IS THERE AN INTERACTION BETWEEN H_2-ANTAGONISTS AND ALCOHOL?

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SUMMARY

H_2-antagonists are commonly prescribed drugs and alcohol use is widespread in the community. Any possible interaction may be important because of the frequent co-administration of both drugs and the potential for unexpected impairment of pyschomotor function, in particular, driving skills. Hepatic ADH is the major site of alcohol metabolism. ADH is also found in the stomach, but it is uncertain whether gastric ADH is able to metabolise a significant amount of alcohol *in vivo*. Significant first-pass metabolism can be demonstrated at lower doses of alcohol, and if alcohol is given after meals. Varying degrees of extraction of alcohol from the portal circulation probably explains the data regarding first pass metabolism rather than gastric metabolism by gastric ADH. H_2-receptor antagonists inhibit gastric ADH activity to a variable extent. If gastric metabolism of alcohol is negligible then this inhibition has no relevance. Given the uncertainty regarding a mechanism of interaction, only carefully conducted studies in controlled environments will answer the question. The large inter-subject variability of alcohol absorption means that any study which seeks to determine the effect of an H_2-receptor antagonist on ethanol metabolism *must have sufficient numbers*. A *cross-over design, with each subject acting as his own control, is preferable* to avoid ascribing an effect to treatment rather than to chance.

The alcohol dosing studies are reviewed and the results summarised according to dose of alcohol given. At a dose of 0.15 g/kg of alcohol, four commonly used H_2-antagonists may cause a small increase in blood alcohol concentrations in certain conditions. This absolute increase is very small. The magnitude of effect is far less than the effect of taking a meal before alcohol. At doses of 0.3 g/kg and above the majority of evidence favours no interaction between H_2-antagonists and alcohol. There is no interaction at doses that would be expected to impair psychomotor skills (above 25 mg/dl). There remains a question regarding the cumulative effect of repeated small doses of alcohol and further studies are required.

The relationship between ethanol absorption and gastric emptying raises the possibility that the effects of H_2-receptor antagonists observed at very low doses of alcohol may be due to the acceleration of gastric emptying by these drugs. This is an attractive hypothesis that

explains many aspects of the debate, but studies of the effect of H_2-antagonists on gastric emptying have been conflicting.

1. INTRODUCTION

The frequent use of alcohol together with H_2-antagonists gives any pharmacokinetic interaction potential clinical significance. *['Alcohol' is used in this manuscript but refers only to ethanol.]* The interactions between drugs and alcohol can be studied in many different settings. Acute ingestion studies with younger healthy volunteers are the most frequent study design. This is easy to perform, but may have some limitations when applied to more general situations. Acute ingestion studies are often quite different from the manner in which alcohol is usually consumed. Chronic ingestion studies can detect important effects from the induction of hepatic enzymes. Some studies have attempted to reproduce a situation more akin to social drinking.

There is considerable inter- and intra-individual variability of alcohol bioavailability /1-3/. One study compared alcohol given after a meal and in the fasted state. The coefficient of variation for AUC (area under the plasma ethanol time curve) for inter-subject variability was 44% (fed) and 21% (fasted) and the coefficient of variation for AUC for intra-subject variability was 35% (fed) and 22% (fasted) /2/. Intra-subject variability is probably determined by the day-to-day variation in gastrointestinal function - particularly gastric emptying, intestinal transit time and portal blood flow /4/. Significant inter- and intra-subject variability in gastric emptying has been demonstrated even with a strictly standardised protocol of meals /5/. Small variations in the composition of the meal can have very significant effects on alcohol absorption, which can make post-prandial studies more difficult to perform /6-7/.

The implication of the large inter-subject variability is that any study which seeks to determine the effect of an H_2-receptor antagonist on alcohol metabolism *must have sufficient numbers.* A *cross-over design with each subject acting as his own control is preferable,* to avoid ascribing an effect to treatment rather than to chance because of the great inter-individual variability.

2. ALCOHOL ABSORPTION AND METABOLISM

A description of normal alcohol absorption and metabolism is necessary to understand any potential interaction. Alcohol metabolism appears to follow Michaelis-Menton kinetics at low doses and first order kinetics at higher doses /8/. The liver is the site of the majority of alcohol metabolism and hepatic alcohol dehydrogenase is the enzyme primarily responsible for this process /8-10/; its activity (as measured *in vitro*) does not appear to decline with age /11/. Other enzymes, in particular the microsomal ethanol-oxidising system (involving the microsomal cytochrome CYP2E1 [P450IIE1]), are also involved at higher doses of ethanol and may metabolise up to 10% of the ingested alcohol /9,12,13/. This enzyme is involved in metabolism of numerous substrates (both endogenous and exogenous) but alcohol (ethanol) is the substrate of most clinical importance. Enzyme induction of cytochrome CYP2E1 occurs after prolonged heavy alcohol intake whereas acute binge drinking is likely to cause inhibition of this enzyme group by direct competition for binding with cytochrome CYP2E1 /13/.

