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Metabolic Disposition of Antipyrine in Patients with Lung Cancer[1]

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SUMMARY

The metabolism of antipyrine (10 mg/kg i.v.) was studied in nine patients with cancer of the lung and in a cancer-free control group matched for age, sex, drug intake, and smoking and drinking history. The mean plasma clearance of antipyrine was 0.0475 ± 0.009 liter/kg/hr in the tumor group and 0.0557 ± 0.007 liter/kg/hr in the control group ($p > 0.05$). The antipyrine plasma elimination half-life was longer in the group with tumors (9.5 ± 1.3 hr) compared to the control group (7.7 ± 1.3 hr), but the difference was not statistically significant ($p > 0.05$). There was no difference between the groups in the excretion of two major antipyrine metabolites, 4-hydroxyantipyrine and *N*-demethylantipyrine, in a 48-hr urine sample. Thus, the presence of lung cancer in humans does not significantly alter antipyrine elimination.

INTRODUCTION

In animals, the presence of some tumors is associated with inhibition of hepatic microsomal drug metabolism (14). Zoxazolamine hydroxylation is decreased in liver microsomes from rats bearing the Walker 256 carcinosarcoma, Flexner-Jobling sarcoma, Sarcoma 45, and the uterine epithelioma of Queren (7) compared to non-tumor-bearing controls. In contrast, adenocarcinoma R-3230 AC did not exert this effect (22). There was good correlation between the tumor size and enzyme inhibition with a maximum effect observed when the tumor was greater than 10% of the body weight of the animal. Injection of tumor extracts into normal rats also produced an inhibitory effect on hepatic drug metabolism. A polypeptide, toxohormone, has been isolated from tumor extracts and partially purified by Nakahara and Fukuoka (18). This substance also inhibited hepatic drug metabolism in rats when injected i.p. Kato *et al.* (13) have demonstrated a reduction in both liver cytochrome P-450 and substrate P-450 binding by toxohormone. The humoral nature of toxohormone was corroborated in parabiotic rats in which only 1 of the pair bore a nonmetastasizing tumor (4) whereas inhibition of drug metabolism was observed in both.

Information concerning drug metabolism in humans with cancer is particularly important, since patients usually receive a number of drugs that are metabolized by the liver microsomal system. For example, the alkylating agent cyclophosphamide must be metabolized to an active form (5) whereas busulfan is metabolized to an inactive form (2). Thus, it is obvious that knowledge about alterations in drug metabolism in cancer patients would be particularly useful to the chemotherapist.

In contrast with the animal studies, Ambre *et al.* (1) reported a shortened plasma elimination half-life of antipyrine in patients with lung cancer compared to normal volunteers. This apparent discrepancy might be due to inadequate matching of the control group since cigarette smoking (9), age (21), and exposure to other drugs (11, 19, 20) and to environmental pollutants (17) may alter the rate of antipyrine metabolism. We report here the metabolism of antipyrine in patients with lung cancer matched with a cancer-free control group for age, sex, weight, smoking habits, and utilization of alcohol and other drugs.

MATERIALS AND METHODS

Patients. Patients with a biopsy-proven diagnosis of lung cancer and a cancer-free control group were selected from the medical and surgical services of the Kansas City Veterans Administration Hospital. There was no evidence of hepatic metastases in the liver scan of any of the tumor-bearing patients. Each cancer patient was matched to a control volunteer on the basis of drug exposure, alcohol intake, smoking, age, weight, and sex (in order of relative importance). Subjects with a creatinine clearance less than 50 ml/min, serum bilirubin greater than 2.0 mg/dl, or with a systemic disorder other than cancer, known to alter drug metabolism, were excluded from the study. None of the cancer patients was receiving chemotherapy or radiation therapy at the time of this study. None of the patients was on a restricted diet or malnourished.

Written, informed consent was obtained from each volunteer before he was accepted into the study.

Antipyrine Study. Each volunteer was given antipyrine (10 mg/kg) i.v. at 8 a.m. Blood samples were drawn into tubes containing sodium heparin (base line, 2, 4, 6, 8, 12, 24, 36, and 48 hr.) Urine was collected before the drug was given and then from 0 to 4, 4 to 8, 8 to 12, 12 to 24, and 24 to 48 hr. Blood samples were centrifuged, and the plasma and the urine fractions were stored at −20° until assayed.

