

Effect of Liv52, A Herbal Preparation, on Absorption and Metabolism of Ethanol in Humans

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ABSTRACT

In 8 social drinkers the effect of a single dose of Liv.52 or placebo on ethanol absorption has been studied after ingestion of 30 ml whisky in 5 min. The $t_{1/2}$ absorption with Liv.52 was 3.62 min., significantly less than after placebo, 6.29 min. The peak concentration after Liv.52 (49.9 mg/100 ml) was significantly higher than with placebo (40.5 mg/100 ml).

Whisky 120 ml consumed by regular alcohol users in 1h, before and following 15 days of Liv.52 treatment produced significantly higher ethanol levels at 2, 3 and 4 h and significantly lower acetaldehyde levels at 3 and 4 h after Liv.52 treatment.

Liv.52 enhanced the rate of absorption of ethanol and rapidly reduced acetaldehyde levels, which may explain its hepatoprotective effect on ethanol-induced liver damage.

INTRODUCTION

Chronic alcohol consumption is a prime cause of liver disease.^{1,2} Present evidence indicates that acetaldehyde, the intermediate metabolite of ethanol, is directly injurious to liver.^{3,4} Significantly higher levels of acetaldehyde in blood are reported after ethanol ingestion by chronic alcohol users as compared to non-alcoholics, as a result of a primary reduction in hepatic acetaldehyde dehydrogenase activity.^{5,6} Acetaldehyde via its covalent binding to hepatic proteins may be the critical event leading to liver injury.⁴

Hepatoprotective agents of herbal origin have been available on the Indian market for many years and are regularly prescribed by physicians. Liv.52, a herbal formulation based on Ayurvedic principles, contains a number of hepatoprotective ingredients which are known to protect the liver from damage produced by toxic substances, including alcohol.⁸⁻¹¹

Using ¹³¹I-labelled Rose Bengal and a whole body linear scanner body segment counter, Harshe *et al.*, demonstrated reversible depression of liver function, even after a single episode of social drinking and the protective effect of Liv.52 (Harshe *et al.*, 1978, unpublished data).

The present study was designed to examine the effect of Liv.52 on the absorption and metabolism of ethanol in moderate and occasional drinkers.

MATERIAL AND METHODS

Twenty-five healthy male subjects with a mean age of 36.7 (± 2.95) y and mean weight of 59.2 (± 1.72) kg., volunteered for the study. After ascertaining the history of alcohol intake they were classified as occasional, mild, moderate or chronic alcohol users¹². Their informed written consent was obtained.

Study of ethanol absorption

Eight mild to moderate drinkers, whose alcohol consumption was from 10 to 20 units/week, were enrolled in the trial to study the effect of a single dose of Liv.52 on the absorption of ethanol.¹³ On the first occasion, subjects received 6 tablets of placebo and on the second occasion after 3 days, 6 tablets of Liv.52 at 08.00h whilst fasting. Two h later and after collection of a fasting blood sample, 75 proof Peter Scot Whisky 30 ml, containing 44.8% v/v ethanol, was given with 70 ml chilled soda, to be consumed over 5 min. Further blood samples were collected 2, 5, 10, 15, 20, 30, 40, 60, 90 and 120 minutes after alcohol ingestion. Blood samples were immediately processed for ethanol estimation by a modified GC method.¹⁴ The method was validated by doing 10 replicates of the assay. The coefficient of variation was less than 3%.

Study of ethanol metabolism

The effect of Liv.52 on ethanol metabolism was studied in 17 subjects. Nine were moderate alcohol users who had consumed more than 20 units/week for more than 5 years and 8 were occasional drinkers.

Ethanol metabolism was checked by estimating the blood ethanol and acetaldehyde levels. In the fasting state, after the '0' hour blood collection, each subject consumed 60 ml Peter Scot whisky with 100 ml soda and 3 cubes of ice in 30 minutes, at 09.00 h. The next portion of 60 ml whisky was consumed over the next 30 minutes, i.e., between 09.30 and 10.00 h. Blood was sampled at 1 h, i.e., at the end of alcohol consumption and hourly thereafter for 6 h. A standard lunch was allowed at 12 noon. Blood samples were immediately processed for ethanol and acetaldehyde assay.

All subjects then took Liv.52, 3 tablets b.i.d. for 14 days, and on Day 15 ethanol metabolism was again studied by the same procedure.

RESULTS

The effect of a single dose of Liv.52 on ethanol absorption in mild to moderate alcohol users is depicted in Table 1.

