4-Methylpyrazole and the Cutaneous Vascular Sensitivity to Alcohol in Orientals

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Twelve healthy subjects of Oriental ancestry were challenged with topical applications of lower aliphatic alcohols and aldehydes after topical pretreatment consisting of 4-methylpyrazole in hydrophilic ointment on the volar aspect of one forearm and hydrophilic ointment alone on the contralateral volar forearm. Cutaneous blood flow was monitored by laser Doppler velocimetry. Pretreatment with 4-methylpyrazole, a specific inhibitor of alcohol dehydrogenase, led to a significant decrease in the cutaneous vascular response to the alcohols as a group, but did not lead to changes in the cutaneous vascular response to the aldehydes as a group. Among the individual alcohols, pretreatment with 4-methylpyrazole reduced the response significantly to all concentrations of 1-propanol and 1-butanol. The means of the vascular response to the different concentrations of ethanol decreased, but not significantly. Additionally, 4-methylpyrazole did not have an independent effect on cutaneous blood flow. These results are consistent with the view that the cutaneous vascular reaction to primary alcohols applied topically to the skin of Orientals is provoked, in large part, by the corresponding aldehyde. J Invest Dermatol 91:117–119, 1988

Diverse Mongoloid populations share an enhanced vascular sensitivity to ethanol. Systemic administration of ethanol leads to a generalized cutaneous erythema (flush) in a substantial number of Orientals [1]. Some Orientals demonstrate a contact urticaria to primary alcohols and aldehydes [2]. Orientals who flush after oral alcohol are more likely to have cutaneous erythema after topical ethanol or propanol [3]. Additionally, the frequency of erythogenesis for lower aliphatic primary alcohols correlates strongly and significantly with the rate of substrate utilization by alcohol dehydrogenase [4].

Because the results of these studies are consistent with the view that the reaction to primary alcohols applied topically to human skin is provoked, in large part, by the corresponding aldehyde, the availability of an effective in vivo inhibitor of alcohol metabolism provides a pharmacologic tool which can separate the direct effects of primary alcohols from those associated with their cognate aldehydes [5]. Because the conversion of the primary aliphatic alcohol to the cognate aldehyde may be necessary for the provoked increase in cutaneous blood flow, I examined the vascular responses to three each of lower aliphatic primary alcohols and aldehydes in 12 Oriental subjects after pretreatment with the potent and specific inhibitor of alcohol dehydrogenase, 4-methylpyrazole.

MATERIALS AND METHODS

Human Subjects Twelve healthy subjects of Oriental ancestry, 4 men and 8 women, ages 21–34 years, consisting of students, faculty, laboratory technicians, and their spouses, participated in a study approved by the local institutional review board. Either both parents or all grandparents were originally from a single East Asian nationality: Cambodian (2), Korean (3), and Chinese (7). All subjects had been previously characterized as flushers by monitoring ambient, oral, and cutaneous temperatures and by monitoring cutaneous vascular reactivity using laser Doppler velocimetry during a challenge by mouth with 0.4 g/kg of ethanol diluted in sugar-free 7UP to a volume of 300 ml [6].

Reagents The reagents used were Acetaldehyde (99%), propionaldehyde (99%), propanol (99%), and butanol (99%) (Aldrich Chemical Co., Milwaukee, Wisconsin); butyraldehyde (98%) (Eastman Kodak Co., Rochester, New York); and, ethanol (99.9%) (AAPER Alcohol & Chemical Co., Louisville, Kentucky).

Pharmacologic Challenge Patch tests to aqueous solutions of ethanol, 1-propanol, 1-butanol, acetaldehyde, propionaldehyde, and butyraldehyde were performed after pretreatment of one forearm with 1% 4-methylpyrazole (4MP) in hydrophilic ointment and the other forearm with hydrophilic ointment alone (control) 1 h before the patch test challenges. Primary alcohols were tested in concentrations of 1, 3, and 10M. Aldehydes were tested in concentrations of 0.15, 0.5, 1.5, and 5M. The three concentrations of alcohols, the four concentrations of aldehydes, and water alone were tested in duplicate on each forearm. Volumes of 25 μl of the solutions tested saturated coarse porosity, quantitative, ashless grade filter paper squares (1.23 cm²) placed on the volar forearms. The patches were covered with Parafilm M for 5 min and then removed. The area was gently blotted and the laser Doppler velocimeter (7–10) (LD 5000 MedPacific, Inc., Seattle, WA) probe was attached to the test site and cutaneous blood flow was monitored continuously for 5 min. The ambient temperature varied on different days from 21.0 to 23.9°C, but never varied more than 1.0°C during the observation period for a single subject.

Data Analysis Global analyses of the data were performed with the general linear model (GLM) of the statistical analysis system (SAS) package [11]. All variations in numerical data and error bars in the figures represent standard errors of the mean.
RESULTS

In a preliminary analysis of raw data at the control level (the challenge to water alone), the mean erythrocyte flux for skin pretreated with hydrophilic ointment alone (control) was 25.33 ± 1.80 mV. Pretreatment with hydrophilic ointment containing 4-methylpyrazole gave a mean value of 23.94 ± 1.74 mV. Because results with 4-methylpyrazole did not differ significantly from those with vehicle alone, mean adjusted erythrocyte flux values reduce intersubject variability.

