THE NORTHERN HOSPITAL

PSEUDOEPHIDRINE

"Brandy Smugglers Loading Boats at the Mouth of a Rocky Cave by Moonlight", oil on canvas, 18th Century, John Thomas Serres.

"Everything is good as it leaves the hands of the Creator of things; everything degenerates in the hands of man".

Jean-Jacques Rousseau, opening lines of "Emile, or On Education", 1762.

"To live is not simply to breath but to act. It is to make use of our organs, our senses, our faculties, of all the parts of ourselves which give us the sentiment of our existence. The one who has lived the most is not the one who has counted the most years, but the one who has most felt life.....

Hold childhood in reverence, and do not be in any hurry to judge it for good or ill. Leave exceptional cases to show themselves, let their qualities be tested and confirmed, ***before*** *special methods are adopted. Give nature time to work before you take over her business, lest you interfere with her dealings. You assert that you know the value of time and are afraid to waste it. You fail to perceive that it is a greater waste of time to use it ill than to do nothing, and that a child ill taught is further from virtue than a child who has learnt nothing at all.*

You are afraid to see children spending their early years doing nothing. What! is it "nothing" to be happy, nothing to run and jump all day? They will never be so busy again in all their life. Plato, in his Republic which is considered so stern, teaches the children only through festivals, games, songs, and amusements. It seemed as if he had accomplished his purpose when he had taught them to be happy: and Seneca speaking of Roman boys, in ancient days, says, "They were always on their feet, they were never taught anything which kept them sitting". Were they not the worse for it in manhood?

Do not be afraid, therefore, of this so called idleness. What would you think of the person who refused to sleep lest it should waste a part of their life? You would say "That person is mad, they are not enjoying their life, they are robbing themselves of a part of it; to avoid sleep they are hastening their own deaths!". Remember that these cases are alike, and that childhood is simply the sleep of reason.

The apparent ease with which children learn is their ruin. You fail to see that this very faculty proves that they are not learning. Their shining polished brains reflect, as in a mirror, the things you show them, but nothing sinks in. The child remembers the words and the ideas are reflected back; their adult hearers understand them, but to the child they are meaningless.

Although memory and reason are wholly different faculties the one does not really develop apart from the other. Before the age of reason the child receives images, not ideas; and there is this difference between them: images are merely the pictures of external objects, while ideas are notions about those objects determined by their relations...

Jean-Jacques Rousseau, "Emile, or On Education", 1762.

The great Age of Reason, or the "Enlightenment" of the Seventeenth and Eighteenth centuries, is perhaps better remembered today by most for laying the scientific foundations of the modern world. But the period was far more than that. It also saw the foundations of modern social and political philosophies, and it would be these ideas that would have profound effects, leading directly to the American and the French Revolutions, which entirely swept away untold centuries of archaic traditions.

Amoung the very greatest of the exponents of these revolutionary ideas was Jean-Jacques Rousseau. His books were banned and burned by the French Ancien Regime, but this did little to limit the dissemination of his radical philosophies both throughout the Old World and the New. Rousseau's work, "The Social Contract" written in 1762, directly challenged the idea of the "divine right" of Monarchs to rule. He asserts that only the people were are sovereign, and that political leaders could only rule by the consent of the people. It was a shocking and powerful idea, that a generation later, would act as the foundation stone of both the American and French Revolutions.

But this was not the only radical influence Rousseau had. In his book Emile (or On Education) he explored the ideal way that children should be educated. Shockingly he discounted religious instruction, substituting instead an appreciation for nature, which would form the basis of ideas on secular education during the time of the Revolution of 1789. It need hardly be said that "Emile" was banned and burnt along with the "Social Contract" under the rule of Louis XV.

One of the great intellectual debates of the 18th Century concerned the innate good or evil of humanity. Jean-Jacques Rousseau believed that all people were born good, and that society was then responsible for them becoming evil. The more advanced the society, the more selfish and evil it would make people. Conversely the more primitive the society the closer to nature it was and the more pure would be its people, ideas he explored in "Emile". Many of his more illustrious Philosophers however disagreed with him, notably Voltaire who sarcastically rebuked Rousseau's notion of the primitive idyll by claiming he had "given up the habit of walking on all fours". Diderot remarked, "I don't care for acorns and dens and hollow oaks. I require a carriage, a convenient apartment, fine linen and a perfumed girl, and after that I would gladly accommodate to all the other curses of our civilized state" - perhaps proving Rousseau's point!

