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Effects of xylene and alcohol on vestibular and visual functions in man

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SAVOLAINEN K, RIIHIMÄKI V, VAHERI E, LINNOILA M. Effects of xylene and alcohol on vestibular and visual functions in man. Scand j work environ health 6 (1980) 94—103. Ten healthy male volunteers were exposed for 4 h to two concentrations [6 and 11.5 μmol/l (636 and 1,218 mg/m3)] of m-xylene or/and given single doses (0.4 and 0.8 g/kg) of ethyl alcohol. Exposure to two xylene concentrations combined with the higher dose (0.8 g/kg) of alcohol was also conducted. Vestibular functions (positional nystagmus with electronystagmography, body balance) and visual function (flicker fusion) were measured. Both alcohol doses increased body sway and the intensity of nystagmus more than either concentration of xylene did, but they had little effect on visual functions. The effects of alcohol on vestibular functions were dose-dependent. The effects of xylene alone on the vestibular system were rather small, and those on the visual functions negligible. The combined effect of alcohol and the lower concentration of xylene (6 μmol/l) on body sway was additive, but the higher xylene concentration (11.5 μmol/l) antagonized the effect of alcohol on body sway and positional nystagmus. Two subjects experienced nausea and vomited during exposure to alcohol and the higher xylene concentration. Mild impairment in visual functions was noted in the combined exposure. Alcohol significantly increased the blood m-xylene concentrations, a finding that suggests that their antagonism was pharmacodynamic rather than pharmacokinetic.

Key terms: alcohol, interaction, man, vestibular system, visual function, xylene.

Industrial exposure often means simultaneous exposure to a mixture of chemical agents. Many aliphatic and aromatic industrial solvents cause neurotoxic symptoms similar to alcoholic inebriation (8). Inebriation and late sedation by alcohol impair psychophysiological functions (37). Short-term exposure to xylene also disturbs these functions (11, 32, 33). Alcohol causes positional nystagmus by disturbing central oculovestibular pathways (3) or the vestibular apparatus (26). Short-term exposure to industrial solvents, eg, xylene, also causes positional nystagmus, at least in the rabbit (5).

There are several reports of alcohol-drug interaction on psychophysiological functions in man (34), while less attention has been paid to the combined effects of industrial solvents and alcohol. Such interaction might, however, occur during or after workhours and might thus contribute to occupational (18) and traffic accident hazards.

We have studied the effects of xylene and alcohol, both separately and combined, on vestibular and visual functions of volunteers.

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Subjects and methods

Subjects

Ten healthy male students volunteered as subjects. Their mean (± SD) age was 22.8 ± 1.9 a, mean height 178.5 ± 4.3 cm, and mean weight 69.2 ± 7.6 kg.

An informed consent, according to the principles of The Declaration of Helsinki (39), was obtained from every subject. Each subject underwent a medical and neurological examination, including electroencephalography and routine pure-tone audiometry, as well as complete clinical electronystagmography with caloric tests. No abnormal findings were noted. None of the subjects used drugs, and all were social users of alcohol.

Exposure

The exposure to m-xylene (laboratory grade, Merck, Darmstadt) was carried out in an exposure chamber (30) with a controlled dynamic environment.

The subjects were divided into two groups, A and B, of five persons. The exposures were conducted once a week, always on the same day of the week, for nine consecutive weeks. The two groups were exposed on consecutive weekdays (Tuesday and Wednesday). The exposures were single-blind, and the subjects served as their own controls. The order of the experimental days for the two groups was reversed to cloud the effect of sequence (22) and learning.

On each experimental day the subjects arrived at about 0800 for base level tests. Alcoholic or nonalcoholic bitters were administered between 0930 and 1000, after which the subjects entered the exposure chamber and stayed until 1400. A standardized meal was served in the morning prior to exposure and at noon in the chamber.

On all days a small amount of peppermint oil vapor was used to mask the presence or absence of xylene in the chamber air. The subjects were sedentary throughout the day. The sequence of the experimental days and the amount of alcohol given, as well as the measured xylene concentrations, are presented in table 1.

Arrangement of tests

Electronystagmographic (ENG) and psychophysiological investigations were conducted in the morning before the subjects entered the chamber, usually twice in the chamber, and once after they left the chamber. Prior to the study, the subjects practiced the tests until their performance was rather stable. The program of the experimental day, which was always the same, is shown in table 2.

Psychophysiological methods

Body sway was studied with a strain gauge transducer platform (32). Maximal swaying amplitudes were used as a measure of body balance.

