GAMMA HYDROXYBUTYRIC ACID (GHB) INTOXICATION
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ABSTRACT
- Gamma-Amino Butyric Acid (GABA) is the major inhibitory neurotransmitter in the CNS; GHB was discovered in a search for therapeutic GABA analogs
- GHB is popular as a dietary supplement and drug of abuse
- Overdose leads to sedation and respiratory depression
- Most patients recover fully within six hours, although respiratory arrest and death are reported
- GHB withdrawal is similar to withdrawal from other sedative/hypnotic agents, such as ethanol
- Congeners such as gamma-butyrolactone (GBL) and 1,4-butanediol have similar toxicity to GHB

INTRODUCTION
- GHB used in models of absence seizures, and may have tissue protective effects in some conditions
- Used as an anesthetic in the 1960’s and 1970’s; fell out of favor due to abnormal EEG patterns
- GHB is FDA approved only for the treatment of narcolepsy

METABOLISM
- Occurs naturally in brain tissue
- Major elimination via the Kreb’s (aka Tricarboxylic Acid)
  - GHB → succinic semialdehyde → succinate → into Kreb’s cycle
- Very little eliminated in urine, but enough to test for poisoning

PHARMACOKINETICS
- Peak blood levels in 15-45 minutes; peak clinical effects in 30-60 minutes; half-life (20-53 minutes)

PHARMACOLOGY
- Several possible mechanisms of action by which GHB produces CNS sedation
  - Direct activation of GHB receptors
  - Modulation of GABA (especially GABA$_B$) receptors to make GABA more effective
  - Increasing total CNS GABA pool
  - Modulation of other CNS neurotransmitters, such as dopamine, acetylcholine, 5-hydroxytryptamine (serotonin) and naturally occurring opioids.

GHB AS A DRUG OF ABUSE
- Intentional misuse first reported in 1990’s in California, Georgia and Florida
- Has been used as an agent of drug-facilitated sexual assault (date rape)
- Made Schedule I by the US DEA in March 2000

CLINICAL FEATURES
- The manifestations of GHB intoxication are primarily as a result of its CNS and respiratory depression.
- Frequently transported to ED from a nightclub; may also be transported from a gym or workout facility.
- Minor intoxications
  - Euphoria similar to low-dose alcohol; may also see ataxia, nystagmus, somnolence or aggression
- Major intoxications
  - CNS depression—the major clinical finding
    - May border on coma
    - May be unresponsive yet arouse with very noxious stimuli (i.e. intubation attempts)
    - Rapid awakening common as drug wears off
  - Respiratory depression
    - May produce changes ranging from minor depression to respiratory acidosis/apnea
    - Patients may also cycle between apnea and hyperventilation
  - Vomiting common
  - Seizures and/or myoclonic jerking may occur
  - Bradycardia common; hypotension occurs but rarely
CLINICAL FEATURES/Major Intoxications, continued
- Hypothermia common
- Nonspecific ECG changes reported *infrequently*
  - U waves, 1\(^{st}\) AV block, inverted P waves, T wave changes, transient RBBB (one patient only)
  - If significant ECG changes are present, consider coningestants (i.e. cocaine)

CLINICAL COURSE
- Outcome usually good if patient survives to seek medical care
- Patients generally recover respiratory and CNS function in 2-6 hours
- If symptoms last more than 6 hours, an alternative diagnosis should be sought

DRUG INTERACTIONS
- Case report of possible potentiation of GHB with ritonavir and saquinavir
- Synergistic with ethanol, 1-4 butanediol, and probably all other sedative/hypnotic agents

MANAGEMENT/TREATMENT
- The management of GHB intoxication consists of supportive care
- Important to consider coningestants and occult trauma
- Intubation may be necessary in profoundly sedated patients
  - Intubation indicated if: severe respiratory depression, apnea, loss of airway reflexes, concern for aspiration
  - Short acting agents (midazolam—Versed\textsuperscript{®}) if necessary for intubation/post-intubation sedation
  - GHB poisoned patients who require intubation may occasionally be extubated and discharged from the ED due to rapid recovery from this drug
- Cardiovascular effects are unlikely to require aggressive therapy
  - Hypotension should respond to fluids; need for pressors not reported
  - Symptomatic bradycardia may require atropine, but this is rare
- Hemodialysis not necessary (drug rapidly eliminated)
- Not included in standard drug screens, but may be detected by specialized tests (i.e. gas chromatography/mass spectrometry)

ANTIDOTES
- There is no effective antidote for GHB
- Flumazenil and naloxone are not effective
- Physostigmine should not be used. Although advocated by some, the data supporting its use are very weak, there is no evidence it improves outcome, and its use IS NOT RECOMMENDED

PRODRUGS OF GHB
- Gamma-butyrolactone and 1-4 butanediol have similar clinical effects to GHB

GHB WITHDRAWAL
- A withdrawal syndrome similar to that of ethanol and other sedative/hypnotic agents I swell reported.
- Symptoms: tremors, agitation, auditory and visual hallucinations, tachycardia, and hypertension.
- Benzodiazepines are the mainstay of treatment; extremely large doses may be required
- Similar syndrome seen with gamma-butyrolactone and 1,4-butanediol
- Usually begins within hours of last use in addicted patients; symptoms may last 5-15 days.

CONCLUSIONS
- GHB, GBL and congeners are popular at rave parties
- CNS and respiratory depression are the major toxicities
- Supportive care usually suffices for treatment
- Abrupt cessation in habituated patients may produce withdrawal