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# A PRELIMINARY STUDY ON THE INTERACTION BETWEEN ETHANOL AND PROPRANOLOL IN NORMAL HUMAN SUBJECTS

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**Abstract:** Ethanol significantly increased the steady-state peak concentration of propranolol while propranolol significantly reduced the total body clearance of ethanol in healthy human volunteers. Ethanol *per se* caused tachycardia and rise in systolic blood pressure while propranolol administration resulted in bradycardia. In combination, ethanol and propranolol caused significant fall in diastolic blood pressure without any significant changes in the heart rate and systolic blood pressure compared to the control readings of four healthy male volunteers. The kinetic and haemodynamic interactions observed between ethanol and propranolol in the preliminary study are of clinical relevance and need further exploration.

**Key words:** ethanol, propranolol, human volunteer, zero-order, kinetics

## INTRODUCTION

Ethanol is a commonly consumed social drink and propranolol is a widely prescribed non-selective beta adrenoceptor antagonist. However, there are very few reported studies pertaining to the kinetic and dynamic interactions between ethanol and propranolol in human beings. Further, the documented results of such studies are equivocal in nature (1, 2). Therefore, a preliminary study was designed to investigate the kinetic and haemodynamic interactions between a single moderate dose of ethanol and propranolol under steady state-plasma concentration in normal human subjects.

## METHODS

The study was approved by the In Ethical Institutional Committee. Four normal male volunteers gave written consent to participate. Their mean ± S.E. weight was 63.50±1.60 kg (range 61-68 kg) and age was 32±4.40 years (range 27-45 years). All the subjects had normal hepatic and renal functions. They were non-smokers and occasional social drinkers who consumed no ethanol for at least one week prior to the study. They were taking no medications. An open, crossover, pilot study was designed as follows :-

*Day 1* : For each volunteer the baseline resting heart rate (HR), systolic blood pressure (SBP) and diastolic blood pressure (DBP) were recorded in the sitting posture at 08.00 hr.

*Day 2* : The study commenced at 07.00 h, the subjects having fasted for 12 h. Alcohol (a local brand of whisky containing 40 g% ethanol) was administered by staggered dosing at every 20 min intervals to the volunteers. 60 ml of whisky was diluted with 180 ml of lemon juice to give a final concentration of 10 g/100 ml of ethanol and each volunteer was asked to consume 240 ml of the final mix along with a standardized breakfast in 10 min. Venous blood samples (1 ml each) were collected at 0 (before ethanol consumption), $\frac{1}{2}$, 1, 1 $\frac{1}{2}$, 3 and 6 h after ethanol consumption. Sitting HR, SBP and DBP were recorded 1 h after ethanol intake.

*Day 3-day 6:* Volunteers were asked to take propranolol (80 mg twice a day) at 06.00 h, and 18.00 h every day.

*Day 7:* The volunteers consumed the morning dose of propranolol at 06.00 h. At 08.00 h, 8 ml venous blood was drawn to estimate plasma propranolol.

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Sitting HR, SBP and DBP were recorded after the venous blood sampling. The volunteers consumed 18.00 h dose of propranolol also.

*Day 8 :* Each volunteer consumed the 06.00 h dose of propranolol; 07.00 h onwards staggered dose of ethanol with standardized breakfast was served to the volunteers as mentioned above. Venous blood samples were collected at the same time intervals as stated under day 2. 0, $\frac{1}{2}$ , 1 $\frac{1}{2}$ , 3 and 6 h samples of 1 ml each were meant for blood ethanol assay while the 1 h sample (9 ml) drawn to estimate both ethanol and propranolol. 1 h after ethanol intake the SBP, DBP and HR were recorded under sitting posture.

**Drug assays**

*Blood ethanol assay :* Blood ethanol concentration (mg $ml^{-1}$) was estimated by the measurement of NADH increase on enzymatic dehydrogenation from NAD (3) by UV-method at 340 nm wavelength adopting a diagnostic kit supplied by Boehringer Mannheim GmbH diagnostica. Blood ethanol estimation was done on the same day of collection of the samples.

*Plasma propranolol assay :* Plasma propranolol concentration (ng $ml^{-1}$) was measured spectrophotofluorometrically. Blood samples were centrifuged at 3000 rpm. Plasma was separated and stored at –20°C till assay. The sensitivity of the assay in our laboratory was 2 ng $ml^{-1}$ with intra assay coefficient of variation of 7.96%.