Critical flicker fusion (CFF) thresholds were studied with a commercial apparatus (Takei & Co, Ltd). The intensity and the light/dark ratio (1/1) of the rectangular orange stimuli were kept constant. Background illumination and the distance between the flickering light and the eyes was always the same. On every occasion three binocular determinations of the CFF threshold were made. The mean was used as a measure of the cortical visual processes (16), particularly drowsiness and sedation (14). The frequency of the light impulses was automatically increased from an initial value of 10 Hz.

| Day | Xylene (g/kg) | Alcohol (g/kg) |
|-----|---------------|----------------|
| 1   | Control       | Control        |
| 2   | 7.7 (816)     | Control        |
| 3   | 5.9 (626)     | 0.4            |
| 4   | 5.9 (626)     | 0.8            |
| 5   | Control       | Control        |
| 6   |               | 0.8            |
| 7   | 10.7 (1,135)  | 11.5 (1,218)   |
| 8   | 11.9 (1,261)  | 11.9 (1,261)   |
| 9   | Control       | Control        |

Table 1. Exposure schedule — The xylene concentrations are the time-weighted average concentrations of xylene in the chamber air during the different exposures of group A and B. The order of exposure for group A was from 1 through 9; for group B the order was reversed (from 9 through 1). Xylene concentrations in g/mol/l, with the equivalent in mg/m³ in parentheses, are presented.
Table 2. Experimental program — The program of each experimental day was similar, and the days differed from each other only in regard to the exposure.

| Time of day | Procedure |
|-------------|-----------|
| 0800—0930   | All tests and electronystagmography (ENG) were performed as a control prior to entering the chamber. A blood sample was drawn. |
| 0930--1000  | Placebo or alcoholic bitter was served. |
| 1000        | The subjects entered the chamber. |
| 1020        | Lateral gaze nystagmus and Maddox wing test |
| 1035        | Body sway |
| 1100        | Blood sample |
| 1150        | Critical flicker fusion (CFF) and questionnaire |
| 1200        | ENG and blood sample |
| 1220        | Lateral gaze nystagmus and Maddox wing test |
| 1235        | Body sway |
| 1300        | Blood sample |
| 1350        | CFF and questionnaire |
| 1400        | The subjects left the chamber. All the different tests and ENG were performed. |
| 1500        | Blood sample |

Extraocular muscle balance was studied by means of the Maddox wing test, which indicates the relative position of the eyes directly in prism diopters (15).

Gaze deviation nystagmus was measured with a simple nystagmometer (21). The nystagmus sign was considered positive if it lasted for more than 10 s and appeared in a deviation angle of less than 50° from the visual axis. A questionnaire was used to assess the subjective feelings and symptoms caused by the exposure.

Electronystagmography

Nystagmus was recorded only three times a day (table 2) because of various other test recordings; thus the eventual duration of alcohol or xylene nystagmus could not be determined. The ENG recordings were performed by means of a direct-writing three-channel Elema Mingograph 34 AC-Recorder. The time constant was 5 s and the paper speed 5 mm/s. Electrodes were placed near the lateral canthus of each eye and above and below the left eye. A ground electrode was placed on the forehead. During all the recordings the subject lay in a supine position in the chamber, the recording apparatus being outside the chamber. On all days recordings were taken of two to five subjects.

Spontaneous nystagmus with the eyes closed and with the eyes open in darkness
was recorded first. Calibration (10°) and fixation, as well as gaze deviation nystagmus forwards and 30° to each side, were recorded next. Positional nystagmus was recorded in the left and right lateral head positions and in both side positions with the subject’s eyes open in darkness. The entire procedure lasted about 7 min.

Pharmacokinetics

Venous blood samples were drawn for xylene and alcohol analysis from an antecubital vein prior to the exposure, during the exposure, and after the subjects left the chamber (table 2).

m-Xylene concentrations were analyzed with gas chromatography by the headspace method (28); the analytical details have been reported elsewhere (29).

Alcohol concentrations were analyzed with gas chromatography (24) and by the alcohol dehydrogenase method (7); the mean of the concentrations was used as a measure of the blood alcohol concentration (BAC).3

Statistics

The Student’s t-test (two-tailed) of paired observations was used to compare the average changes of performance in the different psychophysiological tests between exposure and nonexposure (control) situations. The average changes were calculated separately for each test performance, the morning value being used as a reference. The measures of each performance on the three nonexposure days were combined into one, and the means were used as control values (tables 1 and 2). For statistical calculations groups A and B were combined with N = 10.