Table 1 : Mean C_{max}, t_{max}, area under plasma concentration (AUC) and $t_{1/2}$ absorption of ethanol following ingestion of 30 ml whisky and effect of single dose of Liv.52				
Treatment	C_{max}	t_{max}	AUC mg. 100 ml min 0-120 min.	$t_{1/2}$ min
Placebo	40.5* ±3.99	17.5 ±0.94	2330 ±255	6.29* ±0.89
Liv.52	49.9* ±2.31	12.1 ±1.9	2330 ±249	3.62* ±0.54

Mean (SEM). Unpaired t test. * $p < 0.05$

The peak concentration of blood ethanol from 30 ml whisky was significantly higher and the rate of absorption was significantly faster after a single dose of 6 tablets of Liv.52 as compared to placebo treatment. The area under the plasma concentration time curve (AUC) was not affected. The single dose of Liv.52 increased the rate of absorption of ethanol.

The mean ethanol level was significantly lower and the mean acetaldehyde level was significantly higher in 9 moderate alcohol users as compared to 8 occasional drinkers (Fig.1), indicating the induction of Phase I metabolism.

Following 14 days of Liv.52 treatment, the ethanol levels were 98.2 (± 5.39) and 98.2 (± 5.85) $\mu\text{g/ml}$ at 1 and 2 h in moderate drinkers, which were significantly higher than on Day 0. The rate of elimination of ethanol was not affected (Table 2). The mean acetaldehyde levels produced by 2 doses of whisky in moderate alcohol users before and after Liv.52 treatment are shown in Fig.2. Before Liv.52 administration, the mean acetaldehyde levels were 4.12 (± 0.50), 3.90 (± 0.67), 3.44 (± 0.73) and 2.63 (± 0.49) $\mu\text{g/ml}$ at 3, 4, 5 and 6 h, and they were significantly reduced to 2.58 (± 0.26), 2.10 (± 0.24), 1.73 (± 0.20) and 1.47 (± 0.19) $\mu\text{g/ml}$ respectively by Liv.52. $t_{1/2}$ elimination ($t_{1/2}$) of acetaldehyde was significantly shortened from 6.18 (± 1.68) to 2.79 (± 0.37) h ($p < 0.05$ unpaired 't' test). This suggests a faster rate of elimination of acetaldehyde after 14 days of Liv.52 administration.

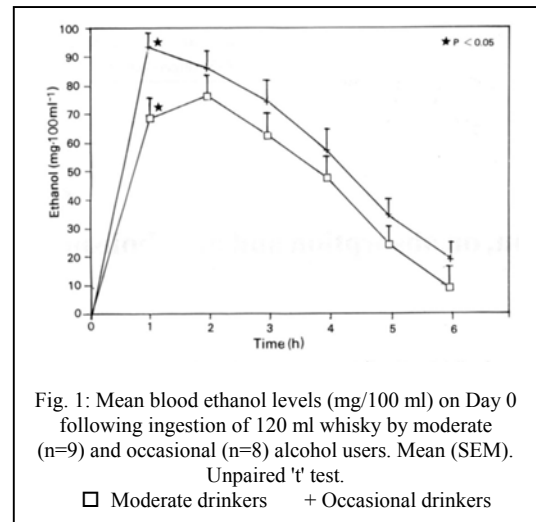


Fig. 1: Mean blood ethanol levels (mg/100 ml) on Day 0 following ingestion of 120 ml whisky by moderate (n=9) and occasional (n=8) alcohol users. Mean (SEM). Unpaired 't' test.
 □ Moderate drinkers + Occasional drinkers

Table 2 : Mean blood ethanol levels (mg/100 ml) on Day 0 and after 14 days of Liv.52 treatment following ingestion of 120 ml whisky by moderate alcohol users (n=9)								
Day 0 time (h)	0	1	2	3	4	5	6	$t_{1/2}$ (h)
Mean (SEM)	0.00 ± 0.00	68.4* ± 6.61	76.9* ± 4.73	63.0 ± 2.47	47.9 ± 3.67	24.3 ± 3.38	9.44 ± 1.61	1.90 ± 0.14
Day 15 time (h)	0	1	2	3	4	5	6	$t_{1/2}$ (h)
Mean (SEM)	0.00 ± 0.00	98.2* ± 5.39	98.2* ± 5.85	75.2 ± 5.98	56.0 ± 4.38	29.8 ± 2.08	10.2 ± 1.78	1.98 ± 0.16

Mean (SE). Unpaired 't' test. * $p < 0.05$.

