

OPIUM USE IN TRANSITIONAL CELL CARCINOMA OF THE URINARY BLADDER

A. Nourbakhsh^{1*}, M. G. Mohseni¹ and Z. N. Hatmi²

1) Department of Urology, Sina Hospital, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran

2) Department of Epidemiology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran

Abstract- Opium use is one of the most common forms of substance abuse in Iran and there are some evidence indicating it is a risk factor of transitional cell carcinoma (TCC) of the urinary bladder. The majority of opium users are also cigarette smokers, so consideration of the high prevalence of smoking which is the most important risk factor of TCC of the urinary bladder among opium users is essential to assess the role of opium use as a possible risk factor of TCC. This study was done to evaluate the role of opium as a risk factor of TCC. A case-control study was performed on 255 individuals diagnosed with TCC of the urinary bladder by pathologic light microscopic examination of the tumor biopsies. Control population was chosen from individuals who had no history or presenting signs or symptoms of urinary problems. Case and control groups were matched by sex and age and also by cigarette smoking habits. Forty-one (18.1%) of the cases and 12 (5%) of controls were recognized to be opium users. Mantel-Haenszel analysis showed an odds ratio of 3.88, with 95% confidence interval of 1.99-7.57 and *P* value of < 0.001. Results indicate that opium use is a risk factor for TCC. The majority of opium users are also cigarette smokers, which is another important risk factor for TCC. Routine urine cytology and early evaluation in the patients presenting with any of the symptoms of urinary bladder malignancy by means of cystoscopy and urine cytology are highly recommended.

Acta Medica Iranica, 44(4): 263-267; 2006

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Key words: Opium, transitional cell carcinoma, cigarette smoking, urinary bladder

INTRODUCTION

Opium has been found to be the most prevalent form of opioid used in Iran (1). In a medico-social survey in a rural population in the northern part of Iran, data collected from randomly chosen households showed an addiction rate of 69/1000 (2). In a survey done on Iranian cardiovascular patients with the mean age of 52.6 yr, 5.2% were opium dependent (3), and Ahmadi *et al.* found it to be 9.4%

among nephrologic patients with mean age of 49.39 years (4). Opium has been considered to be one of the three most prevalent forms of substance abuse among Iranian high school students (5).

There are many forms of usage according to the cultural and geographical features of different parts of the country, either eating opium in its crude form or inhaling the pyrolysates. In the Caspian littoral of Iran, eating opium pipe scrapings (opium dross, called 'sukhteh' locally) and inhaling the pyrolysates are the most common forms of opium usage (6).

Ghadirian *et al.* conducted a study in northern Iran in areas of very high, high and moderately low incidence of oesophageal cancer and concluded that

Received: 20 Jan. 2004, Revised: 22 Oct. 2005, Accepted: 2 Nov. 2005

*** Corresponding Author:**

A. Nourbakhsh, Department of Urology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran

Tel: +98 21 22603475

Fax: +98 21 22613026

E-mail: hannaneh@yahoo.com

opium use, in the form of its pyrolysates, is one of the risk factors of oesophageal cancer in the region (6). Opium has also been considered as one of the risk factors of transitional cell carcinoma (TCC) of the urinary bladder (7). In 1979 Sadeghi *et al.* performed a case-control study on 99 bladder cancer patients admitted to Namazee Hospital in Shiraz, Iran (8). Cancer patients and controls, matched by age and sex, were analyzed as to their opium and/or cigarette smoking habits. A high correlation between opium addiction and bladder cancer was observed and the correlation was significantly stronger than the one observed in relation to cigarette smoking alone. It was concluded that opium and, more likely, its pyrolysis derived fractions may have potential bladder carcinogenic role in man. In 1981 Behmard *et al.* found a high incidence rate of TCC of the urinary bladder among opium addicts (15 of 3500) and no carcinoma in 1750 control cases (7).

Malaveille *et al.* collected samples of opium pipe scrapings (opium dross), but not of crude opium, in an area with a high incidence of oesophageal cancer in north-east of Iran and showed it contain pro-mutagens (9).