Results

Body sway

Maximal body sway with the eyes open diminished in the anteroposterior, but not in the lateral, axis at noon during exposure to a xylene concentration of 6 μmol/l (636 mg/m³), as contrasted to the corresponding change on the nonexposure days (fig 1). After exposure the maximums increased in the anteroposterior axis with the eyes closed, probably indicating a mild deleterious aftereffect (fig 2). Alcohol increased the maximal body sway dose-dependently (fig 2). Exposure to a xylene concentration of 11.5 μmol/l (1,218 mg/m³), which raised the blood xylene con-

3 Courtesy of R Lindbohm, MSc, Central Public Health Laboratory, Alcohol Unit, Helsinki Finland.
Table 3. Venous blood m-xylene concentrations ($\mu$mol/l) on different experimental days. (Means and standard deviations)

| Time of day | Exposure $^a$ | Xylene, 6 $\mu$mol/l | Alcohol & xylene, 6 $\mu$mol/l | Xylene, 11.5 $\mu$mol/l | Alcohol & xylene, 11.5 $\mu$mol/l |
|-------------|---------------|------------------------|-------------------------------|--------------------------|----------------------------------|
| 0915        | —             | 14.4 ± 1.3             | 19.4 ± 6.0                    | 21.4 ± 5.8               | 47.8 ± 8.8                       |
| 1100        | —             | 22.1 ± 2.5             | 32.9 ± 8.2                    | 43.2 ± 13.7              | 69.5 ± 13.3                      |
| 1330        | —             | 22.1 ± 2.5             | 32.9 ± 8.2                    | 43.2 ± 13.7              | 69.5 ± 13.3                      |

$^a$ Xylene air concentration: 6 $\mu$mol = 636 mg/m$^3$, 11.5 $\mu$mol = 1,218 mg/m$^3$.

**Flicker fusion**

Alcohol or xylene alone had no significant impairing effects on the CFF thresholds during exposure, but an improvement was observed ($p < 0.05$) after the higher xylene exposure. Combined exposure to alcohol and a xylene concentration of 6 $\mu$mol/l (636 mg/m$^3$) tended to impair the CFF thresholds somewhat, but alcohol and the higher xylene concentration had no significant effect. A tendency towards improvement was noted also after the latter exposure (fig 3).

**Maddox wing test**

Only slight exophoria was caused by the higher alcohol dose alone, as well as in combination with the lower and higher xylene concentrations, but not by xylene alone or by the smaller alcohol dose.
Gaze deviation nystagmus

None of the subjects showed nystagmus on the nonexposure days or in the mornings. Alcohol caused nystagmus dose-dependently. The higher xylene concentration caused nystagmus in one, and the lower in none, of the subjects. Combined exposure to alcohol and xylene at both xylene exposure levels caused less nystagmus than did alcohol alone (table 4). This decrease was more pronounced with the higher xylene concentration.

Electronystagmography

Neither fixation nor gaze deviation nystagmus were observed in the ENGs. Weak spontaneous nystagmus was noted in several ENGs, but it exceeded 5°/s only twice during the morning recordings, without any other abnormalities. The effects of exposure were mostly observed in the positional nystagmus recordings, especially in side positions.

The intensity of positional alcohol nystagmus (PAN I) (3) correlated dose-dependently with the BACs at noon 120 min after the intake of the alcohol dose and was less than 5°/s after the lower alcohol dose and more than 5°/s after the higher alcohol dose (fig 4 A and B). Exposure to the lower, but not to the higher, xylene concentration caused weak nystagmus (less than 5°/s) similar to PAN I after the exposure in the afternoon (fig 4 C).

The lower xylene concentration combined with alcohol caused clear nystagmus (more than 5°/s) similar to PAN I at 1235 and 1435.

Table 4. Gaze deviation nystagmus — Percentage of subjects showing gaze deviation nystagmus on different experimental days. (95 % confidence intervals are given in parentheses)

| Exposure a | Time of day |
|------------|-------------|
| 0835       | 1035        | 1235        | 1435        |
| Control (nonexposure) | 0 | 0 | 0 | 0 |
| Xylene (6 μmol/l) | 0 | 0 | 0 | 0 |
| Alcohol (0.4 g/kg) | 0 | 30.0 | (6.7—65.2) | 0 |
| Xylene (6 μmol/l) & alcohol | 0 | 66.7 | (29.9—92.5) | 62.5 | (24.5—91.5) | 12.5 | (0.4—57.9) |
| Alcohol (0.8 g/kg) | 0 | 88.9 | (51.8—99.7) | 77.8 | (40.0—97.2) | 11.1 | (0.3—48.2) |
| Xylene (11.5 μmol/l) | 0 | 11.1 | (0.3—48.2) | 11.1 | (0.3—48.2) | 0 |
| Xylene (11.5 μmol/l) & alcohol | 0 | 55.6 | (21.2—86.3) | 57.1 | (18.4—90.1) | 28.6 | (3.7—71.0) |

a Xylene air concentration: 6 μmol/l = 636 mg/m³, 11.5 μmol/l = 1,218 mg/m³.

