THE NORTHERN HOSPITAL

GAMMA HYDROXY BUTYRATE (GHB)

"The Sleeping Venus", oil on canvas, Paul Delvaux, 1944, Tate Gallery London.

"The psychology of that moment was very exceptional, full of drama and anguish. I wanted to express this anguish in the picture, contrasted with the calm of the Venus"

Paul Delvaux

Paul Delvaux (1897-1994) was a Belgian surrealist painter who began his early career with naturalistic landscapes, but by 1933 had developed a surrealist style under the influence of the works of the proto-surrealist Giorgio Chirico. In the 1930s he visited the Brussels fair where skeletons and a mechanical Venus made a strong impression on him and would influence a number of his future works.

Delvaux delighted in the provocative and incongruous juxtaposition of precisely rendered objects, persons, and situations to create surrealist dreamscapes. Under the influence of de Chirico he adopted the use of arresting settings characterized by receding diagonals and classical architecture.

Delvaux's goal in many of his works was to produce what he called "poetic shock" by, as he explained, "putting heterogeneous but real things together in an unexpected way." He put these disparate objects together in a dreamlike - but also in a disturbing way. In his "Sleeping Venus" of 1944 we see a classic example of his work. The Venus sleeps calmly it seems, but we see by the figures around her she is dreaming nightmares. The elegantly dressed figure on the left - perhaps herself - seems lost in her own thoughts but then is suddenly startled by the specter of a skeleton – a universal symbol of death - in her path.

The figure on the right appears to be calling out an anguished warning to the woman. A distant figure in the far background seems to recognize some danger and begs for help from some unseen possible rescuer. A group of three figures behind the sleeping Venus are wailing perhaps in response to some tragedy. Delvaux later explained that he had composed the work during the war when Brussels was being bombed, an atmosphere charged with anguish and extreme anxiety.

In the "raves" of the 21 Century lurks a malicious drug with an increasing presence. It lulls those who use it into a false sense of emotional well being. But like Delvaux's "Sleeping Venus", amidst her apparent calm there lurks contrasting and disturbing specters of doom. These specters cry out their warning, they call out for help to save them from an unseen assailant, they wail over some unknown assault. This drug is GHB and despite the sense of warmth and well being it can induce, it may also leave those who use it vulnerable to assault - or - as the skeletal specter suggests – a fait even worse than this.

GAMMA HYDROXY BUTYRATE

Introduction

Gamma hydroxy butyric acid, (GHB) was synthesized in 1960 in an attempt to create a new anesthetic agent.

It is an analogue of the inhibitory brain neurotransmitter GABA that is capable of readily crossing the blood-brain barrier.

Today it has become an illicit drug of abuse, used predominantly because of its alcohol like effects.

In overdose it causes **rapid CNS** and **respiratory depression**, which can be **lethal.**

The duration of toxic effects is relatively short at **4-8 hours.**

Treatment is supportive.

Uncomplicated ingestions have a benign course and respond well with supportive treatment.

Full recovery is usually seen within 8 hours if there are no coingestants or secondary complications.

GHB may induce a **severe withdrawal syndrome** in very frequent users which is difficult to treat.

Related agents:

Two chemical precursors with similar effects are also commonly available:

- Gamma butyrolactone, (GBL) which is an oily liquid and is used as an industrial solvent.

- 1,4- butanediol, a water soluble liquid.

Once ingested these agents are metabolized to GHB.

Clinical effects therefore are experienced more *slowly* than is the case for GHB.

Legal Status

The law in Australia states that it is illegal to supply, manufacture, import, possess, sell or use the drug GHB. [2]

Illicit Use

GHB is a white crystalline powder. It is usually dissolved in water to produce a clear colorless liquid, which may be ingested directly or added to drinks.

