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SHORT COMMUNICATION

Pharmacokinetic Studies of the Fragrance Compound 1,8-Cineol in Humans during Inhalation

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Abstract

The present study was undertaken to investigate the pharmacokinetics of 1,8-cineol in human subjects during prolonged inhalation. The results showed that 1,8-cineol is well absorbed from breathing air, with a peak plasma concentration after ~18 min. The elimination of this fragrance compound from the blood is biphasic, with a mean distribution half-life of 6.7 min and an elimination half-life of 104.6 min. **Chem. Senses 21: 477–480, 1996.**

Introduction

Volatile rosemary oil shows an effect on minor gastrointestinal disorders, improves blood circulation and leads to hyperaemia of the skin after local administration (Kovar *et al.*, 1987). An increase in locomotor activity was demonstrated for rosemary oil and its main component 1,8-cineol in mice after peroral or inhalatory application (Kovar *et al.*, 1987; Ammon, 1989; Buchbauer *et al.*, 1993a, b) and correlated with the level of 1,8-cineol in the blood (Kovar *et al.*, 1987). In humans an increase of global cerebral blood flow after prolonged inhalation of 1,8-cineol was found, which could also be correlated with the concentration of 1,8-cineol in blood. (Našel *et al.*, 1994; Stimpfl *et al.*, 1995). The aim of this study was to determine the pharmacokinetics of 1,8-cineol in human subjects after prolonged inhalation in order to get more information about the absorption, distribution and elimination process of this fragrance compound.

Material and methods

Four healthy subjects (two females, two males) were chosen for the pharmacokinetic study. 1,8-Cineol (99%; Aldrich, Germany) was introduced into a closed breathing circuit with the air passing over 4 ml of the fragrance compound for 20 min. Blood samples (5 ml) were drawn from the left cubital vein at 0, 5, 10, 15, 20, 25, 30, 35, 45 and 60 min after the application of 1,8-cineol had been started and were collected in evacuated tubes (Vacutainer A3200LH; Becton Dickinson, UK). Quantification of the fragrance com-

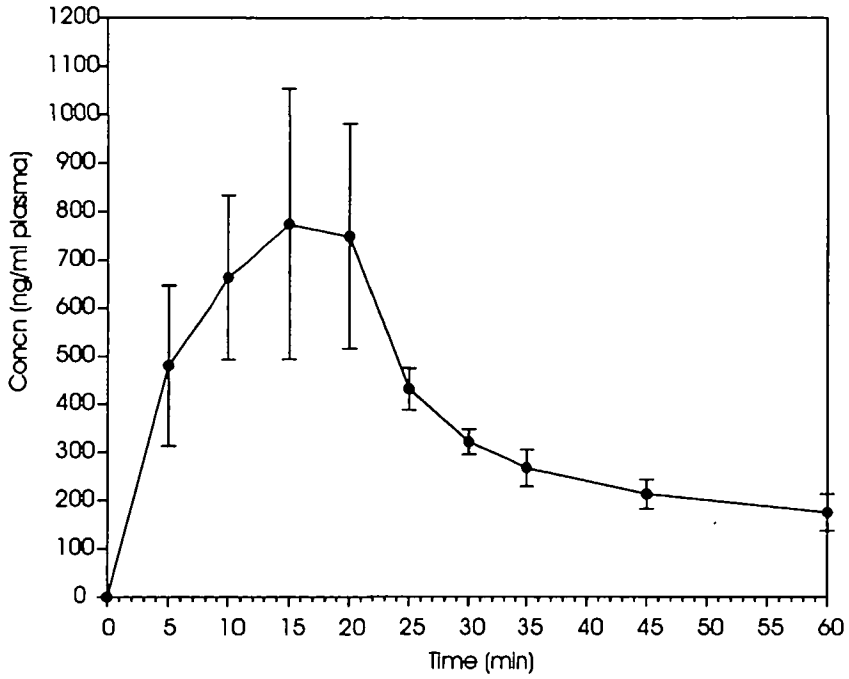

Figure 1 Blood concentration of 1,8-cineol during prolonged inhalation.