Assays. Antipyrine and its 4-hydroxy metabolite were

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determined in plasma and urine by a modification of the gas chromatographic method of Huffmann *et al.* (10) with acetophenetidin as an internal standard. The *N*-demethylantipyrine metabolite was measured by gas chromatography-mass spectrometry with 4-chlorobenzhydrol (Aldrich Chemical Co., Milwaukee, Wis.) as an internal standard. One ml of urine was acidified with 0.2 ml of 2 N hydrochloric acid and hydrolyzed in a boiling water bath for 45 min. After this was cooled, 5 ml of nanograde chloroform (Mallinckrodt Chemical Works, St. Louis, Mo.), containing 25 μg of 4-chlorobenzhydrol, were added, and the mixture was shaken for 10 min. After centrifugation, the aqueous layer was removed by aspiration, and 4 ml of the chloroform layer were transferred into conical, siliconized tubes and evaporated to dryness at 50° under an air stream. The residue was dissolved in 20 μl of methanol, and 0.2 to 0.3 μl of the resulting solution was analyzed by gas chromatography-mass spectrometry (Finnigan 3300 with 6000 data system) using a 40-m × 0.5-mm OV-1 support-coated open tubular column at 110° (8). The ratio of the areas of the peaks in the mass chromatograms of the ions at m/e = 174 (molecular ion of *N*-demethylantipyrine) and m/e = 139 (fragment ion of 4-chlorobenzhydrol) for each sample was determined. The concentration of *N*-demethylantipyrine was obtained by comparison of this ratio to that of a standard curve prepared by addition of varying amounts of *N*-demethylantipyrine (Aldrich) to blank urine.

Mass spectrometry was used for these analyses to obviate interferences due to the presence of compounds in the urine which could not initially be resolved by gas chromatography alone. Subsequently, we have developed a satisfactory gas chromatographic method using support-coated open tubular columns with a flame ionization detector, which will be described in detail elsewhere.[3]

Pharmacokinetic Analyses. Plasma elimination half-life was calculated from the least-squares regression slope of the terminal log-linear plasma data points. C_0, the concentration at zero time, was estimated by extrapolation of the β slope back until it crossed the ordinate (zero time). The area under the plasma concentration × time curve from 0 → 48 hr ($AUC_{0\to48}$) was calculated by the trapezoidal rule. $AUC_{0\to\infty}$ was the sum of $AUC_{0\to48} + C_{48}/\beta$. The apparent volume of distribution (V_d) was calculated from the relationship $V_d = D/C_0$, where D = dose, and plasma clearance (Cl) was calculated by $Cl = D/AUC_{0\to\infty}$.

The paired Student t test was used to test for the probability that a significant difference existed between the means of the 2 groups. A p value less than 0.05 was considered statistically different.

RESULTS

The characteristics of the volunteers are recorded in Table 1. Four patients had squamous cell carcinoma of the lung, 3 had adenocarcinoma of the lung, and 2 had undifferentiated carcinoma of the lung. Although the control patients had a variety of diagnoses, they were clinically well at the time of the study. There were no significant differences in the ages, weights, or smoking and drinking habits of the patients (Table 1). Although it was not possible to match the groups completely for drug exposure, no patient was receiving a drug believed to alter the rate of hepatic drug metabolism.

Laboratory Findings. The blood urea nitrogen, creatinine, and creatinine clearance of the cancer patients and the control group were not significantly different. Similarly, there were no differences in the serum glutamic oxaloacetic transaminase or bilirubin. The serum alkaline phosphatase was normal in 11 and increased in 7 patients. Serum alkaline phosphatase activity was significantly greater in the cancer patients than in the control group ($p < 0.025$).

The pharmacokinetic data for the matched pairs are listed in Table 2. There were negligible differences between the 2 groups in the C_0 or apparent volume of distribution. Although the mean plasma clearance of antipyrine [0.0475 ± 0.009 (S.E.) *versus* 0.0557 ± 0.007 liter/kg/hr] was decreased and the mean antipyrine half-life (9.5 ± 1.3 *versus* 7.7 ± 1.3 hr) was longer in the cancer patients than in the controls, the differences between these 2 groups were not significant. The percentage of antipyrine excreted as 4-hydroxyantipyrine [19.6% (range 10.8 to 32.1) *versus* 16.4% (8.4 to 25.3)], *N*-demethylantipyrine [17.2% (8.8 to 24.6) *versus* 18.2% (6.0 to 24.0)], and unchanged antipyrine [2.0% (0.08 to 3.9) *versus* 2.8% (0.08 to 5.9)] in urine was similar for the 2 groups of patients (Table 2). Neither the rate (Chart 1) nor the cumulative excretion (Chart 2) of 4-hydroxyantipyrine or *N*-demethylantipyrine was significantly different in the 2 groups.

