

## Longitudinal Study of Excretion of Metabolites of Polycyclic Aromatic Hydrocarbons in Urine from Two Psoriatic Patients

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Coal tar, which is widely used in the treatment of patients with atopic dermatitis, chronic eczema, and psoriasis, contains a large amount of polycyclic aromatic hydrocarbons (PAH). Some of the PAH compounds are known either to be carcinogenic or to potentiate the effects of other carcinogenic substances. In the present study, the excretion patterns of 1-hydroxypyrene (metabolite of pyrene) and  $\alpha$ -naphthol (metabolite of naphthalene) in urine were studied in 2 patients, both treated once a day with coal tar pitch covering more than 50% of the skin. After 1 week of treatment, the concentration of both  $\alpha$ -naphthol and 1-hydroxypyrene increased approximately 100 times. However, the concentration after 3 weeks of treatment was decreased to approximately the concentration measured before initiation of the treatment, even though the patients were coal tar-treated with unchanged intensity. The measured concentrations of  $\alpha$ -naphthol and 1-hydroxypyrene in the urine of the 2 patients exceeded by order of magnitude the levels measured in the urine of occupationally exposed workers, and in view of the present study, epidemiological studies are needed to clarify to what extent coal tar treatment results in an increased risk of skin cancer, and e.g. bladder cancer. **Key words:** Coal tar; PAH-exposure; Cancer risk.

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Coal tar is widely used in the treatment of patients with atopic dermatitis, chronic eczema, and psoriasis. One of the major groups of components in coal tar is polycyclic aromatic hydrocarbons (PAH). More than 300 PAH components have been identified in coal tar, and it has been estimated that as many as 10,000 components may exist (1). Detailed information on the metabolism of several of the PAH compounds is provided by the International Agency for Research on Cancer (2). In contrast to the small volatile PAH compounds, several of the larger particulate PAH compounds are – based on long-term observations in laboratory animals, occupational medicine and epidemiology – classified as carcinogenic in humans (2). The earliest association of a human cancer with PAH was made more than two centuries ago by Pott (3), who reported an increased incidence of scrotal cancer among chimney workers. Since then, epidemiologic studies have shown a possible correlation between PAH exposure and increase in the frequency of cancer in organs directly related to the route of exposure (4). Recently, it has been shown that molders in iron foundries have an increase in bladder cancer, which may be associated with PAH exposure (5). Stern and coworkers (6) showed that exposure to large amounts of tars and ultraviolet radiation may increase the risk of skin cancer in psoriatic patients.

However, in general there is no increase in skin cancer in psoriatic patients (7, 8).

Each PAH compound produces several metabolites, which are excreted as glucuronide, sulfates and mercapturic acids in the urine (9), making this fluid the preferable medium for biological measurements. The excretion of 1-hydroxypyrene, the metabolite of pyrene, was described by Jongeneelen et al. (10), who followed 5 patients during the first 4 days of the coal tar treatment and found that within 1 day the urine concentration of 1-hydroxypyrene was elevated to 500  $\mu\text{mol/mol}$  creatinine. This high level was maintained during the next 3 days. In a recent study Clonfero and coworkers (11) found that there might be a correlation between urine level of 1-hydroxypyrene and mutagenicity of the urine in urinary samples of psoriatic patients undergoing topical treatment with mineral coal tar.

Recently, two new reversed-phase high-performance liquid chromatography methods for measurements of 1-hydroxypyrene and  $\alpha$ -naphthol (metabolite of naphthalene) has been published by Hansen et al. (12, 13). The aim of the present study was to use these two methods to estimate the level of body burden of different PAH compounds during coal tar treatment of psoriatic patients, and to compare the results with the burden resulting from occupational PAH exposure.

### MATERIALS AND METHODS

#### Patients

The present study included 2 patients, one non-smoking female (age 53 years) and one smoking male (age 35 years) with psoriasis in progress covering more than 50% of the skin. Both patients were treated once a day for 4 weeks with 10 g of coal tar pitch on the eczematous skin. In both patients the treatment was successful, and particularly within the first 2 weeks the skin condition showed a marked improvement.

The patients volunteered to collect the following urine samples: one urine sample 1 day before the start of the coal tar pitch treatment, one sample after approximately 1 week and one sample after approximately 3 weeks of treatment. The urine samples were stored at  $-20^{\circ}\text{C}$  until analysis.

#### Analysis of PAH compounds and metabolites

The concentrations of pyrene and naphthalene in the coal tar used in the treatment and the concentrations of 1-hydroxypyrene and  $\alpha$ -naphthol in the collected urine samples were measured using reversed-phase high-performance liquid chromatography with fluorescence detection as described previously (12–14).

### RESULTS AND DISCUSSION

The coal tar pitch contained 11.8 mg/g naphthalene and 1.43 mg/g pyrene.

