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Major article

Assessment of transpulmonary absorption of ethanol from alcohol-based hand rub

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Background: Alcohol-based hand rubs (ABHRs) have been associated with a reduction of nosocomial infections. Despite the worldwide introduction of these products in health care settings, the aim of this study was to assess the transpulmonary absorption of ethanol contains in ABHRs used by health care workers (HCWs) in real conditions of work shift.

Methods: Twenty-six HCWs of Nancy University Hospital were included. Research consisted in monitoring participants during 4 hours of work shift to assess their exposure to ethanol. The measurement of ethanol vapors in exhaled breath was performed using a class B ethylometer (Alco-Sensor FST). Ethanol concentration in inhaled breath was measured using Gilian pump LFS-113. Concentration of ethanol, acetaldehyde, and acetate in blood and urine samples were determined using gas chromatography with flame ionization detector.

Results: Participants were 12% male and 88% female. The mean age was 40 $\pm$ 8 years. None of the employees included in the study presented any traces of ethanol or its metabolites in the blood or urine. Ethanol (0.08 $\pm$ 0.07 mg/L) was detected in the breath of 10 HCWs at 1 to 2 minutes postexposure. The mean concentration of ethanol in the inhaled air was 46.2 mg/m^3.

Conclusion: Absorption of ethanol vapor from ABHRs among HCWs during their care activities was not detected. Quantification of ethanol fumes inhaled during 4 hours of work shift was below the regulatory limitations of exposure to ethanol.

The importance of hand hygiene in the prevention of nosocomial infections[1,2] and in reducing the transmission of pathogenic microorganisms[3] has been proven several times over.[4] The use of alcohol-based hand rubs (ABHR) as compared with antiseptic soap[5] increased the compliance with hand hygiene[6,7] and decreased the rate of nosocomial infections.[8] Intensive use of ABHR is also one of the objectives of several national programs to prevent the spread of health care-associated infection.[9] Health care workers (HCW) exposure to ethanol contained in ABHR can result in systemic inhalation and transdermal absorption (and occasionally ingestion). The metabolism of ethanol varies from one individual to another, and prolonged exposure can cause serious adverse effects. Several studies have investigated absorption of ethanol content in ABHR, but the results remain controversial. Two of Miller et al's studies[10,11] investigated absorption of ethanol. In the first study, 5 volunteers applied an ABHR containing 62% ethanol 50 times over a period of 4 hours. Blood levels remained below 0.05 g/L. In the second study, an emergency physician applied an ABHR containing 62% ethanol to his hands 25 times over a period of 2 hours. Serum levels remained below the detection limits according to the method used in this laboratory. These 2 studies tend to show that ethanol is absorbed through the skin barrier gradually. However, they were conducted in volunteers free of dermatologic lesions and without taking into account subjects' variability (sex, age, skin type, and others) that could influence the transcutaneous absorption. Inversely, another study[12] tackled the problem of detection of alcohol while driving after using ABHR. In this study, 20 subjects carried out 30 rubs per hour during a working day. Ethanol was detected in exhaled breath of 6 subjects 1 to 2 minutes after exposure and in the blood of 2 subjects 5 to 7 minutes after

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exposure. The clinical trials were controlled, double blind, and randomized, and cross over to analyze the transdermal absorption of ethanol and 1-propanol after dermal application on 14 healthy male volunteers.[13] The results showed 0.35 mg/L ± 0.14 mg/L ethanol/1-propanol in the blood samples. The absence of transcutaneous absorption and/or associated with pulmonary absorption of ethanol is not proven. The half-life of ethanol evaporation on the skin is 12 seconds.[14] The absorption rate of a toxin (air distribution into the blood) depends on its concentration in alveolar air and the Nernst partition coefficient for blood (solubility coefficient). Under these conditions, the respiratory route must be taken into account. A recent study assessed the inhaled dose of alcohol during hand disinfection using 2 hand disinfection procedures and 2 types of commercially available ABHRs (ethanol and combined alcohols, which contained 700 mg/g of ethanol and 560 mg/g of ethanol and 90 mg/g of isopropanol). This research provided experimental data, using a simple method to show that the use of ABHRs leads to the absorption of very low doses of alcohols, but repeated inhalation of high alcohol concentrations raises the question of possible adverse health effects.[15] To our knowledge, no previous study has focused on ethanol concentration in inhaled air during use of ABHRs in real conditions of work in health care settings; most of the studies have focused on exposure to alcohols in experimental conditions by measuring blood alcohol concentrations. Consequently, the principal aim of this study was to assess the pulmonary exposure to ethanol during hand disinfection in real conditions at workplace. A simple method was used to estimate the amount of ethanol inhaled during 4 hours of work shift in hospital. The concentration of ethanol in biologic fluids and exhaled breath was performed.

