

Antitussives and expectorants

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Cough

- reflex
 - afferent – center – efferent
 - central – peripheral
- purpose
 - cleaning the airways
 - removal of alien material and secretum/excretum

Definitions, clinical use

- antitussive
 - cough suppressant
 - used in non-productive, exhaustive/racking cough
 - e.g. inflammation, tumor, bronchoscopy
 - not suggested in productive cough
 - airway obstruction / atelectasis
 - inhibition of cough reflex
 - central and peripheral
- expectorant
 - enhance the airway clearance
 - used in productive cough
 - enhance removal of debris / alien material

Antitussives

- centrally acting
 - opioids
 - codeine / dihydrocodeine
 - dextromethorphan
 - levopropoxyphene
 - noscapine
 - butamirate
- peripherally acting
 - prenoxdiazine
 - levodropropizine
 - lidocaine (local anesthetic for bronchoscopy)

non-pharmacologic methods: fluid intake / misting

Opioids

- antitussive effect is usually in sub-analgesic dose
- stereoisomers without opioid characteristics have antitussive effect (different receptors?)

- **codeine** / dihydrocodeine
 - chemically similar to morphine
- **dextromethorphan**
 - levorphanol > methylation > **dextrorotatory stereoisomer**
- levopropoxyphene
 - stereoisomer of dextropropoxyphene
 - seems to have no analgesia and addiction liability
 - sedation has been reported
- noscapine
 - not available

Codeine / dihydrocodeine

- chemically similar to morphine
- **lower binding affinity to μ -opioid receptors**
- used in sub-analgesic dose
- less first pass effect > oral
- demethylated by CYP2D6 to morphine
 - genetic polymorphism – PM and UM
 - in UM more morphine > respiratory depression
 - FDA banned codeine use for any purpose in young children

Dextromethorphan

- levorphanol > methylation > dextrorotatory stereoisomer
- seems to have **no addiction liability** and analgesic effects
 - may enhance the analgesic action of morphine and other u-receptor agonists
 - abuse has been reported and dangerous
- **less constipation** than codeine
- **do not use under age 6**
 - due to increasing reports of death FDA banned the use of OTC dextromethorphan formulations in children younger than 6 years of age

Butamirate

- not related to opioids
 - nor chemically neither pharmacologically
- mechanism of action is unclear
 - probably central
 - may have non-specific anticholinergic effect
- extensive and quick oral absorption
- no addiction liability
- no respiratory depression

Peripherally acting antitussives

- ↓ excitability of afferent neurons / receptors
- prenoxdiazine
 - may have some bronchodilator effect
 - may help during bronchoscopy
 - oral
- levodropropizine
 - oral, no central adverse effects
- lidocaine
 - applied locally before bronchoscopy

Expectorants

- secretolytics
 - increased secretion
- mucolytics
 - decreased viscosity of mucus
- secretomotorics
 - increased movements of cilia

- more than one mechanism of action
- efficacy is not well established
- when used: increase fluid intake

Secretolytics

- indirect effect – stomach > bronchi
 - herbal remedies
 - ipecac
 - saponine containing expectorants
 - extract of leaves of *Plantago lanceolata* (English plantain)
 - guaiaicol/guaifenesin
- direct effect
 - herbal remedies
 - volatile oils
 - e.g. cinnamon oil, lemon oil, oil of thyme
 - iodine salts
 - ammonium chloride

Mucolytics

- bromhexine > ambroxol
 - increased lysosomal activity > cleaving mucus polysaccharides
 - also: increased secretion and ciliary activity
 - ambroxol: may increase surfactant
- acetylcysteine
 - free SH-groups > cleaves disulfide bridges > viscosity↓
- erdosteine
 - metabolism > free SH-groups
- carbocysteine
 - no free SH-groups
 - effect unclear / less viscous secretum is produced
- dornase alpha
 - deoxyuribonuclease > degrade extracellular DNA

Acetylcystein

- SH-groups -> cleaves disulfide bridges
 - mucolytic (oral)
- glutathione regenerator
 - antidote in paracetamol intoxication (iv)
- problems, adverse effects
 - generally well tolerated
 - contraindications: peptic ulcer / bronchial asthma
 - do not combine with antibiotics – 2 hour difference