The history of Human civilization is sadly one endless litany of insatiable greed, war, and unrelenting struggle for power and wealth at any price. Whether these traits are the result of innate, evolutionary hard wiring or whether they are simply the result of learned behaviour passed from generation to generation is very difficult to know. It is a question that has vexed the great Philosophers for countless centuries. Whatever the cause, we can be sure that, given human nature, anything at all that can be exploited for personal gain will be by someone at some time. It is therefore unsurprising that the innocuous cough and cold medication, pseudoephedrine, requires rigorous systems of identification and/or medical prescription in order to control its dispensing. Pseudoephedrine, is a key chemical component in the manufacture of illicit amphetamine based drugs, such as methamphetamine or "ice" - the conversion of pseudoephedrine into methamphetamine was a process that was always going to be exploited.

PSEUDOEPHIDRINE

Introduction

Pseudoephedrine (trade name in Australia "**Sudafed"** amoung others), like ephedrine, is a mixed, directly and indirectly acting, **sympathomimetic, *non-selective* adrenergic agonist.**

It acts both peripherally and centrally within the CNS, but is a somewhat less potent **CNS stimulant** than the closely related, **ephedrine**.

It is a very effective nasal decongestant, and used to be readily available "over the counter" as a standalone medication or in a large number of combination "cold and flu" medications.

Pseudoephedrine however is a precursor for the illicit sympathomimetic agent, methamphetamine (or "**ice**"). As such pseudoephedrine is commonly procured for the purpose of **illicit methamphetamine production**.

In consequence **strict controls** were introduced into Australia for the sale of pseudoephedrine.

Phenylephrine containing "cold and flu" formulations were offered by pharmacists as freely available "over the counter" (OTC) agents (i.e agents not requiring a doctor's prescription), as an alternative to pseudoephedrine, however, this agent has been shown to be **no more effective than placebo** at relieving nasal congestion in seasonal allergic rhinitis. [2]

Illicit pseudoephedrine use:

Pseudoephedrine is the key and essential ingredient for the manufacture of **methamphetamine.**

Pseudoephedrine based mediations such as the cold and flu preparations sold in pharmacies have been identified as a major source of the pseudoephedrine used to manufacture methamphetamine in Australia.

In keeping with the Quality Use of Medicines guidelines which form part of the National Medicines Policy and the concern about the use of pseudoephedrine based products for illicit drug manufacture, the Australian Government and the Pharmacy Guild of Australia implemented Project STOP in 2005 in Queensland, to decrease the sale of pseudoephedrine for illicit use. This program is now Australia wide.

Larger doses of Pseudoephedrine now require a Doctor's prescription.

Lesser doses require a screening process by Pharmacists.

This screening process involves the following steps: [5]

1. Upon requesting a pseudoephedrine-based product, the pharmacist asks to see an acceptable form of photographic identification:

    - A State or Territory issued driver's license
    - A State or Territory issued Proof of Age card
    - Any other State or Territory assigned form of photographic identification.

2. Your pharmacist records your identification card number in a protected database held and operated by the Pharmacy Guild of Australia.

3. Your pharmacist also records the name of the product and the quantity you have requested in the database.

4. The database checks to see if your identification number was previously entered into the database within an appropriate threshold period.

5. The pharmacist decides whether or not to supply the product based on a determination of your therapeutic needs.

6. The database records whether or not the sale was made.

History

The plant alkaloids **ephedrine** and **pseudoephedrine** are natural compounds produced by members of the genus Ephedra. These compounds are sympathomimetics with potent stimulant actions. Chemically they are substituted amphetamines.

Ephedra is a genus of gymnosperm shrubs, the only genus in its family, Ephedraceae, and order, Ephedrales.

The Chinese name for the Ephedra species is **mahuang**, which has been used in traditional medicines for centuries.

Historically ephedrine was used medicinally for a wide range of conditions including, CHB, narcolepsy, asthma and depression.

Chemistry

Pseudoephedrine is a sympathomimetic drug of the phenethylamine and amphetamine chemical classes.

It is a diastereomer of **ephedrine** and is readily reduced into **methamphetamine** (**see Appendix 1**) or oxidized into **methcathinon.**

Although pseudoephedrine occurs naturally as an alkaloid in certain plant species (such as Ephedra species, in which it occurs together with other isomers of ephedrine), for commercial use it is usually derived from yeast fermentation of dextrose in the presence of benzaldehyde.

