OBI 836
The Autonomic Nervous System-Sympathomimetics
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August 29, 2012

Learning Objectives Lecture II

The student should be able to explain or describe

1. The potential sites of action for sympathomimetics and the difference between a direct and indirect acting agonist.

2. The pharmacologic and therapeutic actions of selected sympathomimetic drugs.

3. How the presence of sympathomimetics alters the dental management of patients.

Prototype Drugs
Amphetamine-Adderall – 16th leading prescription drug in the US in 2010- source-rxlist.com
Albuterol – 129th leading prescription drug in the US in 2010-
Cocaine
Methylphenidate – Ritalin, FocalinXR - 140th leading prescription drug in the US in 2010
Pseudoephedrine
Methamphetamine

FYI; a more complete list of sympathomimetics and their trade names can be found on p. 110-111 of the Yagiela text.
SYMPATHOMIMETICS:

Direct acting sympathomimetics

1) Synthetic analogs of epinephrine or norepinephrine that are agonists at alpha and/or beta adrenergic receptors.
2) The structural modifications result in
   - drugs that are orally active
   - have longer plasma half-lives
   - are highly selective for a specific receptor

Indirect acting sympathomimetics

Drugs that can mimic activation of the sympathetic nervous system by mechanisms other than direct receptor activation.
BETA<sub>2</sub> AGONISTS

Agents, such as albuterol, are selective beta<sub>2</sub> agonists. These agents have a higher affinity for and therefore selectively activate beta<sub>2</sub> receptors when compared to beta<sub>1</sub>.

Implications in Dental Practice
1) Albuterol and the other beta<sub>2</sub> agonists can be given via inhaler. Xerostomia is a common side effect when these drugs are given by this route of administration.

Implications in Medical Practice and Drug Therapy
1) Selective beta<sub>2</sub> agonists are used to treat COPD (chronic obstructive pulmonary disease, bronchial asthma, chronic bronchitis, emphysema) - due to the ability to decrease airway resistance. A specialized use is in premature labor - due to the ability to relax uterine smooth muscle.

ALPHA<sub>1</sub> AGONISTS
These drugs activate the alpha<sub>1</sub> receptor resulting in vasoconstriction. Drugs such as pseudoephedrine are often found in over-the-counter cough and cold preparations.

Implications in Dental Practice
These drugs can;
1) Potentiate the hypertensive effects of systemically absorbed epinephrine.
Implications in Medical Practice and Drug Therapy

These drugs can be:

1) Used in cough and cold preparations for the symptomatic relief of nasal congestion by inducing constriction of nasal mucosal blood vessels and decreases resistance to air flow.
2) Used by an ophthalmologist to induce mydriasis.
3) Used by an anesthesiologist to increase blood pressure during a surgical procedure.

BETA₁ AGONISTS ****FYI, not testable****

Drugs such as dopamine or dobutamine activate the myocardial beta₁-receptor.

Implications in Dental Practice

1) It is highly unlikely that a dental practitioner will treat a patient taking these drugs in an out-patient setting.

Implications in Medical Therapy

1) These drugs are short acting, given by the IV route and used only in intensive care situations to treat congestive heart failure and cardiogenic shock.

INDIRECT ACTING SYMPATHOMIMETICS
Drugs that can mimic activation of the sympathetic nervous system by mechanisms other than direct receptor activation. Potential mechanisms and drugs include:

1) Cause the release of norepinephrine from presynaptic nerve terminals- **amphetamine** and **amphetamine-like drugs**

2) Blockade of the norepinephrine transporters (NET) - **cocaine, amphetamine, amphetamine-like drugs** and tricyclic antidepressants. To varying degrees, they can also block dopamine (DAT) and serotonin (SERT) transporters.

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**Cocaine**

1) Has multiple actions; a) blocks monoamine transporters, b) local anesthetic activity.

2) Has limited use as a local anesthetic and vasoconstrictor in surgical procedures involving the oral, laryngeal and nasal cavities. This local anesthetic action is due to its ability to block Na-channels and **not** to effects on monoamine transporters.

3) Has significant abuse liability. This euphoria is thought to be due to a blockade of dopamine uptake (blockade of the DAT).
4) Is extremely cardiotoxic. It can produce hypertension, ventricular arrhythmias, myocardial ischemia and infarction. This toxicity is due to:
   - Coronary vasoconstriction (enhance alpha₁-receptor vasoconstriction)
   - Increased cardiac automaticity (enhance beta₁-receptor effects on conduction)
   - Local anesthetic activity on the heart - alters impulse propagation
   - Central effects leading to an increase in cardiac sympathetic tone

Amphetamine and Amphetamine-like Drugs
1) Amphetamine and amphetamine-like drugs available for therapeutic use include:
   - **Adderall** (a combination of d- and l- amphetamine),
   - **Methylphenidate** (Ritalin) and **Focalin** (the more potent isomer of methylphenidate)
   - **Methamphetamine** - available by prescription, also produced illegally

2) CNS actions result in increase in wakefulness, cognition and a reduction in appetite.

3) Therapeutic uses include:
   - appetite suppression
   - narcolepsy
   - attention deficit disorder with hyperactivity (ADHD)

4) These drugs carry a significant abuse liability

5) Toxicity similar to cocaine-elevated blood pressure, ventricular arrhythmias, myocardial ischemia and infarction and CNS manifestations.

