Antipyrine clearance and metabolism in patients with psoriasis

K. KUBOTA, T. ISHIZAKI, K. CHIBA, A. TAKAGI¹, A. NAKAGAWA² & K. NAKAMURA²

Division of Clinical Pharmacology, Clinical Research Institute, National Medical Center, Tokyo,

¹Takagi's Dermatological Clinic, Obihiro City, Hokkaido, and ²Analytical and Metabolic Research Laboratories, Sankyo Co. Ltd, Tokyo, Japan

1 The kinetic parameters of antipyrine obtained from saliva samples and the appearance of major antipyrine metabolites (4-hydroxyantipyrine, norantipyrine and 3-hydroxymethylantipyrine) in urine samples were measured in 10 patients with psoriasis (six nonsmokers and four smokers) and in 20 healthy subjects (11 nonsmokers and nine smokers).

2 The volume of distribution and total clearance of antipyrine were not significantly different between psoriatic patients and control subjects subdivided according to smoking habit. However, antipyrine half-life was significantly ($P < 0.05$) shorter in nonsmoking psoriatics than in nonsmoking controls.

3 There were no significant differences in mean values for the amounts (% dose) and partial clearances for production of major antipyrine metabolites between non-smoking patients and non-smoking controls, between smoking patients and smoking controls, and between patients overall and controls overall.

4 The total clearance of antipyrine and the partial clearances of antipyrine to its three main metabolites were significantly ($P < 0.05$ to 0.01) greater in smoking controls than in nonsmoking controls, and the total clearance of antipyrine and the partial clearance to 4-hydroxyantipyrine were significantly ($P \leq 0.05$) greater in smoking patients than in nonsmoking patients.

5 These findings provide no evidence that psoriasis is associated with an alteration in hepatic microsomal monooxygenase activity, at least insofar as the formation of major antipyrine metabolites is concerned.

Keywords psoriasis antipyrine metabolites smoking aryl hydrocarbon hydroxylase hepatic microsomal monooxygenase

Introduction

Aryl hydrocarbon hydroxylase (AHH) is a component of the microsomal monooxygenase system responsible for the oxidation of a wide variety of drugs and other chemicals (Alvares *et*

al., 1973; Kapitulnik *et al.*, 1976, 1977). Attention has been paid to AHH activity in the skin of patients with psoriasis (Shuster *et al.*, 1979, 1980; Chapman *et al.*, 1979, 1980; Finnen *et al.*,

Correspondence: Dr Takashi Ishizaki, Division of Clinical Pharmacology, Clinical Research Institute, National Medical Center, Toyama, 1-21-2, Shinjuku-ku, Tokyo 162, Japan

1983; Bickers *et al.*, 1984), because polycyclic hydrocarbons contained in tar, which is used as a main therapy for this skin disorder, are converted into carcinogens by AHH. If epidermal AHH activity is lowered in psoriasis as originally reported (Chapman *et al.*, 1979, 1980; Shuster *et al.*, 1980), an attractive hypothesis can be proposed that patients with psoriasis are resistant to skin cancer from environmental chemicals. Epidemiological studies, however, do not support this hypothesis (Stern *et al.*, 1980, 1982).

The relationship between the clearance of antipyrine (AP), a drug metabolized primarily by hepatic microsomal monooxygenase activity (Park, 1982), or the partial clearance of AP to each metabolite and AHH activity is uncertain. Kalamegham *et al.* (1979) have shown a weak correlation ($r = 0.52$) between the *in vivo* AP elimination rate and *in vitro* benzo[a]pyrene hydroxylase activity, but concluded that the AP test is not satisfactory for predicting AHH activity in human liver. On the other hand, Kapitulnik *et al.* (1977) have reported a higher correlation ($r = 0.85$) between the 4-hydroxylation of AP and benzo[a]pyrene hydroxylase activity in 32 specimens of human liver *in vitro*. The clearance of AP has been reported to be lowered in patients with psoriasis who do not smoke as compared to nonsmoking controls (Chapman *et al.*, 1981). This was confirmed using a larger sample size (Marsden *et al.*, 1984). These observations suggested that psoriasis is likely to be associated with a defect in some of the cytochromes concerned with microsomal oxidation. However, previous studies (Chapman *et al.*, 1981; Marsden *et al.*, 1984) have examined only the total clearance of AP, and not that to its individual metabolites. This study was designed to determine any selective effect of psoriasis on the formation of AP metabolites.

