

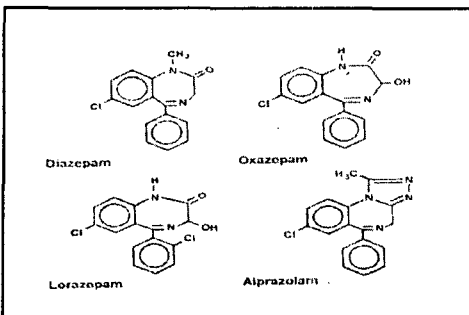
Benzodiazepine계 약물과 그 문제점

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History

- 1st. BZ : Myanesisin - sedative, muscle relaxation
- 1st patented BZ.(1959)
: Librium(=methaminodiazepoxide, chlordiazepoxide)
- 1963 : Diazepam-more potent, broad spectrum
- 1963 ~ present : 30 or more BZs available
- 1992 : Alprazolam approval for panic dis. (FDA)

Structures



Pharmacological Properties of Benzodiazepines

- Anxiety-reducing
- Sedative-hypnotic
- Anticonvulsant
- Muscle relaxation
- Others : ataxic, amnesic, respiratory depression

Advantages and Disadvantages of Benzodiazepines

Advantages	Disadvantages
- Rapid onset	- Dependence/withdrawal
- Well tolerated	- Sedation
- Generics available	- Interaction with alcohol
- Few drug-drug interactions	- Impaired motor coordination
- Little effect on cardiovascular status	- Impaired short-term memory

Indications of Benzodiazepine

- Anxiety Disorders : GAD, Panic Disorder, S.P, O.C.D, PTSD
- Sleep Disorders : Insomnia, PLMS
- Alcohol withdrawal syndrome
- Extrapryamidal Syndrome
- Seizure Disorders
- Schizophrenia-associated stress/anxiety
- Other Stress-related Disorders
- Bipolar disorder-acute manic phase

Major Benzodiazepines

- Alprazolam(Xanax)
- Diazepam(Valium)
- Lorazepam(Ativan)
- Prazepam(Centrex)
- Triazolam(Halcion)
- Flurazepam(Dalmane)
- Quazepam(Doral)
- Mirtazepam
- Loprazolam
- Flunitrazepam
- Clonazepam(Klonopin)
- Chlordiazepoxide(Librium)
- Oxazepam(Serax)
- Clorazepate(Tranxene)
- Temazepam(Restoril)
- Midazolam(Versed)
- Flumazenil(Romazicon)
- Lormetazepam
- Clobazam
- Brotizolam

Approximate Therapeutic Equivalent Dose of BZ

Genetic Name	Trade Name	Dose(mg)
Alprazolam	Xanax	1
Chlordiazepoxide	Librium	25
Clonazepam	Klonopin	0.5-1
Clorazepate	Tranxene	15
Diazepam	Valium	10
Flurazepam	Dalmane	30
Lorazepam	Ativan	2
Oxazepam	Serax	30
Triazolam	Halcion	0.25
Zolpidem	Ambien	10

Benzodiazepines as Anxiolytics (I)

- Indications
 - short - term anxiety related conditions
(e.g. adjustment disorder)
 - short-term stabilization of anxiety symptoms in specific Anxiety Disorders
 - long-term Tx. of Panic disorder, Social Phobia, G.A.D., O.C.D, P.T.S.D.
 - as needed use for sudden surges of anxiety symptoms

Benzodiazepines as Anxiolytics (II)

Advantages

- Rapid onset of action
- Other helpful auxiliary effects
(muscle relaxation, sedative-hypnotic effect, ...)
- Favorable side-effect profiles

Disadvantages

- Tolerance
- Dependence & Withdrawal problems
- Cognitive dysfunctions

Benzodiazepines in the Treatment of GAD

- Widely used
- Long-term Tx. : controversial on BZs
- Effect sustained remission of anxiety symptoms
without dose escalation over 6 month or longer
- Not used as 1st line
- Gradual tapering regimen needed due to long-term use
(switch to long half life, or use other Tx.)

