Malignancies of the urinary tract and their relation to analgesic abuse

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The first observations of a relationship between analgesic abuse and urothelial renal pelvic tumors came from Sweden. In 1965, Hultengren, Lagergren, and Ljungqvist [1] described the epithelial renal pelvic tumors in six patients who had renal papillary necrosis. Five of these patients were known to abuse phenacetin-containing drugs. In 1968, Bengtsson et al [2] reported on the development of such tumors in nine out of 104 patients with previously known nephropathy associated with analgesic abuse. Two other patients in this series developed uroepithelial bladder tumors. The average follow-up period was five years. All of the patients had taken compounds containing phenacetin, phenazone, and caffeine. A consumption of one gram of phenacetin daily for at least one year was classified as abuse. Even patients with a smaller daily intake often reached a total consumption of several kilograms and were therefore included in the group of abusers. This study from the Medical Department I, Sahlgren's Hospital, Göteborg, prompted us to perform further studies of all patients with epithelial renal pelvic tumors admitted to the cooperating Surgical Department I during the years 1960 to 1967. Fourteen of the 29 patients reviewed had been abusers of phenacetin-containing drugs. The mean age of the patients in this group was lower, and females were in majority, while in the nonabusers (15 patients) elderly men with prostatic hyperplasia predominated.

Our further studies on the relationship of renal pelvic tumors to analgesic abuse were then focused to Huskvarna-Jönköping, a district with a known high consumption of phenacetin-containing drugs [3]. The high incidence of analgesic nephropathy in this district had earlier been reported by Nordenfelt and Ringertz [4] and Grimlund [5]. In the county hospital, 15 cases of urothelial tumors of the renal pelvis had been diagnosed between 1960 and 1968 [3]. Ten, possibly 12, of the patients had been abusers of a phenacetin-containing powder.

In the 1970's, there have been several reports on cases of epithelial tumor of the renal pelvis or the bladder in abusers of phenacetin-containing drugs from other parts of the world, although the number of patients in these reports usually has been small [6–18]. The experience of a total of 62 patients from Sweden with abuse of phenacetin-containing drugs and urothelial tumors of the renal pelvis was reported by Johansson et al in 1974 [19]. In a later publication, the prognosis in patients with renal pelvic tumors was studied with respect to the influence of different clinical and morphologic variables [20].

Epidemiology

The total incidence of epithelial tumors of the renal pelvis in Sweden is low. During the early 1960's, the average yearly incidence was one case per 183,000 inhabitants, and during the later 1960's it was one case per 156,000, according to the Swedish Cancer Registry [21]. This disease has usually been described as a predominantly male disease, with a ratio of four men to one woman [22]. In Sweden, this sex ratio was 2:1 in 1958. The sex ratio, however, has been reversed in the reports on renal pelvic tumors in analgesic abusers. In the study by Hultengren et al [1], all six patients were females, and in our first study [2] the sex ratio was 1:2.5. This fits with the epidemiology of analgesic abuse, since women have more frequently been addicted to phenacetin-containing drugs than men [23–25]. The only exception from this pattern is the findings among the workers at the Huskvarna factory. A traditionally heavy abuse of phenacetin-containing drugs predominantly in males had prevailed there since the Spanish influenza pandemic in 1918–1919. This was reflected in a higher death rate due to uremia in males, than in females [4, 5]. In the investigation by Angervall et al, it turned out that 10 out of 15 patients with renal pelvic tumors in the nearby county hospital had
come from Huskvarna [3]. Later on, 1973, Zetterlund [26] reported on an additional number of 14 cases of renal pelvic tumors in phenacetin abusers from this district. The Huskvarna factory has 1,800 workers, the town of Huskvarna has 13,000 inhabitants, and the county has 100,000 inhabitants. The Swedish Cancer Registry has disclosed no accumulation of renal pelvic carcinoma in other places with factories manufacturing similar products as in Huskvarna. The total consumption of phenacetin-containing drugs had been recorded to be ten times higher in Huskvarna than in other comparable towns [5]. In Göteborg, the city with the largest number of reported cases of renal pelvic tumors in analgesic abusers, there were few factory workers. Instead, housewives were in majority. Thus, there are no data speaking in favor of an environmental or occupational factor.

Clinical history and clinical findings

In the Swedish series, the great majority of patients had taken compounds containing 0.5 g of phenacetin, 0.5 g of phenazone (antipyrine), and 0.1 g of caffeine. The other patients had used similar compounds, only the dose relations of phenacetin, phenazone, and caffeine varied somewhat. A few patients had for shorter periods of time also used compounds of phenacetin and salicylates. In 38 patients of the Göteborg study [19], fairly detailed data of the abuse were available, and these data are given in Table 1. For the remaining patients it could only be stated that there had been a heavy abuse of the aforementioned drugs over several years. The manifest development of the tumor often came after cessation of the drug abuse.

