



REVIEW ON DRUG INTERACTIONS OF ALPRAZOLAM ON PHARMACODYNAMIC AND PHARMCOKINETIC ACTIONS

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ABSTRACT

Alprazolam is the one of the mostly prescribed benzodiazepines in the all over the world. It is commonly regarded as a safe and efficient drug for the treatment of anxiety disorders and panic disorders. Some overdoses that are due to the sole ingestion of alprazolam has been reported. The paper documents is a fatality due to alprazolam intoxication & describes the distribution of alprazolam and an active metabolite, (x-hydroxyalprazolam, in tissues obtained at autopsy. Qualitative identification of the drugs is achieved by full-scan mass spectroscopy and gas-chromatograaphy, and quantitative analysis was performed by high-performance liquid chromatography. High concentrations of alprazolam are found in all specimens analyzed, but the metabolite was detected only in subclavian blood, urine, bile, and liver. heart blood alprazolam concentration of 2.1 mg/t is the highest reported in the postmortan.

KEYWORDS: x-hydroxyalprazolam, subclavian blood, urine, bile, and liver.

INTRODUCTION

Alprazolam, is one of the most widely prescribed benzodiazepines in the all over the world. It is commonly prescribed for the treatment of anxiety and depression and for sedation. It is an effective anxiolytic dose of 0.75-4 mg daily, and doses of 6-9 mg per day are prescribed to treat panic attacks and panic disorders. Its precise mechanism of action is unknown, but, presumably, it acts in a manner similar to other benzodiazepines by potentiating GABA. Following oral administration, it is rapidly absorbed with peak plasma concentrations occurring 1-2 h after ingestion. McCormick et al. reported steady-state serum concentrations of 25-55 ng/mL of alprazolam in six individuals after chronic daily oral administration of 1.5-6 mg. Dose-related increases in steady-state plasma concentrations were reported with average concentrations reaching 102 ng/mL after doses of 9 mg/day.

Alprazolam has a rapid and short duration of action with an average plasma half-life of 11 h. It is actively metabolized by oxidation and conjugation with only 20% of the parent drug appearing unchanged in urine. The major metabolites are α -hydroxyalprazolam, 4-hydroxyalprazolam, α -alprazolam, and 3-hydroxy-5-methyltriazolyl chlorobenzophenone (HMTBP). α and 4-hydroxyalprazolam are pharmacologically active with approximately 66 and 19% of the potency of alprazolam,

respectively. Smith and Kroboth mentioned and finally reported that unconjugated forms of these two metabolites were detected at plasma concentrations of less than 10% of the parent drug concentration even after chronic dosing, and, thus, their contribution to pharmacological effects may be frequently less than therapeutic cases. Adverse reactions to alprazolam are typically observed at the beginning of therapy and diminish under continued treatment. The most common effects reported are fatigue & drowsiness. Other adverse reactions include confusion, headache, nausea and vomiting, tachycardia, hypotension, and blurred vision. Abrupt cessation of chronic alprazolam therapy has resulted in withdrawal symptoms, the most important being seizure activity. However, alprazolam is mostly considered a safe and effective drug with a high therapeutic index level studies. Few overdoses attributable to alprazolam have been reported, and even fewer fatalities due to alprazolam intoxication without the combination of other drugs are documented. In this study, we reported the issue of the tissue distribution of alprazolam and α -hydroxyalprazolam in a death due (solely to the ingestion of alprazolam).

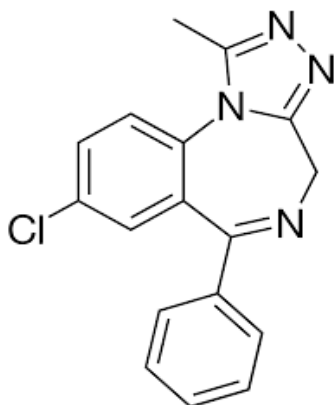
STRUCTURE OF ALPRAZOLAM

Fig.1
IUPAC
8-chloro-1-methyl-6-phenyl-4H-[1,2,4]triazolo[4,3-a][1,4]benzodiazepine

Chemical names : Xanax, Alprazolam Intensol, Xanax XR, Niravam.

MECHANISM OF ACTION: Benzodiazepines(BZA) binds unspecifically to the benzodiazepines receptors BNZ1, which induces sleep, and BNZ2, which effects the muscular relaxation, anticonvulsant activities, motor coordination, and brain memory. The benzodiazepines receptors is thought to be binded to gamma-aminobutyric acid receptors, thus enhances the effects of GABA by increase in gamma -amino butyric affinity for the GABA receptor. Binding to the inhibitory neurotransmitter gamma -aminobutyric acid to the site open the cl⁻ ion channel, thus resulting in a hyperpolarized cell membrane that objects further excitation of the cell as shown in figure 3.