Benzodiazepines in the Treatment of Panic Disorder

- Alprazolam, Clonazepam : approved by FDA
- Lorazepam, Diazepam : small information
- Effective for
 - frequency of panic attack ↓
 - severity of anticipatory anxiety ↓
 - avoidance behavior ↓
- Dose

	Initial	Maintain
alprazolam	0.25-0.5mg X 3,4/day	2-6mg X 3,4/day
clonazepam	0.25-0.5mg X 2,3/day	1-3mg X 2,3/day

Benzodiazepines in the Treatment of Social Phobia

- Clonazepam, Alprazolam : most widely studied
- Others : Bromazepam : small informed
- Generalized type : long-term Tx.
- Non-generalized type : as-needed Tx.
- Effective for
 - performance anxiety
 - generalized social anxiety
 - fear and phobic avoidance
 - fear of negative evaluation
- Dose
 - clonazepam : 1-3mg/day
 - alprazolam : 2-5mg/day

Benzodiazepines in the Treatment of Posttraumatic Stress Disorder

- Alprazolam, Clonazepam : 1 double, 3 open trials
- Effective for
 - intrusive recollections
 - flashback
 - nightmare, insomnia
 - panic like anxiety attack
- Combined with other drugs
- Dose
 - alprazolam : 3-5mg/day
 - clonazepam : 1-6mg/day
- Disadvantages
 - : withdrawal symptom (rage reaction)
 - : cautiously use pt. With poor impulse control, prone to severe depression

Benzodiazepines in the Treatment of Obsessive Compulsive Disorder

- Used as augmentation

- Clonazepam : serotonergic property(?)

- SRI + clonazepam

Summary of Rational Benzodiazepines Use in Anxiety		
Anxiety State	Duration of Tx.	Other Tx.
Mild anxiety	Not recommended	Psychological Tx.
Acute Stress Reaction	1-7 days	Psychological Tx.
Adjustment disorder	Single dose or a few days And initially	Antidepressants Psychological Tx.
Eplaudic Anxiety Chronic Generalized Anxiety	Single or intermittent course (2-4 wks followed by 1-2 wks in tapering) Use with other Tx.	Antidepressants Beta-blocker Psychological Tx.
Panic dis. Phobic dis.	Initial course 2-4 weeks Followed by 1-2 wks in tapering Use with other Tx.	Antidepressant Blockers Psychological Tx.
Generalized Anxiety dis.	4-6 Mo. Or longer	Antidepressant Psychological Tx.

Benzodiazepines Effects on Sleep and EEG(I)
<ul style="list-style-type: none"> • Decreased alpha activity • Increased low-voltage fast activity(especially, beta activity) • Decrease sleep latency • Reduce the number of awakening / Increased total sleep time • Shorten REM sleep time • Increased number of cycles of REM • Complex effects on dream process

Benzodiazepines Effects on Sleep and EEG(II)
<ul style="list-style-type: none"> • Ultra-short acting BZ <ul style="list-style-type: none"> : rebound insomnia, worsen insomnia (worsening of sleep beyond baseline levels on discontinuation) • Usefulness of BZs in Insomnia : temporal use • BZs <ul style="list-style-type: none"> : can not provide normal sleep : can make disruption in various aspects of normal cycle

Rational Benzodiazepines Use in Insomnia

Type of insomnia	Dosage and administration
Transient insomnia	1-2 nights only, minimal dose
Short term insomnia (e.g. temporary stress)	not for more than 2 wks intermittent if possible (1 night in 2 or 3 nights) minimal dose
Chronic insomnia (e.g. secondary to physical, psychiatric causes)	treat primary cause first intermittent if possible course repeated with interval

Toxic Effects of Benzodiazepines

- Over-sedation, hypnotic effect
- Cognitive dysfunctions : short-term memory, confusion, delirium..
- Paradoxical Effects, Disinhibition, other behavioral aberrations
: agitation, psychosis, depression, suicide
- Withdrawal : anxiety, insomnia, psychosis, seizure
- Rebound : more intense anxiety, insomnia
- Addiction

Benzodiazepines induced Over sedation / sleepiness

- Residual daytime somnolence
: complains of sleepiness the following day
- Two factors
 - 1) half-life : longer-acting BZs > short-acting BZs
 - 2) dosage : higher dose(short or long)
- Impairment of performance
: require warning in driving, engaging in dangerous physical activity, using hazardous machinery

Benzodiazepines induced Cognitive Dysfunction

- Memory impairments, confusion, delirium
- Amnesia(anterograde) : difficulty in learning new material
- Can appear in any BZ
- More common in lorazepam, triazolam, alprazolam, flunitrazepam :
- Intravenous Adm. > Oral Adm.
- Dose related
- Elderly group > Younger group

Probability of Permanent Brain Damage by BZ use

- High doses / Long-term use BZ
- : brain atrophy associated
- (Lader and Petursson,1984 ; Schmauss and Krieg,1987)
- Ashton(1995)
- "it remains possible, that subtle, perhaps reversible, structural changes may underlie the neuropsychological impairments shown in long-term BZ users."

