COMMENTARY
RESPONSES TO CARDIOVASCULAR DRUGS DURING ALCOHOL WITHDRAWAL
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Abstract — Aim: To present findings on the kinetics and dynamics of cardiovascular drugs during alcohol withdrawal (AW), compared with that observed in remission. Method: Studies were reviewed and summarized. Results: A single-dose study in alcoholic patients with propranolol, a β-adrenergic antagonist, showed that the negative inotropic effect was decreased and the bradycardiac effect increased during AW as compared with during early remission. The hypotensive effect of isosorbide dinitrate, commonly used as a vasodilator, was weaker at the onset of AW, being associated with the decreased bioavailability of the drug. Verapamil, which is a L-type Ca²⁺ channel antagonist, produced a bradycardiac effect at the onset of AW, but no effect was observed in early remission. The effect was probably due to changes in L-type Ca²⁺ channels because no differences in verapamil concentrations between AW and early remission were observed. Conclusion: Taken together, AW modifies the dynamics and kinetics of cardiac drugs, which may have an impact on the treatment of alcoholic patients with cardiac diseases.

INTRODUCTION
Alcohol-dependent subjects undergo different phases of their disorder including acute intoxication, withdrawal and remission, all of which may affect drug kinetics and dynamics. Acute and long-term alcohol intake is known to modify the pharmacokinetics of many drugs. When administered simultaneously, alcohol can potentiate effects of several drugs, whereas long-term alcohol abuse may have an inhibitory effect due to pharmacokinetic interactions (for review, see Fraser, 1997; Lieber and Abittan, 1999). In this overview, recent findings will be discussed showing that alcohol withdrawal (AW) also modifies drug kinetics and dynamics producing drug responses different from those observed in early remission.

CARDIOVASCULAR CHANGES DURING ALCOHOL WITHDRAWAL
Alcohol withdrawal is a severe complication of alcohol dependence that develops after cessation of alcohol intake in alcohol-dependent patients. It is characterized by increased anxiety, tremulousness, paroxysmal sweating, and reduced sleep (American Psychiatric Association, 1994). In severe forms, AW may precede the development of delirium tremens, seizures, and complications such as arrhythmias which can lead to sudden death (Puddey et al., 1999). Cardiovascular changes that occur in AW, as a result of over-activity of the sympathetic nervous system are tachycardia, arterial hypertension, elevated cardiac output, and increased total peripheral resistance (Beckman et al., 1981; Saucler et al., 1981; Clark and Friedman, 1985; Kähkönen and Bondarenko, 2000). These changes are mostly transitory abnormalities soon subsiding if abstinence is continued (Saunders et al., 1981; Clark and Friedman, 1985; Kähkönen, 1997). However, after one month of abstinence some alcoholics with transitory hypertension during AW continued to show high systolic blood pressure in response to isometric handgrip test, higher total peripheral resistance and heart rate, and lower stroke volume than patients without hypertension (King et al., 1991, 1996). Cardiovascular changes in AW are mediated by several central and peripheral mechanisms. The level of the activation of the sympathetic nervous system is the most important factor regulating the functioning of the cardiovascular system in AW directly and indirectly with the renin-angiotensin-aldosterone system, vasopressin, cortisol, and sodium sensitivity (for review, see Kähkönen, 2004).

EFFECTS OF BETA BLOCKING DRUGS
Kähkönen (2003) reported a study in six male alcoholics. On Day 1 following AW, 80 mg of propranolol reduced the heart rate by 25 ± 3.8 beats/min, whereas the reduction on Day 10 was 19 ± 2.1 beats/min (P = 0.05). Resting heart rate was 82 ± 6.2 and 73 ± 3.4 beat/min, respectively (P = 0.05). The higher heart rate on day one reflects increased sympathetic activity, associated with initial AW (see above). The blood level reached on Day 1 was 70 ± 13.8 mg/ml and on Day 10 was 50 ± 9.5 mg/ml, thus more pronounced bradycardiac effect on Day 1 is hardly unexpected. Another factor explaining the greater bradycardiac effect on Day 1 is higher initial heart rate. It is evident that if an increase in heart rate is due to strong adrenergic stimulation, it is easier for an adreno-receptor antagonist to reveal its anti-adrenergic effect. In the same study, the extent of the negative inotropic effect did not differ between Days 1 and 10. However, when the inotropic effect based on changes in cardiac output was plotted against changes in propranolol concentration, the curve was shifted to the left on Day 10. This may indicate that sensitization to the inotropic effect of propranolol occurs at early remission.