Pyrolysis of opium and its major alkaloid, morphine, yielded smoke condensates with mutagenic activities 10 and 100 times higher than that of the sukhteh samples tested, respectively. Heterocyclic aromatic hydrocarbons and primary aromatic amines present at different concentrations in these three pyrolysates are considered to be the major active fragments. Pyrolysates of opium and particularly of morphine, a major opium alkaloid, were both shown to contain similar highly mutagenic substances that were also clastogenic in mammalian cells and which transformed hamster embryo cells in culture (10).

To evaluate the association between opium consumption and TCC of the urinary bladder we performed a case-control study in Sina Hospital, Tehran University of Medical Sciences, in Tehran. Cigarette smoking is the main contributing factor for TCC of the urinary bladder (11). So besides age and gender and status of opium consumption, cigarette smoking habits of the two groups were also identified.

MATERIALS AND METHODS

A case-control study was designed in which the cases were the patients who had been admitted to Sina Hospital and had been diagnosed with TCC of the urinary bladder by pathologic light microscopic examination of the tumor biopsies (according to WHO classification) and had a complete medical record necessary for the study. Sina Hospital is one of the major referral hospitals in Tehran responsible for diagnosis and treatment of urological diseases which is being affiliated to Tehran University of Medical Sciences. Medical records of all patients referred to this hospital during 10 years (1990-2000) were reviewed. Reliability and validity of opiate use self-report has been assessed previously by Abnet *et al.* in a large cohort study in a rural Iranian population and they concluded that self-reported opiate use is reliable and valid in the population. This is a subjective method and has its limitation and advantages. The reliability of ever opium use and duration of opium use had kappa's of 0.96 and 0.74, respectively. The validity of self-reported opium use was also high. Using urine codeine or morphine as the gold standard for use of opium, self-report had a sensitivity of 0.93 and a specificity of 0.89 (12).

A total of 255 of patients had the complete data required for the study and also met the criteria of being or not being either opium user or cigarette smokers, and thus were interred in the analysis. None of the patients had a previous history of urological problems.

Control population were chosen from individuals who had been admitted into Sina Hospital during 1990-2000 in trauma ward and had no history or presenting signs or symptoms of urinary problems.

Individuals were categorized into smokers (at least 10 cigarettes per day for the past 3 years), and non smokers who had no previous history of cigarette smoking. These criteria were chosen according to the Smoker and Non Smoker Guidelines and also cigarette smoking habits in the country.

Being an opium user was defined as inhalation of the smoke of ignited opium or/and eating it, in the crude form (both types are very common among the addicts and separation of them is almost impossible because almost all of the addicts have experienced

using both types) for at least 3 times a week for at least 5 years. Non opium users were those who had no previous history of opium use. Criteria for definition of being opium user are arbitrary due to the lack of any internationally validated criteria on this issue and were defined according to the opinion of epidemiologists and authors.

On the basis of a significant association between opium use and cigarette smoking (13), we not only matched the case and control groups by sex and age but also by cigarette smoking habits which had not been considered in the previous studies. Cases and controls were matched individually (one control for each case) according to the gender, age (with a range of 2 years), cigarette smoking habits and then the status of opium use was compared between two groups.

The analysis protocol included basic descriptive and univariate statistics, Mantel-Haenszel odds ratio as bivariate analysis which was performed by SPSS 10 computer package.

RESULTS

A total of 510 individuals, 255 in case and 255 in control group entered the study. The mean ages were 63.3 (SD = 10.35) and 63.1 (SD = 10.06) years in cases and controls, respectively.

In case group, 227 (89%) were male and 28 (11%) were female (the sex ratio was 9 males to 1 female). The number of cigarette smokers in case group was 156 (61.2%) and only one of them was female; cigarette smoking was significantly more prevalent among men (P value < 0.001). None of females had a previous history of opium use. The prevalence of opium use was much higher in smokers than in non-smokers (24.4% versus 3%, P value < 0.001) in the case group. Only 3 individuals out of 41 of opium users were not cigarette smokers, while all 12 opium users in the control group were also cigarette smokers.

Forty-one (18.1%) of the cases and 12 (5%) of controls were opium users. The difference was statistically significant. Mantel-Haenszel analysis showed an odd ratio of 3.88, with 95% confidence interval of 1.99-7.57 and P value of < 0.001 for Mantel-Haenszel X^2 .

