mood
• 2- Increase Motor Activity
• 3- Increase Alertness
• 4- Decrease need for Sleep
• In case of overdose lead to convulsion and death.
MOA of CNS Stimulants

1- Block neurotransmitters reuptake (Most reuptake inhibitors affect either NE or Serotonin: Cocaine
2- Promote neurotransmitters release: Amphetamine
3- Block Metabolism - MAO inhibitors (monoamine oxidase): ex. Phenelzine
4. antagonize the effect of inhibitory neurotransmitter: Picrotoxin & Strychnine.
A CNS stimulant produces most or all of the following effects in experimental animals:

1. Increase in heart rate
2. Increase in respiratory rate
3. Instability and restlessness
4. Muscle twitching
5. Hair erection and protrusion of the eye ball
6. Convulsions
According to their site of action, CNS stimulants are classified into three main groups:

1. Cerebral stimulants
2. Medullary stimulants
3. Spinal stimulants
Cerebral stimulants

- Caffeine, Amphetamine, Nicotine, Cocaine
- Act mainly on the cerebral cortex.
- Their effects are seen more clearly in higher animals (Mammalians).
- In large doses these drugs produce mixed convulsion.
• **Actions of caffeine in the CNS:**
  • Caffeine in 1-2 cups of coffee (100-200mg) causes a decrease in fatigue and increased mental alertness as a result of stimulating the cortex and other areas of the brain.
  • Consumption of 1.5 g of caffeine (12-15 cups of coffee) produce anxiety and tremors.
  • The spinal cord is stimulated only by very high doses (2-5 g) of caffeine.
  • Caffeine can lead to a withdrawal syndrome which consists of feelings of fatigue and sedation.
Medullary stimulants

EX. Picrotoxin: can be used to counter barbiturate poisoning, that can occur during general anesthesia or during overdose.

These drugs act on the medull oblangata.

In large doses produce convulsion characterized by:

1. Asymmetry: both sides of the body of the animal do not convulse at the same time.
2. Intermittent, convulsions are not continuous.
3. Spontaneous in origin, convulsions develop of their own not in response to external stimuli.
4. Coordinated, when the flexors convulse the extensors are relaxed.
Spinal stimulants

EX. Strychnine

Its primary action is on the spinal cord. Large doses, produces tonic convulsion characterized:
1. Symmetric, two sides of body convulse simultaneously.
2. Sustained
3. Reflex in origin, they develop in response to external stimuli.
4. Uncoordinated in nature, both the flexor & the extensor muscles contract at the same time & the body becomes arched into a posture know as *opisthotonus*. 
MOA of Strychnine

- Strychnine is a competitive antagonist of glycine, an important inhibitory neurotransmitter in the spinal cord and brainstem.
• Strychnine is a very toxic substance, used as a pesticide, particularly for killing small vertebrates such as rodents.

• Is one of the most bitter substance in the world is taste is detectable as conc. As low 1 ppm.
• 10-20 min after exposure, every muscle in the body will start to simultaneously contract, starting with head & neck.
• The spasm spread to every muscle in the body with nearly continuous convulsion.
• They get worse at the slightest stimulus they progress, increase in intensity & frequency until the back bone arches continually (opisthohotonus)
• Death come from asphyxiation caused by paralysis of the brain breathing apparatus, or by exhaustion from convulsion.
Effect of drugs on the eye

Dr. Raz Mohammed
**Mydriasis and miosis**

- **Mydriasis** is the dilatation of the eye pupil.
- **Miosis** is the constriction of the eye pupil.
- Pupil size is controlled by
  1. Light (Normally, the pupil dilates in the dark and constricts in the light)
  2. Parasympathetic stimulation (miosis)
  3. Sympathetic stimulation (mydriasis)
• Mydriasis is controlled by the dilator muscle, which is controlled primarily by sympathetic innervation.
• Miosis is controlled by the sphincter muscle, which primarily receives parasympathetic innervation.
Mechanisms involved in controlling pupil size.

