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Alteration of Warfarin Kinetics in Man Associated with Exposure to an Operating-room Environment

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The plasma half-life of warfarin (mean ± SE) in five normal, nonmedicated control subjects given a single 40 mg/m² oral dose of warfarin was 38.8 ± 4.1 hours. It was essentially the same (37.7 ± 2.6 hours) in these subjects when determined again four months later. The effect of the single dose of warfarin on prothrombin complex activity (prothrombin response) was determined by calculating the area under the curve obtained by plotting prothrombin time (seconds) versus time after the warfarin dose (hours). The prothrombin response in control subjects was 1670 ± 64 sec-hr initially and essentially the same at the end of the four-month interval (1730 ± 96 sec-hr).

Plasma warfarin half-life and prothrombin response in seven anesthesiology residents were 32.1 ± 3.6 hours and 1337 ± 78 sec-hr at the start of their training period, *i.e.*, before working in the operating room. Four months later, their plasma warfarin half-lives were significantly prolonged (49.3 ± 4.8 hours) and the prothrombin responses were significantly greater (1552 ± 22 sec-hr) compared with their initial values. The alteration of warfarin kinetics appeared to be due mainly to inhibition of warfarin metabolism, presumably related to the repeated exposure of these subjects to an operating room environment. (Key words: Biotransformation, warfarin; Anesthetics, gases, trace concentrations.)

ENVIRONMENTAL FACTORS may play an important role in determining the activity of hepatic drug-metabolizing enzymes.[1] Operating-room personnel, particularly anesthesiologists, are subject to a unique environment in which they are continually exposed to small amounts of volatile anesthetics and other chemicals.[2] Exposure to subanesthetic amounts of some volatile anesthetic agents has been shown to influence drug metabolism in animals.[3] In this study, we made an attempt to evaluate the effect of this exposure on drug metabolism in man. We determined plasma warfarin half-lives and the prothrombin responses to warfarin in seven subjects before and after they had worked for four months in the operating room. Another five subjects who did not work in the operating room served as a control group.

Methods

Seven normal volunteer male subjects starting their residency training in anesthesiology participated in the study. Another group of five normal volunteer male subjects served as controls. The control subjects were medical students who lived in the same area and were in training at the same hospital as the anesthesiology residents, but did not work in the operating room. Ages of the subjects ranged from 21 to 30 years. They had no history of drug intake immediately before or during the investigation, and they were asked to keep their use of alcohol, coffee, tea, and cigarettes constant during the study period. The study was approved by the Institutional Committee on Research Involving Human Subjects, and informed written consent was obtained from each subject.

A single oral dose of sodium warfarin (Coumadin¶), 40 mg/m² body surface area, was administered early in the morning. Fifteen-milliliter venous blood samples were taken at 0, 3, 6, 9, and 12 hours, and then every 12 hours until 60 hours after warfarin administration.

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for measurement of plasma warfarin levels. Venous blood samples of 4.5 ml were also taken at 0, 3, and 12 hours and then every 12 hours until 96 hours after administration for measurement of prothrombin time. Plasma levels of warfarin were determined spectrophotometrically.[4] The log plasma concentration was plotted against time and a line was fitted to data points from 24 to 60 hours by the least-square method. The plasma half-life was calculated from the slope of this line. One-stage prothrombin times were determined using an automatic timer and the prothrombin response was calculated by plotting prothrombin time (seconds) versus time, from 24 to 96 (hours) after warfarin administration, and then calculating the total area under the curve by the trapezoidal method.

Plasma warfarin half-lives and prothrombin responses in the anesthesiology residents were determined by the above procedures just prior to the start of their training. The residents administered various anesthetic agents, though nitrous oxide and halothane were the most common agents used. All residents had approximately the same exposures to all agents. None of the operating rooms had equipment for scavenging overflow anesthetics. Warfarin half-lives and prothrombin responses were determined again in the anesthesiology residents four months after they started to work in the operating room. In two subjects, the procedure was repeated after a year. The control subjects were each studied on two occasions separated by four months.