*Pharmacodynamic measurements :* BP (mm Hg) was measured by the same observer throughout the study using the same mercury sphygmomanometer and stethoscope. The 1st and 5th korotkoff sounds were considered for documenting the systolic and diastolic blood pressures respectively. HR (beat/min) was measured from the lead I of a direct writing electrocardiograph by determining the time taken for five complete cardiac cycles (5). Under the pharmacokinetic study, the blood concentrations of ethanol were analyzed by zero order kinetics. The following parameters were calculated : Cmax from the plasma data; Tmax from the plasma data; BEDR (Blood ethanol disappearance rate) from the slope of the regression line of ethanol elimination by the least square regression analysis; the desired ethanol concentration at the start of ethanol administration (Co) from the Y-intercept of the regression line; apparent volume of distribution ($V_z$) by dividing the total dose by Co; the total body ethanol elimination rate (Widmark's $B_{60}$) from the product of BEDR and Vz (6); $AUC_{0-3}$ by trapezoidal rule and the post-ethanol 3 h concentration of ethanol from the plasma data.

For propranolol, the steady-state anticipated peak concentration at 2 h after the morning dose of the drug was estimated.

Data were expressed in terms of mean±S.E. Two tailed paired 't' test was applied for statistical purposes and $P < 0.05$ was considered to be statistically significant.

## RESULTS

Table I shows the mean ± S.E. of the pharmacokinetic data of single dose of ethanol (24 g per volunteer) given with and without five days of propranolol pretreatment to four normal volunteers. No significant difference could be observed in the Cmax, Tmax, $AUC_{0-3}$ and Vz between the two groups. Both Cmax and $AUC_{0-3}$ were higher in the propranolol administered group but failed to attain statistical significance. However, BEDR and Widmark's $B_{60}$ parameters were significantly lower in the propranolol administered group compared to the control group and post-ethanol 3 h concentration was significantly higher in the propranolol treated group compared to the control group suggesting a slower clearance of ethanol after multiple dose treatment with propranolol in human volunteers.

TABLE I : Pharmacokinetic data (Mean±SEM) of ethanol obtained from four healthy volunteers : A zero order analysis.

| *Group* | *Dose of Ethanol (g)* | *Cmax (mg. $ml^{-1}$)* | *Tmax (min)* | *$AUC_{0-3}$ (mg. $ml^{-1}$ h)* | *BEDR ($gl^{-1}$ $h^{-1}$)* | *Vz ($LKg^{-1}$)* | *Widmark's $B_{60}$ ($gh^{-1}$ $kg^{-1}$)* | *3h concentration (mg. $ml^{-1}$)* |
|---|---|---|---|---|---|---|---|---|
| Ethanol treated | 24 | 0.62±0.04 | 37.50±7.50 | 1.09±0.01 | 0.20±-0.01 | 0.50±0.03 | 0.099±0.0015 | 0.14±0.04 |
| Propranolol + ethanol treated | 24 | 0.66±0.09 | 45.00±8.66 | 1.32±0.16 | 0.16±0.01* | 0.50±0.04 | 0.076±0.004* | 0.29±0.05* |

*Statistically significant difference between the two groups at $P < 0.05$

Table II shows the individual values and mean ± S.E. from four healthy volunteers of the 2 h concentration of propranolol after the early morning (06.00 h) dose at steady state in presence and in absence of an acute dose of ethanol. In the ethanol treated group, the obtained concentration of propranolol (94.30 ± 15.40 ng/ml) was significantly higher compared to the concentration of propranolol in the ethanol untreated group (34.80 ± 7.60 ng/ml). However, wide interindividual variation was reflected in the obtained data. The concentration ranged from 17.20 - 53.70 ng/ml in the ethanol untreated group while it ranged from 58.00-132.80 mg/ml in the ethanol treated group. Each volunteer showed rai-sed propranolol concentration after ethanol in the range between 2 - 3.5 times that obtained without ethanol.

TABLE II : Post dose 2 h plasma concentration of propranolol at steady-state obtained from four healthy volunteers.

| *Volunteer* | *Plasma propranolol concentration (ng/ml)* | |
|---|---|---|
| *No.* | *Propranolol treated* | *Propranolol + ethanol treated* |
| 1 | 53.70 | 132.80* |
| 2 | 37.60 | 88.90* |
| 3 | 30.80 | 97.60* |
| 4 | 17.20 | 58.00* |
| Mean ± S.E. | 34.80 ± 7.60 | 94.30 ± 5.40* |

*Statistically significant difference at P<0.001.

