SEDATIVE/HYPNOTICS: Ethyl Alcohol (p.1)

Ethyl alcohol = ethanol = ETOH
"alcohol is the excrement of yeast"!
sugars & water consumed by yeast --- output is CO2 & ETOH

History:
Most likely discovered by humans about 8,000 years B.C.
Probably by chance ate naturally fermenting fruits, grains
e.g. baboons
6400 B.C. evidence of fermentation of beers, 12-15% ETOH
3700 B.C. 1st brewery (Egypt)
400-300 B.C. grape wines made
all of above mainly used for medicinal or religious purposes, not widespread use
800-900 A.D. 1st evidence of distillation (Arabia), 95-98% ETOH

by 1500's widespread use of distilled spirits throughout Europe
1606 1st law against public intoxication (Great Britain)
1733 "Gin Riots" in England (against attempts to limit access to gin)
1749 England's population was decreasing due to ETOH-related deaths

ETOH taken to No.Amer. by Puritans, where its use became common
By late 1700's/early 1800's start of temperance movements
Jan.16, 1920 start of Prohibition, ended 1933
Now attempt to tx alcoholism, control alcohol use

1. Pharmacokinetics of Ethanol

administered PO
Absorption
molecule is very small, cannot be ionized easily, only moderately polar
very soluble in water, somewhat soluble in fat (25:1)
readily crosses out of GI tract (abut 20% gastric, 80% intestinal) & into bloodstream & across BBB
food in GI tract slows absorption, esp. high-fat foods…why?

SEDATIVE-HYPNOTICS: Ethyl Alcohol (p.2)

1. Pharmacokinetics of Ethanol (cont.)

Absorption (cont.)

carbonation speeds up absorption…why?

With no food in GI tract, peak plasma levels occur in 20-30 minutes

Distribution

Distributed freely & uniformly throughout body, proportional to water content of tissues

e.g. muscle tissue – 70% water; fat – 10-40% water

In very *obese S* (incl. women, who have more fat than muscle tissue generally), ETOH distributes less rapidly & plasma levels remain high longer vs. males; *larger Ss* need more ETOH to feel intoxicated vs. smaller Ss

Metabolism

By *alcohol dehydrogenase* (in stomach & liver)

Note: females do not have this enzyme in stomach

By *alcohol dehydrogenase* (in liver) (85% in males, 100% in females)

ETOH (acted on by *alcohol dehydrogenase*) --- acetaldehyde

Acetaldehyde (acted on by *aldehyde dehydrogenase*) --- acetic acid --- CO2 + water + energy

Alcohol dehydrogenase is a *rate limiting enzyme* (metabolizes ETOH at a steady rate* independent of amount of ETOH in body

* for a *non*-tolerant *S*, mean is 10-15 mg ETOH/100 ml blood/hour (range is 5-30 mg, Std.Dev. = 4.5 mg)

in order to become intoxicated, *S* must "outrace" one's metabolism of ETOH…becomes an issue of *how much ETOH is consumed how fast*

There is also a 2nd microsomal liver enzyme system = *MEOS*

"microsomal (liver) ethanol oxidizing system"

enzyme system related to the P-450 enzymes

induced by high doses of ETOH, benzodiazepines, barbiturates

SEDATIVE-HYPNOTICS: Ethyl Alcohol (p.3)

1. Pharmacokinetics of Ethanol (cont.)

Excretion: for low to moderate dose levels
- 2-8% excreted unchanged by kidneys
- an even smaller % unchanged through exhaled breath, sweat, skin, etc.

