SHORT COMMUNICATION

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Effect of Ethanol in Paclitaxel Injections on the Ethanol Concentration in Exhaled Breath

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Abstract

Background: Ethanol is included in certain injectable preparations of anticancer drugs to increase their solubility. Since the volume of ethanol in these preparations is approximately half of the total injection volume, the potential inhibitory effects of ethanol on the central nervous system cannot be disregarded, especially considering that patients may drive immediately after administration of the medication. Therefore, the concentration of ethanol was examined in exhaled breath after administration of paclitaxel, an anticancer medication containing ethanol.

Methods: The ethanol concentration in exhaled breath immediately after an intravenous infusion of paclitaxel was measured in 30 patients, using a balloon-type gas detector tube. Correlations between the concentration of ethanol in exhaled breath and the total amount of ethanol administered or the intravenous infusion speed were calculated.

Results: The mean ethanol concentration in exhaled breath was 0.028 ± 0.015 mg/L. The correlation between the ethanol concentration in exhaled breath and the total dose of ethanol was weak ($R^2 = 0.25$; $p = 0.055$), while the intravenous infusion speed showed a stronger positive correlation with the concentration of ethanol in the breath ($R^2 = 0.49$; $p = 0.11$). The maximum concentration of ethanol measured in exhaled breath (0.06 mg/L) was equivalent to 40% of the threshold for drunk driving, as specified in the Road Traffic Act in Japan.

Conclusion: In this study, no patient had a breath ethanol concentration exceeding the legal threshold for drunk driving. However, it is still advisable for patients to avoid driving after receiving paclitaxel injections. When driving cannot be avoided, patients should wait for a sufficient time after receiving the injection before driving.

Background

Paclitaxel is an antineoplastic drug isolated from a bark extract of *Taxus brevifolia* (Taxaceae).[1] The governments of the US and Canada approved paclitaxel for sale in 1992, and a parenteral solution of paclitaxel subsequently became commercially available in Japan in 1997. Paclitaxel induces formation of excess disordered microtubules by promoting microtubule polymerization and stability. Since paclitaxel inhibits depolymerization of microtubules,[2,3] cell division is inhibited. Thus, paclitaxel has antitumor activity. Paclitaxel is used clinically in the treatment of ovarian, breast, endometrial, stomach, and non-small cell lung cancers in Japan. The main adverse drug reactions to paclitaxel include gastrointestinal symptoms, peripheral neuropathy, arthralgia, muscular pain, nausea and vomiting, epilation, and pyrexia.

Paclitaxel tends to be soluble in *N,N*-dimethylacetamide, acetonitrile, methanol, and ethanol but is relatively insoluble in water. Because 50% ethanol is used as the solvent for clinical paclitaxel injections,[4] we hypothesized that impairment of specific central nervous system (CNS) functions by ethanol or its cleavage product, acetaldehyde, as well as adverse reactions related to intoxication, may occur following treatment with this preparation. Thus, the possibility of adverse reactions following intake of ethanol accompanying paclitaxel administration should not be overlooked.

Since many hospitals in Japan are located in rural areas and are not conveniently accessible by public transportation, most patients drive to the hospital. Thus, it is important to consider the possible CNS depressant actions of ethanol contained in injectable drug formulations, in order to reduce the risk of serious car accidents. Furthermore, in the Road Traffic Act in Japan, the breath ethanol concentration that constitutes drunk driving is 0.15 mg/L.[5] This threshold is lower than those in the UK, USA, and Canada (0.40 mg/L), and those in Australia, Germany, and France (0.25 mg/L). It is important to ensure that patients who receive paclitaxel injections containing ethanol do not have breath ethanol concentrations exceeding the legal threshold. Although research on plasma ethanol concentrations following paclitaxel administration has been published previously,[6] only a few reports have evaluated the correlation between ethanol intake during chemotherapy and the ethanol concentration in exhaled breath.

Here, we investigated the concentration of ethanol in exhaled breath after chemotherapy with an intravenous paclitaxel infusion.

Methods

Patients

Thirty Japanese outpatients (mean age 55 ± 8.6 years [range 35–74]; 2 male and 28 female) who received treatment with paclitaxel (80–330 mg/day) for breast, ovarian, or gastric cancer were eligible subjects for this research. This clinical study was approved by the Institutional Review Board for Clinical Trials at Gunma University Hospital (Maebashi, Japan). Written consent was obtained from all patients after they were informed of the study procedure.

Analysis of Ethanol Concentrations in Exhaled Breath

The volume of ethanol administered and the infusion rate of ethanol were calculated from the volume of the paclitaxel infusion and the administration time. Immediately after administration of the intravenous infusion to a subject, a balloon-type gas detector tube (Kitagawa Gas Detector Tube System; Komyo Rikagaku Kogyo KK, Kanagawa, Japan) was used to measure the concentration of ethanol in exhaled breath. The levels of aspartic acid aminotransferase (AST) and alanine aminotransferase (ALT) were noted from the medical records, and the alcohol drinking history was taken from each patient.

