THE NORTHERN HOSPITAL

AMPHETAMINES

"The Ecstasy of Saint Therese", Gian Lorenzo Bernini, sculpture in marble, 1644-47
Cappella Cornaro, Santa Maria della Vittoria, Rome

"Who can look at Bernini's Ecstasy of St Theresa, 1644-7, with an innocent eye?

On a scalding Roman summer afternoon some years ago a trio of sandaled nuns came into the dark church of Santa Maria della Vittoria and approached the Cornaro Chapel in the left arm of the crossing. I was sitting on one of the pews opposite, unsettled as usual by what I was seeing- intermittently illuminated rapture. Every so often a coin would clunk into the pay-for-light box, and the most astounding peep show in art would proceed: the saint's head thrown back, her mouth, its upper lip drawn back, opened in a moan, heavy lidded eyes half-closed, shoulders hunched forward in both recoil and craving. Beside her, a smiling seraph delicately uncovers Theresa's breast to ease the path of his arrow.

The nuns stayed for ten minutes, stock still, then two of them genuflected, crossed themselves, as well they might, and left the church. The third sister, small, round, bespectacled, sat down in another pew, dipped her head in prayer and occasionally caught my eye as I tried not to wonder what she was thinking and feeling. Bernini's sculpture, after all, is a spectacle that hovers on the moving borderline between sacred mystery and indecency. Scholars have fallen over themselves to warn us that what we are looking at could not possibly be a moment of sensual surrender, Bernini being so famously devout and the saint herself insisting in her autobiography that the "pain is not physical but spiritual". Typical is the authority who writes that to see the work as being in any way erotic "limits it severely"- although, equally typical of this kind of comment, he doesn't bother to say why. We are left with the wagged finger and imputation that, if we are to understand Bernini's intentions, we had better banish any such modern vulgarity from our heads. It is utterly unhistorical, these interpreters insist, to imagine that the Pope's architect, and supreme sculptor of Rome, a man who practiced Jesuitical discipline every day, could conceive of representing the mystical levitation of a saint as a moment of orgasmic convulsion."

Simon Schama, Power of Art, 2006

Simon Schama's startling essay on Bernini's "Ecstasy of St. Theresa", expounds the hidden modern dichotomy of those who gaze upon the work, that of the spiritual side and the "darker," yet somehow unavoidable to 21st century sensibilities, sensual side.

St Theresa sought her ecstasy by divine inspiration. In the 21st Century, however, we live in a far more secular world and now unfortunately ecstasy tends to be sought by pharmacological means rather than divine. Like Bernini's depiction of ecstasy these pharmacological agents also present a dark dichotomy. A sensual, physical or even spiritual experience may be achieved; however there is also a darker aspect to this experience, in the potentially lethal effects they may exert.

AMPHETAMINES

"Rave party", the modern face of "ecstasy".

Introduction

Amphetamine (**phenyl iso-propylamine**) is the prototype of a class of synthetic biogenic amines that produce a strong **sympathomimetic toxidrome, particularly of the CNS.**

The naturally occurring biogenic amines include:

- The catecholamines, (adrenaline and noradrenaline).
- Dopamine.
- Serotonin.

Strictly speaking amphetamine refers specifically to **phenyl iso-propylamine**, however the term has now come to include a range of structurally related compounds with similar effects. The basic structure of these compounds is the **sympathomimetic amine nucleus.**

Amphetamines are a common drug of abuse. They are produced in clandestine laboratories and vary significantly in purity and potency.

Prescription amphetamine type medications are common and are also used as drugs of abuse.

Formulations:

Prescription medications include:

- Dexamphetamine
- Methylphenidate
- Diethylpropion

Illicit amphetamine derivatives include:

- Methamphetamine: **(Ice, Speed).**
- 3, 4-methylenedioxy-amphetamine (**MDA**)
- 3, 4-methylenedioxy-metamphetamine (**MDMA** commonly known as **Ecstasy)**

In recent years a multitude of clandestine laboratory produced synthetic derivatives of sympathomimetic chemicals have been produced. These are now widely available in clubs and via the internet.