Physiology

The principle clinical effects of the adrenergic receptors are as follows:

Alpha - 1 receptor stimulation:

1. Vasoconstriction:
    - Arterioles of heart, brain, kidneys, lungs, skeletal muscle, skin, splanchnic
    - Venoconstriction.
2. Mydriasis
3. Ureter contraction
4. Metabolic
    - Inhibition of insulin release

Alpha - 2 receptor stimulation:

1. Negative feedback:
    - This is a pre-synaptic receptor, **causing negative feedback** on, for example, norepinephrine. When norepinephrine is released into the synapse the α_2 receptor, causes **less** norepinephrine. release from the presynaptic neuron.
2. Metabolic:
    - **Inhibition** of **insulin** release in the pancreas.
    - **Stimulation** of **glucagon** release from the pancreas.

Beta - 1 receptor stimulation:

1. Heart:
    - Positive inotrope (i.e. increased contractility
    - Positive chronotrope (i.e. increased rate - SA node)

- Positive dromotrope (i.e. increased A-V node conduction velocity)
- Decreased refractory period.

2. Increased renin secretion from the kidney

3. Metabolic:

   - Increased liver glycogenolysis
   - Adipose tissue lipolysis

Beta - 2 receptor stimulation:

1. Vasodilation:

   - Skeletal muscle

2. Bronchial smooth muscle relaxation

3. Uterine relaxation (if pregnant)

4. Metabolic:

   - Hypokalaemia (due to stimulation of the sodium-potassium pump)
   - Stimulates insulin secretion

Beta - 3 receptor stimulation:

1. Enhancement of lipolysis in adipose tissue

Classification

Chemical Structural Classification

Drugs that mimic the effects of sympathetic nervous system stimulation may be broadly structurally divided into catecholamines and non-catecholamines.

Catecholamines contain the organic molecule, **catechol** which is **1,2 dihydrobenzene**, (this has a benzene ring with two hydroxyl groups, an intermediate ethyl chain, and a terminal amine group).

1. **Catecholamines**:

   - Naturally occurring:

     Biosynthesis in the body occurs as follows:

Phenylalanine → L-Tyrosine → L-Dopa → Dopamine → Noradrenaline → Adrenaline.

- ♥ Adrenaline:

  The major *hormone* of the adrenal medulla

- ♥ Noradrenaline:

  The *neurotransmitter* acting at most sympathetic postganglionic adrenergic nerve terminals

- ♥ Dopamine:

  The immediate biological precursor of noradrenaline

- Synthetic:
  - ♥ Dobutamine
  - ♥ Isoprenaline

2. **Non-catecholamines**:

   Examples include:

   - Naturally occurring:
     - ♥ Ephedrine
   - Synthetic:
     - ♥ Phenylephrine
     - ♥ Metaraminol
     - ♥ Salbutamol

Chemical Action Classification

Sympathomimetic agents may alternatively be classified according to their principle mode of action.

1. Directly acting sympathomimetics:

Listed examples mostly have *relative* specificity rather than absolute specific for the receptors. In general terms receptor specificity becomes *less pronounced* with *increasing* dosages.

- Alpha agonists:
  - ♥ Alpha -1 selective agonists

    Examples include:

    - ♥♥ Phenylephrine
    - ♥♥ Noradrenaline
  - ♥ Alpha - 2 selective agonists

    Examples include:

    - ♥♥ Clonidine
    - ♥♥ Moxonidine
    - ♥♥ Dexmedetomidine
- Beta agonists:
  - ♥ Beta -1 selective agonists

    Examples include:

    - ♥♥ Dopamine
    - ♥♥ Dobutamine
  - ♥ Beta -2 selective agonists

    Examples include:

    - ♥♥ Salbutamol
    - ♥♥ Salmeterol
  - ♥ Non-selective beta agonists

    Examples include:

    - ♥♥ Adrenaline

- ♥♥ Isoprenaline

2. Indirectly acting sympathomimetics:

   - Stimulate release of noradrenaline

     Examples include:

     - ♥ Amphetamine and derivatives
     - ♥ Tyramine

   - Inhibit reuptake of noradrenaline

     Examples include:

     - ♥ Cocaine

   - Inhibit the metabolism of catecholamines.

     - ♥ MAOI inhibitors
     - ♥ COMT inhibitors

3. Mixed (i.e. Directly Acting and Indirectly Acting) Sympathomimetics:

   Examples include:

   - Ephedrine
   - **Pseudoephedrine**
   - Metaraminol

Preparations

Pseudoephedrine hydrochloride as:

Tablets (standard release):

- 60 mgs

Tablets (controlled release):

- 120 mgs

Mechanism of Action

Ephedrine is a non-selective sympathomimetic agent which stimulates both α and β-adrenergic receptors

It is directly acting and indirectly acting sympathomimetic as it directly stimulates adrenergic receptors and also releases noradrenaline from its presynaptic storage sites.