Figure 2: For Alprazolam binding sites.

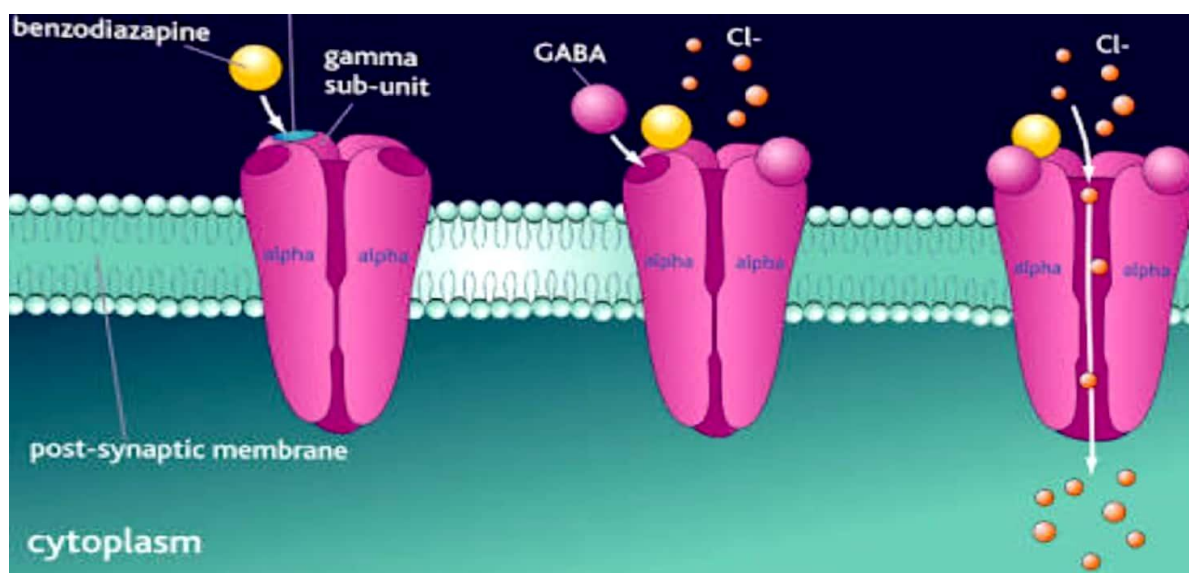


Figure 3: mechanisam of action.

DRUG INTERACTIONS: Drug interactions might change your medications work or increase their risk for major side effects. The document does not contain most possible drug interactions. Keep the list of overall the products you use (including prescription or nonprescription drugs & herbal products) and consult it with your doctor & pharmacist. Don't discontinue, stop, or change the dose of any drugs without your doctor's approval.

Some of the products that might interact with this drug include: sodium oxybate, kava.

Other medicinal products can effect the removal of alprazolam from the body, which might effect the way alprazolam works. Examples include azole antifungals (such as ketoconazole, itraconazole.), cimetidine, certain anti-depressants (such as nefazodone, fluvoxamine, fluoxetine.), drugs they treat HIV or AIDS (protease inhibitors such as indinavir), delavirdine, rifamycins (such as rifabutin), macrolide antibiotics (such as erythromycin), St. John's wort, the drugs used to treatment for seizures (such as phenytoin), among others drugs.

The deadly risk of serious side effects (such as slow/shallow breathing, severe drowsiness/dizziness) might be increased if the medication is taken with other products they might also cause breathing or drowsiness. Consult your doctor or pharmacist if you are using other products such as cough relievers or opioid pain (such as codeine, hydrocodone), alcohol, marijuana, other drugs for sleep or anxiety (such as lorazepam, diazepam, zolpidem), muscle relaxants (such as cyclobenzaprine, carisoprodol), or antihistamines (such as diphenhydramine, cetirizine).

Check the labels markings on all your medicinal dosages (such as allergy or cough-and-cold products) because they might contain ingredients that may cause drowsiness. Ask your pharmacist about using that product safely.

Cigarette smoking induces decreases blood levels rate in overall body for this medication. Mention to your doctor that if you smoke or if you recently stopped smoking.

Clinical Uses of alprazolam : Treat a variety of anxiety disorders

- 1) Muscle relaxants.
- 2) Hypnotics.
- 3) Alcohol & other CNS depressant withdrawal
- 4) To produce anterograde amnesia
- 5) Anti-convulsants.