The excretion patterns of 1-hydroxypyrene and  $\alpha$ -naphthol in urine are presented in Figs. 1 and 2. After 1 week of

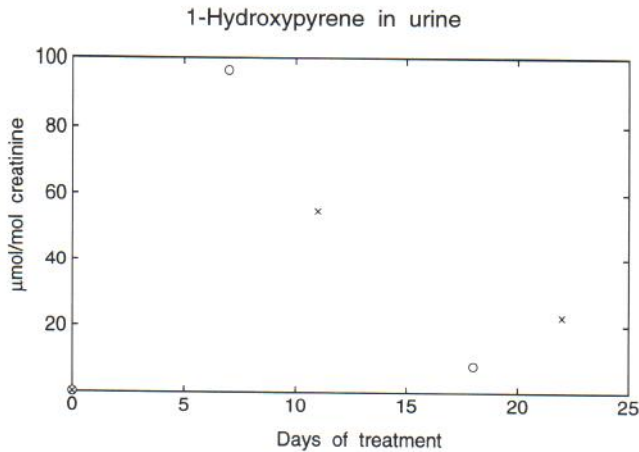


Fig. 1. Number of days of coal tar treatment plotted against the urine concentration of 1-hydroxypyrene of 2 psoriatic patients. Patient no. 1 (○), patient no. 2 (×).

treatment the concentration of 1-hydroxypyrene increased approximately 100 times, reaching the same order of magnitude as measured by Jongeneelen et al. (10) at 1–4 days of treatment. However, the concentration after 3 weeks of treatment was decreased to approximately the concentration measured before the treatment, even though the patients were coal tar-treated with unchanged intensity.

The same pattern was seen for  $\alpha$ -naphthol, but the concentration of  $\alpha$ -naphthol was 5–10 times higher than that of 1-hydroxypyrene, corresponding to the difference in concentration of the two compounds in the coal tar used.

The present study raises two important questions:

- 1) Does the decreasing urinary concentration of 1-hydroxypyrene during treatment reflect an induction of liver enzymes, rendering the patients better fitted to metabolize the PAH compounds?
- 2) Is the skin getting less permeable for PAH compounds?

The relatively fast recovery from the severe eczematous skin conditions within the first 2 weeks of treatment may support the second suggestion. The two questions must be clarified before conclusions can be drawn regarding the clinical applicability of 1-hydroxypyrene and  $\alpha$ -naphthol measurements for e.g. indirect monitoring of recovery of the skin barrier or indirect measurement of liver activity.

Jongeneelen and coworkers (10) found up to 500  $\mu\text{mol}$  1-hydroxypyrene/mol creatinine in the urine of 5 psoriatic patients after a few days of treatment with coal tar. In the present study, approximately 100  $\mu\text{mol}$  1-hydroxypyrene/mol creatinine was found in the urine of one of the patients after 7 days of treatment, and the other patient had approximately 55  $\mu\text{mol}$  1-hydroxypyrene/mol creatinine after 11 days of treatment. One explanation of the discrepancy between the two cases may be that the two patients were treated for a longer period before sampling, and for this reason their skin may have become less permeable for PAH. Nevertheless, both studies have demonstrated that high amounts of PAH compounds penetrate the skin and are excreted during tar coal treatment.

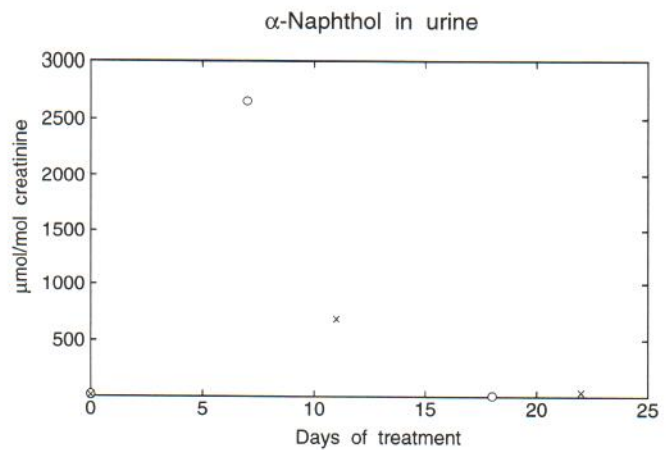


Fig. 2. Number of days of coal tar treatment plotted against the urine concentration of  $\alpha$ -naphthol of 2 psoriatic patients. Patient no. 1 (○), patient no. 2 (×).

The urine concentration of 1-hydroxypyrene and  $\alpha$ -naphthol of exposed iron foundry workers was up to 1.5  $\mu\text{mol/mol}$  creatinine and 70  $\mu\text{mol/mol}$  creatinine, respectively (12, 13). Hence, the urine concentration of 1-hydroxypyrene and  $\alpha$ -naphthol was at least 40 times higher in the 2 psoriatic patients treated with coal tar. If PAH exposure is responsible for increased incidence of bladder cancer among molders at iron foundries (5), then coal tar treatment may constitute a cancer risk for psoriatic patients as well. It should, however, be emphasized that epidemiological studies on skin cancer among psoriatic patients are controversial, i.e. one study showed that exposure to large amounts of tars and ultraviolet radiation increases the risk of skin cancer in psoriatic patients (6), whereas other studies failed to demonstrate a general increase in skin cancer of psoriatic patients (7, 8). Even though some of the patients have presumably been treated with tar coal, the latter studies did not focus specifically on the relationship between tar coal treatment and cancer. The use of psoralen and ultraviolet A radiation (PUVA) therapy for treatment of psoriasis may not be an attractive alternative, since an increased incidence of skin cancer has been reported among PUVA-treated patients (15, 16).

In view of the present investigation, epidemiological studies are needed to clarify to what extent coal tar treatment results in an increased risk of skin and bladder cancer.

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