Methods

Subjects

Ten outpatients with chronic discoid psoriasis (six nonsmokers and four smokers) and 20 healthy volunteers (11 nonsmokers and nine smokers) were the study subjects. Their demographic characteristics are shown in Table 1. Written informed consent was obtained before the study. Women taking oral contraceptives were excluded from the study. Each patient was judged to be free of disease except for psoriasis by a medical history, physical examination and laboratory tests (haemogram, urinalysis, serum albumin, total protein, serum bilirubin, alanine aminotransferase, creatinine, cholesterol, uric

acid, blood sugar level, serum electrolytes). All drug therapy was stopped in the patients at least 3 weeks before and during the study. An estimate of the extent of psoriasis (% affected per body surface) was recorded for each patient and this ranged from 8 to 21% in the 10 patients (Table 1). The normal controls were judged to be healthy on the basis of a history, physical examination and laboratory tests.

Details of tobacco, alcohol, tea (and/or coffee) consumption and dietary status were recorded. All of the smokers smoked more than an average of 20 cigarettes per day. Diet is known to affect the clearance of AP (Vestal *et al.*, 1975; Kappas *et al.*, 1976; Fraser *et al.*, 1977). However, there were no obvious differences in diet between the patients and normal control subjects. All subjects took Japanese tea regularly and some took coffee, but the total daily consumption of caffeine did not differ between the groups. In addition, there was no difference in alcohol consumption between the two groups.

Antipyrine test

AP ($10 \text{ mg kg}^{-1} \text{ kg body weight}$) in 200 ml water was administered orally to all subjects after an overnight fast. Saliva samples were collected at 2, 4, 6, 9, 12, 24, 28 and 32 h postdose. Urine samples were collected up to 48 h after dosing. Sodium metabisulphite (500 mg) was added to the urine collection bottles as an antioxidant to stabilize AP metabolites (Danhof *et al.*, 1979; Nakagawa *et al.*, 1982). Saliva and urine samples were stored at -20°C until analyzed.

Assay

AP in saliva was measured by the gas-liquid chromatographic method of Knights *et al.* (1981). AP, 4-hydroxyantipyrine (4OHA), norantipyrine (NORA) and 3-hydroxymethylantipyrine (3HMA) in urine were measured after enzymatic hydrolysis of the conjugates with glucuronidase by an automated high-performance liquid chromatographic method (Nakagawa *et al.*, 1982).

Calculations

AP half-life ($t_{1/2}$) was calculated by least-squares regression analysis of the log saliva concentration-time curve. The apparent volume of distribution (V) was calculated by dividing the given dose by the extrapolated value of the AP concentration at zero time. Total AP clearance (CL) was calculated from $\text{CL} = 0.693 \cdot V/t_{1/2}$. The partial clearance of AP to each metabolite was calcu-

lated by multiplying total drug clearance by the fraction of the dose excreted as the metabolite in the urine (Danhof *et al.*, 1982; Teunissen *et al.*, 1982). CL_{4OHA} , CL_{NORA} and CL_{3HMA} are the partial clearances for production of 4OHA, NORA and 3HMA, respectively. The fraction excreted was obtained by extrapolation of the amounts excreted in 48 h to infinity using the AP $t_{1/2}$. CL_{rest} , the clearance to unmeasured products plus the renal clearance of unchanged AP was calculated from the difference between CL and ($CL_{4OHA} + CL_{NORA} + CL_{3HMA}$). Renal clearance of AP is negligible (Danhof *et al.*, 1982).