In one chronic alcohol user, the lower ethanol levels and trend to faster elimination of acetaldehyde was confirmed on 5 occasions over 2 y following 15 days of Liv.52 treatment. The $t_{1/2}$ of acetaldehyde of 6.14 h on Day 0 was reduced to 1.74 h on Day 15. The effect of Liv.52 seemed to wear off 28 days after stopping the treatment.

The mean ethanol levels up to 6 h before Liv.52 treatment in occasional drinkers and after 15 days of Liv.52 treatment in moderate alcohol users are shown in Table 3. Although Liv.52 administration caused higher ethanol levels in moderate drinkers, they were comparable to those observed in occasional drinkers before Liv.52 treatment. Liv.52 seemed to normalise blood ethanol levels in moderate alcohol users.

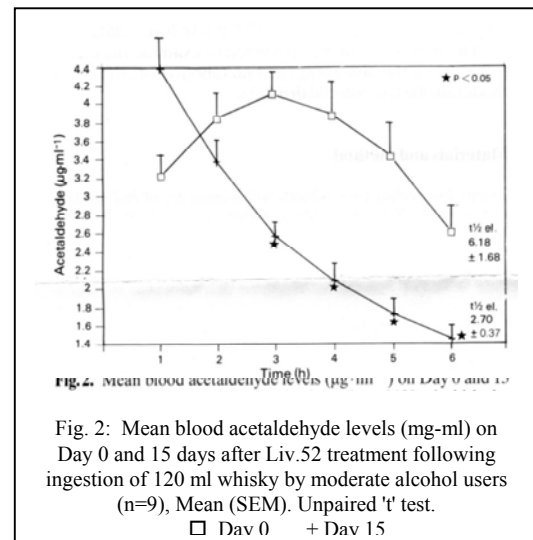


Fig. 2: Mean blood acetaldehyde levels (mg/ml) on Day 0 and 15 days after Liv.52 treatment following ingestion of 120 ml whisky by moderate alcohol users (n=9), Mean (SEM). Unpaired 't' test.
 □ Day 0 + Day 15

Table 3 : Mean blood ethanol levels (mg/100 ml) on Day 0 in occasional drinkers and 15 days after Liv.52 treatment following ingestion of 120 ml whisky by moderate alcohol users							
	Time (h)	1	2	3	4	5	6
Moderate alcohol users (n=9)	Day 15	98.2 ±5.71	98.2 ±6.20	75.2 ±6.34	56.0 ±4.64	29.8 ±2.21	10.2 ±1.89
Occasional alcohol users (n=8)	Day 0	93.6 ±9.87	86.4 ±6.79	74.8 ±6.25	57.8 ±7.68	34.4 ±7.92	19.1 ±5.84

DISCUSSION

A single dose of Liv.52 increased the rate of absorption of ethanol, leading to earlier and higher peak concentrations. The increased level of ethanol produced by Liv.52 in moderate users might be due to an enhanced rate of absorption. Pre-systemic metabolism of ethanol has been demonstrated¹⁵ and its stimulation in chronic alcohol users is well documented.¹⁶ Herbal drugs have been shown to inhibit pre-systemic metabolism of other drugs and so to enhance their bioavailability.¹⁷ The effect of Liv.52 on absorption was more striking in moderate alcohol users, in whom there was evidence of enhanced pre-systemic metabolism of ethanol, and it had virtually no effect in occasional drinkers. The inhibition of pre-systemic metabolism following Liv.52 may be responsible for the higher ethanol levels.

Lower blood ethanol and higher acetaldehyde levels in blood have been reported in chronic alcohol users.¹⁸ This is probably the result of induction of the Phase I metabolism of ethanol, leading to faster acetaldehyde formation. This together with decreased Phase II metabolism, causes higher levels of acetaldehyde.⁷ Liv.52 caused higher ethanol and lower acetaldehyde levels in moderate alcohol users. It did not affect ethanol levels in occasional drinkers but it did significantly reduce acetaldehyde levels. The initial higher levels of acetaldehyde and their rapid subsequent decline suggests the possibility that the binding of acetaldehyde to a receptor or acceptor was prevented.

The unique action of Liv.52 in lowering the accumulation of acetaldehyde by its rapid removal may reduce the injurious effects of ethanol on the liver and possibly on the brain. This action of Liv.52 is most probably responsible for its hepatoprotective effect in alcoholic liver disease.

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