MATERIALS AND METHODS

Twenty-six HCWs of the Nancy University Hospital, France (1,700 beds), participated in the study. Participants were from all wards of hospital. Volunteers used 3 mL of the product usually used in the hospital ANIOSGEL 85 NPC (Anios Laboratories, Lille, France) for each hand rub, containing 70% ethanol + emollients. The study followed the guidelines for Good Clinical Practice and was approved by the Ethics Committee of the University Hospital of Nancy. The main criteria for inclusion were volunteers aged 18 to 50 years, working in the Nancy University Hospital, and having participated in hand hygiene rubbing training. Subjects were excluded if over 50 years old because this study was the first in a longitudinal study to be conducted over 10 years (DEESSES cohort). All former alcoholics or those who left the hospital within 2 years were not accepted. Participants were asked to stop consuming alcohol from 48 hours before the beginning of the experiment and throughout the entire study period.

The data collected included the following: demographic characteristics (age, weight, height, body mass index, ward, position); medical and surgical history; Fitzpatrick skin types[16]; start and finish time for the exposure assessment; content before and after of the ABHR bottle to estimate the amount of ABHR used; concentration of ethanol, acetaldehyde, and acetate in blood and urine; and ethanol concentration in inhaled and exhaled breath.

This study was conducted in a hospital. HCWs can use ABHRs in any situation (when the opportunity for hand rubbing arises): in the care rooms, hallways, and patient rooms. Measurements were performed under standardized conditions of temperature and humidity. Building ventilation is provided by a constant air exchange rate of about 25 to 50 m^3/h per room.

The quality of hand rubbing (percentage of surface coverage, time spent rubbing, and respect of the standard rub procedure)[17] was assessed using the method described by Hautemaniere et al.[18] Ethanol concentrations in blood, urine, and exhaled breath were measured at the beginning of the work shift and 4 hours later under real-life conditions at workplace. This study was carried out on the subject's duty ward without changing the care program in any way.

Blood samples

For blood samples collection, the skin was disinfected with a non-alcoholic antiseptic solution to prevent contamination of the blood with ethanol. The blood samples were collected in an anticoagulant EDTA collection tube (BD vacutainer; Becton Dickinson, Franklin Lakes, NJ) and centrifuged at 800*g* for 10 minutes at room temperature; the plasma was taken and aliquoted into 200-μL vials and stored at −20°C until analysis.

Urine samples

Samples of urine were collected in urine collection bottles 60 mL of size. Samples are centrifuged at 1,000*g* for 15 minutes at +4°C and stored in closed microsample containers at −20°C until analysis.

Ethylotest breathalyzer

Breath ethanol concentration was measured using an electronic Ethylotest Alco-Sensor FST (Intoximeters, Inc, St. Louis, MO). The Ethylotest measures with a precision of ±0.01 mg/L of breath; measurement range is 0.00 mg/L to 2.00 mg/L of breath. Measurement was made at baseline and 1 to 2 minutes after 4 hours of work shift.

Sampling method for measurement of ethanol vapor in inhaled breath

To estimate exposure levels to ethanol during hand disinfection in workplace for 4 hours, air samplings in the breathing zone of HCW were taken with sampling pump (Model LFS-113, Sensidyne, Inc., Clearwater, FL). The LFS-113 is a compact, low-flow, air-sampling pump with sorbent tubes designed for flow rates between 1 mL/min and 350 mL/min. Compact size and light weight of this pump allow it to fit easily inside a shirt pocket. Flow rates were measured at the start and end of the sampling period using a soap bubble flow meter and SKC sorbent sample activated charcoal tubes (100 + 50 mg) (SKC Inc., Eighty Four, PA). The sampling flow rate was fixed at 200 mL/min; this was accurately measured at the start and end of the sampling period. Sorbent tube was placed near the breathing zone of the subject to be representative of the distance between the hands and the respiratory tract. At the end of the sampling process, SKC sorbent sample tubes were rapidly transferred to the laboratory and stored at +4°C for a maximum period of 10 to 15 days.