Data are expressed as means $\pm$ standard deviation (s.d.). Student's *t*-test, Mann-Whitney U-test and Fisher's exact probability test were used for the statistical evaluation of the data as appropriate. A *P* value of ≤ 0.05 was taken to indicate statistical significance. The minimum detectable difference with $\beta = 0.2$ was used to evaluate the type 2 error (Lachin, 1981).

Results

The mean ($\pm$ s.d.) values for age and body weight were not significantly different between the psoriatic and normal groups as a whole and among the four subgroups according to the absence or presence of habitual smoking. Four of 10 patients and two of the control subjects were females ($P = 0.076$, Fisher's exact probability test), all of these being nonsmokers (i.e., four of six nonsmoking patients and two of 11 nonsmoking normal subjects, Table 1, $P = 0.072$ Fisher's test).

The individual and mean kinetic parameters of AP obtained from saliva samples are listed in Table 1. The mean data on the amounts (% dose) and partial clearances of AP to its metabolites are summarized in Table 2. The individual values for the partial clearances of AP to 4OHA, NORA and 3HMA are shown in Figure 1.

When all data (from nonsmokers and smokers) were compared, the mean AP $t_{1/2}$ was significantly ($P < 0.05$) shorter in patients with psoriasis. Otherwise, all other kinetic parameters of AP obtained from saliva samples, the amounts excreted in urine and the partial clearances were not significantly different (Tables 1 and 2, Figure 1).

No statistically significant differences were observed in the mean values of *V* and CL between nonsmoking patients and nonsmoking controls, while the mean $t_{1/2}$ value was significantly ($P < 0.01$) shorter in the nonsmoking psoriatics compared to the nonsmoking normal group (Table 1). Habitual smoking influenced

Figure 1 Individual data for the partial clearances for production of major antipyrine metabolites, 4-hydroxyantipyrine (4OHA), norantipyrine (NORA) and 3-hydroxymethylantipyrine (3HMA).

Circles (○, ●) and triangles (△, ▲) indicate the data obtained from normal subjects and patients with psoriasis, respectively. Open and solid symbols indicate nonsmokers and smokers, respectively. Solid and dotted horizontal bars indicate the mean and 1 s.d. in each of the groups.

AP disposition and the formation of major AP metabolites in the two groups (Tables 1 and 2). Thus, in the normal group, the mean AP $t_{1/2}$ was significantly ($P < 0.01$) shorter, and the mean values for CL, CL_{4OHA} , CL_{NORA} and CL_{3HMA} were significantly ($P < 0.05$ to < 0.01) greater in smokers than in nonsmokers; in the psoriatic group, CL showed a marginal difference of statistical significance ($P < 0.06$ by *t*-test, but not by U-test) and CL_{4OHA} was significantly ($P < 0.05$ by *t*-test and by U-test) greater in smoking vs nonsmoking patients. Although not significant, a similar trend as observed in the normal group was also seen in the psoriatic group when the mean data for CL_{NORA} and CL_{3HMA} in nonsmoking and smoking patients were compared (Table 2). The respective mean values for CL_{rest} were 12.1 ± 5.0 , 16.0 ± 6.6 and 13.6 ± 5.7 ml h^{-1} kg^{-1} in the nonsmoking ($n = 6$), smoking ($n = 4$) overall groups of psoriatic patients, and 9.8 ± 2.9 , 12.5 ± 3.3 and 11.0 ± 3.3 ml h^{-1} kg^{-1} in the nonsmoking ($n = 11$), smoking ($n = 9$) and overall groups of normal subjects. There were no significant differences in these mean values, except for the data in normal non-

Table 1 Demographic characteristics of patients with psoriasis and normal healthy subjects, and their antipyrine (AP) kinetic parameters obtained from saliva samples

