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SHORT COMMUNICATION

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The effects of acute ethanol intake on isoniazid pharmacokinetics

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Abstract *Aim*: To assess effects of acute ethanol intake on the pharmacokinetics of isoniazid in healthy male volunteers.
Methods: Sixteen healthy male, drug-free subjects were studied. Each received in the fasting state, on two occasions separated by at least 1 week, isoniazid (200 mg orally). On one occasion (assigned randomly), subjects received ethanol 0.73 g/kg, 1 h before isoniazid, followed by 0.11 g/kg ethanol orally every hour thereafter for 7 h. Plasma isoniazid and acetylisoniazid concentrations were measured by means of high-performance liquid chromatography. Blood ethanol concentrations were measured hourly by breath analysis. Plasma concentrations of isoniazid and acetylisoniazid were analysed using TOPFIT software.
Results: Peak concentrations of isoniazid were reached within 90 min, in both the ethanol-treated and control groups. The ethanol dosage regimen used resulted in peak blood ethanol concentrations between 78 mg/l and 103 mg/l. There was no significant difference in area under the curve, half-life of elimination or the ratio of acetylisoniazid to isoniazid (AcINH/INH) in the sample withdrawn 3 h after isoniazid dose. Acetylator phenotype for patients was the same in both phases, whether assessed by half-life of isoniazid or the AcINH/INH ratio at 3 h.
Conclusions: Acute ethanol intake at this dose is unlikely to affect results of acetylation studies in which isoniazid is used as a substrate, whether the half-life of isoniazid or the AcINH /INH ratio at 3 h is used to phenotype patients.

Keywords Isoniazid · Ethanol · Acetylator status · Acetylation · Pharmacokinetics · Drug interaction

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Introduction

The rate at which an individual acetylates a drug is bimodally distributed, with subjects being classified as either slow or fast acetylators. From a clinical point of view, this polymorphism is of great importance with respect to adverse reactions and therapeutic effects. In general, at any given dose, the occurrence of adverse reactions to polymorphically acetylated drugs is greater in slow acetylators whilst therapeutic effects may be sub-optimal in rapid acetylators when they are taking dosages appropriate for slow acetylators [1]. For this reason, acetylation phenotyping has often been used as a predictor of toxicity or of dose requirement [2].

Many complex factors are known to interfere with the ability to measure reliably the acetylating capacity of an individual. For example, sulphamethazine and procainamide clearance by non-renal routes is enhanced by acute administration of ethanol in man [3–5]. In some slow acetylators, the extent of acetylation measured in blood increased so much that they would have been misclassified as rapid acetylators, according to conventional criteria [5]. Since both these drugs are acetylated, we investigated the effects of acute ethanol administration in volunteers receiving isoniazid (INH), which is also acetylated in man. This compound is of particular interest in that it is widely used to examine acetylator status [6] and has several advantages over other substrates used for this purpose [7–9]. Furthermore, a single sample (plasma or saliva) INH test has proven to be as reliable as the conventional tests whilst being less invasive [10–12].

Methods

Subjects

Sixteen healthy male volunteers with a mean age of 22 years (range 18–31 years), mean body weight of 83 kg (range 61–150 kg) and a mean height of 183 cm (range 173–192 cm) were included in the study. All subjects had standard haematological values within the normal range. Only subjects who were considered moderate social alcohol drinkers (less than 20 units per week) were selected. Exclusion criteria included anyone taking medication 1 week prior to the trial and anyone with a drug allergy or impaired kidney or liver function. Women of child-bearing potential were also excluded due to the potential teratogenic effects of INH. Subjects abstained from alcohol 24 h prior to each experimental session.

Study protocol

The South East Wales Local Research Ethics Committee approved the study protocol, and written informed consent was obtained from all subjects. The study was performed according to a randomised, un-blinded, two-way crossover design and was conducted on two occasions separated by at least 1 week. Subjects were assigned randomly to receive either ethanol or act as controls. Following an overnight fast, each patient received a single oral dose of 200 mg INH. Ethanol-treated subjects were given a loading dose (0.73 g/kg) of ethanol (vodka and orange juice 50:50 v/v) 1 h before INH, followed by a maintenance dose (0.11 g/kg) of ethanol orally every hour thereafter for 7 h. The control group received an equivalent volume of orange juice, at the same time interval as the alcohol regime. A 7-day washout period was allowed, and the experiment was repeated with the ethanol-treated and control groups being reversed. In this way, each subject acted as his own control.