Results

Plasma half-lives of warfarin for individual subjects in both groups are shown in table 1. Half-lives determined on two occasions at an interval of four months did not change significantly in the control subjects. The changes in half-life was 3.5 ± 0.9 hours (mean ± SE) for this group. Plasma warfarin half-lives obtained in the anesthesiology residents before they started to work in the operating room were not significantly different from those of the control group. All of these values agreed with those found previously in groups of normal subjects.[5] However, after exposure to the operating room environment for four months, plasma warfarin half-lives in the anesthesiology residents were significantly increased above their initial values. The increases in half-lives averaged 18.4 ± 5.6 hours (mean ± SE). In all but one subject warfarin disappearances from plasma were prolonged. In that subject, who had a slight shortening of the warfarin half-life, the magnitude of the change was small and similar to that seen in the control group. In two residents, the plasma warfarin half-lives, which were prolonged after four months, showed the same or even greater prolongation after a year of work in the operating room. Apparent volumes of distribution of warfarin in control subjects were 9.6 ± 0.4 liters and 8.9 ± 0.5 liters (mean ± SE) for the two determinations. Apparent volumes of distribution of warfarin in the anesthesiology residents were 8.9 ± 1.2 liters initially and 10.7 ± 1.0 liters after they

TABLE 1. Plasma Half-lives of Warfarin (Hours), Single Oral Dose, 40 mg/m²

Anesthesiology Residents				Control Subjects		
	Initial (before Working in Operating Room)	4 Months Later	12 Months Later		Initial	4 Months Later
Subject 1	37.9	64.2	66.0	Subject 8	32.1	34.0
Subject 2	31.2	38.7	74.5	Subject 9	29.9	34.0
Subject 3	33.0	70.0		Subject 10	44.1	42.3
Subject 4	11.7	42.3		Subject 11	52.1	45.6
Subject 5	34.8	48.1		Subject 12	35.5	32.5
Subject 6	41.0	36.7				
Subject 7	35.2	45.3				
Mean	32.1	49.3			38.8	37.7
SE	3.6	4.8			4.1	2.6
t	3.12*			0.58		

* Significant, $P < 0.05$, by t test for paired data.

TABLE 2. Plasma Levels of Warfarin, Single Oral Dose, 40 mg/m²

	Warfarin in Plasma (μg/ml)*							
	3 Hours	6 Hours	9 Hours	12 Hours	24 Hours	36 Hours	48 Hours	60 Hours
Anesthesiology residents (n = 7)								
Initial	6.9 ± 0.9	6.6 ± 0.5	6.3 ± 0.4	6.5 ± 0.6	4.8 ± 0.2	4.2 ± 0.2	2.5 ± 0.1	2.3 ± 0.1
4 months later	6.7 ± 0.9	6.6 ± 0.6	6.6 ± 0.6	6.1 ± 0.5	4.8 ± 0.5	4.4 ± 0.5	3.3 ± 0.5	3.0 ± 0.4
Control group (n = 5)								
Initial	6.4 ± 0.8	7.0 ± 0.3	6.7 ± 0.2	6.7 ± 0.3	5.0 ± 0.2	4.2 ± 0.2	3.3 ± 0.2	2.6 ± 0.3
4 months later	6.5 ± 1.0	7.5 ± 0.3	7.1 ± 0.2	6.8 ± 0.2	5.5 ± 0.2	4.5 ± 0.3	3.5 ± 0.2	2.8 ± 0.2

* Mean ± SE.

had worked for four months in the operating room. There was no significant difference among these values.