Study group	Age (years)	Weight (kg)	Sex	Skin affected (% body surface)	Daily consumption of cigarettes	AP kinetic parameters		
						t _½ (h)	V (l kg ⁻¹)	CL (ml h ⁻¹ kg ⁻¹)
Patients with psoriasis								
Nonsmokers								
M.K.	52	67	M	10	0	14.4	0.58	28.1
K.M.	29	75	M	13	0	16.4	0.56	23.7
H.N.	49	63	F	21	0	13.6	0.62	31.5
N.K.	36	61	F	16	0	10.8	0.58	37.1
H.O.	25	55	F	8	0	12.4	0.53	29.4
S.A.	59	54	F	11	0	15.8	0.46	20.3
mean	41.7	62.5		13.2		13.9†‡§§	0.56	28.4
±s.d.	±13.6	±7.8		±4.7		±2.1	±0.06	±5.9
Smokers								
N.Y.	40	86	M	10	35	10.7	0.60	38.6
Y.N.	31	65	M	13	20	10.9	0.73	46.5
I.N.	43	61	M	12	20	14.6	0.52	25.2
K.K.	23	53	M	12	20	9.5	0.67	50.6
mean	34.3	66.3		11.8		11.4	0.63	40.2*
±s.d.	±9.1	±14.1		±1.3		±2.2	±0.09	±11.2
Overall								
mean	38.7	64.0		12.6		12.9†§	0.59	33.1
±s.d.	±11.4	±9.7		±3.7		±2.4	±0.08	±9.9
Normal healthy subjects								
Nonsmokers								
C.K.	31	52	M	—	0	19.1	0.65	23.6
E.T.	27	56	M	—	0	14.8	0.50	28.5
F.T.	26	53	F	—	0	14.8	0.61	26.8
K.S.	32	80	M	—	0	14.8	0.54	25.2
N.K.	40	73	M	—	0	17.2	0.73	29.4
S.T.	29	68	M	—	0	18.6	0.63	23.5
S.T.	29	65	M	—	0	17.9	0.71	27.5
S.I.	24	55	F	—	0	18.5	0.68	25.4

Study group	Age (years)	Weight (kg)	Sex	Skin affected (% body surface)	Daily consumption of cigarettes	AP kinetic parameters		
						$t_{1/2}$ (h)	V (l kg ⁻¹)	CL (ml h ⁻¹ kg ⁻¹)
F.M.	43	65	M	—	0	22.0	0.48	15.2
G.S.	33	66	M	—	0	20.7	0.56	18.9
K.M.	32	68	M	—	0	16.4	0.54	20.9
mean	31.5	63.7				17.7	0.60	24.1
±s.d.	±5.7	±8.9				±2.4	±0.09	±4.3
<i>Smokers</i>								
A.M.	28	58	M	—	25	13.7	0.67	33.9
I.T.	41	66	M	—	25	11.5	0.62	37.4
N.F.	28	70	M	—	25	15.3	0.68	30.9
S.T.	27	68	M	—	20	12.0	0.63	36.6
S.K.	23	60	M	—	20	11.7	0.68	40.4
K.S.	43	60	M	—	40	12.4	0.53	29.5
J.U.	38	63	M	—	20	18.5	0.58	21.6
S.I.	32	65	M	—	20	10.1	0.66	45.5
G.T.	44	70	M	—	55	10.4	0.70	46.9
mean	33.8	64.4				12.8††††	0.64	35.9††††
±s.d.	±7.8	±4.5				±2.7	±0.06	±8.0
<i>Overall</i>								
mean	32.5	64.1				15.5	0.62	29.4
±s.d.	±6.7	±7.1				±3.5	±0.07	±8.5
<i>Minimal detectable difference^a</i>								
nonsmokers	14.3	13.4						
smokers	15.4	15.6						
overall	9.9	9.3						