- **Adrenoceptor agonists**
  - sympathetic stimulation
  - adrenoceptor agonists

  Radial muscles contract resulting in pupil dilation

- **M3 muscarinic acetylcholine receptor agonists**
  - parasympathetic stimulation
  - muscarinic agonists

  Sphincter muscle contracts resulting in pupil constriction
Accommodation:

- It’s the mechanism that focuses the image on the retina.
- Therefore accommodation is the ability of the lens to change its radius of curvature.
A. Loss of accommodation

• When the ciliary muscle relaxes, the suspensory ligaments are tense, stretching the lens into an ellipsoid shape (far or distant vision).

• **Cycloplegia** is paralysis of the ciliary muscle of the eye, resulting in a loss of accommodation. Because of the paralysis of the ciliary muscle, the curvature of the lens can no longer be adjusted to focus on nearby objects.

• Cycloplegic drugs are generally muscarinic receptor blockers.
B. Spasm of accommodation

• When the ciliary muscle contract as a result of parasympathetic stimulation, the suspensory ligaments relax, and the lens takes up a more spherical shape.

• The curvature of the lens therefore focuses near objects onto the retina (near vision).

• This causes vision to blur when attempting to view objects from a distance.

• The contraction of the ciliary muscle explains why the eye gets tired after reading for long periods of time.
Eye drops

1. Antimuscarinic drugs (Atropin, Tropicamide)
   • Atropine eye drops contain the active ingredient atropine, which as an antimuscarinic agent. It is also known as a mydriatic and a cycloplegic agent.
   • It relaxes the ciliary muscle, resulting in loss of accommodation for near objects (distant objects are viewed clearly).
   • There is no reaction to light.
2. Muscarinic agonist (Pilocarpine)

- Is a non-selective muscarinic receptor agonist. Pilocarpine has been used in the treatment of chronic open-angle glaucoma and acute angle-closure glaucoma, it produces miosis.
- It causes spasm of accommodation, which means the ciliary muscle of the eye remains in a state of contraction, it can not relax to view distant objects (blurred vision for far objects).
3. Sympathomimetics

- **Phenylephrine**: is a selective $\alpha_1$-adrenergic receptor agonist used as an agent to dilate the pupil (mydriasis), also certain eye surgeries, certain inflammatory conditions of the eye, or glaucoma. It may also be used in certain diagnostic procedures.

- Has no effect on accommodation.
4. Topical local anesthetic

- **Tetracaine**: is a potent local anesthetic. It is mainly used topically in ophthalmology and as an antipruritic.
- Tetracaine works by interfering with entry of sodium ions into nerve cells. This reduces the ability of nerves to generate an impulse and send pain sensations.
- Tetracaine is prescribed as local anesthetic before eye procedures like removal of corneal foreign bodies, and for short corneal and conjunctival procedures.
- **It has no effect on accommodation, light reflex, and size of pupils**
Procedure

• Each student receives a drop of the one solution (Atropin, Tetracaine and pilocarpine) only in one of his or her eyes.

• Observe the following:

1. Size of the pupil.
2. Reaction to light
3. Accommodation for near and far vision.
4. Corneal sensation
Drug Excretion

Dr. Raz Mohammed
• The major organ for the excretion of drugs is the kidney.

• **Renal elimination of a drug**

  1. Glomerular filtration
  2. Proximal tubular secretion
  3. Distal tubular reabsorption
1. Free drug enters glomerular filtrate

Bowman's capsule

2. Active secretion

Proximal tubule

Loop of Henle

Distal tubule

Collecting duct

3. Passive reabsorption of lipid-soluble, un-ionized drug, which has been concentrated so that the intraluminal concentration is greater than that in the perivascular space

Ionized, lipid-insoluble drug into urine

Drug

Proximal tubule

Loop of Henle

Distal tubule

Passive reabsorption of lipid-soluble, un-ionized drug

Phase I and II metabolism

Ionized or polar metabolite
1. Glomerular filtration

• Most drugs are readily filtered from blood into the glomerulus, except drugs that are extensively bound to plasma proteins.
• But the overall renal excretion is controlled by what happens in the tubules.
• More than 90% of the filtrate is reabsorbed into circulation.
2. Proximal tubular secretion

- Secretion occurs by energy-requiring active transport (carrier-requiring) system.