Sample collection and analysis

Venous blood was collected via an indwelling cannula inserted into a forearm vein. Blood samples were drawn at 0, 15, 30, 45, 60, 90 min and thereafter at 2, 3, 4, 5, 6, 7 h post-dose into lithium heparin tubes. Plasma was separated by centrifugation and stored at −70°C until analysis, to avoid breakdown of INH or acetylisoniazid (AcINH) [13].

Blood ethanol concentrations were measured hourly by breath analysis, using a hand-held alcolmeter (Lion Laboratories, Cardiff, UK). INH and AcINH were measured in plasma by means of high-performance liquid chromatography [14].

Pharmacokinetic analysis

Plasma concentrations of INH and AcINH were analysed using TOPFIT software. The following pharmacokinetic parameters were estimated: terminal half-life ($t_{1/2}$), area under the concentration curve (AUC), apparent oral clearance (CL/F), maximum INH concentration measured (C_{max}), time taken to reach C_{max} (t_{max}) and apparent volume of distribution (V_d).

Acetylator phenotyping using the ratio of acetylisoniazid to isoniazid (AcINH/INH) in the plasma sample at 3 h, with 1.5 as the antimode, has been shown to be just as reliable as using the half-life method [12]. In this study, acetylator phenotype was determined from both the half-life of INH and by the AcINH/INH ratio in the plasma sample at 3 h.

Statistical analysis

Pharmacokinetic parameters for the two phases of the study were compared using Wilcoxson's paired rank test and a P value < 0.05 was set as the minimum level of significance. All results are given as mean ± SD.

Results

Pharmacokinetics of INH in slow and rapid acetylators

Of the 16 subjects studied, 9 had an INH half-life of less than 130 min and were thus classified as rapid acetylators. All these subjects, had AcINH/INH ratios greater than 1.5 in their 3-h plasma sample. In the remaining 7 subjects, INH half-life was greater than 130 min and were classified as slow acetylators. These subjects had AcINH/INH ratios less than 1.5 in the 3-h plasma sample.

Ethanol effect on INH pharmacokinetics

Peak serum concentrations of INH were reached within 90 min, in both the ethanol-treated and control groups. The ethanol dosage regimen used resulted in peak blood ethanol concentrations between 78 mg /l and 103 mg /l. Ethanol was not detected in the blood of any subject during the control phase. Individual serum concentrations of INH in the seven slow and nine rapid acetylators declined gradually in accordance with first-order elimination kinetics, in both the absence and presence of ethanol, over the course of the experiment. Pharmacokinetic values for the ethanol and control phases for slow and fast acetylators are shown in Table 1. There was no significant difference in AUC, $t_{1/2}$ or the AcINH/INH ratio in the sample withdrawn 3 h after the INH dose, for either the slow or the fast acetylators.

More importantly, ethanol did not induce a change in the acetylator phenotype in any of the volunteers, whether this was assessed by the half-life of INH or by the AcINH/INH ratio in the 3-h sample (Figure 1).

Table 1 Pharmacokinetics of isoniazid (INH) in control and ethanol-treated groups