Pharmacodynamics: How do benzodiazepines work Pharmacodynamically Benzodiazepines bind to sub-receptor on the GABA(a) receptor complex in the brain (GABA: gamma amino-butyric acid).

– This BZD binding causes Gamma amino butyric acid to more readily bind to own sub-receptor.

– In turn, gamma amino butyric acid binding causes the chloride (Cl-) channel to open, allowing chloride to enter the intracellular environment.

- Influx of Cl- results central nervous system (CNS) depressant effect (inhibitory).

- as same areas of the brain affected by barbiturates & alcohol in a similar manner.

- CNS agents of 1,4 benzodiazepine class were presumably exert their effects by binding at stereo receptors at several sites within the central nervous system (CNS).

- Thus exact mechanism of action was unknown. Clinically, all the benzodiazepines results a dose-related central nervous system(CNS) depressant activity varying from the mild unpairment of task performance to hypnosis.

Pharmacokinetics of BZD:

• BBB– Example: Imodium

• Benzodiazepines cross the barriers easily – Blood brain barrier (BBB) – Placental barrier – These effects identical to other CNS depressants as well as psychostimulants.

Variable for half-lives.

Absorption:- from the Following oral administration, alprazolam is fastly absorbed. The Peak concentrations in the plasma occur in 60 to 120 mins following administration. Plasma levels were proportionate to a dose given; above the dose range of 0.5 to 3.0 mg, the peak levels of 4.0 to 18 ng/mL was observed. Using the specific assay methodology, a mean plasma elimination to half-life of alprazolam has been found to be 12 hours (range: 8 -25.9 hours) in healthy adults.

Distribution:- In vitro method, alprazolam is bound (80 %) to human serum protein. Serum albumin results for the majority of the binding sites.

Metabolism/Elimination: Alprazolam is mostly metabolized in humans, primarily by cytochrome CYP3A4 (CYP3A4), to 2 major metabolites in the plasma: 4-hydroxyalprazolam(4HA) and α -hydroxyalprazolam. The benzophenone derived from alprazolam is also found in humans. Thus their half-lives appear to be identical to that alprazolam. The plasma concentrations for 4-hydroxyalprazolam (4HA) and α -hydroxyalprazolam was relative to unchanged alprazolam concentrations was always less than 4%. a reported relative potencies of benzodiazepines receptor binding experiments and in all animal models of induced seizure inhibition of 0.20 and 0.66, respectively, for 4-hydroxyalprazolam (4HA) and α -hydroxyalprazolam. Such at low concentrations and the low potencies of 4-hydroxyalprazolam(4HA) and α -hydroxyalprazolam suggest they are unlikely to contribute more to the pharmacological effects of alprazolam. The benzophenone metabolite is requirably inactive.

Alprazolam and its metabolites are eliminated mostly in the urine.

Tolerance

- Decrease regulation and/or increase in liver enzymes
- Occurs at even therapeutic doses
- Doesn't occur as readily for the anti-anxiety effects much as with the sedative (or) muscle relaxant properties of Benzodiazepines.
- cross-tolerance with Benzodiazepines, the barbiturates and alcohol.

CLINICAL STUDIES

The anxiety Disorders (XANAX) Tablets was compared to placebo in 2 blind clinical studies (doses upto 6 mg/day) in patients with a diagnosis & treatment of anxiety and (or) anxiety with associated to depressive symptomatology. XANAX is significantly better than the placebo at each of the determination or evaluation periods of these 4-week studies as judged by the representing psychometric instruments: The Physician's Global Impressions(PGI), Hamilton, Target Symptoms, Anxiety Rating Scale, Global Patient Impressions and Self-Rating Symptom Scale.

Alprazolam recent abuses

In the body, it raises the effects of other substance called GABA, which was an neurotransmitter that down regulates the excitatory brain activities, slows down the firing of neurons. The results of alprazolam to produces the tranquilizing and sedating effect. since the alprazolam additionally promotes a pleasant euphoria and other changed responses in the brain, users can become addicted to this feelings – using more and more in an attempt to recreate these effects. The more drug is has considered, the greater the likelihood that tolerance will starts to develop.

Tolerance: a condition that commonly occurs with alprazolam use, as when the body adapts to the increased amounts of the substance resulting in higher levels of the drug needed to produce the previously experienced effects. When highest levels of drug are needed or when the substance is used in combination with opioids like methadone or alcohol, thus increased risk of overdose, which can lead to: dangerously slow breathing, extreme sedation, coma.

One of the most devastating effects of alprazolam abuse is addiction. This is characterized by a compulsive desire to continue obtaining using the drug even when negative events are happening to you. examples of addiction signs included.