Plasma warfarin levels (mean ± SE) for the two groups are shown in table 2. There was no significant difference among these values at any time point. *Prothrombin responses* for individual subjects in both groups are shown in table 3. Prothrombin responses determined on the two occasions at an interval of four months did not change significantly in the control subjects. However, after exposure to the operating room environment for four months, prothrombin responses in the anesthesiology residents were significantly greater than their initial values. The three subjects with the greatest changes in the half-lives (Subjects 2, 3, and 4) had the greatest increases in prothrombin responses, so changes in prothrombin response paralleled changes in plasma warfarin half-life.

Discussion

Warfarin is cleared from the plasma primarily by metabolism. Changes in plasma half-life of warfarin are considered to reflect, therefore, alterations in the rate of its metabolism by hepatic microsomal enzymes.[6] In our study the plasma half-life of warfarin appeared to be a highly reproducible characteristic of normal, nonmedicated subjects. Vesell *et al.* have shown this to be true for other drugs such as antipyrine and dicumarol.[7] For this reason, a change in the plasma warfarin half-life in a given individual over a period of time indicates that some environmental factor has influenced the rate of warfarin metabolism. Assuming no change in the availability of vitamin K, a change in prothrombin response to a given dose of warfarin would indicate a similar influence, since the effect of warfarin on prothrombin complex activity

TABLE 3. Prothrombin Time (Seconds) Versus Hours after Warfarin Dose, Area under the Curve (sec–hr)

Anesthesiology Residents				Control Subjects		
	Initial (before Working in Operating Room)	4 Months Later	12 Months Later		Initial	4 Months Later
Subject 1	1,482	1,560	1,848	Subject 8	1,443	1,326
Subject 2	1,449	1,572	1,722	Subject 9	1,884	1,932
Subject 3	978	1,544		Subject 10	1,649	1,785
Subject 4	1,140	1,644		Subject 11	1,732	1,882
Subject 5	1,342	1,476		Subject 12	1,640	1,724
Subject 6	1,554	1,488				
Subject 7	1,416	1,578				
Mean	1,337	1,552			1,670	1,730
SE	78	22			64	96
t	2.45*				1.25	

* Significant, $P < 0.05$, by t test for paired data.

is related to warfarin plasma levels.[8] Alterations in the volume of distribution of warfarin could theoretically account for changed plasma warfarin half-lives. However, in this study the apparent volumes of distribution of warfarin were too similar on repeated determination to explain the large change in warfarin half-life observed in the anesthesiology residents.

Our data suggest that exposure of an individual to the operating room environment is associated with a change in warfarin metabolism. Although other factors could be involved, one possibility is that this represents the result of frequent exposure to subanesthetic amounts of volatile anesthetics. Other studies have shown that anesthetic gases are present in the operating room air[7] and in the blood of the anesthetist.[9]

Repeated exposure of animals to low or subanesthetic amounts of these agents stimulates drug metabolism.[3] Cascorbi *et al.* reported than anesthesiologists metabolized halothane at a faster rate and to a greater extent than a group of subjects not exposed to anesthetic agents.[10] A later preliminary report suggested absence of such a difference with respect to fluroxene metabolism.[11] We have not been able to find reports of inhibition of drug metabolism in either animals or man after low-level exposure to anesthetic agents.

Since the development of hepatic disease may change the plasma half-lives of various drugs,[12–14] prolongation of warfarin half-life in anesthesiologists might also represent some nonspecific hepatotoxic effect of exposure to the operating room environment. Chenoweth *et al.* described histologic evidence of hepatic toxicity in rats chronically exposed to subanesthetic concentrations of halothane and methoxyflurane.[15] There was no consistent change in results of standard liver function tests of the animals. Although anesthesiologists have a higher incidence of hepatic disease than other physicians working outside the operating room,[16] we have not been able to find histologic or liver function test studies of alterations in occupationally exposed populations. The prolongation of plasma warfarin half-life may be a more sensitive indicator of low-grade hepatic injury than the standard liver function tests.

The results of this study indicate the need for additional studies of the effects of exposure to the operating room environment.

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