Hematuria was the major symptom leading to the diagnosis of the renal pelvic tumor in the analgesic abusers. Gross hematuria, often combined with renal colic, was found in 75% of the patients. Microscopic hematuria was found in 14% of the patients. Retrospectively, it could be noted that gross hematuria had often been heralded by microscopic hematuria for several months. Five to 17 yr earlier, one-fourth of the patients had had episodes of hematuria and/or acute attacks of pyelonephritis, probably due to temporary obstruction of the urinary tract by seques-

Pathologic findings

The renal pelvic tumors in phenacetin abusers have been urothelial with varying degree of differentiation, the majority of them wholly or partly papillary. In occasional cases, areas of squamous cell differentiation have been observed. There has been no case of pure squamous cell carcinoma in the Swedish series, but a few such tumors were reported in a Swiss series [16]. One investigator has even discussed a relationship between phenacetin abuse and renal cell carcinoma [18]. Some five percent of the patients have had simultaneous bilateral pelvic tumors. Most of the papillary tumors have been smaller than 3.5 cm, and most of the solid tumors, larger than 3.5 cm.

A significant, higher relative frequency of women has been observed among patients with the larger tumors. With increasing tumor size, a tendency to lower differentiation of the tumor has been observed. Infiltration has been noted, particularly among the high grade tumors [19]. In some instances, the tumors have been localized wholly or partly to the renal papilla, but in most cases the tumors were localized to the calyces or pelvic ampulla [2] (Fig. 1).

Table 1. Consumption of phenacetin in 38 patients with uroepithelial tumors of the renal pelvis

<table>
<thead>
<tr>
<th>Consumption kg</th>
<th>Exposure time yr</th>
<th>Induction time yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>9.1</td>
<td>17</td>
</tr>
<tr>
<td>Range</td>
<td>1.5—27</td>
<td>4—30</td>
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Swedish series had papillary necrosis, including papillary necrosis with calcification (Fig. 1), and in three instances bone formation [19]. The papillary necrosis was usually bilateral. In this series, there were three patients with a heavy abuse history, tumors of the renal pelvis without signs of nephropathy and papillary necrosis clinically, roentgenologically, and histologically, indicating that a preexisting nephropathy is not a sine qua non for the development of renal pelvic tumors in abusers of phenacetin-containing drugs.

**Prognosis**

In our first study [2], we found that the tumor differentiation tended to be lower in patients with analgesic abuse than in nonabusers. Furthermore, the death rate within two years was twice as high in the abusers, despite the fact that the mean age was 11 yr lower among them than among the nonabusers (56 and 67 yr, respectively). In a later prognostic study of a Swedish national series of renal pelvic tumors [20], the five-year survival rate in patients operated upon was 33% among females and 50% among males. Out of 94 patients with epithelial tumors, 25 patients had a verified or probable abuse of phenacetin-containing drugs, and out of them only six (24%) survived five years. The five-year survival was 6/15 (40%) among those who could be submitted to curative operative procedures. These data indicate a poorer prognosis in patients with analgesic abuse, and the relatively high frequency of females in this group may explain the sex difference in five-year survival in the total series. The main predictor of the prognosis was the extent of the invasive growth of the tumor. Tumor grade and tumor structure also exhibited some influence on the prognosis. One major factor contributing to the poorer prognosis of renal pelvic carcinoma in analgesic abusers is the coexisting chronic nephropathy in the great majority of patients. With advanced renal impairment, operative removal of the tumor cannot be extensive enough. Only resection of the kidney and/or the renal pelvis can be performed, and in azotemic patients only palliative operations or no operation at all can be carried out.

The progress of analgesic nephropathy is usually slow, providing the analgesic abuse has ceased and if factors which might accelerate renal impairment, such as hypertension and urinary tract infections, are adequately treated. We have seen several patients...
with a glomerular filtration rate of 15 to 20 ml/min and serum creatinine levels of 3 to 4 mg/100 ml who have maintained an unchanged renal function after 10 to 15 yr. To avoid a progressive course into uremia, it is therefore important that an operation should not leave a patient with a renal function below the aforementioned levels. Split function studies may be necessary to determine the surgical approach: nephrectomy or parenchyma-saving resection.

Carcinogenic factors

Occupational bladder cancer was first described by Rehn, 1895, in dye factory workers [29]. Later, experimental and epidemiologic investigations provided evidence for carcinogenicity of 1- and 2-naphthylamine, 4-aminodiphenyl, and benzidine [30—33]. These chemical products were removed from the dye and rubber industry. Also chloramphenicol, a drug used against hemato logic malignancies, and a derivative of 2-naphthylamine were shown to induce epithelial bladder tumors [34, 35].