	Control	After ethanol
$t_{1/2}$ (min)		
All subjects	164 ± 97	148 ± 72 (NS)
Slow acetylators	217 ± 115	187 ± 82 (NS)
Fast acetylators	123 ± 58	119 ± 49 (NS)
AcINH/INH ratio		
All subjects	3.23 ± 3.01	3.02 ± 2.37 (NS)
Slow acetylators	0.77 ± 0.37	0.66 ± 0.31 (NS)
Fast acetylators	4.99 ± 3.02	4.6 ± 1.68 (NS)
AUC $(INH)_{0-\infty}$ (mg min/l)		
All subjects	328 ± 176	382 ± 219 (NS)
Slow acetylators	709 ± 376	683 ± 354 (NS)
Fast acetylators	240 ± 108	292 ± 165 (NS)
Apparent oral clearance (ml/min)		
All subjects	653 ± 420	523 ± 356 (NS)
Slow acetylators	550 ± 317	469 ± 427 (NS)
Fast acetylators	733 ± 489	565 ± 310 (NS)
C_{max} (mg/l)		
All subjects	1.90 ± 1.02	2.66 ± 1.39 (NS)
Slow acetylators	2.5 ± 1.22	2.89 ± 1.48 (NS)
Fast acetylators	1.44 ± 0.55	1.98 ± 1.38 (NS)
t_{max} (min)		
All subjects	47.8 ± 22.7	46.3 ± 38.3 (NS)
Slow acetylators	36.4 ± 11.8	40.7 ± 7.32 (NS)
Fast acetylators	56.7 ± 25.7	50.6 ± 51.6 (NS)
Vd (l)		
All subjects	115 ± 34.1	104 ± 58.9 (NS)
Slow acetylators	104 ± 37.0	98.8 ± 83.0 (NS)
Fast acetylators	125 ± 30.7	108 ± 35.9 (NS)

NS not statistically significant ($P < 0.05$)

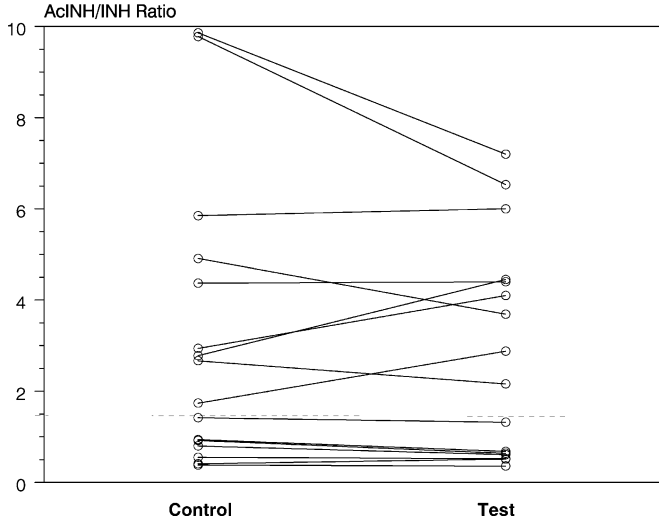

Fig. 1 Effect of ethanol administration on acetylisoniazid/isoniazid (AcINH/INH) ratio in the 3-h plasma sample. The value of 1.5 was taken as the antimode (*broken lines*)

Discussion

The enzyme, *N*-acetyltransferase, which catalyses drug acetylation, requires acetyl-coA as a co-substrate [15]. Acetylation of sulfadimidine and procainamide has been shown to be increased by ethanol administration. This was attributed to increased formation of acetyl-CoA, originating from acetate production during ethanol metabolism, enhancing *N*-acetyltransferase activity [3, 5]. However, the authors failed to illustrate a clear relationship between ethanol oxidation and drug acetylation, thus making it difficult to explain their conclusion that acute ethanol consumption increases acetylation. Furthermore, the theoretical assumption that an introduction of acetyl groups enhances acetylation has been disproved in another study on sulfadimidine [16].

To our knowledge, the effects of ethanol on INH pharmacokinetics have not previously been fully studied in man. Administration of ethanol (1.5 mg/g and 4 mg/g, i.v.) in mice increased the concentration of AcINH but did not affect the total concentration of INH in blood [17]. Although this has been attributed to ethanol-induced increase in acetylation of INH, the failure to demonstrate a reduction in the parent drug concentration invalidates the author's conclusion. Lester [18] described a 25% reduction in INH half-life in two healthy volunteers after alcohol, but we have been unable to demonstrate any acute effect of ethanol on the pharmacokinetics of INH after oral administration to a larger number of healthy subjects.

Our results are similar to those observed with dapsone in that the ratio of acetylated drug to the parent compound at 3 h after drug administration was not significantly changed by the administration of ethanol [19].

Conclusion

We conclude that acute ethanol intake at this dose is unlikely to affect results of acetylation studies in which INH is used as a substrate, whether the half-life of INH or the AcINH/INH ratio at 3 h is used to phenotype patients. However, any possible effects of higher acute ethanol dosing than that used in this study or of chronic alcohol intake on INH pharmacokinetics cannot be excluded by this study.

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