- GHB may be added to drinks without visible trace, or taste, hence may be used to spike drinks, a practice used to facilitate sexual assault or "date rape".
- On the "street" GHB is available as a powder or colorless liquid form.
- Common street names include, fantasy, liquid ecstasy, liquid E, liquid and Easy lay, but there are many others that come and go according to the fashion of the moment.

History

Gamma hydroxy butyric acid, (GHB) was synthesized in 1960 in an attempt to create a new anesthetic agent.

Toxicology

GHB is a naturally occurring short chain carboxylic acid in the brain and is a metabolite of GABA (gamma amino butyric acid). It may act as a neurotransmitter in its own right.

Its mechanism of action is uncertain, but one theory is that it acts on **GABA - B receptors**, (and **not** on GABA - A receptors, which benzodiazepines act on).

Pharmacokinetics

Absorption

- GHB is rapidly absorbed following oral ingestion.
- Peak plasma levels occur within 20 - 60 minutes.
- Food in the stomach will reduce bioavailability.

Distribution

- GHB readily crosses the blood brain barrier
- GHB readily crosses the placental barrier.

Metabolism

- GHB is predominantly metabolized to succinate, with saturable kinetics. which subsequently enters the Krebs cycle to ultimately produce CO_2 and water.
- Half-life is around 30 minutes and proceeds in a dose dependent saturable manner.

This means that the margin between the usual clinical effects and toxicity is narrow.

A small increase in amount therefore can result in a dramatic increase in effect and toxicity.

- It is normally eliminated within 4-8 hours.

Risk assessment

GHB is often presented at a strength of **1 gram /ml**, however accurate dose estimation is impossible as there is, of course, no "standard" of preparation, and in practice concentrations vary widely.

Overdose often occurs when a preparation of higher than usual concentration is ingested.

"Therapeutic" index is also narrow with this drug. Just twice the "standard" dose of 30-40mg/kg can induce coma.

Death can occur from respiratory depression, and/or airway compromise and/or pulmonary aspiration.

Effects is enhanced by other CNS depressants, in particular alcohol.

Any ingestion in **children** may be associated with rapid onset of coma, and must be treated as potentially lethal.

Clinical Effects

When used in "recreational" doses:

- Effects are generally experienced within **20 minutes** of ingestion
- Effects peak at **30 - 60 minutes.**
- Maximal effects may last for approximately **2-3 hours**, often followed with a relatively abrupt recovery of consciousness.
- Complete recovery from the effects of GHB mat take up to **8 hours**.

It should be noted however that effects can vary greatly between individuals and effects are not reliably predicable.

Recreational effects:

The "recreational" effects of GHB include:

Effects that are very similar to alcohol (though the potential toxicity is much greater).

1. Mild euphoria:
    - Feelings of “enhanced sensuality” and “emotional warmth” are described.
2. Disinhibition.
3. Anterograde amnesia.
4. Sedation that increases with dosage.
5. Impaired coordination/ judgment and slurring of speech.

Overdose effects:

The risk of overdose is high with illicit use as there is no way of being sure of the dose ingested.

CNS effects are greatly enhanced with other CNS depressants, including alcohol and benzodiazepines.

Effects include:

1. CNS:
    - Conscious state may initially fluctuate.
    - Delerium.
    - *Profound and rapid* onset of CNS depression may occur.
    - Myoclonus is common
    - Seizures, (uncommon)
    - Coma:
        - ♥ Note the resolution of the coma can be quite abrupt. Patients can be quite confused and agitated on awakening.
        - ♥ Coma that lasts greater than **8 hours** suggests another/ additional diagnosis.
2. Respiratory depression:
    - Death can occur from respiratory depression, and/or from airway compromise, (particularly in the presence of other CNS depressants, including alcohol) or from pulmonary aspiration.

3. Autonomic effects:

- Sweating
- Miosis

3. CVS:

- Hypotension
- Tachycardia.
- Bradycardia is also common.

5. GIT:

- Nausea and vomiting may occur, particularly upon awakening.