Tricyclic Antidepressants****FYI, not testable on this exam*****
1) The use of tricyclic antidepressants such as **imipramine** to treat depression has been supplanted by newer and safer drugs such as the **Selective Serotonin Reuptake Inhibitors (SSRIs)**.

Implications in Dental Practice
1) Cocaine, amphetamine-like agents and tricyclic antidepressants could potentiate the cardiovascular effects of systemically absorbed epinephrine on blood pressure
and heart rate.

2) In addition to the catastrophic effects on teeth, inhaled methamphetamine can produce xerostomia.

Drug Abuse

Prescription drugs
1) Adderall, methylphenidate and related stimulants are misused by parents seeking an “academic advantage” for their children or by college students seeking “study aids.”

Illicit drugs
1) Cocaine is often vaporized and then inhaled. This can result in very high blood levels increasing the likelihood of toxicity.
2) An analog of amphetamine, methamphetamine, is produced illegally and is a widely abused substance. Methamphetamine can be produced from over-the-counter cough and cold medications such as pseudoephedrine. Lithium, muriatic acid, sulfuric acid, red phosphorus and lye are used in this preparation. When smoked, these highly corrosive agents are vaporized resulting in significant damage to teeth and gums.

REVIEW OF OBJECTIVES AND LECTURE SUMMARY

Objective # 1-- The potential sites of action for sympathomimetics and the difference between a direct and indirect acting agonist.

Direct agonists bind to and activate alpha or beta receptors.

Indirect agonists potentiate the actions of endogenous neurotransmitters by blocking the uptake of norepinephrine into nerve terminals and/or promoting its release into the synapse.

Objective # 2-- The pharmacologic and therapeutic actions of selected sympathomimetic drugs.

Beta$_2$ –agonists albuterol- COPD, asthma and premature labor.

Beta$_1$ –agonists- congestive heart failure and cardiogenic shock.

Alpha$_1$ agonists pseudoephedrine- OTC cough and cold preparations, hypotension during surgery, ophthalmic preparations.
Indirect acting agonists **cocaine, amphetamine, methamphetamine, methylphenidate**- ADHD, narcolepsy, appetite suppression, drugs of abuse.

**Objective # 3 -- How sympathomimetics alters the dental management of patients.**

Inhaled Beta_2-_agonists **albuterol** - Xerostomia

Beta_1-_agonists- No selective agonists are available for oral use as drug products.

Alpha_1_ agonists- **pseudoephedrine** - Hypertension, potentiation of the pressor responses to epinephrine.

Indirect acting agonists- **cocaine, amphetamine, methamphetamine, methylphenidate** Potential for abuse, hypertension, potentiation of the pressor responses to epinephrine.

Methamphetamine-Xerostomia
### TABLE 2

**ADVERSE DRUG INTERACTIONS IN DENTISTRY: VASOCONSTRICTORS.**

<table>
<thead>
<tr>
<th>POSSIBLE DRUG INTERACTION</th>
<th>CUMULATIVE RATING*</th>
<th>MECHANISM AND CLINICAL PRESENTATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasoconstrictor with tricyclic antidepressant (levonordefrin with imipramine)</td>
<td>1</td>
<td>Sympathomimetic effects may be enhanced. Use of levonordefrin should be avoided.</td>
</tr>
<tr>
<td>Vasoconstrictor with nonselective β-adrenoceptor antagonist (epinephrine with propranolol)</td>
<td>1</td>
<td>Hypertensive and/or cardiac reactions are possible. Use of vasoconstrictor should be used cautiously; blood pressure and heart rate should be monitored.</td>
</tr>
<tr>
<td>Vasoconstrictor with general anesthetic (epinephrine with halothane)</td>
<td>1</td>
<td>Increased possibility of cardiac arrhythmias exists. Consultation with anesthesiologist is recommended.</td>
</tr>
<tr>
<td>Vasoconstrictor with cocaine (epinephrine with cocaine)</td>
<td>1</td>
<td>Arrhythmias and hypertensive responses possible. Concurrent use should be avoided.</td>
</tr>
<tr>
<td>Vasoconstrictor with antipsychotic or other α-adrenoceptor blocker (epinephrine with chlorpromazine)</td>
<td>4</td>
<td>Hypotension resulting from overdose of antipsychotic agent may be worsened. Use of vasoconstrictor should be used cautiously.</td>
</tr>
<tr>
<td>Vasoconstrictor with adrenergic neuronal blocker (levonordefrin with guanadrel)</td>
<td>4</td>
<td>Sympathomimetic effects may be enhanced. Use of vasoconstrictor should be used cautiously.</td>
</tr>
<tr>
<td>Vasoconstrictor with local anesthetic (lidocaine with epinephrine)</td>
<td>4</td>
<td>Multiple effects on systemic toxicity, which may be self-limiting.</td>
</tr>
<tr>
<td>Vasoconstrictor with thyroid hormone (epinephrine with thyroxine)</td>
<td>4</td>
<td>Summation of effects possible when thyroid hormones are used in excess. Use of vasoconstrictor should be used cautiously if signs of hyperthyroidism are present.</td>
</tr>
<tr>
<td>Vasoconstrictor with monoamine oxidase inhibitor (epinephrine with phenelzine)</td>
<td>5</td>
<td>No substantial evidence of an interaction.</td>
</tr>
</tbody>
</table>

***From J.A. Yagiela, Adverse drug interactions in dental practice, interactions associated with vasoconstrictors. JADA, 139:701-709, 1999. **This information is presented for your knowledge.***