Pharmacodynamics

Pseudoephedrine is an effective nasal decongestant.

Like ephedrine, pseudoephedrine acts both peripherally and centrally within the CNS, but is a somewhat less potent **CNS stimulant** than the closely related, **ephedrine**.

Pharmacokinetics

Absorption:

- Pseudoephedrine is administered orally

  It is readily absorbed from the gastrointestinal tract.

Distribution

- Distribution into extravascular sites is extensive with the apparent volume of distribution between 2.6 and 5 L/kg.
- The degree of protein binding is unknown
- Pseudoephedrine can cross the human placenta.
- Pseudoephedrine is excreted into human breast milk, in amounts.

Metabolism and excretion:

- Pseudoephedrine is largely excreted unchanged in the urine
- There is a small amount of hepatic metabolism.
- Half-life ranges from 9 - 16 hours.

Indications

Relief of nasal and sinus congestion associated with acute and chronic rhinitis

Relief of nasal and sinus congestion associated with acute sinusitis

Contra-indications/precautions

These include:

1. Known hypersensitivity to pseudoephedrine

2. Patients with tachyarrhythmias.

3. Contraindicated in patients with HCM - may aggravate obstruction secondary to increased myocardial.

4. Use with caution in patients with active cardiovascular disease including angina, cardiac arrhythmia and coronary insufficiency, myocardial infarction as the cardiovascular effects of ephedrine may exacerbate these conditions.

5. Hypertension:

    - Use carefully in hypertension as blood pressure may increase.

      A meta-analysis has found that, on average, pseudoephedrine only slightly increased systolic blood pressure and heart rate in people who were normotensive or had controlled hypertension; however, the elderly were not represented in the trials, and, in practice, this effect may be greater in some individuals than others. [2]

6. Contraindicated in patients with phaeochromocytoma - severe hypertension may result.

7. Closed angle glaucoma, (may exacerbate the condition).

8. Drug interactions:

    - Monoamine oxidase inhibitors:

        - ♥ Current use or within 14 days of ceasing therapy - these may prolong and enhance the cardiac and pressor effects of ephedrine.

    - Halogenated hydrocarbons:

        - ♥ These agents may increase cardiac irritability which may lead to arrhythmias.

9. Use with caution in patients with hyperthyroidism

10. Patients with psychosis or neurosis.

11. Age extremes:

Children:

- Avoid using for rhinitis due to common cold in children < 6 years; may be used in children 6 - 11 years on professional advice.

  Do not use controlled release products in children

Elderly

- Use lowest effective dose as the elderly are particularly susceptible to adverse effects.

Pregnancy

Pseudoephedrine is a category B2 drug with respect to pregnancy.

Category B2 drugs are those drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of fetal damage.

From the limited information available, maternal use of pseudoephedrine has not been associated with an increased risk of birth defects.

However, pseudoephedrine *may* increase the risk of gastroschisis, small intestinal atresia and vascular disruption defects due to the vasoconstrictive effects of the medicine.

Therefore, consider an **alternative medicine during pregnancy.**

Breast feeding:

Small amounts of pseudoephedrine are excreted into breast milk, but the amounts are unlikely to adversely affect the breastfed infant.

However, as pseudoephedrine has CNS stimulating effects, observe the breastfed infant for potential adverse effects such as irritability, poor feeding and sleeping problems.

Pseudoephedrine may also reduce breast milk production, and oral administration of the medicine during breastfeeding should be avoided, especially in women who are at risk of low milk supply.

The use of topical nasal decongestants is preferred.

Adverse Effects

Adverse effects may include:

1. CVS:
    - Tachycardia
    - Hypertension
    - Precipitation of angina pectoris (usually in those with atherosclerotic disease).
    - Arrhythmias:
        - ♥ Serious / life-threatening malignant arrhythmias (e.g. VT/ VF) may occur in patients with organic heart disease or those receiving other drugs that sensitize the heart to arrhythmias, (such as halogenated anesthetics).
2. CNS:
    - Anxiety / restlessness / agitation.
    - Tremor
    - Diaphoresis
    - Insomnia (chronic use)
    - Confusion / euphoria / delirium is **larger** doses.
    - Psychosis characterised by paranoia, hallucinations, depression and bizarre mentation in cases or **chronic** abuse
3. GIT:
    - Nausea / vomiting
    - Mild abdominal pains
4. Acute urinary retention (particularly in those with prostatic hypertrophy).
5. Extravasation with IV use may cause tissue necrosis and sloughing of skin tissue
6. Tachyphylaxis
7. Psychological and physical addiction:
    - Long term (oral) pseudoephedrine use can lead to psychological and physical addiction.