Excretion: for high dose levels
- Up to 15% excreted unchanged by kidneys

Remainder (85-98%) oxidized by liver (a slow process)

Amount of ETOH in urine can be increased by increasing fluid volume in body (increasing amount of urine)

Note: ETOH causes a decrease in ADH (vasopressin) levels in body --- Less H2O reabsorbed by kidneys --- more urine output --- dehydration (ETOH acts like a diuretic) --- contributes to handover Sxs

2.Pharmacologic Effects

ETOH acts at the ***GABA*** *receptor complex* (which has 5 subunits)
- Acts on the *alpha subunit*, which is the same one that Valium & other BZDs act on
- Both BZDs & ETOH disrupt fine motor control
  - GABA RSs in cerebellum are necessary for fine motor control, BZDs & ETOH can interfere with these cerebellar RSs
- When is bound to alpha subunit, will *potentiate GABA's effects*
  - Lets in more Cl-, which increases the IPSP effects of GABA

ETOH also may increase the release of ***DA***, esp. in mesolimbic pathway (reward pathway)
- may be an indirect effect, by increasing ***5HT*** --- which then increases release of DA in nucleus Accumbens

ETOH also inhibits the release of ***glutamate*** --- less activity in NMDA RSs --- less memory (amnestic effects) & less neural activity (antiseizure effects)

ETOH selectively inhibits ***MAO type B*** --- should thus be a catecholamine Agonist

ETOH increases activity of ***cyclic AMP*** at 2nd messenger RS

SEDATIVE-HYPNOTICS: Ethyl Alcohol (p.4)

2. **<u>Pharmacological Effects</u>** (cont.)

Blood Alcohol Levels (BAL) – conc. of ETOH in blood

These data are for "non" drinkers (infrequent, small users)

BAL @ 0.04-0.05 disinhibition of subcortex, cortex inhibited

Excitement, stimulant effects ("ED"50)

BAL @ > 0.05 get more & more cortical/subcortical depression

0.08 legally drunk in CA

0.10 greatly impaired motor functions, drowsy

0.40-0.60 unconscious (LD50), respiratory arrest

Note: for frequenct/mod-severe ETOH users, because of tolerance

Such a person may show no/few behavioral Sxs of intoxication until the BAL => than 0.10, e.g. Lady Diana's driver

Such a person may suddenly die of respiratory arrest…why?

<u>3. Physiological Effects of Ethanol</u>

High affinity for *reticular formation* neurons --- decreased arousal, attention

Mild effects on *cortex* --- mild euphoria, impaired judgment, impaired discrimination, impaired concentration, impaired fine motor movement, mood changes, impaired impulse control

Effects *limbic system* --- increased aggression, amplified moods, sudden shifts in mood (lability), increased depression

All of which leads to increased risk-taking, anger, violence, lack of coordination, decreased ability to evaluate the consequences of one's actions

which leads to …

Slows cortical EEG frequencies (less focus, less attention, less reasoning)

Increased influx of Cl- ions at GABA RSs, increased K+ efflux and decreased influx of Ca++ ions generally --- less neural activity (these latter two effects may be caused by fatty acid ethyl esters which are breakdown products of ethanol)

Sleep effects: decreased REM sleep, TST, & SOL, increased SMI

SEDATIVE-HYPNOTICS: Ethyl Alcohol (p.5)

3. Physiological Effects (cont.)

Note: when suddenly D/C ETOH --- REM rebound & "dream anxiety
attacks = nightmares
also get EEG arousal, cortical excitement, hyperexcitability --- seizures
withdrawal from alcohol should be medically supervised
use of BZDs temporarily

Causes vasodilation --- heat loss, drop in core body temp, hemorrhages
Of small facial/nose/upper cheek blood vessels

Causes irritation of stomach lining --- increase in HCl & pepsin ---
Decreased appetite, ulcers, IBS

Increases liver P-450 enzymes
--- increased metabolism of testosterone --- decreased libido
--- increased metabolism of BC pills --- increased failures of contracept.

Perhaps impaired fertility in males
(based on rat data)

Decreased sensitivity to pain (analgesia), perhaps via both inhibition of
Spinal cord circuits and/or central brain areas
Via increasing CNS endorphin levels?

