Metabolic Disposition of Antipyrine in Patients with Lung Cancer

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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...
determined in plasma and urine by a modification of the gas chromatographic method of Huffman 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 (Mal- 
tinckrodt 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 chromatog- 
raphy-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 chroma-
tography alone. Subsequently, we have developed a satis-
factory 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. C0, the concen-
tration 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 (AUC0–48) was calculated by the trapezoidal rule. 
AUC0→∞ was the sum of AUC0–48 + C0/β. The apparent 
volume of distribution (Vd) was calculated from the rela-
tion Vd = D/C0, where D = dose, and plasma clearance (Cl) 
was calculated by Cl = D/AUC0→∞.

The paired Student t test was used to test for the proba-
bility 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 undif-
fferentiated carcinoma of the lung. Although the control 
patients had a variety of diagnoses, they were clinically

3 C. E. Hignite, C. Tschanz, D. H. Huffman, and D. L. Azarnoff. Quantita-
tion of N-Demethylantipyrine in Biological Samples and Isolation of Charac-
terization of Its Glucuronic Acid Conjugate, submitted for publication.

DISCUSSION

In an attempt to resolve the apparent discrepancy be-
tween the studies in which inhibition of hepatic drug metab-
olism 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. In-
deed, 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 fre-
quently 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-
### Table 1
Patient characteristics and laboratory results

<table>
<thead>
<tr>
<th>Pair</th>
<th>Patients (tumorous and nontumorous)</th>
<th>Diagnosis</th>
<th>Age (yr)</th>
<th>Wt (kg)</th>
<th>Social history</th>
<th>Laboratory data</th>
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* BUN, blood urea nitrogen; Cr, serum creatinine; Cr Cl, creatinine clearance; SGOT, serum glutamic oxaloacetic transaminase; Bilirubin, serum bilirubin; Alk phos, serum alkaline phosphatase; NS, not significant.

\(^a\) Calculated from nomogram of Kampmann et al. (12).

\(^b\) 0, nonsmoker; 1, 10 to 20 cigarettes/day; 2, >20 cigarettes/day.

\(^c\) Pints of beer per day or equivalent in alcohol content.

\(^d\) Mean ± S.E.
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 (C₀), apparent volume of distribution (Vd), 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.

<table>
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<th>Pair</th>
<th>Patients (tumorous and nontumorous)</th>
<th>C₀ (µg/ml)</th>
<th>Vd (liter/kg)</th>
<th>Plasma clearance (liter/kg/hr)</th>
<th>Plasma t₁/₂ (hr)</th>
<th>4-OH-AP (%)</th>
<th>N-Dem-AP (%)</th>
<th>AP (%)</th>
<th>Total recovery (% administered dose)</th>
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* Obtained by extrapolation of log-linear β slope to ordinate (zero time).
* Vd = Dose/C₀
* Plasma clearance = Dose/AUC₀-∞
* 4-OH-AP, 4-hydroxyantipyrine; N-DEM-AP, N-demethylantipyrine; AP, antipyrine; NS, not significant.
* t₁/₂ = 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 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...
Antipyrine Metabolism in Lung Cancer Patients

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

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


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REFERENCES


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