Fig 4. Horizontal positional nystagmus, weak positional alcohol nystagmus (PAN I), of one subject (PL) at 1155 after the intake of alcohol, 0.4 g/kg (A) and 0.8 g/kg (PAN I) (B), as well as nystagmus similar to PAN I at 1515 after exposure to xylene [6 μmol/l (636 mg/m³)] (C). (R = right lateral side position, L = left lateral side position, Cal = calibration; the time constant is also shown in the figure)
noon 120 min after the intake of the alcohol dose in three subjects out of five. Combined exposure to the higher xylene concentration and alcohol caused weak nystagmus (less than 5°/s) similar to PAN I at the same time in only one subject out of five.

Symptoms caused by the exposure

The subjects still felt inebriated 2 h after the intake of the lower and 4 h after the higher alcohol dose. When the BAC reached its peak value (0.7 g/l), alcohol combined with the lower xylene concentration (in blood 20 μmol/l) caused transient vomiting and nausea in one subject, and in combination with the higher xylene concentration (in blood 30 μmol/l) it correspondingly affected two subjects. These subjects discontinued their exposure on these days.

Pharmacokinetics

The concentration of m-xylene in venous blood increased rapidly during the first hour of exposure. After an initial rapid rise a slower increase of the concentration was observed. Interestingly, the simultaneous ingestion of alcohol significantly increased the venous blood m-xylene concentration during the 6 μmol/l (636 mg/m³) exposure to xylene (p < 0.01, Student's paired t-test), as well as during the 11.5 μmol/l (1,218 mg/m³) exposure (p < 0.05, Student's paired t-test) (table 3). The possible mechanism behind this phenomenon will be discussed elsewhere (Riihimäki et al, unpublished results).

Table 5. Venous blood alcohol concentrations on different experimental days. (Means and standard deviations)

| Time of day | Alcohol, 0.4 g/kg | Alcohol, 0.8 g/kg | Alcohol & xylene, 6 μmol/l | Alcohol & xylene, 11.5 μmol/l |
|-------------|-------------------|-------------------|---------------------------|-------------------------------|
|             | mmol/l g/l        | mmol/l g/l        | mmol/l g/l                | mmol/l g/l                    |
| 0915        | —                 | —                 | —                         | —                             |
| 1100        | 5.8±0.9           | 14.8±2.2          | 16.3±1.5                  | 15.6±3.9                      |
| 1330        | 0.6±1.1           | 9.3±2.4           | 10.0±1.5                  | 10.2±3.2                      |

a Xylene concentration: 6 μmol/l = 636 mg/m³, 11.5 μmol/l = 1,218 mg/m³.

The peak BACs were reached about 60 min after the intake of the higher alcohol dose and a little earlier after the lower dose of alcohol on different experimental days. Xylene did not seem to have any effect on the BAC (table 5).

Discussion

The disturbance of equilibrium is of vital importance in human activities. Besides being related to changes in cerebellar function, it may be due to impaired vestibular function, a sign of which is nystagmus (3).

Positional nystagmus caused by alcohol and appearing in two phases (PAN I: left beating in the left lateral position and right beating in the right lateral position; PAN II, which appears after PAN I in the hangover phase: right beating in the left lateral position and left beating in the right lateral position) is a constant finding already at low BACs, such as 0.5 g/l (2). The intensity of PAN, as well as postural equilibrium, correlates with the BAC (10, 13). Subjective symptoms of alcoholic inebriation, such as dizziness and nausea, are also closely related to the intensity of PAN (3). Aschan et al (4) suggested that PAN is due to a dual nervous mechanism including a central and peripheral component and thus involves at least one functioning labyrinth. Money & Myles (25, 26) suggested that PAN is caused by the low specific weight (0.8) of alcohol changing the buoyancy of the cupula in the inner ear endolymph.

Several industrial solvents cause vertigo and dizziness. In the rabbit xylene (5),
styrene (20), methyl chloroform (19), and trichloroethylene (36) cause positional nystagmus, the beat direction of which is opposite to PAN. The specific weights of these solvents (xylene 0.86 — trichloroethylene 1.5) differ. The results obtained thus contradict the suggestions of Money & Myles (25). Ödkvist et al (27) suggested, therefore, that the chemical (biochemical) rather than the physical properties of solvents determine their effect on the vestibular system and that a neuropharmacological explanation is needed to describe the mechanism of this action, the site of which might be in the central vestibular pathways.