- 1) Increased conflict with friends, family and coworkers.
- 2) Decreased performance at work or school.
- 3) Financial changes with more money being spent on the substance.

ADDICTION TREATMENT:

Due to the risks of alprazolam withdrawal symptoms, professional treatment should always be sought when ending use. when done under the supervision of medical staff, the effects can be diminished leading to safer withdrawal process where any complications can be addressed.

It is strongly recommended to undergo an evaluation by a physician or substance abuse professional before ending use so that the best course of care can be recommended. when ending use, several options mostly recommended – the precise program will be dependent on the frequency and amount of use. These options include.

Detox

Residential rehab

Outpatient treatment.

Support groups.

Detoxification : It is the process of allowing the body to process and eliminate the substance. compared to treatment, detox is a necessary to treatment. You must rid the body of the dosage before beginning of your recovery. Practically, detox is completed on an inpatient basis to monitor vital signs of the patient.

From the following detox, someone fighting a xanax addiction might be referred for rehab or outpatient treatment. Rehab will be appropriately in some cases for more severe addiction, for those with poor financial support at home, or those who might benefit from removed from an unhealthy environment for the duration of their recovery program. It is an medicinal program where the users will be living in the treatment centre for period that typically ranges between 1 to 3 months. Their time and efforts will focus on learning new skills to be happy and healthy without the drugs or medicinal substance.

Outpatient treatment takes several forms : The intensive and safe programs requiring multiple time and numerous hours of therapy. The others programs will require few required weekly hours. They share the common methods for establishing a relapsed prevention plan and exploring underlying the triggers of addiction while allowing the patient in treatment to live in their own home or premises and resume their normal activities.

Statistics.

According to the Drug enforcement Administration

- More than 20 million people have used benzodiazepines unprescribedly in their lifetime.
- Benzodiazepines were responsible for mostly 6,50,000 emergency room visits in 2010.
- Alprazolam accounted for more than 1/3 of ER visits, nearly doubles that of the next benzodiazepine.

Teen Alprazolam Abuse

Prevention is recommended to stop use before it can begin. consider:

- Having a honest conversation with your teen about the risks of alprazolam abuse.
- Keep medications safe & accounted for in the home.
- Be aware and safe of behavioral changes in your teen.
- Note sudden changes in the friends and family members with whom your teen in spending time.

Panic Disorder

The effectiveness of XANAX for the treatment of panic disorder came across the 3 short-term, placebo-controlled studies (up to 80 days) in patients with diagnoses and treatment for the closely corresponding to DSM-II-R criteria for panic disorder and treatment.

Uses: Alprazolam is used to treat anxiety and panic disorders. It belongs to a class of medications called benzodiazepines which act on the brain and nerves (central nervous system) to produce a calming effect. It works by enhancing the effects of a certain natural chemical in the body (GABA).