Effects on Cardiopulmonary and Vascular System

- Pre-anesthetic application
- : often lower B.P, increase H.R.
- High dose / IV adm.
- : decrease cerebral blood flow,
- : can cause cardiopulmonary depression / arrest
- Patients with COPD or sleep apnea
- : may experience decreased respiratory drive – CO2 narcosis or increase apneic episodes
- : sudden death in severe pulmonary disease

Effects on Gastrointestinal System

- Rare, but can cause GI troubles
- : abdominal discomfort or pain, diarrhea, nausea or vomiting
- Liver enzyme elevation
- : BZ alone or combination with Antidepressants(MAOI)

Effects on Renal and Genitourinary System

- New incontinence or exacerbation of existing incontinence
- : often associated with confusion in elderly
- Sexual dysfunctions
- : decreased libido, inability to initiate or sustain an erection, anorgasmia
- : major cause of non-compliance

Effects on Other System

- Joint pain, muscle fatigue or weakness, sweating, dyspnea
- Neutropenia / other blood dyscrasia
- Chills, fever, burning sensations in feet / hands, dry mouth
- Weight gains
- Phlebitis / venous thrombosis : IV use
- Skin rashes
- : urticaria, pruritus

Paradoxical Effects

- 5% of BZ users
- Increased excitement, irritability, aggression, hostility, impulsivity
(Attack of rage or violence or antisocial behaviors)
- Depression
- Personality changes
- Commonly occur in children, elderly, developmental disabilities
- Short-acting(lorazepam, triazolam) > long-acting
- Can occur in short-term use, even in 1st medication

Disinhibition

- Results of disinhibition of behavioral tendencies normally suppressed by social restraints(like alcohol)
- Showing increased excitement, irritability, aggression, hostility, impulsivity
- Rarely attack of rage or violence or antisocial behaviors
- Commonly occur in children, elderly, developmental disabilities

Depression and Emotional blunting

- Depressive symptoms and suicide ideation : newly occur or worsen
- Mechanism : unclear, possibly physiologic result of reduction in central monoamine activity
- “ Emotional anesthesia ”
 - : can be seen in drug addicts
 - : progressively more incapable of tolerating their emotions and life stressors

Benzodiazepines as Instruments of Suicide

- Less toxic than TCAs and barbiturates
- Combined with alcohol or other drugs : elevate lethality
- Top rank among poisoning with psychotropic medications
- Hypnotics(e.g. flurazepam, temazepam)
 - : most death per million prescription(high lethality)
 - : flurazepam>temazepam>flunitrazepam>triazolam>nitrazepam

Tolerance

- Loss of wanted / adverse effects after medication
- To all BZ actions : can develop
- At variable rates and to different degrees
- Tolerance to hypnotic effects : more rapid than anxiolytic effects
- Dosage escalation
 - : maintain cycle of tolerance and dependency
 - : increase difficulty discontinuing drug therapy

BZ Tolerance Mechanism

- Down-Regulation of GABA receptors
 - : decreased GABA receptor density
 - : diminished response to GABA agonist
 - : decreased density of benzodiazepine binding sites

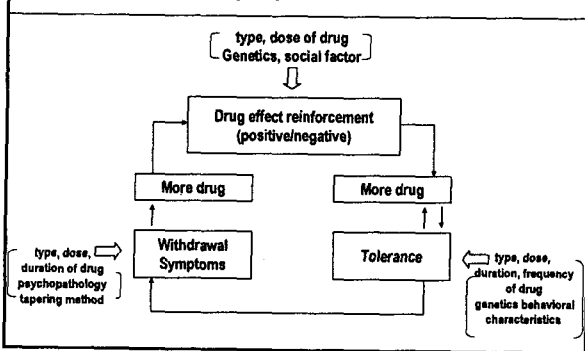
Abuse Liability

- Potential for recreational abuse
- Actual recreational abuse : occur in other substance abusers
- Euphoric / reinforcing effects : relatively low
- Diazepam, alprazolam : more widely abused in risk group
- Drug-liking or preference in normal human subjects
: BZ – much less drug liking than traditional drugs of abuse