Many of these agents in addition to having strong sympathomimetic effects, are also **hallucinogenic.**

Some of these newer derivatives include:

- Phenyl ethyl amine derivatives
- Cathinone derivatives
- Piperazine derivatives

See also separate documents on:

- **Alpha - PVP (in Toxicology folder)**
- **NBOMEs (in Toxicology folder)**
- **Para - methoxy - amphetamine (PMA) (in Toxicology folder)**

- **Cocaine(in Toxicology folder)**

Pharmacokinetics

Absorption:

- Amphetamines are well absorbed orally and following insufflation.

Distribution:

- Amphetamines are lipid soluble weak bases, with large volumes of distribution, (methamphetamine is 3.6 L/kg)

Metabolism and excretion:

- Most undergo hepatic metabolism and renal excretion of metabolites.
- Half-lives vary from 8 -30 hours.

Pathophysiology

Amphetamines are structurally related to ephedrine. Substitutions on the basic amphetamine structure yield numerous derivatives with varying receptor affinities.

They produce a sympathomimetic toxidrome that includes both central nervous system and peripheral nervous system stimulation.

They have a dual sympathomimetic action:

- Enhancement of catecholamine release, ie act as indirectly acting sympathomimetics, (like metaraminol and ephedrine)
- Blockade of catecholamine reuptake.

This results in central and peripheral increases in catecholamines, dopamine and serotonin.

Risk Assessment

Small doses in non-tolerant persons can result in significant toxicity.

In **children** as little as **one** illicit amphetamine derivative pill (eg MDMA) may be life threatening.

Potentially life threatening symptoms include:

- Hyperthermia.

- Chest pain:
    - ♥ ACS/ STEMI/ aortic dissection
- Headache/ focal neurological signs/ altered conscious state/ coma
    - ♥ Hyponatremia/ ICH/ SAH/ carotid dissection
- Seizures occur in up to 4 % of cases.

Clinical Features

Patients may present with one of 3 ways:

- An acute sympathomimetic toxidrome.
- Secondary hypertensive and cardiac medical complications
- Psychiatric sequelae

Acute sympathomimetic toxidrome:

Unlike cocaine which causes a relatively short lived sympathomimetic toxidrome, the duration of amphetamine action is generally very much longer and may persist for up to 24 hours.

Features of the toxidrome include:

Central Effects:

There is central stimulation, especially of the reticular activating system and the cerebral cortex.

In milder cases this can result in:

1. Increased mental alertness.
2. Euphoric effects.
3. Increased physical performance.

In moderate toxicity:

4. Dysphoria.
5. Agitation/ aggression, which can be extreme.
6. Tremor

7. Psychosis with:
    - Hallucinations
    - Paranoid delusions.
    - The margin between euphoria and psychosis is small.

In severe toxicity:

8. Hyperthermia:
    - With muscle rigidity
    - Rhabdomyolysis.
    - Dehydration and renal failure.

9 Seizures

10 Coma

Peripheral Effects:

1. Diaphoresis.
2. **Mydriasis**
3. GIT
    - Nausea/ vomiting.
4. CVS:
    - Tachycardia will be the most common manifestation.
    - Hypertensive crisis.

Secondary medical complications:

Headache, chest pain and focal neurological signs suggest the presence of a potentially serious secondary medical complication.

Serious secondary complications can include:

1. Hypertensive:

- Intracranial hemorrhage:
  - ♥ Intracerebral hemorrhage
  - ♥ SAH
- Acute cardiogenic pulmonary edema
- Hypertensive encephalopathy.
- Arterial dissections:
  - ♥ Aortic artery dissection.
  - ♥ Carotid artery dissection.

2. Cardiac:

- Arrhythmias
  - ♥ Sinus tachycardia is the commonest, but lethal VF or VT may also occur.
- Acute coronary syndromes.

3. Secondary electrolyte disturbances:

- Acute symptomatic **hyponatremia:**

  This can be a particular problem with **MDMA** and **cathinones**

  These agents can have a specific **ADH action** and so can induce an acute **SIADH syndrome.**

  This situation can be aggravated by those who take **excessive fluids** in the belief that this will protect them from the dehydration effects of sympathomimetic agents and hyper - activity .

  Significant acute hyponatremia can develop leading to serious symptoms.

Psychiatric sequelae

Psychotic symptoms such as paranoid ideation may be a feature of acute intoxication, but may also persist as part of a **post amphetamine psychotic state** when other features of the sympathetic toxidrome have resolved.