The SKC tubes were then desorbed in 1 mL of dichloromethane. After 30 minutes of shaking, the desorbed ethanol was analyzed with a gas chromatograph GC 3900 (Varian Analytical Instruments, Walnut Creek, CA) equipped with a flame ionization detector. The conditions of the gas chromatography for the injection and column temperature were 220°C and 55°C, respectively. The flame ionization detector temperature was set at 200°C. The flow rates of hydrogen and air were fixed at 25 mL/min and 300 mL/min, respectively. The flow rate in column was 5 mL/min. The detailed analytical procedures have been described elsewhere.[19]

Samples analysis

Concentrations of ethanol, acetaldehyde, and acetate were determined using a gas chromatograph GC 3900 (Varian Analytical Instruments) equipped with an injector 1177 EFC 21 Split/Splitless and a flame ionization detector. Capillary column was used (CP-SIL 19CB: 25 m × 0.53 mm × 2.0 μm; Varian Analytical Instruments). The detailed analytical method was described by Ahmed-Lecheheb et al.[20]

Statistical analysis

Results of analysis were obtained using Galaxie software version 1.9 SP1 (Varian Analytical Instruments). The peak heights were used to calculate the concentration of ethanol and its metabolites in the samples. Data were analyzed using SPSS version 17 (SPSS Inc, Chicago, IL).

RESULTS

Twenty-six volunteers, 12% male and 88% non-pregnant female, participated in this study. Participants were 50% nurses, 23% auxiliary nurses, 15% hospital cleaners, and 8% radiology technicians. The mean age was 40 ± 8 years, the mean weight was 64 ± 12 kg, the mean size was 1.63 ± 0.08 m, and mean body mass index was 24 ± 4 kg/m^2. Subjects were 96% right-handed, and 85% had Fitzpatrick skin type II. Fifty percent of subjects never consumed alcohol or consumed only at parties. No volunteers were suffering from hepatic problems, but 3 suffered from asthma and 6 from skin pathologies. Table 1 show demographic and physical characteristics of participants.

The quality of hand rubbing was judged as excellent or good in 100% of cases and the rubbing time sufficiently long (more than 30 seconds) in 42%. Seventy-three percent of HCWs had the palms of their hands covered 100% with the ABHR. In the 7 subjects whose hand surfaces were not completely covered, the discrepancy was on average 9% (Table 2). The amount of ABHR used during 4 hours of assessment was on average 33 g or 34.5 mL, which corresponds to 11.5 hand rubs (with 3 mL of product for each hand rub). This average reflects significant differences in consumption from 8 g (2.7 rubs) to 59 g (20.5 rubs). We decided to exclude the result for 1 SKC sorbent sample activated charcoal tube for misuse of the Gillian pump by HCW that resulted in damage to the tube. The mean concentration of ethanol in the inhaled air of 25 HWCs was 46.2 mg/m^3 (Table 3). There is a significant correlation of 0.388 ($P = .05$) between the amount of ABHR used and the ethanol concentration in inhaled air (Fig 1).

Before the beginning of work shift, none of the HCWs included in the study presented any traces of ethanol or its metabolites in the blood, urine, and expired air. After 4 hours of ABHRs professional use, all the concentrations of ethanol and its metabolites were nil or nondetectable in blood and urine. The ethanol level in the expired air was measured at 1 to 2 minutes after the last rub with ABHR. We measured the mean value of 0.03 ± 0.06 mg of ethanol per liter of expired air (95% confidence interval: 0.00-0.23) (Table 3). No clinical effects were described during the 4 hours of ABHR use for subjects with health problems.