Ephedrine and pseudoephedrine are commonly used as a base compound for the production of illicit sympathomimetic drugs of abuse.

Dosing

Usual adult dosing is:

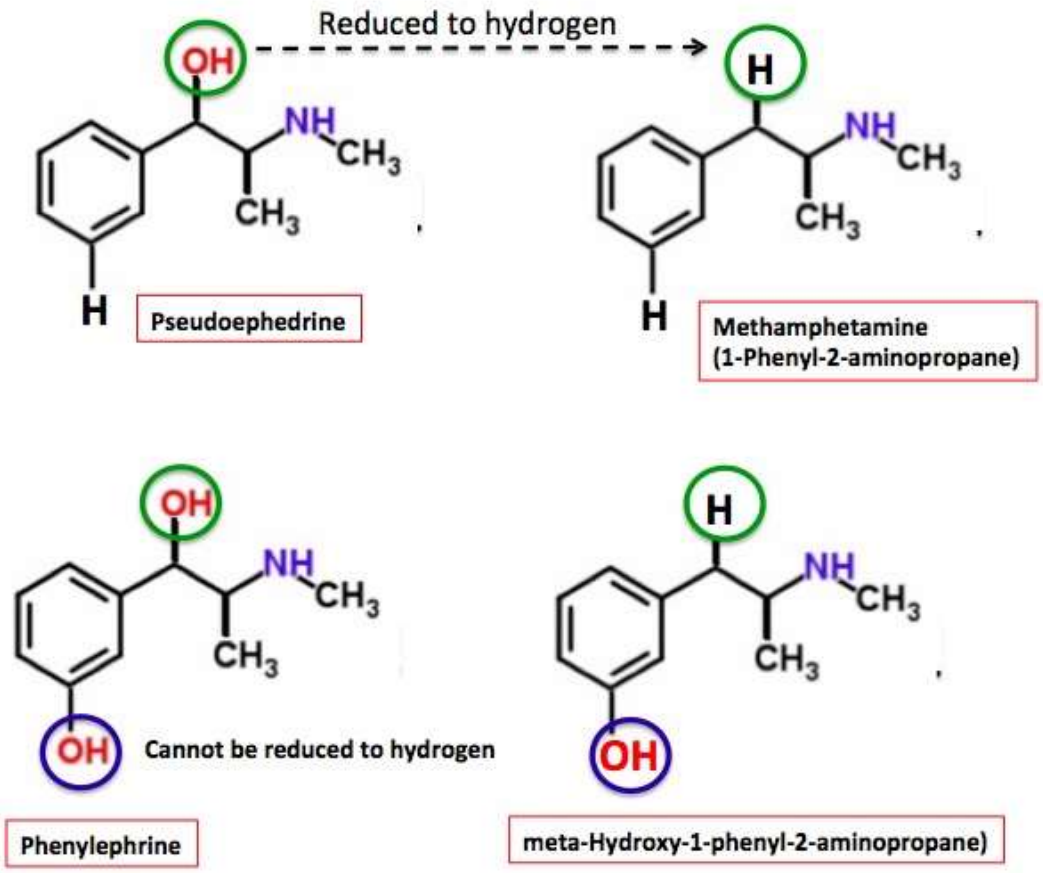
Oral standard release:

- 60 mg every 4 - 6 hours; maximum 240 mg daily.

Oral controlled release tablet:

- 120 mg every 12 hours until symptoms improve, then reduce to 120 mg once daily, if needed.

Appendix 1



(From American Council of Science & Health)

*In the first reaction (above), a simple chemical transformation of a hydroxyl (OH) group (green circle) into a hydrogen atom - a process called reduction- is all that is needed to convert (relatively) harmless pseudoephedrine into methamphetamine (or "**ice**")*

*There are a number of chemical reagents that can be used for this transformation. Walter White, from the Drama Series, "**Breaking Bad**" of 2008-2013, used phosphorous and iodine, a method that no organic chemist in his right mind would use due to the danger this would impose...however it does work well enough.*

*The second reaction (below) is quite different. Phenylephrine, the alternative agent used as a decongestant, contains **two** different hydroxyl (OH) groups, shown by the blue and green circles. The blue hydroxyl group (called a phenolic group) is chemically unreactive. So if you react phenylephrine with phosphorous and iodine, only the OH in the green circle is affected. The product of this reaction is an aminopropyl phenol (the drug gepefrin), a mediocre sympathomimetic agent without central stimulant effects.*

Phenylephrine in consequence has been put forward as an alternative to pseudoephedrine. The only problem is, however, it is useless.

References

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5. Project Stop:

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