Tolerance

Marked tolerance develops after repeated amphetamine use and leads to rapid escalation of drug doses.

Increasing doses produce increasing toxicity and complications.

Dependence

Psychological dependence may occur, but true physical dependence is not commonly seen.

Investigations

These will be done according to the index of suspicion for secondary complications or to rule out alternative diagnoses.

Blood tests:

1. FBE
2. U&Es/ glucose:
    - **Urgent sodium level**

      SIADH with severe hyponatremia may occasionally occur with **MDMA.**
3. LFTs
4. CK
5. Troponin
6. ABGs/ VBGs/ lactate
7. Coingestion:
    - Blood alcohol / paracetamol level.

ECG:

- Arrhythmias
- ACS

CXR:

- Pulmonary edema

CT Scan/ CT angiogram:

- Suspected ICH
- Suspected aortic dissection.

Urine drug screen

- Some amphetamines and cocaine can be detected on urine drug screen.
- Many newer agents cannot be readily detected

Management

1. Immediate attention to any ABC issues.
2. Charcoal:
    - This is *not* advised as amphetamines are rapidly absorbed and are associated with the risk of seizures and delirium.
3. Delirium and agitation:

    IV benzodiazepines:

    - Sedation with titrated doses of **benzodiazepines.**
        - ♥ Oral administration may be sufficient in mild cases of agitation, but more severe cases will require IV administration.
    - **Early** use of benzodiazepine is an important aspect of treatment. They will decrease many of the sympathomimetic effects.

    Neuroleptic agents:

    - For extreme agitation with psychotic features, titrated doses of **olanzapine** or **droperidol** may also be given.
    - There is some controversy about neuroleptics in amphetamine toxicity. However they are very effective. The main concern is lowering seizure threshold. Of all neuroleptics, haloperidol is rarely associated with seizures and has minimal effects on seizure threshold.

    Physical restraint:

    - This may also be necessary in some cases to treat very agitated patients.

4. Seizures:

   - IV benzodiazepines

5. Hypertension:

   - Sinus tachycardia and hypertension can initially be controlled with IV titrated benzodiazepines.

   If refractory to the above, further options include:

   - Phentolamine 1 mg IV repeated every 5 minutes, as required.
   - GTN infusion
   - Nitroprusside infusion

   Note that beta blockers are contraindicated in amphetamine toxicity.

   Beta-blockers are **not** recommended, as they will leave alpha effects unopposed. Treating with beta-blocker to control the heart rate will leave an unopposed alpha activity that aggravates vasoconstriction, (beta $_2$ effects are blocked)

6. Hyperthermia:

   - IV cooled fluids
   - IV Benzodiazepines
   - Paralysis and ventilation may be required in severe cases.

7. Hyponatremia:

   - Look for and treat as indicated in cases of MDMA toxicity.
   - Immediate correction with **hypertonic saline (3%)** is indicated if profound and associated with altered conscious state or seizures.
   - 4 mls/kg over 30 minutes can be given

8. ACS:

   - Thrombolytics may be considered if *standard criteria* are met, however there is more risk with their use in the setting of amphetamine toxicity an **specialist advice** should be sought.

Thrombolytics are problematic in amphetamine induced STEMI. This is more commonly due to vasospasm or arterial dissection rather than to thrombotic disease.

They should not be used in hypertensive patients and aortic dissection must be excluded.

- **Coronary angiography, if readily available is a better option than thrombolysis. Vasodilators can be given or angioplasty performed if indicated.**

9. Arrhythmias:

    - Are treated along standard lines, although the use of beta blockers are contraindicated.

Disposition:

Amphetamine effects can be relatively long lasting, (**up to 24 hours**), so a prolonged period of observation may be necessary.

Patients with chest pain or ECG changes will require ECG monitoring

Patients who are *symptom free* with normal vital signs including normal blood pressure and a normal ECG at 4 hours may be medically cleared.

References

1. Amphetamines in L Murray et al. Toxicology Handbook 3rd ed 2015.

2. eTG - March 2016

    - Wilderness & Toxicology Guidelines 2nd ed 2012.

Further reading:

Schama, S. Power of Art. BBC Books, 2006.

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Reviewed August 2016