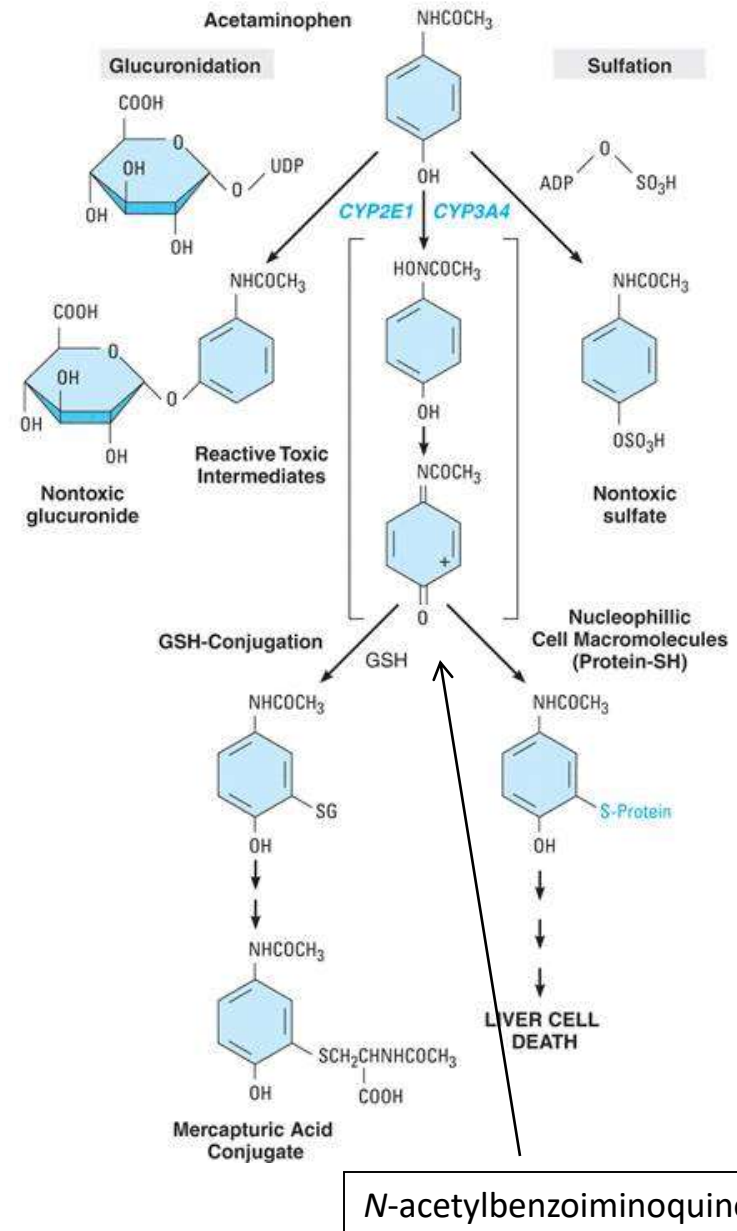
Metabolism of acetaminophen to hepatotoxic metabolites.

Therapeutic dose (1-1.5 g/day max. 4x1 g /day) is safe.

detoxification mechanisms

1. glucuronidation, conjugation (95%)
2. cP450-dependent GSH conjugation (5%)

Antidote: N-acetylcysteine



Secretomotorics

- beta sympathomimetics
 - β 2-receptor agonists (salbutamol, terbutaline)
 - primarily bronchodilators
- volatile oils
 - combined effect (direct secretolytic + secretomotoric)
- bromhexine
 - combined effect (mucolytic + secretomotoric)

Surfactant

- endogenous
- mixture of phosphatidyl-choline, phosphatidyl-glycerine, neutral lipids and proteins
- decreases surface tension in alveoli > prevent collapse, improve O₂ transfer
- in RDS
 - supplement
 - poractant alfa
 - extract of natural porcine lung surfactant
 - beractant
 - modified bovine pulmonary surfactant
 - increase production in premature newborns
 - glucocorticoids before delivery to the mother