* $P < 0.05$ and ** $P < 0.01$ compared with nonsmokers within the same study group (t -test).
† $P < 0.05$ and †† $P < 0.01$ compared with the respective normal control group (t -test).
††† $P < 0.01$ compared with nonsmokers within the same study group (U-test).
§ $P < 0.05$ and §§ $P < 0.01$ compared with the respective normal control group (U-test).
^aA power of 80% ($\beta = 0.2$) and $\alpha = 0.05$ (two-sided) were assumed.
CL = $0.693 \cdot V/t_{1/2}$ where CL = total antipyrine clearance, V = apparent volume of distribution and $t_{1/2}$ = half-life.

Table 2 Mean ($\pm$ s.d.) amounts (% dose) excreted in urine as 4-hydroxyantipyrine (4OHA), norantipyrine (NORA) and 3-hydroxymethylantipyrine (3HMA), and the partial clearances for production of 4OHA, NORA and 3HMA in each study group

Study group	Amount excreted in urine (% dose) ^a			Partial clearance (ml h ⁻¹ kg ⁻¹)		
	4OHA	NORA	3HMA	4OHA	NORA	3HMA
<i>Patients with psoriasis</i>						
nonsmokers (n = 6)	27.9 $\pm$ 3.3	18.8 $\pm$ 5.1	10.9 $\pm$ 1.9	7.9 $\pm$ 0.9	5.3 $\pm$ 1.5	3.1 $\pm$ 0.6
smokers (n = 4)	30.6 $\pm$ 10.0	17.6 $\pm$ 11.0	12.1 $\pm$ 5.7	12.3 $\pm$ 4.0†*	7.1 $\pm$ 4.4	4.9 $\pm$ 2.3
overall (n = 10)	29.2 $\pm$ 10.0	18.2 $\pm$ 8.8	11.5 $\pm$ 1.3	9.7 $\pm$ 3.3	6.0 $\pm$ 2.9	3.8 $\pm$ 1.7
<i>Normal healthy subjects</i>						
nonsmokers (n = 11)	29.8 $\pm$ 6.4	16.7 $\pm$ 5.0	12.1 $\pm$ 3.2	7.2 $\pm$ 1.6	4.0 $\pm$ 1.2	2.9 $\pm$ 0.8
smokers (n = 9)	33.4 $\pm$ 11.4	16.6 $\pm$ 4.6	15.0 $\pm$ 5.7	12.0 $\pm$ 4.1††*	6.0 $\pm$ 1.7††*	5.4 $\pm$ 2.1††*
overall (n = 20)	31.8 $\pm$ 12.8	16.7 $\pm$ 5.8	13.7 $\pm$ 6.5	9.3 $\pm$ 3.8	4.9 $\pm$ 1.7	4.1 $\pm$ 1.9
<i>Minimal detectable difference^b</i>						
nonsmokers	8.7	7.9	4.4	2.1	2.0	1.1
smokers	20.7	18.3	12.0	7.6	5.1	4.0
overall	13.9	8.0	6.3	4.2	2.5	2.1

^aObtained by extrapolation of the amounts excreted in 48 h to infinity using the antipyrine $t_{1/2}$.

^bA power of 80% ($\beta = 0.2$) and $\alpha = 0.05$ (two-sided) were assumed.

* $P < 0.05$ compared with nonsmokers within the same study group (t -test).

† $P < 0.05$ and †† $P < 0.01$ compared with nonsmokers within the same study group (U-test).

smokers vs smokers ($P < 0.05$ by t -test, but not by U -test).