Gastric emptying has a marked effect on absorption of most drugs because it governs the access of the drug to the main absorptive surface, the small intestine. A slower rate of delivery of alcohol to the small intestine increases the effectiveness of portal extraction of alcohol. The area under the plasma ethanol concentration-time curve has been shown to correlate closely with the half-time emptying of liquids from the stomach /14/. Faster gastric emptying gives rise to higher blood alcohol concentrations, and vice-versa. Drinks with a high alcohol concentration delay gastric emptying /15-17/. This explains the observation that blood alcohol concentrations are lower after drinking whisky than after drinking the same amount of alcohol as beer /18/.

Gastric emptying may be delayed in alcoholics and gastrointestinal transit may also be altered /19/. Drugs which increase gastric emptying, such as metoclopramide, erythromycin or cisapride, increase the bioavailability of ethanol /20-22/, and drugs which delay gastric emptying will decrease the bioavailability of ethanol /22/. Intravenous erythromycin increased blood alcohol concentration after a meal by 40% /21/. Smoking also increases the rate of gastric emptying. A randomised crossover study showed that smoking caused a 20%

increase in peak blood alcohol concentrations /23/. Readers are referred to an excellent review of the effect of drugs on gastrointestinal motility /24/. An increased rate of delivery of ethanol to the small intestine is likely to be the reason for the increased bioavailability of ethanol after intra-duodenal instillation of alcohol and in patients who have had a gastrectomy /25/.

3. FIRST-PASS METABOLISM: GASTRIC OR HEPATIC?

First pass metabolism of alcohol is estimated by the difference in bioavailability of ethanol after intravenous or oral administration. This may be between 0-75% for individuals when alcohol is taken after a meal /26-28/. The difference decreases with an increasing dose of alcohol. The apparent difference depends on the methodology of the study. A slower rate of intravenous infusion will give a blood alcohol-time profile very similar to oral dosing /29/. First pass metabolism is also virtually absent in the fasting state /28/.

There is a continuing debate on the role of gastric alcohol dehydrogenase (ADH) in the first-pass metabolism of alcohol /29-31/. This hypothesis forms the basis of a proposed interaction between alcohol and H_2-receptor antagonists. The presence of a gastric alcohol dehydrogenase has been known for some time. The gastric ADH appears to be a separate form of ADH with distinct kinetic properties; three isoenzymes have been detected in the human stomach /32-36/. Total gastric ADH activity is very difficult to measure because of the quite different affinities of the three isoenzymes. There are some racial differences in the isoenzymes present. Eighty percent of Japanese patients lack one of the isoenzymes; however blood alcohol concentrations after oral dosing appear to be similar to those of Caucasians /37-39/. The relevance of any ethnic differences in enzyme activity (both gastric and hepatic ADH) is still debatable. There are also conflicting data on differences in gastric ADH activity with gender /40-42/. A lower ADH activity in females has been suggested as an explanation for gender differences in blood alcohol concentrations after oral dosing, although other factors such as differences in volume of distribution are equally plausible /31,43,44/. Alcoholics have a reduced gastric ADH activity, which is not surprising given the inhibitory effect of heavy ethanol intake on other enzyme systems and the potential for gastric mucosal damage with ethanol /28,40/. Gastric ADH activity

decreases with age /40/. Many elderly patients have atrophic gastritis and as a consequence will have lower gastric ADH levels. Two clinical studies have shown lower gastric ADH levels in patients with atrophic gastritis. However patients with atrophic gastritis did not have higher blood ethanol concentrations compared to patients with normal gastric mucosa and normal gastric ADH activity /45,46/. Gastric ADH activity is decreased in the presence of *H. pylori* infection /47/. Eradication of *H. pylori* increases gastric ADH activity but ethanol first pass metabolism is unchanged /48/.