Table 1
Demographic and physical characteristics of participants

	Epidemiology section		Biologic measurement		
	Frequency	Percent	Mean	SD	95% CI
Sex					
Male	3	11.5			
Female	23	88.5			
Skin type					
Fitzpatrick skin type I	1	3.8			
Fitzpatrick skin type II	22	84.6			
Fitzpatrick skin type III	2	7.7			
Fitzpatrick skin type IV	1	3.8			
Dominant hand					
Right-handed	25	96.1			
Ambidextrous	1	3.8			
Profession					
Auxiliary nurse	6	23.1			
Hospital cleaner	4	15.4			
Nurse	13	50.0			
Radiology technicians	2	7.7			
Laboratory technicians	1	3.8			
Ward					
Surgical	2	7.7			
Consultation	2	7.7			
Medical-technical*	9	34.6			
Medicine	9	34.6			
ICU	4	15.4			
Alcohol consumption					
Never	2	7.7			
Only at parties	11	42.3			
Once per month at least	1	3.8			
Between 2 and 4 times per month	9	34.6			
2 or 3 Times per week	3	11.5			
Pathology					
Asthma	3	11.5			
Eczema	4	15.4			
Psoriasis	2	7.7			
Weight, kg			64	12	44-85
Height, cm			163	8	150-180
Age, yr			40	8	26-50
BMI			24	4	19-32

BMI, body mass index; *CI*, confidence interval; *ICU*, intensive care unit; *SD*, standard deviation.
*Dialysis, functional respiratory exploration, digestive endoscopy, radiology.

Table 2
Hand rub practice

	Epidemiology section		Biologic measurement		
	Frequency	Percent	Mean	SD	95% CI
Quality of hand rub					
Period of hand rub					
Less than 15 seconds	2	7.7			
15 to 30 seconds	13	50.0			
More than 30 seconds	11	42.3			
Method of hand rub					
Good	8	30.8			
Very good	18	69.2			
Surface of hand without ABHR					
Palm %			3	4	0-10
Back %			7	11	0-45
Weight of ABHRs used, g			33	16	8-59

CI, confidence interval; *SD*, standard deviation.

DISCUSSION

Our study did not find any systematic absorption of ethanol vapors from hand disinfection product in HCWs during their care activities. This study confirms the findings of Miller et al's 2 studies.[10,11] HCWs used several products that do not contain only ethanol. This alcohol presents toxicologic characteristics different from the 2 other alcohols usually used in the formulation of hand rub products. These differences may be one of the explanations for the results of the studies that found alcohol in the blood. Although the peak points are all very low (13°C [pure ethanol], 7°C [isopropanol], 15°C [n-propanol]), the molar masses are different (46.0684 ± 0.0023 g/mol ethanol and 60.095 ± 0.0033 g/mol for isopropanol and n-propanol) or 30% higher for those with

Table 3
Concentration of ethanol in the expired and inhaled air

	Minimum	Maximum	Mean	SD
Expired air (mg/L)				
Ethanol T_0	0	0	0	0
Ethanol T_4	0	0.23	0.03	0.06
Inhaled air				
Ethanol (mg)	0.5	6.8	2.2	1.7
Ethanol (mg/m^3)	10.4	141.9	46.2	34.8

SD, standard deviation.
NOTE. T0: At baseline (pre-exposure); T4: After 4 hours work shift (postexposure).

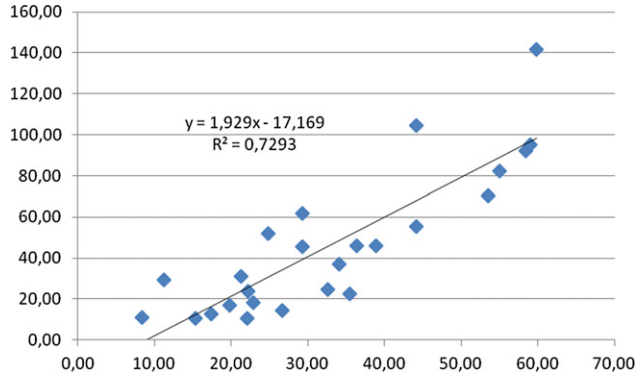

Fig 1. Correlation between the amount of ABHRS used and ethanol concentration in inhaled air.

tri-carbon chains. This toxicologic data could explain a difference in evaporation and skin absorption. In fact, the studies that found plasmatic concentrations were all carried out using isopropanol or n-propanol.[12,13]