DISCUSSION

In an attempt to resolve the apparent discrepancy between the studies in which inhibition of hepatic drug metabolism is observed in tumor-bearing animals and the clinical study of Ambre *et al.* (1) in which an increased rate of drug clearance in lung cancer patients was demonstrated, we have studied the metabolism of antipyrine in patients with lung cancer and in matched patients without cancer. In contrast with the findings of Ambre *et al.* (1), the antipyrine clearance was not increased and plasma elimination half-life was not shortened in patients with lung cancer when compared with appropriately selected control patients. Indeed, there was a trend toward a longer plasma half-life for antipyrine in the cancer patients. This difference was not statistically significant, but it suggests that inhibition of drug metabolism by lung cancer may occur in humans. In this regard, total tumor burden may be quite important. In animal studies, maximum inhibition occurred when the tumor was 10% of total body weight. The tumor burden in the patients that we studied was substantially less.

Ambre *et al.* (1) do not report the smoking habits of their subjects. Patients with carcinomas of the lung are frequently heavy smokers. Smoking accelerates antipyrine elimination (9) and could account for the difference in half-lives between the cancer and control groups observed in their study if the latter contained significantly fewer smok-

[3] C. E. Hignite, C. Tschanz, D. H. Huffman, and D. L. Azarnoff. Quantitation of *N*-Demethylantipyrine in Biological Samples and Isolation of Characterization of Its Glucuronic Acid Conjugate, submitted for publication.

Table 1

Patient characteristics and laboratory results

Pair	Patients (tumorous and nontumorous)	Diagnosis	Age (yr)	Wt (kg)	Social history: Smoking	Social history: Drinking	Laboratory data: BUN[a] (mg/dl)	Cr (mg/dl)	Cr cl[b] (mg/min)	SGOT (units/ml)	Bili (mg/dl)	Alk phos (units/liter)	Drug exposure history
A	P. H.	Squamous cell carcinoma	56	76	2[c]	1[d]	21	1.6	60	15	0.5	75	Acetaminophen, Flurazepam
	S. F.	Ulcer (leg)	43	67	2	1	11	1.2	75	15	0.4	60	Acetaminophen, Flurazepam
B	B. W.	Squamous cell carcinoma	74	55	0	1	6	0.8	65	28	1.2	120	None
	S. F.	Bronchopneumonia	61	90	0	0	18	1.2	115	27	1.0	60	Digoxin, furosemide, warfarin
C	H. J.	Squamous cell carcinoma	63	70	1	3	13	1.2	65	15	0.6	70	Flurazepam, acetaminophen
	W. C.	Varicose veins	68	80	1	4	19	1.0	110	20	1.0	45	Flurazepam, acetaminophen
D	D. L.	Squamous cell carcinoma	64	56	0	1-2	10	0.9	68	14	0.5	160	Digoxin
	M. J.	Ulcer (gastric)	47	80	0	0	10	1.0	110	32	0.2	90	Chlordiazepoxide
E	M. F.	Adenocarcinoma	51	98	2	1-3	11	1.0	125	17	0.5	75	Diazepam acetaminophen
	O. J.	Pneumonitis	53	70	2	2-4	16	0.7	110	30	0.8	70	Flurazepam
F	W. E.	Adenocarcinoma	58	82	1	1-2	12	0.7	120	58	0.6	175	Digoxin, propoxyphene
	D. H.	Hernia	63	73	2	2	20	1.2	70	15	0.5	70	Acetaminophen
G	S. E.	Adenocarcinoma	62	107	1	1-3	14	1.0	115	20	0.9	75	None
	N. T.	Granuloma	45	61	1	1-2	10	1.0	120	35	1.0	65	None
H	S. R.	Undifferentiated carcinoma	55	50	2	2-4	7	0.9	70	22	0.4	90	Acetaminophen
	C. A.	Pulmonary embolus	52	73	1	1	13	0.8	120	45	0.4	90	Warfarin
I	L. E.	Undifferentiated carcinoma	58	70	2	0	9	0.8	100	15	0.5	110	Aspirin, meperidine, flurazepam
	S. O.	Polyarthritis	59	65	1	1-2	13	0.8	85	20	0.3	85	Aspirin, acetaminophen, ibuprofen
	Tumorous		60.1[e] (2.2)	73.8 (6.5)	1.20 (0.27)	1.66 (0.32)	11.4 (1.5)	0.99 (0.09)	87.6 (9.0)	22.7 (4.7)	0.6 (0.09)	10.6 (13)	
	Nontumorous		54.6 (2.9)	73.2 (3.0)	1.11 (0.26)	1.55 (0.44)	14.4 (1.3)	0.99 (0.06)	101.7 (6.5)	26.5 (3.3)	0.6 (0.17)	70.6 (5)	
			NS	NS	NS	NS	NS	NS	NS	NS	NS	0.025	