3- Distal tubular reabsorption

- As a drug moves toward distal convoluted tubule, its concentration increases & exceeds that of the perivascular space.
- Uncharged drug may diffuse out of the lumen, back into the systemic circulation.
- Changing the pH of the urine to increase the ionized form of the drug in the lumen may be used to minimize the amount of back-diffusion, and increase the clearance of an undesirable drug.
• Weak acids can be eliminated by alkalization of urine
• Weak bases may be eliminated by acidification of urine.
• The excretion of weak acidic drugs (patient who has taken overdose of aspirin) can be increased by taking sodium bicarbonate.
Weak acids can be eliminated by alkalinization of urine. Weak bases may be eliminated by acidification of urine. This process is called **ion trapping**.

• EX- a patient with phenobarbital (weak acid) overdose can be given bicarbonate, which alkalinizes the urine and keeps the drug ionized, thereby decreasing its reabsorption.

- If overdose is with a weak base like cocaine, acidification of the urine with NH4Cl, increases its clearance.
Drug-induced coloration of urine

- Discoloration could be due to:
- Serious adverse effects of drugs such as hemolysis.
- Harmless discoloration of urine is induced by some drugs.
• A patient taking drugs like rifampicin, phenazopyridine, metronidazole, levodopa..etc

• Should be informed in advance, otherwise, he might alarmed by the changes of his/her urine color.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Color</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifampicin</td>
<td>Orange-red</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>Dark brown</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>Yellow</td>
</tr>
<tr>
<td>Phenazopyrididine</td>
<td>Orange-red</td>
</tr>
<tr>
<td>Levodopa</td>
<td>Dark brown</td>
</tr>
<tr>
<td>Phenolphthalin</td>
<td>Red</td>
</tr>
<tr>
<td>Salicylates</td>
<td>Pink to brown</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>Yellow to brown</td>
</tr>
<tr>
<td>Cascara</td>
<td>Red (in alkaline urine)</td>
</tr>
</tbody>
</table>
Procedure:

• One student (volunteer) in each group after emptying his bladder and preserving a sample of blank urine, will receive two capsules of rifampicin (300mg) and the other will receive nitrofurantoin.

• Urine is then collected after 45 minutes and the color is compared to the blank sample.
Notes

• Color changes may interfere with laboratory tests.
• Food and food additives might also change the color of urine (beet root)
• Drugs might interfere with urine tests,
• Drug, in addition, could discolor stool (iron, charcoal, and red wine)
• Rifampicin $t_{1/2} = 3 \text{ hrs}$
• Metronidazole $t_{1/2} = 8 \text{ hrs}$
• Tetracycline $t_{1/2} = 16 \text{ hrs}$
• Nitrofurantoin $t_{1/2} = 30 \text{ min.}$
<table>
<thead>
<tr>
<th>Drug</th>
<th>Onset of action</th>
<th>Duration of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tropicamide</td>
<td>30 minutes</td>
<td>5 hours</td>
</tr>
<tr>
<td>Phenylephrine</td>
<td>30 minutes</td>
<td>3 hours</td>
</tr>
<tr>
<td>Tetracaine</td>
<td>6.6 minutes</td>
<td>10 minutes</td>
</tr>
<tr>
<td>Pilocarpine</td>
<td>10-30 minutes</td>
<td>4-8 hours</td>
</tr>
</tbody>
</table>