The existence of gastric alcohol dehydrogenase is not disputed but the hypothesis that the enzyme has sufficient opportunity and ability to metabolise significant amounts of ethanol is in question. Orally ingested ethanol, when taken after a meal, is only in contact with the stomach for approximately one hour. The activity of the stomach ADH is 100 times less than that of the liver ADH. Moreno and Pares predicted from their data that the total activity of human stomach ADH would be able to metabolise only 1.2 mmol/l of ethanol/h, about 0.25% of the ethanol ingested in a 0.3 g/kg dosing study /49/. Advocates of a significant gastric component to alcohol metabolism present very different calculations /31/. Levitt has reviewed these calculations and finds many flaws, drawing similar conclusions to Moreno and Pares /30/. Experimental data have shown that there is no arterial to venous gradient for acetaldehyde in the rat stomach suggesting that there is negligible metabolism of ethanol in the stomach /50/.

The observed difference between systemic and oral dosing may be due to varying efficacy of extraction of alcohol from the liver. Pharmacokinetic modelling has suggested that the difference between equivalent intravenous and oral doses of ethanol can be explained by varying portal extraction depending on the different rate of delivery of ethanol to the liver with oral and intravenous dosing /51,52/. The same observations have been made in the comparison of bioavailability of propanolol in standard or slow-release preparations /53/. It is interesting that food increases the clearance of ethanol given by intravenous infusion by 60%. The mechanism for this may be due to varying efficacy of extraction of alcohol from the liver /54/.

4. INHIBITION OF GASTRIC ADH BY H_2-RECEPTOR ANTAGONISTS

In vitro evidence of inhibition of gastric alcohol dehydrogenase by H_2-receptor antagonists has been shown in several studies /55-57/. For these *in vitro* observations to be relevant to the proposed *in vivo* interaction, it must be assumed that a similar concentration of H_2-receptor antagonist is present in the cytosol of the cell with the gastric ADH. Studies with radiolabelled H_2-receptor antagonists show that some accumulation of this class of drugs does occur in the gastric mucosa /55/. Inhibition *in vitro* is most significant for cimetidine, then ranitidine, and virtually absent for famotidine. The conclusion from these *in vitro* studies was that therapeutic doses of ranitidine and cimetidine should cause significant effects *in vivo*, but that the effect of nizatidine and famotidine would be negligible /56/. Recent studies with gastric mucosal cells in culture have confirmed that alcohol metabolism can occur but this *in vitro* model is much removed from the *in vivo* situation. In this study, there was a 59% reduction in gastric ADH activity by cimetidine but no inhibition by ranitidine. Famotidine and nizatidine were not tested /58/.

5. CLINICAL STUDIES

5.1 Study design

The interpretation of the volunteer studies is crucial to the debate. If there is no clear mechanism for the proposed interaction then only carefully conducted studies in controlled environments will answer the question. The issue of gastric metabolism and decreased first pass metabolism clouds the debate. Some investigators have stated that only studies that perform intravenous dosing as well as oral dosing are relevant. In fact, if the mechanism of the proposed interaction is unclear, then the only real issue at stake is whether peak alcohol concentrations change with concurrent use of H_2-antaganist, and if so, is there any impairment of pyschomotor performance. Some investigators have excluded subjects who do not demonstrate any significant first pass metabolism. Such a protocol is based on an *assumption* regarding the mechanism of drug interaction with alcohol (which may be flawed). Given the data on variability of oral absorption, the observed first pass metabolism calculated from dosing

TABLE 1

A summary of all studies of H_2-antagonists and alcohol sorted by the dose of alcohol given

Ref	Dose	Meal	Trial type	Time	Drug	(n)	Control	Treated	Sig
Brown[59]	0.15	Fed	S	MD	Ranitidine	29	10.0	21.0	p = 0.03
	0.15	Fed	S	MD	Ranitidine	6	7.0	16.9	NS (p=0.06)
Burnham[60]	0.15	Fed	XO	M	Famotidine	24	7.5	9.2	p < 0.01
Bye[31]	0.15	Fed	XO	M	Ranitidine	24	13.3	15.9	p < 0.03
Caballeria[62]	0.15	Fed	S	M	Cimetidine	6	≈6.4	≈10.0	NA
Clemmesen[63]	0.15	Fast	S	?	Cimetidine	6M	15.2	15.2	NS
						6F	19.8	23.5	NS
Cook[64]	0.15	Fast	PG	M	Cimetidine				
					Social	5	17.2	20.4	NS
					Heavy	6	16.9	28.7	NS
Fraser[65]	0.15	Fed	XO	E	Ranitidine	20	4.92	6.47	p<0.05
Palmer[66]	0.15	Fed	XO		Ranitidine				
				M	Breakfast	24	8.2	12.1	p<0.0003
				E	Dinner	23	9.8	10.6	NS
	0.15	Fed	XO	E	Cimetidine	23	9.8	8.8	NS
	0.15	Fed	XO	M	Nizatidine	24	8.3	12.8	p < 0.0005
Gupta[67]	0.15* (x4 over 135mins)	Fed	S	M	Cimetidine	20	27	39	p < 0.01

TABLE 1 cont.

