Drugs Affecting Uterine Contraction

Drugs Acting on the Uterus

Uterine-Stimulating Agents (Oxytocic)
- Oxytocin
- Ergot Alkaloids
- Prostaglandins

Uterine-Relaxing Agents (Tocolytic)
- beta 2-adrenergic agonists
- Magnesium sulfate
- Ethanol

Pharmacokinetics
- PO: inactive
- usually administered intravenously for stimulation of labor
- nasal spray: induce lactation postpartum
- not bound to plasma protein
- catabolized by the kidneys and liver
- half-life: 5 min

Pharmacodynamics
- alter transmembrane ionic currents in myometrial smooth muscle cells to produce sustained uterine contraction
- sensitivity of uterus increases during pregnancy
- also caused contraction of myoepithelial cells surrounding mammary alveoli: leads to milk ejection
- weak antidiuretic and pressor activity

Oxytocin
- nine-amino acid peptide hormone secreted by the posterior pituitary

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**Clinical Uses**
- Diagnostic uses: fetal heart rate response to a standardized oxytocin challenge test provides information about placenta circulatory reserve (abnormal response suggests intrauterine growth retardation)
- Therapeutic uses:
  * induce labor and augment dysfunctional labor (uterine inertia, incomplete abortion)
  * control postpartum uterine hemorrhage
  * impaired milk ejection

**Adverse Reactions**
- used properly: serious toxicity is rare
- report adverse reactions: maternal deaths due to hypertensive episodes, uterine rupture, water intoxication, and fetal death, afibrinogenemia

**Contraindications**
- fetal distress, prematurity, abnormal presentation

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**Ergot Alkaloids**
- Ergot alkaloids are produced by *Claviceps Purpurea*
- variably absorbed from the gastrointestinal tract
- extensively metabolized in the body

**Mechanism of action**
- act on several types of receptors
- their effects include agonist, partial agonist, and antagonist actions at alpha-adrenoceptors and serotonin receptors (especially 5-HT1A and 5-HT1D)

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**Effects of ergot alkaloids at several receptors**

<table>
<thead>
<tr>
<th>Ergot alkaloid</th>
<th>Alpha-adrenoceptor</th>
<th>Dopamine Receptor</th>
<th>Serotonin Receptor (5-HT2)</th>
<th>Uterine Smooth Muscle Stimulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bromocriptine</td>
<td>-</td>
<td>+++</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>Ergonovine</td>
<td>+</td>
<td>+</td>
<td>-(PA)</td>
<td>+++</td>
</tr>
<tr>
<td>Ergotamine</td>
<td>-(PA)</td>
<td>0</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Lysergic acid</td>
<td>0</td>
<td>+++</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>LSD</td>
<td>+/0</td>
<td>+</td>
<td>+(PA)</td>
<td>-</td>
</tr>
</tbody>
</table>

1 agonist effects are indicated by +, antagonist by -, no effect by 0. Relative affinity for the receptor is indicated by the number of + or – signs. PA means partial agonist (both agonist and antagonist effects can be detected).

**Ergot alkaloids**
- (CNS, pituitary)
- (Uterus)
- (Vessels)

LSD, Ergonomine, Ergotamine, Methylsergide
- Bromocriptine
Organ System Effects

1. Central nervous system
   * Lysergic acid diethylamide (LSD) : powerful hallucinogens (agonist effects at prejunctional or postjunctional 5-HT2 receptors in CNS)
   * Dopamine receptors : play important roles in extrapyramidal motor control and the regulation of prolactin release
   * Bromocriptine & pergolide : highly selectivity for the pituitary dopamine receptors (suppress prolactin secretion)

2. Vascular smooth muscle
   * Ergotamine : have a strong vasoconstrictor spectrum of action (partial agonist effects at alpha-adrenoceptors, some at 5-HT receptors)

3. Uterine smooth muscle
   * Ergonovine : is more selective than other ergot alkaloids in affecting the uterus
     * the uterus at term is more sensitive than the earlier in pregnancy
     * very small doses : rhythm contraction and relaxation, high conc : powerful and prolonged contracture

Clinical Uses

1. Migraine
   * ergotamine (often combined with caffeine to facilitate absorption)
   * methysergide : prophylaxis

2. Hyperprolactinemia
   * bromocriptine : reducing the high levels of prolactin that result from pituitary tumors(regression of tumor in some case)

3. Postpartum hemorrhage
   * ergonovine : (IM : at the time of delivery of the placenta or immediately afterward if bleeding is significant)

Toxicity

• most common : GI disturbance (diarrhea, nausea, vomiting)
• overdosage with ergotamine and ergonovine : prolonged vasospasm (is refractory to most vasodilators : infusions of large dose of nitroprusside or nitroglycerine have been successful in some cases)
• chronic therapy with methysergide : associated with development of fibroblastic changes in the retroperitoneal space (drug holidays of 3-4 wk every 6 m)

Prostaglandins

• Myometrium : PGE, PGF : contract
• Cervix : ripening

Adverse Reactions
1. GI : nausea, vomiting, diarrhea
2. Transient pyrexia
3. Bronchoconstriction

Contraindications : obstructive vascular disease and collagen disease
Tocolytic Agents

1. Beta 2-mimetic agents
   (SE: maternal & fetal tachycardia)
2. Magnesium sulfate
   (SE: respiratory depression)
3. Ethanol
   (SE: restlessness, coma)
4. NSAIDs
   (SE: closure ductus arteriosus)
5. Calcium antagonist

Ritodrine

- a selective beta2-adrenergic agonist
- PO: rapidly but incompletely (30%) absorbed, 90% of the drug is excreted in the urine as inactive conjugates
- IV: 50% of ritodrine is excreted unchanged
- therapeutic uses: arrest premature labor
- adverse effect: skeletal muscle tremor, tachycardia