Table III shows the mean ± S.E. of the pharmacodynamic data obtained from four volunteers under control condition, after an acute oral dose of ethanol, after multiple oral doses of propranolol and after acute oral dose of ethanol given at steady-state condition of propranolol. After multiple oral doses of propranolol it was observed that the sitting HR (65.50 ± 1.50 beats/min) was significantly less compared to that of the control value (86.25 ± 4.68 beats/min) although no significant change in either the SBP or the DBP could be observed. The sitting SBP (105.50 ± 5.32 mm Hg) in the propranolol + ethanol treated group was significantly less compared to the SBP (123.00 ± 3.00 mmHg) in the ethanol treated group but did not differ significantly from the control and propranolol treated groups. However, the sitting DBP (66.50 ± 2.06 mmHg) in the propranolol + ethanol treated group was significantly less compared to the value for the same parameter under all other groups i.e. control, ethanol and propranolol treated. The sitting HR ( 79.50 ± 5.36 beats/min) in the propranolol + ethanol treated group was found to be significantly less compared to the sitting HR in the ethanol treated group (102.00 ± 4.64 beats/min) and significantly more compared to the sitting HR inthe propranolol treated group (65.50 ± 1.50 beats/min) but did not differ significantly from the control observation (86.25 ± 4.68 beats/min).

TABLE III : Effect of ethanol, propranolol and the combination on the haemodynamic parameters in healthy human volunteers.

| | *Control* | *Post Ethanol* | *Prop (At SS)* | *Prop + Ethanol* |
|---|---|---|---|---|
| Sitting systolic BP | 111.50±2.99 | 123.00±2.00* | 113.00±4.65 | 105.50±5.32[a] |
| Sitting diastolic BP | 79.50±2.50 | 81.00±9.70 | 78.50±1.76 | 66.50±2.06*,[a,+] |
| Sitting heart rate | 86.25±4.68 | 102.00±4.64* | 65.50±1.50* | 79.50±5.36[a],[+] |

*Compared to the control value at P<0.05
**[+]Compared to the proparanolol (at SS) treated value at P<0.05**
**[a]Compared to the ethanol treated value at P<0.05.**

## DISCUSSION

The present data suggested both pharmacokinetic and pharmacodynamic interactions between ethanol and propranolol. Pharmacokinetically, it would appear that individuals on chronic propranolol would show a slower elimination of ethanol from their body while the peak concentration of propranolol would be greatly accentuated if intake of propranolol is followed by moderate doses of ethanol. Considering the remarkable change in the peak plasma propranolol concentration after ethanol ingestion, it would seem worthwhile to carry out detailed kinetic investigations of propranolol in presence of ethanol. Mechanistically, the slower

elimination of ethanol in the presence of propranolol could be because of decreased hepatic perfusion induced by multidose propranolol treatment (7), since the principal route of ethanol clearance is metabolism by the hepatic enzyme systems. The ethanol induced rise in the 2 h concentration of propranolol could be related to greater extent of bioavailability of propranolol (1). In addition to the kinetic interaction, it was also observed that the two drugs interacted in a complex manner to influence the resting haemodynamic parameters viz. heart rate and blood pressure.

In the present study, it could be observed that an acute dose of ethanol resulted in a significant rise in the systolic blood pressure and heart rate in the sitting position while multidose of propranolol brought about bradycardia without any change in the blood pressure profile compared to the control readings. The bradycardiagenic effect of an adequate dose of propranolol is well documented and is related to the degree of β-adrenoceptor blockade in the heart. The cardiac stimulation and the resultant changes in the haemodynamic parameters induced by an acute dose of ethanol could probably be due to increased catecholamine release by acetaldehyde (8, 9). The catecholamine hypothesis in relation to ethanol induced cardiac stimulation needs further confirmation although it was observed in the present study that both the pressurizing and the tachycardiagenic effects of ethanol could be obliterated by effective beta-adrenoceptor blockade induced by multiple doses of propranolol. Characteristically, neither ethanol nor propranolol could alter the diastolic blood pressure *per se* while the two in combination brought about a significant drop in the aforementioned parameter compared to the control observation in the sitting posture. It was thus concluded, that in the absence of propranolol, an acute dose of ethanol would result in a dominantly cardiac stimulatory effect, resulting in a vasopressor response, while in the presence of propranolol, the vasodilatory effect to an acute dose of ethanol gets unmasked resulting in a vasodepressor response.

It was felt that the nature and extent of the kinetic and haemodynamic interactions between propranolol and ethanol was such that it might have clinical relevance. Ethanol must, therefore, be taken into account while prescribing propranolol or advising patients on it's use. Considering the small number of volunteers in the present study, it was felt that the nature of the interaction could at best be described as a definite trend but conclusive proof would necessitate documentation in larger number of volunteers and also in mild hypertensive patients under close medical supervision.

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