Statistics

Correlations between the total amount of ethanol administered and the ethanol concentration in exhaled breath, and between the intravenous infusion speed and the ethanol concentration in exhaled breath, were calculated using Pearson's correlation coefficient. Regression analysis was applied to each combination.

Results

Patient Characteristics, Treatment, and Breath Ethanol Concentrations

The patient characteristics, the amount of paclitaxel administered, the speed of the intravenous infusion, and the concentration of ethanol in exhaled breath are summarized in table I. The average ethanol concentration in exhaled breath immediately after the intravenous infusion of paclitaxel was 0.028 ± 0.015 mg/L (range 0.00–0.06).

Hepatic function in all patients was assessed to be within the normal range, as indicated by AST and ALT values of 12–33 U/L and 12–62 U/L, respectively.

Table I. Ethanol concentrations in exhaled breath of individual patients

Patient no.	Age (y)	Sex	Primary disease (type of cancer)	Paclitaxel dose (mg)	Total amount of ethanol administered (mL)	Duration of infusion (min)	Infusion speed of ethanol (mL/h)	Ethanol concentration in exhaled breath (mg/L)
1	66	Female	Breast	330	27.5	210	7.9	0.04
2	61	Female	Ovarian	300	25.0	180	8.3	0.05
3	50	Female	Breast	280	23.3	135	10.4	0.05
4	35	Female	Ovarian	270	22.5	180	7.5	0.03
5	58	Female	Ovarian	270	22.5	180	7.5	0.01
6	56	Female	Breast	250	20.8	153	8.2	0.06
7	52	Female	Ovarian	240	20.0	180	6.7	0.05
8	49	Female	Ovarian	240	20.0	180	6.7	0.04
9	56	Female	Ovarian	180	15.0	180	5.0	0.01
10	55	Female	Breast	145	12.1	74	9.8	0.05
11	54	Female	Breast	130	10.8	80	8.1	0.02
12	68	Female	Gastric	120	10.0	108	5.6	0.03
13	45	Female	Breast	120	10.0	70	8.6	0.04
14	60	Female	Breast	120	10.0	99	6.1	0.03
15	60	Female	Breast	120	10.0	95	6.3	0.03
16	53	Male	Gastric	120	10.0	127	4.7	0.02
17	51	Female	Breast	110	9.2	99	5.6	0.03
18	52	Female	Breast	110	9.2	65	8.5	0.04
19	40	Female	Breast	110	9.2	90	6.1	0.02
20	53	Female	Breast	110	9.2	85	6.5	ND
21	52	Female	Gastric	108	9.0	85	6.4	0.04
22	58	Female	Breast	105	8.8	81	6.5	0.03
23	58	Female	Breast	105	8.8	130	4.0	0.01
24	39	Female	Breast	103	8.6	91	5.7	0.01
25	74	Female	Breast	100	8.3	75	6.7	0.03
26	66	Female	Breast	100	8.3	78	6.4	0.03
27	49	Female	Breast	98	8.2	88	5.6	0.03
28	61	Female	Ovarian	90	7.5	185	2.4	0.01
29	64	Female	Breast	86	7.2	90	4.8	0.01
30	55	Male	Gastric	80	6.7	100	4.0	ND
Average ± SD	55 ± 8.6			155 ± 76	12.9 ± 6.3	119 ± 45	6.5 ± 1.7	0.03 ± 0.02

ND = not detectable; **SD** = standard deviation.

Relationship between Ethanol Concentrations in Exhaled Breath and the Total Volume or Infusion Speed of Ethanol

The correlation coefficient between the total amount of ethanol administered via the intravenous infusion and the ethanol concentration in exhaled breath was weak ($R^2 = 0.25$; $p = 0.055$) [figure 1a]. In contrast, the intravenous infusion speed had a relatively stronger positive correlation with the concentration of exhaled ethanol ($R^2 = 0.49$; $p = 0.11$) [figure 1b].