Amin[68]	0.3	Fed	S	E	Ranitidine	8	22	29	p < 0.02
Bye[61]	0.3	Fed	XO	M	Ranitidine	24	33.8	33.0	NS
Casini[69]	0.3	Fed	S	MD	Ranitidine	8	21.2	24.4	NS
					Famotidine	8	18.4	19.8	NS
Di Padova[70]	0.3	Fed	S	M	Ranitidine	8	32	42	p < 0.1
			S	M	Cimetidine	6	30	57	p < 0.1
Fraser[71]	0.3	Fed	PG	E	Ranitidine	12	25.4	25.0	NS
			PG	E	Cimetidine	12	22.7	23.4	NS
			PG	E	Famotidine	12	26.0	23.5	NS
Fraser[72]	0.3	Fed	XO	M	Ranitidine	20	18	21	NS
Holtzmann[73]	≈0.3	Fast	PG	?	Cimetidine	6	≈33	≈32	NS
					Famotidine	6	≈35	≈35	NS
Mallat[37]	0.3	Fed	XO	M	Ranitidine	12	30	30	NS
					Cimetidine	12	30	27	NS
					Famotidine	12	30	30	NS
Raufmann[74]	0.3	Fed	XO	M	Ranitidine	23	13.5	14.1	NS
					Cimetidine	23	13.5	14	NS
Sharma[75]	0.3	Fed	S	E	Cimetidine	11	19.8	27.1	p < 0.05
Teyssen[76]	≈0.3	Fast	XO	E	Famotidine	10	≈19	≈20	NS

TABLE 1 cont.

Ref	Dose	Meal	Trial type	Time	Drug	(n)	Control	Treated	Sig
Brown[77]	0.6 (x3 over 60 min)	Fed	XO	E	Ranitidine	23	33.1	30.1	NS
					Cimetidine	23	33.1	35.2	NS
Bode[61]	0.6	Fed	XO	M	Ranitidine	24	86.6	87.7	NS
Clemmesen[63]	0.45	Fast	S	?	Cimetidine	6M	53.0	54.0	NS
						6F	58.1	53.0	NS
Dauncey[78]	≈0.5	Fed	XO	M	Ranitidine	10	57	49	NS
		Fast	XO	M	Ranitidine	10	57	59	NS
Fraser[79]	0.6	Fed	XO	E	Ranitidine	24	53.8	57.9	NS
Kleine[80]	0.5	Fed	XO	E	Ranitidine 150mg bd	16	15.3	14	NS
					300mg bd	16	15.3	15.5	NS
Toon[81]	0.5	Fed	XO		Ranitidine				
				M	Breakfast	18	43.7	46.4	NS
				MD	Lunch	18	45.4	48.7	NS
				E	Dinner	18	41.3	43.8	NS
		Fast	XO		Ranitidine				
				M	Breakfast	18	80.8	76.4	NS
				MD	Lunch	18	74.6	69	NS
				E	Dinner	18	59.1	64.1	NS

TABLE 1 cont.

Dobrilla[82]	0.8	Fast	XO		Ranitidine	6	≈80	≈74	NS		
					Cimetidine	6	≈80	≈60	NS		
Feely[83]	0.8	Fast	XO	M	Cimetidine	6	146	163	$p < 0.05$		
Fraser[84]	0.8	Fed	PG	E	Ranitidine	16	87	87	NS		
					Cimetidine	16	87	88	NS		
					Famotidine	16	87	84	NS		
Guram[85]	0.75	Fed	XO	E	Ranitidine	6	76	81	NS		
					Cimetidine	6	76	100	$p < 0.002$		
					Famotidine	6	76	75.9	NS		
					Nizatidine	6	76	90.3	$p < 0.02$		
Jonsson[86]	0.8	Fast	XO	M	Ranitidine	12	105.0	103.2	NS		
					Cimetidine	12	105.0	100.9	NS		
Kenda[87]	≈0.7*	Fed	XO	MD	Ranitidine	24	52.9	54.7	NS		
					Cimetidine	24	52.9	53.1	NS		
					Famotidine	24	52.9	56.3	NS		
Seitz[88]	0.80	Fed	XO	M	Ranitidine	8	73	75.5	NS		
					Cimetidine	8	73	86	$p < 0.02$		
Tanaka[89]	0.80	Fast	XO	M	Ranitidine	6	112	110	NS		
					Cimetidine	6	112	111	NS		
Webster[90]	0.7	Fast	XO	M	Ranitidine	7	116	148	$p < 0.05$		
					Cimetidine	7	116	136	$p < 0.05$		

TABLE 1 cont.

