Central Nervous System (CNS)-Acting Chemicals

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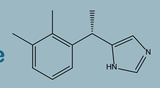
Toxic chemicals that target the central nervous system (CNS). These chemicals can act as anaesthetics, sedatives, and analgesics. Specific CNS-acting chemicals discussed in the context of the Chemical Weapons Convention have included α2-adrenergic receptor agonists, inhaled anaesthetics, fentanils and the Schedule 2A.03* chemical BZ.

α2-adrenergic receptor agonist examples

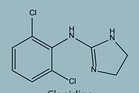
Dexmedetomidine


Dexmedetomidine

Mechanism of action:

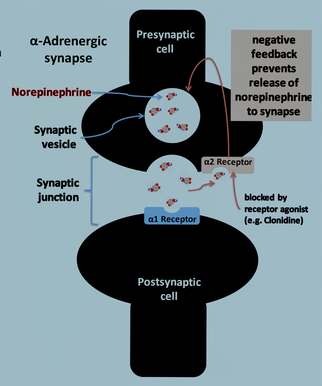
- Presynaptic activation of the α2-adrenoceptor, inhibiting norepinephrine release, preventing entry of the neurotransmitter into the synaptic junction (negative feedback).
- Postsynaptic activation of the α1-adrenoceptor
- inhibiting sympathetic activity. This results in decreased blood pressure and heart rate.
- Produces analgesic, sedative, and anxiolytic effects.
- Occupational exposure band (OEB) 5: control exposure to < 1 µg/m³.

Clonidine


Clonidine

Mechanism of action:

- Reduces release of noradrenaline at both central and peripheral sympathetic nerve terminals.
- Produces dose-related sedation, analgesia and anxiolysis.
- A reduction in the effective dose of other anaesthetic agents and opioids is also observed.
- LC_{50} (rat inh): 19.7 mg/m³/4 Hours
- LD_{50} (rat i.v.): 29 mg/kg

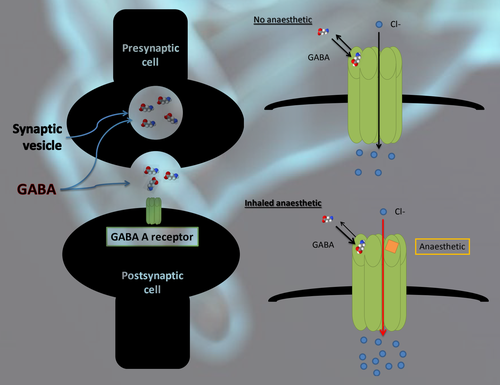


Mechanism of action of Dexmetomidine and Clonidine.

Inhaled anaesthetic examples

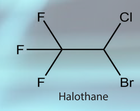
Mechanism of action:

- Enhances γ-aminobutyric acid (GABA) binding to its chloride ion-channel receptor.
- The increase in intra-cellular chloride levels produces an inhibitory effect (anaesthesia).

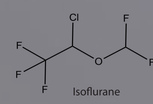


Mechanism of action of Inhaled anaesthetics.

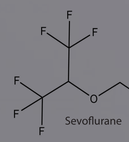
Halothane


Halothane

Isoflurane


Isoflurane

Sevoflurane


Sevoflurane

Toxicity Data	Oral LD_{LO} (Human) (µL/kg)	Oral LD_{50} (rat)	Inhalation LC_{50} (rat) [ppm]	Oral LD_{50} (mouse) [µL/kg]	Inhalation LC_{50} (mouse) [ppm (3 hrs)]
Halothane	-	5680 mg/kg	29000 (1h)	-	-
Isoflurane	1071	4770 µL/kg	15300 (3h)	5080	16800
Sevoflurane	-	10800 µL/kg	28800 (3h)	18200	28300

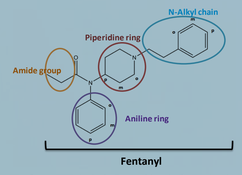
LD_{LO}: the lowest dosage of a substance observed to cause a fatality within a specific subject population under a specific set of exposure conditions. LD_{50}: the median value of all the observed dosages of a substance resulting in a fatality within a specific subject population under a specific set of exposure conditions. LC_{50}: the median value of all the observed concentrations (based on an exposure time) of a substance resulting in a fatality within a specific subject population under a specific set of exposure conditions. Lethal dose and lethal concentration values are statistics derived from specific populations and exposure conditions (typically controlled animal studies), they may not be representative of alternate populations and/or exposure conditions.

Fentanils

- Fentanils are a highly potent family of opioid narcotic analgesic drugs.
- The family includes fentanyl, a narcotic linked to an increased risk of overdose amongst opioid addicts.
- As of May 2018, there were 20 fentanil derivatives scheduled under the Single Convention on Narcotic Drugs

Properties

- Fentanyl and its analogues are solids that require aerosolisation for weaponisation purposes.
- Routes of exposure for fentanils include inhalation (aerosolized form), oral exposure or ingestion. Transdermal absorption is possible (for example, the use of transdermal patches), however as the process is slow, such that brief incidental exposures may not cause significant opioid toxicity.
- Fentanyl and its analogues have higher potency than morphine and heroin.
- Poor drug dosage, poly-drug use and addiction are all contributors to the high rates of overdose, respiratory depres-

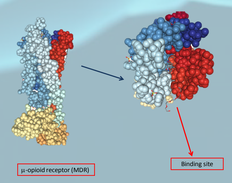


Structure and substitution positions for fentanyl and derivatives.