[a] BUN, blood urea nitrogen; CR, serum creatinine; Cr cl, creatinine clearance; SGOT, serum glutamic oxaloacetic transaminase; Bili, serum bilirubin; Alk phos, serum alkaline phosphatase; NS, not significant.

[b] Calculated from nomogram of Kampmann *et al.* (12).

[c] 0, nonsmoker; 1, 10 to 20 cigarettes/day; 2, >20 cigarettes/day.

[d] Pints of beer per day or equivalent in alcohol content.

[e] Mean ± S.E.

Table 2

Pharmacokinetic parameters of antipyrine after a 10-mg/kg i.v. dose

Patients with biopsy-proven lung cancer were given antipyrine, 10 mg/kg i.v., and plasma levels were determined at various time periods thereafter. The plasma concentration at zero time (C_0), apparent volume of distribution (V_d), plasma clearance, and excretion of 4-hydroxyantipyrine, *N*-demethylantipyrine, and antipyrine in a 0 → 48-hr urine sample were determined and compared to matched controls who did not have a cancer.

Pair	Patients (tumorous and nontumorous)	C_0 (μg/ml)[a]	V_d (liter/kg)[b]	Plasma clearance (liter/kg/hr)[c]	Plasma $t_{1/2}$ (hr)	Excretion in urine (0 → 48 hr) (% administered dose)			
						4-OH-AP[d]	*N*-Dem-AP	AP	Total recovery
A	P. H.	16.5	0.606	0.0366	11.0	14.1	21.2	1.5	36.8
	S. F.	18.0	0.555	0.0899	4.5	23.6	23.7	2.2	49.5
B	B. W.	17.5	0.571	0.0249	13.5	19.5	12.2	3.9	35.6
	S. F.	18.0	0.555	0.0602	6.3	25.3	23.1	1.7	50.1
C	H. J.	16.2	0.617	0.0709	6.0	32.1	16.0	0.8	48.9
	W. C.	21.0	0.476	0.0540	5.4	9.2	11.9	0.5	21.6
D	D. L.	22.0	0.450	0.0210	13.0	17.9	8.8	1.4	28.1
	M. J.	14.5	0.689	0.0328	12.4	18.0	21.0	5.9	44.9
E	M. F.	17.5	0.571	0.0342	10.0	19.1	24.0	3.9	47.0
	O. J.	16.0	0.625	0.0235	15.7	11.6	6.0	5.7	23.3
F	W. E.	19.0	0.526	0.0678	4.5	15.1	12.5	0.8	28.4
	D. H.	18.5	0.540	0.0653	5.2	16.2	16.0	0.9	33.1
G	S. E.	16.5	0.566	0.0310	13.0	10.8	20.7	0.8	28.4
	N. T.	19.0	0.526	0.0422	10.0	17.4	24.0	2.8	44.2
H	S. R.	18.0	0.555	0.0345	10.6	23.7	24.6	1.9	50.2
	C. A.	17.0	0.588	0.0713	4.6	8.4	23.4	1.5	33.3
I	L. E.	16.2	0.617	0.1070	3.9	24.2	14.5	2.8	41.5
	S. O.	18.5	0.540	0.0620	5.5	17.7	14.9	3.6	36.2
	Tumorous	17.7[e] (0.6)	0.564 (0.017)	0.048 (0.009)	9.5 (1.3)	19.6 (2.1)	17.2 (1.8)	2.0 (0.4)	38.8 (2.9)
	Nontumorous	17.8 (0.6)	0.566 (0.021)	0.056 (0.007)	7.7 (1.3)	16.4 (2.0)	18.2 (2.1)	2.8 (0.7)	37.4 (3.6)
	p	NS	NS	NS	NS	NS	NS	NS	NS