When the respective amounts of major AP metabolites excreted in urine or the respective partial clearances of AP to its metabolites in psoriatic patients were compared to those in normal controls, there were no statistically significant differences in the mean data among the groups subdivided according to the smoking habit and between the overall patient and control groups. We evaluated the type 2 error (Lachin, 1981) for all of the above data and estimated the minimal detectable differences with $\beta = 0.2$ in the mean values. The differences with $\beta = 0.2$ in the urinary amounts of AP metabolites or in the partial clearances of AP to its metabolites between psoriatic patients and control subjects were at most 30% for 4OHA, 40% for 3HMA and 50% for NORA of the respective mean values of the nonsmoking controls. However, the minimal detectable differences in the above data between smoking patients and smoking controls were roughly equal to the respective mean values obtained from the normal smoking controls (Table 2). The minimal detectable difference with $\beta = 0.2$ in CL_{rest} was 5.8, 9.3 and 4.9 $\text{ml h}^{-1} \text{kg}^{-1}$ when the nonsmoking, smoking and overall subjects were compared between the psoriatic and control groups.

The extent of psoriasis (% affected per body surface) showed no correlation with any kinetic parameters of AP or partial clearances for production of AP metabolites in this small group of patients.

Discussion

The clearance of AP has been reported to be lower and its $t_{1/2}$ longer in psoriatics compared to control subjects (Chapman *et al.*, 1981; Marsden *et al.*, 1984). However, our results did not support these findings. This discrepancy may be due to the differences in sample size, sex distribution, or environmental factors including diet and ethnic backgrounds. The shorter AP $t_{1/2}$ observed in the nonsmoking and overall patient groups as compared to the respective control groups (Table 1) is possibly due to a larger proportion of females in the psoriatic group (four of 10). Female subjects have been reported to show a shorter AP $t_{1/2}$ compared to male subjects (Teunissen *et al.*, 1982).

The observation that the formation of 4OHA, which has been reported to be well correlated with AHH activity in human liver *in vitro*

(Kapitulnik *et al.*, 1977), was not altered in nonsmoking psoriatic patients as compared to that in nonsmoking control subjects suggests that there would be no appreciable differences in the basal AHH activity between the psoriatic and control groups.

Finnen *et al.* (1983) found that AHH activity in fresh liver specimens biopsied from patients with psoriasis was comparable with values from normal subjects. Although these data are inconclusive because of the small sample size ($n = 2$), Finnen *et al.* (1983) also found that AHH activity in skin and jejunal mucosa from psoriatic patients was similar to that in normal controls. Similar results on basal AHH activity in psoriatic epidermis have been reported by Bickers *et al.* (1984). Therefore, based upon our results, at least insofar as the formation of 4OHA is concerned, our finding is consistent with the previous observation that there seems to be no generalized tissue abnormality of AHH activity in psoriasis (Finnen *et al.*, 1983), but not with the original observation by Chapman *et al.* (1980).

One of the influences of smoking on drug disposition is a selective effect on drug metabolism (Jusko, 1978; Dawson & Vestal, 1982). Accordingly, our healthy smokers showed an increase in the partial clearances of AP to its metabolites (Table 2, Figure 1). The extent of the increase appeared to be greater in $CL_{4\text{OHA}}$ and $CL_{3\text{HMA}}$ than that in CL_{NORA} (Table 2). This is in accordance with the observation of Dahlqvist *et al.* (1984) that smoking induces only two hydroxylations of AP (3- and 4-hydroxylation) but not N -demethylation to NORA. A similar trend to that observed in normal subjects was also found in psoriatic patients, although a significant difference between nonsmoking and smoking patients was seen only in $CL_{4\text{OHA}}$ (Table 2).

Although the statistical analyses of our results (using t - and U -tests) showed that all of the mean data as given in Tables 1 and 2, except for AP $t_{1/2}$ (Table 1), did not reach statistical significance in nonsmoking patients vs nonsmoking controls, smoking patients vs smoking controls, and overall patients vs overall controls, a rigorous analysis requires evaluation of the possibility of a Type 2 statistical error (Freiman *et al.*, 1978; Lachin, 1981). The results indicated that we may neither reject nor accept the null hypothesis.

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