Fentanyl derivative	Amide group	Piperidine ring	N-Alkyl chain	Aniline ring
Sufentanil				
Carfentanil				
Ocfentanil				
Remifentanyl				
3-Fluorofentanyl				
Pivaloylfentanyl				
α'-methyl Butyrylfentanyl				
Cyclopentenilfentanyl				
Cyclopropylfentanyl				
para-chloro Valerylfentanyl				
Valerylfentanyl				
Acetylfentanyl				
Furanylfentanyl				
4F-iBF				
Tetrahydrofuranylfentanyl (THF-F)				
Methoxyacetylfentanyl				
ortho-methyl Cyclopropylfentanyl				
Acryloylfentanyl				
2'-fluoro ortho-Fluorofentanyl				

Mechanism of action:

- In the CNS, fentanils bind to opioid receptors, specifically μ-receptors. These receptors are found predominantly in the brain and spinal cord
- They act to depress CNS function.
- Bioavailbility from inhalation exposure can range from 12-100%.



Crystal structure of the μ-opioid receptor bound to a morphinan antagonist (Protein Data Bank Structure 4DKL)

Effects:

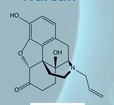
- Loss of pain sensation
- Miosis
- Decreased intestinal paristalsis (constipation)
- Nausea and vomiting
- Dose-dependent respiratory depression (which can lead to death)
- Diminished mental alertness resulting in a feeling of drowsiness, euphoria, sleepiness, and unconsciousness

Time Weighted Average – Occupational Exposure Limits (OEL-TWA)	
Alfentanil	1 µg/m³
Fentanyl	0.1 µg/m³
Sufentanil	0.032 µg/m³

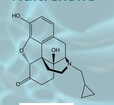
Antidotes: Naloxone hydrochloride (Narcan) or Naltrexone

- Opioid receptor antagonists.
- Bind to the opioid receptors more strongly than a fentanyl derivative, but do not activate the receptor.
- Quickly reverse signs and symptoms, especially life-threatening respiratory depression.
- Short half-life, symptoms may return in an apparently stabilized patient and antidotes might need to be readministered.
- 0.4 mg is the standard starting dose but for some fentanyl derivatives doses up to 2 mg have been required.

Narcan



Naltrexone

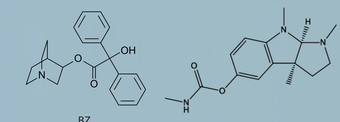


BZ (3-quinuclidinyl benzilate)

BZ is a glycolate anticholinergic compound and is a only "CNS-acting chemical" found in the Annex of Chemicals of the Chemical Weapons Convention (Schedule 2A.03*).

Properties

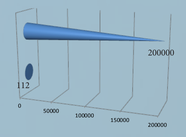
- Odourless crystalline powder with bitter taste.
- Persistent in soil and water and on most surfaces.
- Half-life in moist air ~ 3-4 weeks.


BZ

Antidote: Physostigmine

- Temporarily raises acetylcholine concentrations by binding reversibly to anticholinesterase.

Safety Ratio of BZ

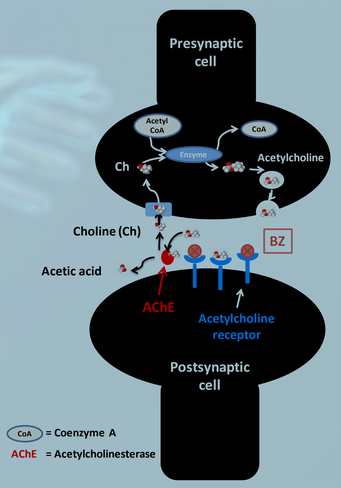


Dose in [mg.min/m³]

The large difference between the median lethal concentration (LC_{150}) and the median incapacitating concentration (IC_{150}) allows for the onset of CNS-acting symptoms to appear at a dosage much lower than a lethal dose.

Mechanism of action:

- Acts as a competitive inhibitor of the neurotransmitter acetylcholine (ACh) in postsynaptic ACh receptors.
- As the concentration of BZ at these sites increases, the proportion of receptors available for binding to acetylcholine decreases, resulting in an understimulation of nerve signal transduction.
- When administered by inhalation (in aerosolised form), absorption to the bloodstream is more pronounced than with oral administration.



Mechanism of action of BZ.

CNS effects:

- Stupor, ataxia, confusion, and confabulation. Induces concrete and panoramic illusions and hallucinations.

Peripheral effects:

- Mydriasis, blurred vision, dry mouth and skin, initially rapid heart rate; later, normal or slow heart rate.

Toxicity