[a] Obtained by extrapolation of log-linear β slope to ordinate (zero time).
[b] V_d = Dose/C_0
[c] Plasma clearance = Dose/$AUC_{0\to\infty}$
[d] 4-OH-AP, 4-hydroxyantipyrine; N-DEM-AP, *N*-demethylantipyrine; AP, antipyrine; NS, not significant.
[e] Mean ± S.E.

ers. Ambre *et al.* (1) demonstrated differences in the rate of antipyrine elimination in the lung cancer patients as a function of the presence of hepatic metastases. In our series, 7 patients (5 tumorous and 2 nontumorous) had elevated serum alkaline phosphatase values. Of these, 2 nontumorous and 1 tumorous patient had levels of 90 units, which was only slightly above the upper limit of normal (85 units) in our laboratory. The remaining 4 cancer patients had approximately a 2-fold elevation in the activity of this serum enzyme. Three of these 4 patients had evidence of bone metastases by radionuclide uptake techniques. All 4 patients had a negative liver-spleen scan and only 1 had a slightly elevated serum bilirubin (1.2 mg/dl). Thus, the elevated serum alkaline phosphatase was most likely of bone origin and and not indicative of hepatic metastases.

Kellerman *et al.* (16) have reported that the inducibility of aryl hydrocarbon hydroxylase in human lymphocytes is higher in patients with lung cancer than in noncancerous subjects. In addition, these investigators found that the inducibility of aryl hydrocarbon hydroxylase activity is highly correlated with the plasma antipyrine elimination half-life in a homogeneous population selected to exclude factors that are known to influence drug metabolism (15). Thus, one might suspect that patients with lung cancer would have shorter half-lives of antipyrine than would a noncancerous group. Our results do not support such a conjecture.

The metabolism of antipyrine is shown in Chart 3. In a previous study (10) we found that the rate of excretion of 4-hydroxyantipyrine in urine correlated quite well with the rate of antipyrine elimination from plasma. However, the overall elimination rate will be the sum of all the pathways of antipyrine metabolism. Therefore, it is possible that

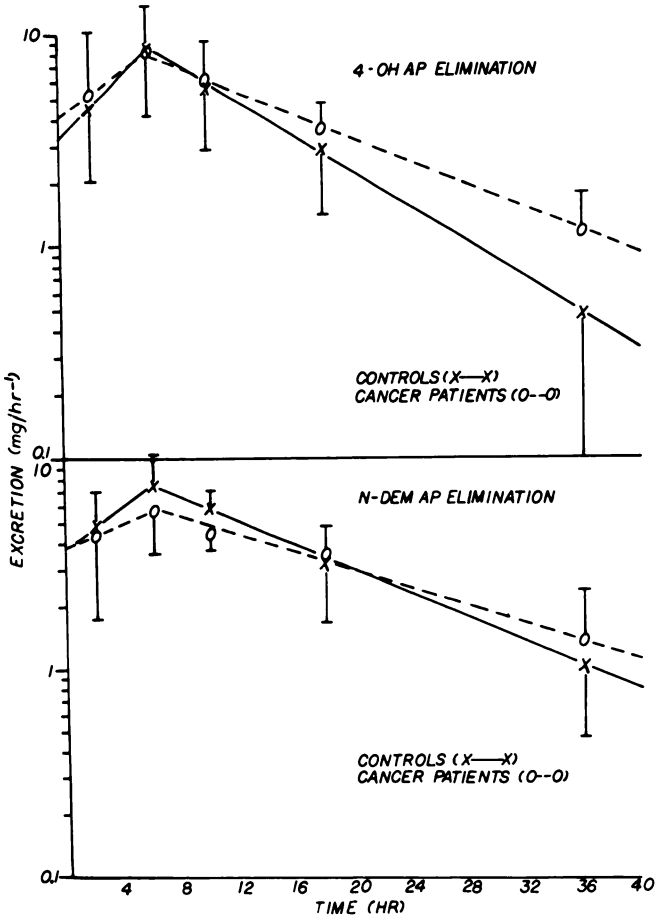

Chart 1. Rate of excretion of 4-hydroxyantipyrine (*4-OH AP*) and *N*-demethylantipyrine (*N-DEM AP*) in urine of patients with lung cancer and in a matched control group. Each value is the mean ± S.E. of 8 individuals.

