Ethanol and Oral Diazepam Absorption

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A recent survey conducted by the US National Institute on Drug Abuse, disclosed that in emergency-room visits resulting from ingestion of 2 or more drugs, the most frequently mentioned drug was ethanol, with diazepam second. In the cases in which ethanol was reportedly ingested with one or other drug the most frequently mentioned other drug was diazepam.

Plasma diazepam levels were estimated in volunteer subjects following the administration of diazepam 0.07mg/kg in solution in distilled water and with 30ml of 50% ethanol. Levels attained after diazepam in ethanol were consistently higher than those attained after diazepam in distilled water, and in some instances, considerably higher. The means were significantly higher between 60 and 240 minutes post-dosing.

The mechanism whereby plasma diazepam levels may be elevated by ethanol is discussed. Plasma levels reflect interaction of 3 first-order processes — absorption of drug into blood, redistribution into available body compartments, and hepatic biotransformation into metabolites. The results could have been explained by any one combination of these possibilities. Ethanol may have enhanced the rate of diazepam absorption; ethanol may have inhibited the metabolic biotransformation of diazepam.

The first of these possibilities is most likely. Passive diffusion of drugs through biomembranous barriers obeys first-order kinetics, that is to say the rate of transfer is directly proportional to the concentration gradient across the membrane. Since diazepam is more soluble in ethanol than in water, the effective diazepam concentration gradient across the mucosa would probably enhance absorption. It is possible also that ethanol may increase the permeability to diazepam as well.

Ingestion of ethanol together with a hypnosedative is a frequent combination leading to hospital admission for drug overdosage. The additive CNS depressant effects of alcohol and other sedatives are well known and, in addition, the ingestion of large quantities of ethanol predisposes to some of the more important complications of drug overdosage, including inhalation of gastric contents.

The present report demonstrating an acceleration by ethanol of the absorption of diazepam is important and provides a more complete explanation of the marked sedation that can follow this combination of drugs. The effect is, perhaps, not surprising as ethanol has been used in some drug formulations to facilitate the absorption of sparingly soluble drugs.

Whilst it is true that overdosage with diazepam alone is remarkably safe, the combination with alcohol
can produce CNS depression and death, usually from respiratory failure or obstruction. As with any sedative drug, patients taking diazepam should be warned of the dangers of drinking alcohol.

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Immediate Effects of Tobramycin on Human Cochlea and Correlation with Serum Tobramycin Levels

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The aminoglycosides are a useful group of antibiotics, and gentamicin has gained widespread popularity for treating Gram-negative infections. Nevertheless, tobramycin is now probably the drug of choice in infections due to Pseudomonas aeruginosa since it is more active, at least in vitro than gentamicin.

These aminoglycosides occasionally produce ototoxicity. Transtympanic electrocochleography provided exact objective indications of the functioning of the cochlea and primary 8th nerve neurones. The compound 8th nerve potential (AP) and the remote cochlea microphonic (eM) were recorded through an active electrode placed through the tympanic membrane onto the promontory under local anaesthesia. These functions were recorded at intervals for up to 2 hours after intravenous tobramycin was given in a bolus injection over 3 minutes. Blood samples from tobramycin assay were taken from a site away from the injection site.

Tobramycin produced an immediate and reversible depression of cochlear function without any otological symptoms in these 3 patients. Reports on the ototoxicity of aminoglycosides have, in the past, concentrated on their delayed effects — deafness or vertigo. These observations suggest that asymptomatic changes might occur undetected in many patients receiving aminoglycosides. The speed of onset of the observed effect suggests that a direct action at a site in the cochlea, involving a temporary metabolic block — for example, interference with an energy requiring process or blocking of transport of cations across cell membranes. How these findings relate to long term ototoxicity is not clear.

Doses of aminoglycosides are often therapeutically insufficient however, and monitoring of the serum levels is required not only for ototoxicity but to ensure that adequate doses are administered. Prolonged serum levels exceeding 8 to 10μg/ml produce damage to the inner ear; however, the immediate and dramatic changes which occurred in cases 1 and 2 did so with levels greater than this. In case 3 lesser changes occurred even though the serum levels were in the ‘safe’ range.

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Rhabdomyolysis and Acute Tubular Necrosis Associated with Carbenoxolone and Diuretic Treatment

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A 61-year-old man with a gastric ulcer who had had haematemesis was treated with carbenoxolone 300mg/day. His blood pressure at that time was 160/100, and serum electrolytes and renal function showed no abnormalities. He then developed ankle oedema and chlorthalidone 50mg, every other day, was added. No potassium supplement was given. Within a month the patient complained of progressive muscle weakness, mental confusion, and disorientation. Drug treatment was continued.