DISCUSSION

Results of this study showed that opium abuse is a risk factor for TCC, independent of cigarette smoking. This can explain sex ratio of 9 males per female in the case group in this study that has also been reported before (3) which is different from Western textbooks where it is mentioned to be 3 to 1 (11). Sadeghi and Behmard supposed that since industrial carcinogens and other predisposing factors, such as schistosomiasis, are rare, the role of other possible etiologic factors, such as cigarette smoking and opium addiction, which can be found predominantly in males, should be considered (14). Ahmadi and Hasani in their study on the Iranian high school children conclude that substance abuse is significantly higher among males than females (5).

As proved above and previously (13), opium use and cigarette smoking are significantly associated. Cigarettes, alcohol, and opium are found to be the most prevalent forms of substance abuse. Agahi and Spencer suggested that the initiation to the use of cigarettes and alcohol is contemporary with, rather than preceding the initiation to opium (13). Cultural attitudes toward substance abuse were found to affect the type and amount of use (4). There are even more studies on different sectors of the society which have found opium abuse to be the most or at least one of the most prevalent forms of substance abuse in Iran (3, 15, 16), and the majority of them are also cigarette smokers which is itself the most important risk factor of TCC and also associated with poor prognosis (17).

Many researches have been done to find the carcinogenic products in the opium pyrolysates or sukhteh. In 1982 Malaveille *et al.* considered heterocyclic aromatic hydrocarbons and primary aromatic amines to be the major active principles (9). Pyrolysates of opium, and particularly of morphine, a major opium alkaloid, were both shown to contain similar highly mutagenic substances as Freisen *et al.* reported the isolation and characterization of nine of the most abundant mutagenic compounds present in morphine pyrolysate, using spectroscopy. The hitherto unknown compounds, all containing a hydroxy phenanthrene moiety, were identified as: I, 3-methyl-

3H-naphth[1,2-e]indol-10-ol; II, 1,2-dihydro-3-methyl-3H-naphth[1,2-e]indol-10-ol; III, 1-methyl-1H-naphth[2,1-g]indol-10-ol; IV, 2-methylphenanthro [3,4-d]-[1,3] oxazol-10-ol; V, 6-methylaminophe-nanthren-3-ol; VI, 2-methyl-3H-phenanthro [3,4-d]imidazol-10-ol; VII, 1,2-dimethyl-1H-phenanthro [3,4-d] imidazol-10-ol; VIII, 2,5-dimethyl-3H-phenanthro [3,4-d] imidazol-10-ol; and IX, 2-ethyl-3H-phenanthro [3,4-d] imidazol-10-ol (10). Long-term usage of other opium derivates may also have such mutagenic effect which merits more research.

These findings show the need for implementing screening programs in opium abusers who are at higher risk of TCC of the urinary bladder. Urine cytology along with cystoscopy remains the gold standard for bladder cancer detection. Urine cytology has excellent specificity with few false-positive results but its overall sensitivity is poor. Urine cytology often results in the identification of high-grade malignant cells even before a cystoscopically distinguishable gross lesion is present (18). Therefore, routine urine cytology at certain intervals with the purpose of early detection of TCC should be considered in opium abusers. Besides screening programs, a thorough work up should be undertaken if an opium abuser presents with any of the signs or symptoms of urinary bladder malignancy such as hematuria or chronic suprapubic pain. Several urine markers have been and are currently being investigated for the diagnosis and prognostication of bladder malignancies, while cystoscopy and urine cytology remain the gold standard in the detection of bladder cancer (19). Because carcinoma *in situ* produces no changes or only subtle gross mucosal changes and early small papillary lesions may be difficult to detect, cystoscopy and biopsy with cytologic examinations are the mainstay of diagnosis (20-22).

As a brief conclusion, opium abuse either eating its dross or crude form or inhaling the pyrolysates are some of the most common forms of substance abuse in Iran. The majority of these patients are also cigarette smokers, and both of these substances are carcinogens for TCC of the urinary bladder. Case finding, like routine urine cytology and also early detection schedules in opium abusers presenting

with any of the symptoms of urinary bladder malignancy by the means of cystoscopy and urine cytology are highly recommended.

Conflict of Interests

We have no conflict of interests.

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