Ref	Dose	Meal	Trial type	Time	Drug	(n)	Control	Treated	Sig
Norpoth[91]	1.4	Fast	XO	M	Ranitidine	12	NA	NA	NS
					Cimetidine	12	NA	NA	NS
Johnson[92]	1.5	Fed	S	E	Cimetidine	8	110	110	NS

≈ blood alcohol concentration derived from figure
≈ dose of alcohol was fixed and not given per weight (estimated for 70 kg person)

XO = crossover
S = sequential (individuals baseline alcohol study compared with a second study after drug treatment)
PG = parellel groups (including placebo study)

M = morning dosing, MD = midday, E = evening

Casini /69/ studied duodenal ulcer patients without *H. pylori*. Brown /59/ studied patients with dyspepsia; Holtzmann /73/ studied volunteers after 3 weeks of regular alcohol intake

on two different days could be non-reproducible data. It is important to randomise *after* any selection process to avoid any order effect and "regression to the mean" effects. It is questionable to exclude any volunteers if these studies are to be applied to the population as a whole.

5.2 Higher dose studies (0.5-1.5 g/kg of alcohol)

The complete list of clinical studies is given in Table 1 /59-92/. The data for high-dose studies (0.5-1.5 g/kg of ethanol) are easier to consider as there is a clear negative conclusion despite the variety of study designs. The great majority of studies assessing the effects of ranitidine, cimetidine and famotidine on high-dose ethanol absorption do not show any interaction. One study with ranitidine /90/, four studies with cimetidine /83,85,88,90/ and one study with nizatidine /85/ have reported an increase in blood alcohol concentration. These positive studies have been with small numbers of subjects. All studies with larger numbers (greater than 15 subjects) have been negative. Two of the positive studies had very high blood alcohol concentrations (one study used breathanalysers to measure alcohol concentration /90/) which are above the maximum concentration that could be achieved with the dose of alcohol given assuming complete absorption /83,90/. These studies must therefore be considered suspect.

5.3 Low dose studies (0.15-0.3 g/kg of alcohol)

The data suggesting a decreasing first pass metabolism with increasing doses of alcohol would imply that if there was a significant interaction involving H_2-receptor antagonists, this would occur at low doses of alcohol /93/. A significant interaction between H_2-receptor antagonists and low-dose alcohol (0.15 g/kg) given after breakfast was first reported by Caballeria *et al.* /62/. The mean peak blood ethanol concentration increased from 6 mg/dl to 10 mg/dl. Three studies from the same centre with ethanol 0.3 g/kg also showed an increase in blood alcohol concentrations after cimetidine and ranitidine /68,70, 75/. Several other centres have attempted to confirm these results and almost all studies have shown no effect of H_2-antagonists on ethanol given at a dose of 0.3 g/kg (with either identical protocols or varying situations). It is difficult to explain the discrepancy in these results. The concentration and type of alcohol may be important. Lieber and

colleagues have always given alcohol as a 10% v/v solution, stating that alcohol given in lower concentrations may not show the effect. However most studies that have been negative have used a similar protocol. The obvious conclusion is that there is no effect at a dose of 0.3 g/kg of alcohol.

The data would appear to be different at the very low dose of 0.15 g/kg of alcohol. Seven studies at 0.15 g/kg of ethanol have shown a statistically significant effect but the magnitude of the effect on peak ethanol concentrations is so small as to be insignificant. Positive studies have been reported for ranitidine /59,61,65,66/, cimetidine /62,67/, famotidine /60/ and nizatidine /66/. This does not seem to correlate with the data from *in vitro* studies of the inhibition of ADH which show significant inhibition for cimetidine only.