The different cardiovascular responses to propranolol in AW compared with early remission may arise partly from altered central and peripheral adrenergic nervous activity
during AW. Evidence suggests that AW is associated with rebound β-adrenergic hypersensitivity (Sellers et al., 1976). Further, the level of dihydroxyphenylalanine, dopamine, noradrenaline, adrenaline, and homovanillic acid in alcoholic patients are much higher than those in healthy subjects. With the development of AW symptoms, urinary excretion of catecholamines increases further, returning to normal levels after AW reduction (Mendelson, 1970). On the first day of AW, lymphocyte β-adrenoceptor levels have been found to be reduced and associated with high noradrenaline and adrenaline levels. Catecholamine levels rapidly subsided over the next 3 days and lymphocyte β-receptors were restored to normal levels within the same period (Mäki et al., 1990). High-catecholamine levels have been established to lead to a reduced β-receptor population (Cruickshank and Prichard, 1994).

EFFECTS OF NITRATES

Cardiovascular effects after isosorbide dinitrate (ISDN; 20 mg sublingually) were studied in nine alcoholic patients on Days 1 and 10 of AW (Kähkönen and Zwartau, 2003). No significant difference was observed in the absolute decrease in systolic blood pressure after ISDN administration. However, when the decrease in systolic blood pressure was plotted against changes in concentrations of ISDN and its metabolites, a more marked effect was observed on Day 10. At the same time, the tachycardiac response to ISDN was more pronounced on Day 1 of AW. Increased vasodilatation in response to ISDN in early remission might be associated with changes in nitric oxide (NO) function during AW. ISDN has been suggested to induce vasodilatation through NO function (Bennett and Marks, 1984; Brien et al., 1987). ISDN undergoes bioformation to NO and S-nitrosothiol, resulting in activation of guanylate cyclase to produce cyclic GMP, which initiates relaxation of vascular smooth muscle (Gruetter et al., 1981). Some evidence also indicates that ISDN given to rats undergoing withdrawal from ethanol worsens withdrawal signs, suggesting that NO is involved in AW (Adams et al., 1995). This was confirmed by findings of the same authors that administration to rats, of an NO synthase inhibitor, Nω-nitro-L-arginine methyl ester, decreases the severity of AW (Adams et al., 1995).

Although ISDN-induced vasodilatation was increased in early remission, the effect was accompanied by a smaller rise in heart rate than during AW. Tachycardia is a sympathetic reflex-mediated response to vasodilatation induced by ISDN to maintain the cardiac output at a constant level (Murad, 1990). Sympathetic activity is increased in alcoholic patients undergoing withdrawal (Linnola et al., 1987), which may also result in a higher heart rate response to administration of ISDN. When sympathetic activity decreases after resolution of AW, a lower heart rate response to ISDN can be expected.

EFFECTS OF CALCIUM CHANNEL ANTAGONISTS

Cardiovascular effects of verapamil (5 mg intravenously) were studied in seven alcoholic subjects on Days 1 and 10 of AW. On Day 1, verapamil caused a bradycardiac response, which was absent on Day 10. The relative hypotensive effect of verapamil was concomitantly weakened (Kähkönen and Bondarenko, 2003). These results on Ca2+ channel modulation of cardiovascular symptoms of AW are in line with those obtained in animal experiments. Administration of antagonists of L-type Ca2+ channels decreases withdrawal signs and mortality in alcohol-dependent rats deprived of ethanol (Little et al., 1986; Bone et al., 1989; Colombo et al., 1995; Watson and Little, 2002). Further, long-term alcohol exposure in rats has been reported to increase the number of dihydropyridine binding sites of cardiac L-type Ca2+ channels (Guppy et al., 1995) and enhance their activity (Solem et al., 2000).

CARDIOVASCULAR DRUG KINETICS AND CONCENTRATIONS

Propranolol concentrations on Day 1 of AW were compared with concentrations on Day 10, being significantly higher on Day 1 for the entire 2 h investigation (Kähkönen, 2003). These findings are in line with those of Sandor et al. (1983), who found elevated concentrations of free propranolol in plasma during AW. Furthermore, alcohol consumed during the evening is capable of increasing the plasma clearance rate of propranolol in non-alcoholic subjects 12 h later (Sotaniemi et al., 1981), indicating that the enzymes responsible for metabolism of propranolol in the liver, recover by early remission. On Day 10, the AUC_{0–1.5 h}, C_{max} and t_{1/2} of ISDN were increased compared with those on Day 1 suggesting an increase in bioavailability in early remission. Concentrations of ISDN metabolites did not differ between the two periods of investigation (Kähkönen and Zwartau, 2003). The reason for increased bioavailability of ISDN in early remission is uncertain. ISDN is metabolized by glutathione-S-transferase to nitrite (Hill et al., 1989). Chronic ethanol treatment in rats may activate glutathione-S-transferase (Antonenkov et al., 1988; Ribiere et al., 1992). Thus, changes in drug metabolism induced by AW may underlie the observed alteration in ISDN pharmacokinetics. AW did not affect verapamil and norverapamil plasma concentrations (Kähkönen and Bondarenko, 2004).

In conclusion, AW seems to be an important factor modifying responses to cardiac drugs. More studies are needed to establish the relevance of altered drug responses in alcoholic patients with cardiac diseases.

REFERENCES