The etiology of renal pelvic tumors has not been defined. A high incidence of renal pelvic carcinoma has been reported in cases of interstitial nephritis in the Balkan states [37, 38], but the etiology has not yet been clarified. Renal pelvic tumors have been reported in patients subjected to retrograde pyelography with the radioactive substance thorotrast [36]. The induction time was 22.5 yr, which is almost identical to the induction time for the tumors in the analgesic abusers and close to the induction time for occupational bladder tumors [31]. There is a further similarity between the occupational bladder tumors and renal pelvic tumors associated with analgesic abuse: the induction time often exceeded the exposure or consumption time by some years.

The incidence of bladder carcinoma is 15 times higher than the incidence of renal pelvic carcinoma according to the Swedish Cancer Registry [21]. Thus, there should be some local predisposing factor to account for the localization of the tumor to the renal pelvis. Inflammatory changes and papillary necrosis are suggested to be such factors. These factors per se, however, seem not to cause tumor development, since in a control series of 88 nonabusers with chronic pyelonephritis in the Göteborg study, no tumor developed during the same period of follow-up [2]. In this connection, it is of interest that two out of eight dye workers with renal pelvic tumors [39] had malformed kidneys [40, 41].

Carcinogenic aromatic amines and amides are activated by N-hydroxylation and subsequently by esterification of the N-hydroxy group [42]. Phenacetin is an aromatic amide with N-hydroxylated metabolites [43, 44]. The major pathways in phenacetin metabolism are shown in Figure 2. Peroral administration of N-hydroxyphenacetin to rats induced a high frequency of hepatomas [45]. Nitrosation of phenacetin has been demonstrated to yield a substance which induces tumors locally upon s.c. administration [46]. Nery [44] found azoxy-4-ethoxy-benzene, a condensation product of N-hydroxy-phenacetin or N-hydroxy-4-phenetidine, in the urine of rats fed with phenacetin. This indicates a concentration of N-hydroxylated metabolites in the kidney and a highly probable carcinogenic hazard. Peroral administration of phenacetin to female Sprague-Dawley rats for up to 110 weeks induced a high incidence of urothelial, partly papillary, hyperplasia of the renal papilla. The hyperplastic changes were in most cases associated with vascular changes and/or calcification (Fig. 3) [47, 48].

Phenazone and caffeine were common ingredients of the analgesic compounds used by the patients in the present study. The chemical structure of phenazone indicates no relation to known urinary tract carcinogens, but the metabolism has been less closely studied, and a carcinogenic effect of this agent cannot be ruled out. Caffeine has been shown to be mutagenic in lower organisms, for example, Drosophila and human dividing cells in vitro [49]. An association between coffee-drinking and bladder cancer has been suggested [50], but its etiologic importance seems doubtful. In Sweden, the consumption of coffee per capita is among the highest in the world, but the total incidence of urinary tract carcinoma is lower than in most other western countries.

Conclusions

Accumulating circumstantial evidence for a carcinogenic effect by phenacetin-containing drugs has been presented. The present knowledge of the metabolism of phenacetin and the chemical relationship of some of these metabolites to known urinary tract carcinogens gives support to the view that phenacetin is a crucial factor in the development of urothelial tumors in man. Further support is given by rat experiments, in which a high frequency and a high degree of papillary epithelial hyperplasia have been induced after long-term phenacetin-feeding. Further investigations, however, are needed to rule out a carcinogenic effect by other components in the analgesic compounds.

Summary

A relationship between analgesic abuse and urothelial renal pelvic tumors was first observed in 1965. Since then more than 100 cases of such tumors have been reported in abusers of phenacetin-containing
Fig. 2. The major pathways in the metabolism of phenacetin. Probable carcinogenic substances are indicated (+).

Fig. 3. Severe vascular changes of the vasa recta with thrombus formation and calcification in association with severe diffuse urothelial hyperplasia in a Sprague-Dawley rat fed phenacetin for 110 weeks. Reprinted with permission from Acta Pathol Microbiol Scand [48].
drugs; most of these cases have been from Sweden. Many patients had a preexisting nephropathy with renal papillary necrosis. The total consumption of the drugs could be estimated to several kilograms, and the average period of consumption was 17 yr in the Göteborg study. The manifest development of the tumor often came a few years after the cessation of the drug abuse. The clinical picture and the pathologic findings are described and the five-year survival rate is given. Multiple tumors in the urinary tract were common. Carcinogenic factors are discussed. Phenacetin is an aromatic amide with N-hydroxylated metabolites, closely related to known carcinogenic amines like the naphthylamines which earlier were common. Carcinogenic factors are discussed. Animal experiments of long-term induction time were very similar in occupational bladder cancer. Furthermore, the data on exposition (consumption) time and tumor induction time were very similar in occupational bladder cancer and in renal pelvis cancer related to analgesic abuse. Animal experiments of long-term phenacetin feeding have produced a high degree of papillary epithelial hyperplasia. Further investigations are under way.

Reprint requests to Dr. U. Bengtsson, Department of Nephrology, University Hospital, Lund, Sweden.

References