changes in the rate of formation of the individual metabolites may occur without a change in the overall rate of elimination. In the patients studied, we found the excretion of 4-hydroxyantipyrine in urine to be approximately 18% (8.4 to 32.1) of the i.v. dose, less than the 30 to 40% reported by Brodie and Axelrod (6) using a spectrophotometric method for analysis of this metabolite. Their method depends on a change in absorbance in strong alkali and may not be specific. In addition, only 4 subjects were studied, and no information was given regarding their age or other factors that might alter the rate of drug metabolism. The 24-hr excretion of *N*-demethylantipyrine in urine has been reported to be 6% (3). In contrast, using improved methods, we find substantially more of this metabolite, approximately 15% of the dose being excreted in 24 hr. Again, the investigators only reported the mean for their 6 subjects. *N*-Demethylation of antipyrine is therefore a major route of elimination of this drug in the individuals that we studied.

Since none of the pharmacokinetic parameters, including the excretion of 2 major metabolites, was significantly different between the cancer and the control patients, it is unlikely that the previously published differences in the metabolic fate of antipyrine were due to cancer itself. Studies to evaluate drug metabolism in cancer patients should use appropriately selected control patients.

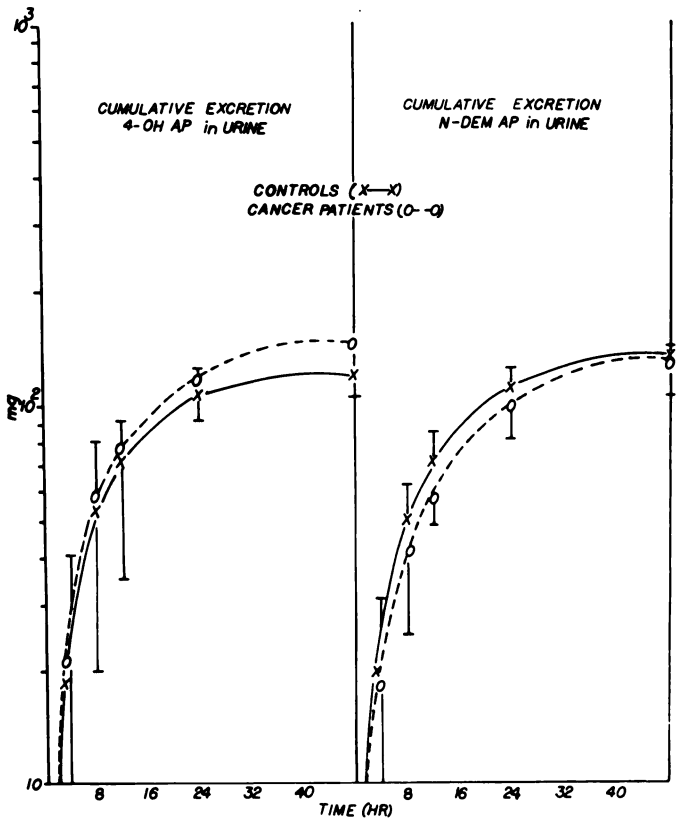

Chart 2. Cumulative 48-hr excretion in urine of 4-hydroxyantipyrine (*4-OH AP*) and *N*-demethylantipyrine (*N-DEM AP*) following an i.v. 10-mg/kg dose of antipyrine.

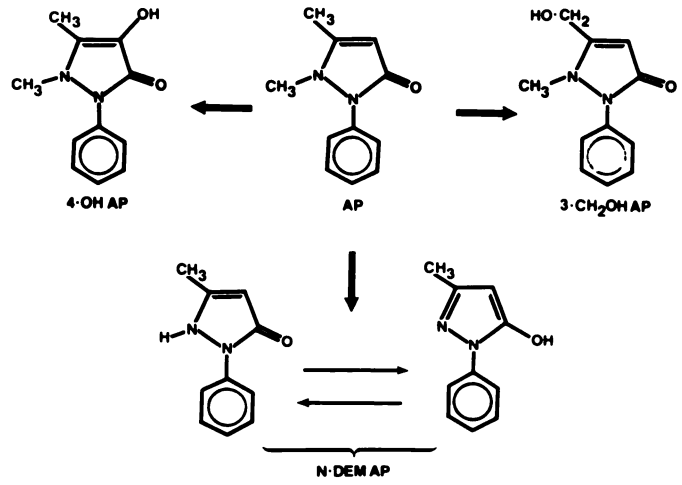

Chart 3. Routes of metabolism of antipyrine in humans. *N-DEM AP*, *N*-demethylantipyrine.

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