Addition, Physical and Psychological Dependency

- Addiction : chronic disorder associated with compulsive use of a drug resulting in physical, psychological, and social harm to user and continued use despite harm
- Physical dependency : physiological state of adaptation to a drug with development of tolerance to the drug's effects and emergence of withdrawal syndrome during prolonged abstinence
- Psychological dependency : emotional craving state for drug's positive effects or to avoid negative effects associated with its, leading to compulsive drug-seeking behavior

Long-term Use & Drug Dependence



Risk factors of Benzodiazepine Dependence

- High dose
- Long-term use
- Potency
- Rapid onset
- Coexistent alcohol or drug dependence
- Family history of alcoholism
- Personality disorder
- Others : Age, Hepatic dis.
- Severity of Symptoms
- Physician discomfort in managing BZ discontinuation

Three Categories of Sign & Symptoms associated with Benzodiazepine Withdrawal

- 1) Recurrence(Re-emergence) of anxiety symptoms
- 2) Rebound symptoms
- 3) True Withdrawal symptoms

Withdrawal Symptoms (I)

Psychological Symptoms

- Perceptual distortion, hallucination, delusion
- Paranoid thoughts and feelings of persecution
- Unreality, Depersonalization
- Agoraphobia
- Depression
- Craving

Withdrawal Symptoms (II)

Somatic Symptoms

- Paresthesia
- Pain : neck, headache(occipital), limb aching
- Ataxia
- Visual disturbances : blurred vision, double vision
- Gastro intestinal symptoms : dysphasia, nausea, vomiting...
- Influenza-like symptoms : prostration, weakness, Postural dizziness, stuffy nose, sinus pain, without fever
- Metabolic and endocrine symptoms : menorrhagia, Breast pain and engorgement, loss of weight, thirst, polyuria

Risk factors of BZ Withdrawal Syndrome

- Dose of BZ
- Duration of BZ Treatment
- Rate of drug taper
- Psychopathology : dependency, neuroticism
- Others
 - pre-withdrawal level of anxiety, depression
 - lower educational level
 - passive-dependent personality dis.
 - sex(female)

Guidelines for BZ Withdrawal Syndrome

- Evaluate and treat concomitant medical and psychiatric conditions
- Obtain drug history, urine, blood sample for drug, ethanol assay
- Determine required dose of BZ for stabilization by history, clinical presentation, drug-ethanol assay, challenge dose
- Detoxification
- Psychological intervention

Drug-Drug Interactions

- Cytochrome P450 system
- Gastrointestinal absorption
- Others

Cytochrome P450(CYP) enzymes and BZs

P450 enzyme	Substrate	Inhibitors	Inducers
CYP 2 C19	diazepam, desmethyldiazepam amitriptyline, clomipramine imipramine, moclobemide, naproxen, piroxicam	omeprazole	rifampin
CYP 3 A4	alprazolam, clonazepam, midazolam, triazolam, cisapride, bupropion, fluoxetine, sertraline, haloperidol, nefazodone, trazodone, venlafaxine, zolpidem	fluoxetine fluvoxamine ketocozazole nefazodone sertraline	

Benzodiazepine and Pregnancy Issues(I)

- First and Second Trimester
 - : facial clefts and skeletal abnormalities in newborn in animal studies
 - : increased risk of oral clefts associated with diazepam in human
 - : other case reports
 - 1) 1st trimester : inguinal hernia, pyloric stenosis, heart defects
 - 2) 2nd trimester : hemangiomas, cardiovascular defects
 - : others – spina bifida, absence of left forearm, CNS abnormalities
- Recent results : no increased risk of major malformations related to BZs

Benzodiazepine and Pregnancy Issues(II)

- **Third Trimester and through delivery**
 - 1) **CNS depression('floppy infant syndrome')**
 - : hypotonia, lethargy, sucking difficulties, decreased fetal movements, loss of cardiac beat to beat variability, respiratory depression
 - 2) **Neonatal withdrawal syndrome : hyperactivity, irritability**
- **During labor**
 - : isolated dose -safe
 - : **lowered APGAR score case**
 - : dose dependent elevation of neonatal serum bilirubin level

Summary

- **Rational Use of BZ**
 - relative safe, widely useful
- **Hidden side effects / disastrous effects in vulnerable patients**
- **Review tolerance, dependency, withdrawal symptoms**
- **Consider Drug interaction**
- **Periodic Evaluation of Risk / Benefit of BZ**
- **Advice to patients planning a pregnancy**