Dependence

Physical and psychological dependence can occur with GHB among frequent and heavy users.

Occasional users are unlikely to become addicted.

Prolonged use has been associated with withdrawal symptoms, which can be **severe** if the drug has been taken frequently, (e.g. 1 - 3 hourly).

Once only users do not suffer major withdrawal symptoms.

The time course of the syndrome is as follows:

1. Withdrawal manifests with **1 - 6 hours** from the last dose.

2. Symptoms escalate **rapidly.**

3. Symptoms can be **protracted** at **1 -2 weeks**.

Withdrawal symptoms are similar to those of alcohol or benzodiazepines and so may result in:

1. Anxiety

2. Agitation

3. Delirium

4. Tremor

5. Adrenergic hyperstimulation.

6. In severe cases frank psychosis and seizures may occur.

Tolerance

A degree of tolerance may be seen in *frequent* users.

Investigations

These will be guided by how unwell the patient is and according to the index of suspicion for alternative diagnoses and/ or secondary complications.

It should be borne in mind that the usual settings in which GHB is taken, ("raves") makes co-ingestion of other agents likely and the concomitant presence of alcohol virtually certain.

The following should be considered:

Blood tests

1. FBE

2. U&Es/ glucose

3. Blood alcohol

Urine drug screen

GHB is not routinely included in standard urine drug screens.

ECG

As for any unwell patient.

CXR

If aspiration suspected.

CT scan brain

As for alcohol intoxication, the threshold for brain CT in patients with an altered conscious state must be low, if there is any doubt over the history, suspicion of concomitant trauma or recovery does not occur within the expected time frames.

Management

1. Immediate attention to any **ABC issues.**

    - The need for intubation will be based on the degree of depression of the conscious state and the degree of preservation of the gag reflex.

    - Intubation may not in fact be nessesary in many cases due to the short duration of action and because of the good response to supportive care. Some patients may be nursed in the coma position with close attention to the airway until the effects of the drug subside.

2. Charcoal

    - This is **contra-indicated** because of the potential for rapid and profound depression of the conscious state.

    - It may be given for co-ingestants in patients who have been intubated.

3. Hypotension

    - This usually responds well to IV fluids.

4. **There is no current specific antidote, management therefore is supportive.**

    - Note that flumazenil is **not** effective as this is a GABA A antagonist, (not a GABA B antagonist)

GHB Withdrawal: [4]

Withdrawal symptoms are generally treated with **benzodiazepines**, however most GHB withdrawal patients have a very high tolerance to these agents.

Early and high doses, of **benzodiazepines** are required, but even with this approach they may be relatively ineffective. This is possibly due to that fact that the benzodiazepines are **indirect** agonists of GABA-**A** receptors while GHB (and its analogues) are mainly GABA-**B** receptor agonists.

For this reason other treatment modalities may be required to control symptoms.

Intubation to manage uncontrolled delirium maybe required, followed by the following options:

1. Midazolam infusion

2. Propofol infusion

3. Phenobarbitone infusion (a long acting **direct** GABA-**A** receptor agonist.

4. Baclofen (a GABA-**B** receptor agonist) administered via nasogastric tube, (5 mg b.d titrating up to 20 mg t.d.s has been used for this purpose). [4]

Disposition

Patients who are clinically well at **2 hours** post ingestion may be medically cleared.

Patients with mild symptoms can be managed in a general ward.

References:

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

2. Gamma Hydroxy Butyrate, NSW Health Fact Sheet, Issued 30 April 2006.

3. Snead O.C, Gamma Hydroxybutyric Acid. NEJM, 352: 26, June 30 2005, p. 2721-2732

4. Rajan Kailainathan, Anselm Wong, Shaun Greene, Zeff Koutsogiannis; Recognition of Gamma - hydroxybutyric acid withdrawal: Rapid progression and prolonged symptomatology. Emergency Medicine Australasia 2017, 29, 119 - 120.

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