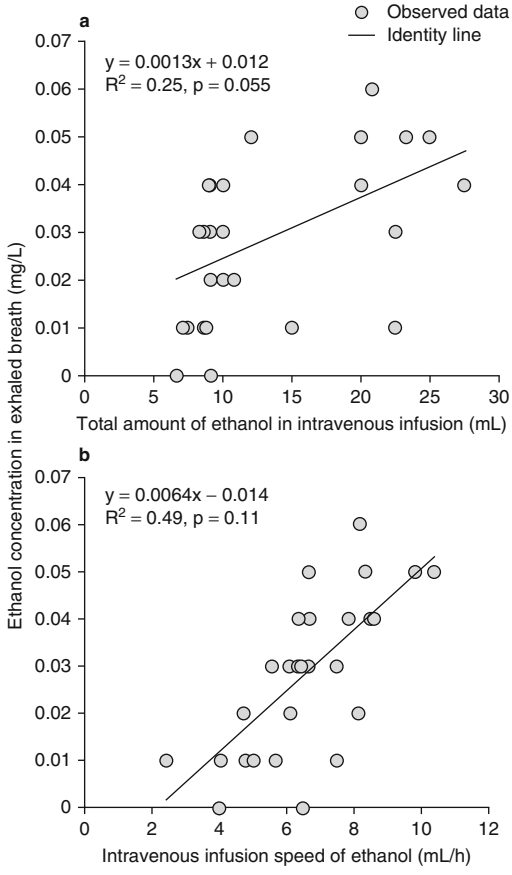

Fig. 1. Relationship between the ethanol concentration in exhaled breath and (**a**) the total amount of ethanol administered via the intravenous paclitaxel infusion; and (**b**) the speed of the paclitaxel infusion. The data-point markers represent observed data. The oblique black data lines represent the fitted curves.

Discussion

More than 90% of ethanol is metabolized by alcohol dehydrogenase (ADH) and aldehyde dehydrogenase 2 (ALDH2) in the liver.[7] It has been reported that people with low ALDH2 activity show hereditary sensitivity to the effects of alcohol, and approximately 50% of Japanese people are poor alcohol metabolizers.[8] Thus, the percentage of Japanese people who experience facial flush and heart palpitations in association with elevated blood aldehyde concentrations after drinking alcohol is larger than that of Europeans and Americans. Inter-individual differences in alcohol metabolism are also larger in the Japanese population. Therefore, there is a greater risk of intoxication leading to a car accident in people who have poor ethanol metabolism, because the blood ethanol concentration remains high even after consumption of a relatively small amount of alcohol.

Ethanol is eliminated primarily by a saturable (Michaelis-Menten) process.[8] Hence, the half-life of ethanol changes according to the dose or the rate of administration. Paclitaxel injections contain 50% (v/v) ethanol; thus, if 300 mg of paclitaxel is injected, 25 mL ethanol is also administered. This amount is equivalent to 500 mL of beer or 60 mL of whisky. Furthermore, because the first-pass effect does not apply to intravenous infusions, the effects of ethanol will be greater than with oral administration. In this study, an ethanol concentration in exhaled breath that exceeded the threshold for drunk driving, as specified in the Road Traffic Act, was not detected in any patient, but there was one case that reached more than 40% of the threshold. Moreover, a previous report described several cases that exceeded the threshold defined by the law.[9]

The relationship between the ethanol concentration in breath and that in blood has been investigated, and a method of deducing the blood concentration from the concentration in breath has been established. Moreover, when considering the CNS effects, the ethanol concentration in breath (which reflects the arterial blood ethanol concentration) is considered to be a more suitable indicator than the venous blood ethanol concen-

tration. The ratio of venous blood ethanol concentrations to exhaled breath ethanol concentrations is approximately 2000 : 1.[7]

The average blood ethanol concentration estimated from our findings was 0.06 ± 0.03 mg/mL. Webster et al. reported that the average plasma ethanol concentration after administration of paclitaxel in Caucasian patients was 0.07 ± 0.10 mg/mL.[6] When the average doses of paclitaxel in both studies (155 ± 76 and 293 ± 35 mg, respectively) are taken into consideration, the estimated blood ethanol concentrations may have been a little higher in our study. The difference in the body size between Japanese and Caucasian subjects may have affected this.

Because ethanol has a fast elimination rate, its concentrations steady state rapidly, and this is why the plasma ethanol concentration at the end of administration depends on the infusion speed. Thus, the ethanol concentration in exhaled breath after administration of paclitaxel is considered to be affected by the infusion speed but not by the total amount of ethanol administered. There were several subjects who complained of facial flush or light-headedness after the end of the intravenous infusion, which may have been a response to the ethanol metabolite, acetaldehyde.[10] In these cases, markers other than the breath ethanol concentration should be considered, in order to assess the degree of intoxication. In general, patients with high sensitivity to ethanol tend to present with symptoms of alcohol impairment and also have impaired decision-making ability.

The gender bias of the patients should be mentioned as a limitation of this study. Because most patients in the study were outpatients with breast cancer or ovarian cancer, the majority of the patients were female. It has previously been shown that when the same dose of ethanol is administered to male and female subjects, higher blood concentrations are reached in females than in males,[11] and this may have affected our results.

Conclusion

We have shown that the ethanol concentration in exhaled breath after administration of paclitaxel is affected by the infusion speed rather than by the total amount of ethanol administered. However, it is difficult to predict from this information which patients will show a high breath ethanol concentration. Hence, all outpatients receiving paclitaxel should avoid driving from hospital when possible and, if driving is unavoidable, they should drive only after taking a sufficient break. The possible effects of the ethanol additive should be considered carefully when administering drugs, such as paclitaxel, with a high volume of ethanol additive.

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