Decreased motor neuron activity --- decreased muscle tonus, more relaxation

4. Clinical Applications of ETOH

Not an acceptable tx for anxiety, although is self-prescribed for this purpose
In past, has been used as a sed-hyp and anesthetic – not presently
In past, has been used as a cleaner/disinfectant – now rare
Is used as a rubdown agent to help cool pt. with fever (evaporative cooling)
Is used for pts. w/ pulmonary edema (who inhale anhydrous ETOH,
Exhalation carries out molecules of H2O)

SEDATIVE-HYPNOTICS: Ethyl Alcohol (p.6)

5. Withdrawal Effects

headache, nausea, thirst (dehydration), fatigue, anxiety, gen. malaise
the higher the BAL --- the worse the "hangover"

Note: if increase the BAL very quickly to 0.12 --- stimulate the *area postrema*--- strenuous vomiting (would protect S from respiratory arrest)
But…can exceed 0.12 w/o triggering the area postrema if drink more slowly…so *slow, steady drinking is more dangerous* in some ways

6. Side-Effects

damage to liver cells:
cirrhosis, jaundice, increased risk of cancer of liver, impaired liver functions, including toxic effects from drugs, etc.
hepatitis (inflammation of liver)
pancreatitis
acute gastritis

increased risk of *cancer* of tongue, mouth, throat, liver, stomach, intestine, breast (esp. if S also smokes cigarettes)

increased risk for *heart attacks & atherosclerosis*, increased HDLs
weakened cardiac muscle in chronic, heavy use --- enlarged heart --- congestive heart failure
HBP, strokes, EKG arrhythmias
note: 6 oz. wine/can beer per day may improve cardiovas. fitness

malnutrition: esp. *depletion of vitamin Bs* (e.g. thiamine --- Korsakoffs)
without vitamin Bs --- less GABA synthesized

SEDATIVE-HYPNOTICS: Ethyl Alcohol (p. 7)

7. Interaction with Other Drugs

e.g. *cimetidine (Tagamet), ranitidine (Zantac)*
potentiate effects of ETOH (92%, 34% respecitively)
inhibit gastric alcohol dehydrogenase

e.g. *aspirin* in males increased BAL by 34%
decreased by 50% the activity of gastric alcohol dehydrogenase
will also produce severe gastric irritation --- bleeding, ulcers

e.g. synergistic with *anxiolytics*, factor of 2-5x

e.g. additive with other *sed-hyp.s*, cross-tolerance (induction of P450s)

e.g. used with *opiates* will lower the LD1 of opiates by 3x
respiratory failure

e.g. will prolong the ½ life of neuroleptics (*antipsychotics*) by occupying microsomal liver enzymes)

although not a "drug", if S is *sleep deprived*, ETOH effects are increased by a factor of 5x

8. RO 15-4513

Developed by Hoffman-LaRoche in 1985
Is a GABA alpha subunit blocker --- an ETOH antagonist, which immediately blocks 90% of ETOHs on the brain (reverses ETOH effects)
Has never been released on the open market for use…why?
Is used in ERs for ETOH ODs

9. Fetal Alcohol Syndrome (FAS)

More than 3-5/1000 live births in USA currently
FAS + ARND (*Alcohol-Related NeuroDevelopmental Disorders*) = 9/1000 infants born to mothers using ETOH while pregnant
400/1000 live births in alcoholic mothers (range 300-500/l000)

SEDATIVE-HYPNOTICS: Ethyl Alcohol (p.8)

9. Fetal Alcohol Syndrome (cont.)

warnings in bars, on bottles of alcoholic beverages *since 1973*

1994 study found that 20% of women continued to drink even after they learned they were pregnant…

retarded pre- and post-natal growth

CNS dysfunction: MR, irritability, poor coordination, more muscle tone, hyperactive (*average IQ = 68*)

Skull/facial deformities: small head, drooping upper eyelids, strabismus (thus, no binocular stereoscopic vision), abnormal inner canthi, thin upper lips, short "pug" nose, no philtrum (midline hollow in upper lip)

Defective organs: eye, ear, mouth, heart, genital, blood vessels, hernias, bones & joints

Deficient immune system

In 1997 was the 3rd leading cause of birth defects in USA (after Down's Syn. #1, and spina bifida #2)

3 oz. ETOH taken rapidly/day --- FAS

esp. vulnerable during *1st trimester*, 60-80 days conceptual age

3rd week of pregnancy (days 14-21) is when brain and craniofacial abnormalities are esp. likely to occur, mother may not know she is pg. …

10. Alcohol Abuse/Dependency

There is a strong *genetic component*, esp. in *males*

under estimate intoxication, show early age of onset (< 20 yrs.)