Results presented in Figs 1 and 2 are mean adjusted erythrocyte flux values. Over all concentrations and as a group, the aldehydes’ effect on cutaneous erythrocyte flux did not differ after pretreatment with 4-methylpyrazole. Over all concentrations the group of alcohols’ effect on the cutaneous erythrocyte flux was significantly lower after pretreatment with 4-methylpyrazole (p < 0.01 for each concentration of alcohol). None of the individual aldehydes (acetaldehyde, propionaldehyde, and butyraldehyde) demonstrated differences in cutaneous erythrocyte flux after pretreatment with 4-methylpyrazole. Although the means of the vascular response to the different concentrations of ethanol decreased, they were not statistically significant. However, the increases in cutaneous erythrocyte flux provoked by 1-propanol and 1-butanol were significantly lower after pretreatment with 4-methylpyrazole (p < 0.05 for each concentration of butanol; and, p < 0.05 for each concentration of 1-propanol). Additionally, there was a dose effect for all the groups, indicating that the dose-response curve is not flat, but that a positive slope is obtained.

DISCUSSION

Except for comments on pretreatment effects on unstimulated cutaneous blood flow, all subsequent results are adjusted values, i.e., flow rate at a specified alcohol or aldehyde level minus flow rate at the test site to water alone. The use of adjusted data is desirable because it imposes a more conservative interpretation of the data. Because pretreatment with 4-methylpyrazole was followed by a lower, although not statistically significant, unstimulated cutaneous erythrocyte flux, raw data will include this effect. It is more rigorous to look for a pretreatment effect after subtracting out the effect of 4-methylpyrazole on a baseline cutaneous erythrocyte flux. Further, the subtraction of each subject’s response to water from the response to nonzero levels of alcohols and aldehydes would reduce any intersubject variability in unstimulated erythrocyte flux.

The cutaneous vascular responses to alcohols as a group and to 1-propanol and 1-butanol, individually, are significantly suppressed after pretreatment with 4-methylpyrazole. In contrast, 4-methylpyrazole pretreatment did not affect the measured cutaneous vascular response to aldehydes as a group or individually, and there was no independent effect of 4-methylpyrazole on cutaneous vascular activity. Because primary alcohols are converted to aldehydes by cutaneous alcohol dehydrogenase [4], it is likely that the inhibitory effect of 4-methylpyrazole on primary alcohols results from the competitive inhibition of cutaneous alcohol dehydrogenase by 4-methylpyrazole.

Pyrazole is an inhibitor of liver alcohol dehydrogenase [12]. Ethanol oxidation is inhibited for prolonged periods after administration of a single dose of pyrazole [13]. Pyrazole forms a ternary complex with alcohol dehydrogenase and nicotinamide-adenine dinucleotide with pyrazole occupying the ethanol binding site [14].

Various 4-substituted pyrazoles inhibit ethanol oxidation in vivo, whereas substitution at other than the 4-position results in loss of the inhibitory effect [14,15]. Repeated oral administration of 4-methylpyrazole to rats is well tolerated in doses which inhibit the alcohol dehydrogenase activity. This is in contrast to the unsubstituted pyrazole, which in equimolar doses causes severe toxicity. Because the 4-methylpyrazole is several times more potent than pyrazole, it has been the compound of choice for pharmacological and metabolic studies of inhibition of ethanol metabolism [16].

As a competitive inhibitor of liver alcohol dehydrogenase, 4-methylpyrazole reduces a variety of ethanol-induced metabolic disturbances [5,12]. 4-Methylpyrazole has been used in the treatment of male alcoholics with the disulfiram-alcohol reaction, and one dose of 4-methylpyrazole has been recommended as sufficient for acute treatment of the disulfiram-alcohol reaction [13]. 4-Methylpyrazole has also been used successfully in the treatment of experimental methanol and ethylene glycol poisoning [17,18].

Not only does 4-methylpyrazole competitively inhibit alcohol dehydrogenase, but it may also have other unrelated pharmacologic effects [5]. Accordingly, it was important in this study to first determine that 4-methylpyrazole did not have an independent effect on cutaneous erythrocyte flux. Further, it is important that 4-methylpyrazole did not limit the increase in cutaneous erythrocyte flux provoked by the aldehydes. Thus, the results of this study are consistent with the view that the effect of 4-methylpyrazole in suppressing the increase in cutaneous erythrocyte flux provoked by primary alcohols is related to its competitive inhibition of cutaneous alcohol dehydrogenase activity.

Accordingly, the cutaneous model of the Oriental sensitivity to alcohol is quite congruous with the systemic reaction. Orientals who flush after oral ethanol are more likely to react to topical ethanol and propanol [3]. In healthy Orientals, ethanol-provoked flushing occurs with a conspicuous rise in blood acetaldehyde levels [19]. A significant elevation of blood acetaldehyde does not occur in Orientals who do not flush after consuming ethanol [19].

Furthermore, considerable evidence supports an important role for aldehydes in the cutaneous reaction to primary alcohols in Orientals. First, only primary alcohols, which can be oxidized to the
corresponding aldehyde, and not secondary or tertiary alcohols, will routinely elicit cutaneous erythema [3]. Second, as presented in this paper, the reaction to primary alcohols can be blocked by pretreatment with a potent inhibitor of alcohol dehydrogenase. Third, the reaction to acetaldehyde occurs earlier than the reaction to ethanol, which is compatible with a time lag requisite for conversion of ethanol to acetaldehyde [3]. Fourth, aldehydes routinely provoke cutaneous erythema [3] and, as shown in this study, an increase in cutaneous erythrobotocyte flux. Fifth, the frequency of erythemogenesis among several lower aliphatic primary alcohols correlates strongly and significantly with the rate of substrate utilization by alcohol dehydrogenase [4].

Thus, it is likely that the local and systemic vascular reactions, contact urticaria and erythema and flushing, respectively, to ethanol among Orientals are based on a common mechanism, and that acetaldehyde has a major role. Further, although acetaldehyde condensation products have opiate-like activity, it is unlikely that an opioid-mediated mechanism exists for these vascular responses [20].

REFERENCES

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