ENGs were recorded in the chamber 100—120 min after the intake of alcohol. At this time the BACs after the lower alcohol dose were negligible and those after the higher alcohol dose were declining, and this had probably decreased the intensity of nystagmus. The ENG was only recorded up to 260 min after the intake of alcohol so that PAN II was not observed (3).

Our finding that alcohol dose-dependently increased body sway or the intensity of PAN agrees with the results of earlier reports (3, 10). Carpenter et al (9) reported that a 15-min exposure to a xylene concentration of 9.4 μmol/l (1,000 mg/m³) caused dizziness in one subject out of seven, and a similar exposure to 28.2 μmol/l (3,000 mg/m³) caused dizziness and a slight loss of balance in one subject and dizziness in three others. Our subjects did not report dizziness, but a slight impairment of body balance by xylene was observed. Xylene at the higher dose seemed to antagonize the effects of alcohol on vestibular functions, although alcohol with the lower xylene concentration additively increased body sway. Nystagmus similar to PAN, observed in one subject after the xylene exposure, might be associated with xylene action on the central nervous system, although no nystagmus was observed during the exposure. This finding might also indicate that some individuals are more susceptible to the effects of xylene than others. Aschan et al (5) found that xylene dose-dependently causes nystagmus opposite to PAN I in the rabbit. We could not confirm the finding in humans, possibly because the xylene concentrations used in the present study were so low.

These findings support the neuropharmacological explanation of Ödkvist et al (27) of solvent action on the vestibular system. Although the action of alcohol on the buoyancy of the cupula in the semicircular canals (25) cannot be rejected as the mechanism behind PAN on the basis of these findings, a labyrinthine action of xylene is not probable because of the low xylene concentrations (26).

Gaze deviation nystagmus and CFF should reflect more central phenomena than, eg, PAN, and they should correlate with the BAC as well (1, 12). The ability to discriminate CFF thresholds has been used as a measure of cortical visual processes (16). Especially, effects on CFF thresholds reflecting drowsiness and sedation have been observed more clearly after the ingestion of psychotropic drugs (14) than after alcohol (23). According to Gamberale et al (11) exposure to a xylene concentration of 12.3 μmol/l (1,305 mg/m³) for 70 min caused no measurable sedation when studied by CFF. Our results were similar, probably indicating that CFF thresholds and, eg, gaze deviation nystagmus reflect different functions of the central nervous system. The improvement in CFF performance after the exposure to xylene and the combined exposure to xylene and alcohol might indicate a recovery phenomenon. As a method, CFF was also definitely less sensitive to the effects of alcohol, as well as to those of xylene, than most of the other methods used in the present study.

In accordance with earlier findings (12, 21), alcohol dose-dependently caused gaze deviation nystagmus. The effect of xylene alone on gaze deviation nystagmus was minor, and it seemed to antagonize the effects of alcohol dose-dependently, a finding which was also made by means of ENG and body sway recordings. Neither xylene nor alcohol seemed to have any significant effects on the ocular muscle balance as measured with the Maddox wing test.

Xylene and alcohol together caused nausea and dizziness, as well as vomiting in two of our subjects, and this occurrence indicates that some humans may be particularly susceptible to xylene-alcohol combinations.
The effects of alcohol were dose-related. A dose-response curve for xylene was difficult to establish because of the rather low doses used. The combined effects of xylene and alcohol did not follow the kinetics of these agents, and they were additive in some instances and antagonistic in others. Therefore this interaction seems to be pharmacodynamic rather than pharmacokinetic in nature.

The general depressant action of alcohol (17, 37, 38), as well as that of xylene (6), was rather small as measured by means of CFF and the questionnaire. The specific effects of these agents on the vestibular system, as measured by means of positional nystagmus, gaze deviation nystagmus and body sway, were clearly more distinct. The observed differences (31) in the phenomena studied might be explained partly by variations in the sensitivity of the methods, in the concentrations of these agents in the different neural structures (35), or by differences in the susceptibility of specific brain areas to the effects of these agents.

Short-term exposure to xylene concentrations below the Finnish threshold limit value (4.1 μmol/l, 435 mg/m³) probably does not cause significant disturbances in the vestibular or central visual system. Higher peak exposure to xylene, particularly combined with the influence of alcohol, might increase accident hazards during or after work.

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