These are often *comorbid conditions/dual diagnoses*

30-50% overlaps with other drug abuse, depression, anxiety, bipolar mood disorder, impulsive behaviors, antisocial personality

About 10% of adult population (2 males: 1 female)

Substance (ETOH) *Abuse*:

A maladaptive pattern of sub. use leading to clinically significant impairment/distress w/i a 12 month period, as defined by 1+ of:

recurrent sub. use resulting in failure to fulfill major roles (work,home,

SEDATIVE-HYPNOTICS: Ethyl Alcohol (p.9)

<u>10. Alcohol Abuse/Dependency</u> (cont.)

Substance *Abuse* (cont.)

or school)

repeated use in situations where such use is dangerous (e.g. driving)

repeated substance use-related legal problems (e.g. arrests for disorderly conduct)

repeated sub. use despite persistent social/interpersonal problems cause by/exacerbated by such use

Substance *Dependency*

Maladaptive pattern of sub. use, leading to clinically significant impairment/distress within a 12 month period, as shown by 3+ of:

tolerance

withdrawal Sxs or active avoidance of w/d Sxs

sub. taken in larger amounts or for longer durations than "intended"

persistent desire for sub., "cravings"

unsuccessful efforts to decrease use of sub.

much effort/time spent to obtain sub.

important social/work/recreational activities given up/reduced because of sub. use

continued use despite knowing that use is causing major problems

withdrawal effects:

early – about 12 – 48/72 hours

tremors, HBP, nausea, diarrhea, DIMS, sweats, irratic heart beat

seizure risk peaks at 8 – 12 hours after last drink (usually)

later – 7 hours – 10 days

overt seizures, DTs (*delirium tremens*) = disorientation, hallucinations, nightmares, fever, "*formication*", agitation

DTs usually start by 2nd or 3rd day, peak on 4th day, then subside by 7th day; deep, long sleep, may be amnestic for w/d effects

Rebound REM

Note: in one study by McKim, pts. given no tx. for w/d effects for ETOH dependency showed 37% mortality vs. those treated

SEDATIVE-HYPNOTICS: Ethyl Alcohol (p. 10)

11. Treatment for Alcohol Dependency

Pharmacotherapy:

assist S during w/d period, during detoxification & acute w/d Sxs
usually use BZDs, both to decrease anxiety & seizure risk
should be done in-patient

after detox. S will still crave ETOH
use *naltrexone* (*ReVia*, *Trexan*), an opiate antagonist, to decrease cravings
use *acamprosate* (*Aotal*), a GABA agonist, glutamate antagonist, to decrease cravings
use *bromocriptine* (*Parlodel*), a DA agonist, or SSRIs to decrease cravings

after detox. can use aversive therapy
disulfiram (*Antabuse*), inhibits aldehyde dehydrogenase
acetaldehyde accumulates 5-10% above normal levels --- flushing, throbbing headache, nausea, vomiting, drowsiness, chest pain, depressed respiration

antidepressant drugs can be used to treat co-morbid depression/anxiety
SSRIs (*Wellbutrin/buproprion* --- DA agonist; *Luvox/fluvoxitine* --- a 5HT agonist)
BuSpar (*buspirone*) used as an anxiolytic in alcoholics, but does not seem to reduce alcohol consumption the way that the above two antidepressants do

Behavioral treatments:

AA, support groups of various kinds (for both family & sub.abuser)
"Harm Reduction Model"
not a very good track record…
from a neurological point of view, may be a matter of boosting up prefrontal cortex & inhibiting amygdala/cingulated gyrus/limbic activity…thus, need to emphasize **prevention**