REFERENCES

1. R.C. Baselt and R.H. Cravey. *Disposition of Toxic Drugs and Chemicals in Man*. 4th ed. Chemical Toxicology Institute, Foster City, CA, 1995.
2. *physicians' Desk Reference*. 48th ed. Medical Economics Data Production, Montvale, NJ, 1994.
3. S.R. McCormick, J. Nielsen, and P. Jatlow. Quantification of alprazolam in serum or plasma by liquid chromatography. *Clin. Chem*, 1984; 30: 1652-55.
4. D.A. Ciraulo, J.G. Barnhill, H.G. Boxenbaum, D.J. Greenblatt, and R.B. Smith. Pharmacokinetics and clinical effects of alprazolam following single and multiple oral doses in patients with panic disorder. *J. Clin. Pharmacol*, 1986; 26: 292-98.
5. G.W. Dawson, S.G. Jue, and R.N. Brogden. Alprazolam. A review of its pharmacodynamic properties and efficacy in the treatment of anxiety and depression. *Drugs*, 1984; 27: 132-47.
6. Litovitz TL, Holm KC, Clancy C, Schmitz BF, Clark LR, Oderda GM. 1992 annual report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. *Am J Emerg Med*, 1993; 11: 494-555.
7. Litovitz TL, Clark LR, Soloway RA. 1993 annual report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. *Am J Emerg Med*, 1994; 12: 546-84.
8. Litovitz TL, Felberg L, Soloway RA, Ford M, Geller R. 1994 annual report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. *Am J Emerg Med*, 1995; 13: 551- 97.
9. Litovitz TL, Felberg L, White S, Klein-Schwartz W. 1995 annual report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. *Am J Emerg Med*, 1996; 14: 487- 537.
10. Litovitz TL, Smilkstein MJ, Felberg L, Klein-Schwartz W, Berlin R, Morgan JL. 1996 annual report of the American Association of Poison Control Centers toxic exposure surveillance system. *Am J Emerg Med*, 1997; 15: 447-500.
11. Litovitz TL, Klein-Schwartz W, Dyer KS, Shannon M, Lee S, Powers M. 1997 annual report of the American Association of Poison Control Centers toxic exposure surveillance system. *Am J Emerg Med*, 1998; 16: 443-97.
12. Litovitz TL, Klein-Schwartz W, Caravati EM, Youniss J, Crouch B, Lee S. 1998 annual report of the American Association of Poison Control Centers toxic exposure surveillance system. *Am J Emerg Med*, 1999; 17: 435-87.
13. Litovitz TL, Klein-Schwartz W, White S, et al. 1999 Annual report of the American Association of Poison Control Centers Toxic Exposure Surveillance system. *Am J Emerg Med*, 2000; 18: 517-74.
14. Litovitz TL, Klein-Schwartz W, White S, et al. 2000 Annual report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. *Am J Emerg Med*, 2001; 19: 337-95.
15. Litovitz TL, Klein-Schwartz W, Rodgers GC Jr., et al. 2001 Annual report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. *Am J Emerg Med*, 2002; 20: 391- 452.
16. Serfaty M, Masterton G. Fatal poisonings attributed to benzodiazepines in Britain during the 1980s. *Br J Psychiatry*, 1993; 163: 386-93.
17. Reith DM, Fountain J, McDowell R, Tilyard M. Comparison of the fatal toxicity index of zopiclone with benzodiazepines. *J Toxicol Clin Toxicol*, 2003; 41(7): 975-80.
18. Buckley NA, Whyte IM, Dawson AH, McManus PR, Ferguson NW. Self-poisoning in Newcastle, 1987-92. *Med J Aust* 1995; 162: 190-3.
19. Whyte IM, Buckley NA, Dawson AH. Data collection in clinical toxicology: are there too many variables? *J Toxicol Clin Toxicol*, 2002; 40: 223-30.
20. Buckley N, McManus P. Fatal toxicity of drugs used in the treatment of psychotic illnesses. *Br J Psychiatry*, 1998; 172: 461-4.
21. Greenblatt DJ, Allen MD, Noel BJ, Shader RI. Acute overdose with benzodiazepine derivatives. *Clin Pharmacol Ther*, 1977; 21: 497-514.
22. Isbister GK, Balit CR, Dawson AH, Whyte IM. Valproate overdose: a comparative cohort study of self poisonings. *Br J Clin Pharmacol*, 2003; 55: 398-404.
23. Buckley NA, Dawson AH, Whyte IM, O'Connell DL. Relative toxicity of benzodiazepines in overdose. *Br Med J*, 1995; 310: 219-21.
24. Mant A. Panic disorders and the listing of alprazolam on authority on the PBS. Beware of overdiagnosis. *Aust Fam Physician*, 1994; 23: 658-60.

25. Lepine JP, Chignon JM, Teherani M. Suicide attempts in patients with panic disorder. *Arch Gen Psychiatry* 1993; 50: 144–9.
26. Chan TYK. Packaging of drugs and the risk of severe toxicity in adult self- poisonings. *J Clin Pharm Ther*, 1997; 22: 157–8.
27. Drummer OH, Ranson DL. Sudden death and benzodiazepines. *Am J Forensic Med*, 1996; 17: 336–42.
28. Bystrycki A, Coleridge J. Drug – and poison-related deaths in Victoria during 1997. *Emerg Med*, 2000; 12: 303–9.
29. Balit CR, Isbister GK, Whyte IM. Quetiapine poisoning: a case series. *Ann Emerg Med*, 2003; 42.
30. National Institute on Drug Abuse. (2014). Treating addiction to CNS depressants.
31. American Addiction Centers, 2018.
32. Meyers, R. J., Smith, J. E., & Lash, D. N. (2005). A program for engaging treatment-refusing substance abusers into treatment:CRAFT *International Journal of Behavioral and Consultation Therapy*, 1(2): 90-100.
33. Whyte IM, Buckley NA, Dawson AH. Data collection in clinical toxicology: are there too many variables? *J Toxicol Clin Toxicol*, 2002; 40: 223–30.
34. Abramowicz M. Alprazolam for panic disorder. *Med Lett Drugs Ther*, 1991; 33: 30–1
35. Lepine JP, Chignon JM, Teherani M. Suicide attempts in patients with panic disorder. *Arch Gen Psychiatry*, 1993; 50: 144–9.