Some authors have suggested that the conflicting data are because studies have been performed at different times of the day. Palmer, dosing with 0.15 g/kg of alcohol, found positive results for ranitidine and nizatidine in the morning but negative results for ranitidine and cimetidine when dosing in the evening /66/. Several centres have conducted studies at varying times of day and have not demonstrated any effect of the time of dosing /71,72,75,81/. This question was specifically addressed in a well-designed double-blind, two-way crossover study. Eighteen normal male subjects, who were dosed with ranitidine 300 mg q.i.d. or placebo q.i.d., took ethanol 0.5 g/kg orally one hour after breakfast, lunch or the evening meal on three separate study days. No treatment effect was observed /81/. Despite this convincing negative study using 0.5 g/kg of alcohol, it remains possible that a diurnal variation exists for dosing with 0.15 g/kg of alcohol.

A study of four doses of 0.15 g/kg of alcohol taken over a total period of 135 minutes did show a significant elevation of blood alcohol concentrations after dosing with cimetidine. The mean increase was 11 mg/dl but did demonstrate that this effect could be cumulative with multiple dosing /67/. Further studies in this area are required.

6. PSYCHOMOTOR PERFORMANCE

An important medico-legal issue is the possibility that co-administration of ethanol and H_2-receptor antagonists may cause a

person to be unexpectantly over the legal drinking limits, or equally important, over the blood ethanol concentration at which significant impairment of psychomotor function (and consequently driving skills) may occur. The majority of evidence supports no interaction at doses that would be expected to impair psychomotor skills (above 25 mg/dl) /94/.

It is doubtful whether tests of psychomotor performance are able to distinguish changes resulting from small increments in blood alcohol concentrations /95/. A study of the effect of a meal prior to taking alcohol on 0.15 g/kg alcohol showed no difference between fed and fasted subjects - mean difference in blood alcohol concentration was 7-8 mg/dl which is more than that observed in the H_2-antagonist studies /96/. Nizatidine has been studied alone and with 0.5 g/kg alcohol. There was no change in a wide range of psychometric variables /97/. High-dose ranitidine 300 mg q.i.d. produced no changes in psychomotor tests after 0.5 g/kg alcohol given in the morning, midday or evening in both fasted and fed subjects. Tests included a line analogue rating scale to assess alertness, digit symbol substitution and a visual search task /81/.

It is important to remember that the peak blood alcohol level for a given individual on a given day cannot be predicted because of the great inter- and intra-individual variability of alcohol absorption and metabolism. Therefore if excellent psychomotor skills are important then one should not take any alcohol!

7. WHAT IS THE EXPLANATION FOR THE POSITIVE STUDIES AT 0.15 g/kg OF ALCOHOL

The relationship between ethanol absorption and gastric emptying raises the possibility that the effects of H_2-receptor antagonists observed at very low doses of alcohol may be due to the acceleration of gastric emptying by these drugs /14,29/. Studies of the effect of H_2-receptor antagonists on gastric emptying of liquid or solid meals have given conflicted results, perhaps dependent on the different methodologies used and variation in the content of meals /98-101/. Cimetidine and ranitidine have been shown to both increase and decrease the rate of gastric emptying. It is interesting to note that the centre which has been the main protagonist for gastric metabolism of ethanol and the effects of cimetidine and ranitidine has now published data showing

that the observed increase in blood ethanol concentration after ranitidine is due to an increase in gastric emptying /68/.

Ethanol may have a variable effect on gastric emptying dependent on intraluminal ethanol concentration and the pH, osmolarity or volume of gastric juice. These are all factors which may be influenced by anti-secretory treatment. However, an argument against the influence of the anti-secretory action of H_2-antagonists is the absence of any effect of proton pump inhibitors on alcohol pharmacokinetics /102-107/. An alternative explanation may be changes in hepatic blood flow and/or efficacy of liver ADH activity.

8. CONCLUSION

The conclusion from dosing studies with volunteers is clear. There is a small effect of H_2-antagonists at the small dose of 0.15 g/kg alcohol. The absolute change in peak levels is very small and would not be expected to cause any additional effect on psychomotor performance. The magnitude of the effect is far less than the effect of taking a meal before alcohol or, indeed, the effect of the type of meal /2,11/. There is no easy explanation for the discrepancy between studies at the higher dose of 0.3 g/kg alcohol. It is prudent to accept that the majority of studies show no effect. At the higher doses there are a few small studies that have shown an effect but larger well conducted studies have shown no effect. There remains a question regarding the cumulative effect of repeated small doses of alcohol which needs further study. This area is the subject of much debate and varying views have been expressed in some summaries of this issue /108-112/.

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