In the literary review on methods for quantification of alcohols and their metabolites, physical methods are the most sensitive. Gas chromatography associated with flame ionizing detector is the most commonly used. This tool enables several molecules whose metabolites are of interest to be dosed simultaneously without pretreatment, which often leads to a loss of product with a detection level of 0.1 mg/L for ethanol. Concerning these data, we cannot claim that there were not a few molecules of ethanol in the blood or urine of HCWs tested. On the other hand, we can confirm that the concentration in ethanol is inferior to the detection limit, which, for our purposes, is 0.1 mg/L. With regard to these results, even if a presence of ethanol was detected by another method such as mass spectrometry, it only shows traces: these traces are harmless to the health. Moreover, these traces could come from an endogenous production of ethanol resulting from bacterial and fungal fermentation of sugars in the intestines. These phenomena have been known for a long time[21] and essentially concern the blood ethanol levels tested on cadavers.

We performed the quantification of pulmonary exposure of HCWs in a real situation of work shift, which had never previously been investigated except in laboratories under experimental conditions with excessive exposure. Our investigation extends knowledge on alcohol vapor concentrations during hand rubbing. In light of our results, we confirm that the concentration of ethanol released into the air from AHBR in workplace (mean 46.2 $\pm$ 34.8 mg/m^3 in 4 hours of exposition) remains far inferior to the French guidelines for professional exposure limits to ethanol over 8 hours (currently 1,900 mg/m^3 and considered as not causing any chronic effects).

Breathalyzer readings registered the mean ethanol level of 0.08 ($\pm$0.07 mg/L) in the breath of 10 HCWs at 1 to 2 minutes postexposure. Values returned to zero in all participants at 10 to 15 minutes after the last ABHR use. These findings confirmed earlier results of our study groups where no significant transpulmonary absorption was detected.[20] Positive breathalyzer readings are resulting from instantaneous inhalation of ethanol vapors during hands disinfection with ABHR. This was not due to skin absorption. The dead space of the airways (trachea and branch) is not the site of gas exchange. However, they corresponding to the quality of the incoming air (loaded air in a fraction of ethanol) and airflows (exchange of CO_2). The breath test was performed after friction often resulting in a penetration in the dead spaces of ethanol without gas exchange and therefore measurable. In the review of the literature, the authors concluded that the values of breathalyzer should not be converted into blood concentration in any case.[22]

The study was conducted in a hospital in which the ventilation is provided by a constant air exchange rate of about 25 to 50 m^3/h per room, which corresponds to poor ventilation. Air exchange took place, and this resulted in no ethanol vapor saturation after repeated ABHR manipulation. HCWs were exposed to alcohol vapors within a short time. The mean amount of ABHR used during a 4-hour shift was 34.5 mL, which corresponds to 11.5 hand rubs, approximately 3 hand disinfections per hour, which is a very short exposure period. HCWs exhibit poor hand hygiene compliance in real-life situation of work shift.

No respiratory clinical effect was observed in fragile populations (asthmatics), but our sample was very small (3 HCWs) and is therefore lacking in scientific basis. However, this result is reassuring and should be confirmed by other studies. It should be noted that our volunteers did not reduce their ABHR use, which suggests that the use of these products was causing them no discernible ill effects.

We are confident to conclude that, under real-life situations, the use of ABHR does not lead to intoxication levels of ethanol, and, therefore, the theoretical risk of systemic toxicity for HCWs could be further excluded. Our findings are important to have confidence in the safe use of ABHR, which encourages HCWs to use these products for hand hygiene in particularly HCWs who have reservation about their exposure to alcohol.

Finally, the major limitation of this investigation is that, in real-life situations, HCWs can work 8 to 12 hours per day, and our experiment was performed in 4 hours. We cannot be sure that intensive use of ABHR for longer than 4 hours results in higher absorption of alcohol. A small amount may be absorbed during intensive use via transcutaneous or inhalation of fumes in closed area.

CONCLUSION

Our findings did not find systematic absorption of ethanol vapors from hand disinfection products in HCW during their care activities, and the exposure concentrations fall well below the limit values fixed by the government guidelines for professional exposure to ethanol in workplace.

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