Table 1 Pharmacokinetic parameters of 1,8-cineol after prolonged inhalation

Subject	1	2	3	4	Mean ± SD
Age (years)	31	30	28	31	30.00 ± 0.41
Gender	male	male	female	female	
Body weight (kg)	92	55	60	61	67.00 ± 16.87
Height (cm)	185	172	170	163	172.50 ± 9.18
Dose (ml)	4	4	4	4	
k_{in} (1/min)	0.0988	0.2110	0.1933	0.1582	0.1653 ± 0.0495
k_{10} (1/min)	0.3463	0.1117	0.0445	0.0086	0.1291 ± 0.1517
k_{12} (1/min)	0.0044	0.0270	0.0445	0.0316	0.0268 ± 0.0167
k_{21} (1/min)	0.0226	0.0276	0.0215	0.0151	0.0217 ± 0.0051
$t_{½\,in}$ (min)	7.01	3.26	3.58	4.38	4.56 ± 1.70
$t_{½\,\alpha}$ (min)	1.98	4.78	6.86	13.10	6.68 ± 4.72
$t_{½\,\beta}$ (min)	31.12	32.56	73.08	281.64	104.60 ±119.62
t(p) (min)	18.98	14.15	13.92	15.22	15.57 ± 2.34
c(tp) (ng/ml)	868	1135	701	459	790.75 ± 284.36
AUC [(ng/ml) × min]	23076	27810	22680	18738	23076 ± 3714.20

k_{in}: invasion rate constant; k_{10}: first-order elimination rate constant from the central compartment; k_{12}: first-order transfer rate constant from the central compartment to compartment two; k_{21}: first-order transfer rate constant from compartment two to the central compartment; $t_{½\,in}$: half-life of invasion; $t_{½\,\alpha}$: initial decay half-life (representing distribution of drug into the tissue); $t_{½\,\beta}$: second decay half-life (elimination half-life); t(p): time to reach the peak; c(tp): concentration at the time to reach the peak; $AUC_{(0-60)}$: area under the curve (0–60 min).

pound was performed with serum (500 ml) by headspace gas chromatography as previously described (Stimpfl *et al.*, 1995). The pharmacokinetic parameters of 1,8-cineol were calculated by means of the Top Fit program, version 2.0 (Heinzel *et al.*, 1993), whereby the area under the curve (AUC0–60 min) was calculated by the linear trapezoidal rule. Curve modelling was performed according to the classical two-compartment open model.

Results and discussion

As previously described for one male subject (Stimpfl *et al.*, 1995), 1,8-cineol is well absorbed from the breathing air. Calculating the kinetic parameters, a half-life of invasion ($t½$ in) of 4.6 min, an initial decay half-life $t½$ α of 3.5 min and an elimination half-life $t½$ β of 19.9 min could be found. In order to investigate the pharmacokinetics of this fragrance compound in a more comprehensive way the protocol was repeated with four volunteers (two males and two females). The mean plasma levels of 1,8-cineol in humans during inhalation are shown in Figure 1; the corresponding pharmacokinetic parameters of each subject are summarized in Table 1. 1,8-Cineol is quickly absorbed from the breathing air and could be detected in the blood 5 min after starting the inhalation procedure. The half-lives of invasion ($t½$ in) and the time to reach the maximum concentration of 1,8-cineol in blood [t(p)] were in a close range between all individuals (~3–7 min and 14–19 min respectively), whereby the maximum measured concentration [c(tp)] ranged between 459 and 1135 ng/ml. As absorption of 1,8-cineol was similar in all subjects, huge interindividual differences for the elimination parameters could be found, indicating different distributions within the bodies after inhalation. The $t½$ α, representing the distribution half-life of 1,8-cineol into tissue, was between 2 and 4.8 min for the two males, whereas the two females exhibited prolonged values of 6.9–13.1 min. These differences between males and females were also observed for the $t½$ β, for which the males had values of 31.1–32.6 min whereas the females had values ~2.5 and 10 times longer. As females generally possess a higher ratio of body fat to body weight (Wissenschaftliche Tabellen Geigy, 1982), we assume that body fat is an important factor influencing the elimination of 1,8-cineol. While the pharmacokinetic microconstant $k12$ (a rate constant which reflects the transition from the central to the peripheral compartment) exhibited nonspecific values in females and males, $k21$ and $k10$ showed some evidence that body fat might be an important factor in determining the half-life of 1,8-cineol. The female subjects 3 and 4 showed the lowest values for $k21$, a constant for the transition of 1,8-cineol from the peripheral compartment to the central one, indicating that, because of the higher affinity of 1,8-cineol to this compartment, it takes longer to transfer 1,8-cineol back to the blood system. Also $k10$, an elimination constant from the central compartment to the elimination organ, was lowest in subjects 3 and 4, indicating a slower elimination process. The area under the curves for these two individuals also showed the lowest values although the dose of 1,8-cineol was the same, indicating that less fragrance compound was available in the blood. The difference to the mean value might therefore be in the fat compartment. To investigate the influence of body fat on pharmacokinetic parameters using 1,8-cineol and other fragrance compounds, a larger study including an obese and a control group is planned.

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