

EFFECT OF OCCUPATIONAL EXPOSURE TO OPIATES ON THE RESPIRATORY SYSTEM

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Abstract. The authors discuss the effect of occupational exposure to opiates. A depressive influence of opiates on the respiratory system is well known. This effect results from stimulation of opioid kappa and delta receptors in the central nervous system leading to a decrease in spirometric parameters and degranulation of mast cells. The studies carried out in the USA indicated that 26% of the pharmaceutical industry workers, occupationally exposed to opiates suffer from bronchial asthma. Some of the cases can be explained by the effect of opiates on the respiratory system mentioned above, but this is not a full explanation. Contribution of immunological mechanisms is also possible. The presence of specific IgG and IgM antibodies was found in workers exposed to opiates. Changes in distribution of individual subpopulations of lymphocytes T were also observed.

The question of asthma and other disorders of the respiratory system in persons exposed to opiates does not receive due recognition in Poland. In view of data presented in this paper this attitude should be changed as this problem is not only the subject of occupational medicine but also of some other fields, particularly in view of a recent increase in the number of users of drugs which also include opiates.

INTRODUCTION

Occupational hypersensitivity to opiates has been reported in few publications (8,44). Neither mechanisms nor clinical symptoms of this kind of hypersensitivity have been fully described so far. Contact dermatitis (1,42) and presence of IgG (7) and IgM (15) class antibodies have been reported in the pharmaceutical industry workers and drug users. Decrease in spirometric parameters in the pharmaceutical industry workers has also been postulated (8). The aim of this study is to review possible mechanisms of the effect of opiates on the respiratory system with regard to the known cases of respiratory disorders in the exposed subjects.

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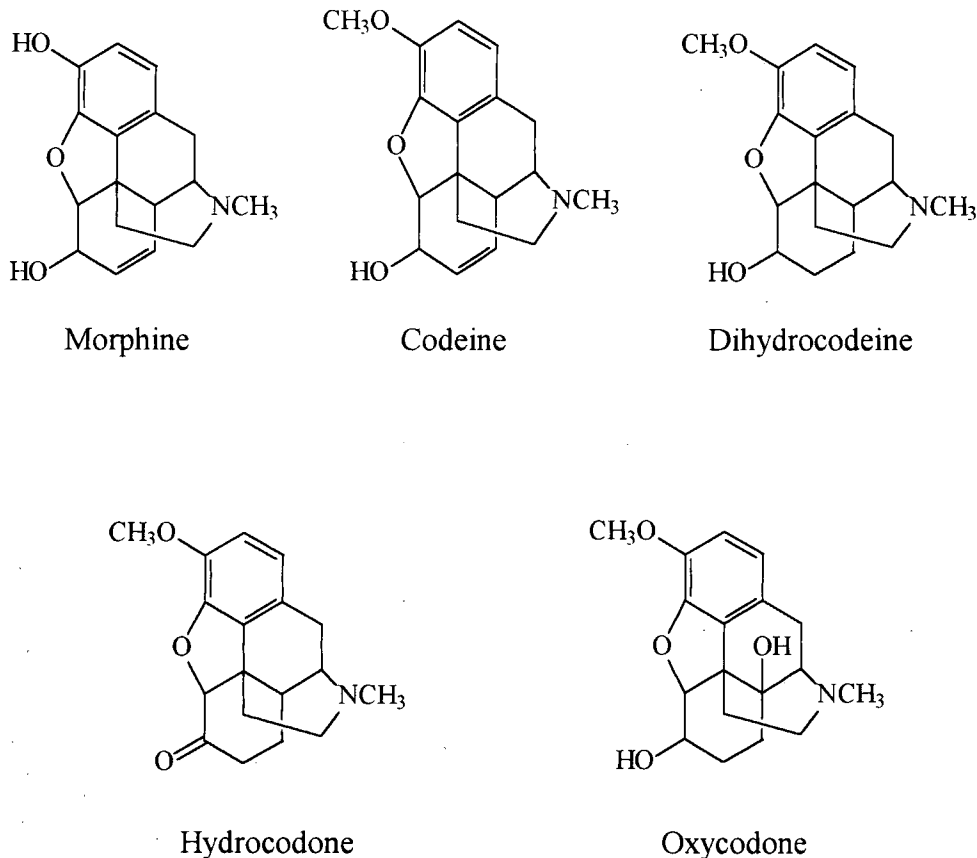


Fig. 1. Chemical structure of selected opiates.

PATHOPHYSIOLOGY OF OPIATES EFFECT IN HUMANS

The ability of opiates to induce respiratory depression is well known. Two mechanisms of this process are fully described. They are:

- stimulation of opioid receptors in the central nervous system leading to a decrease in spirometric parameters and
- degranulation of mast cells due to contact with opiates.

There are four subpopulations of opioid receptors in the central nervous system whose stimulation lead to different effects on the respiratory system.

Mu receptors

There are two subtypes of mu receptors whose properties have been identified using the irreversible mu-1 selective antagonist naloxazone (31,32) and its derivative naloxonazine (16,17). Naloxonazine is capable of binding to the high affinity mu-1 subtype of mu receptor but not to low affinity mu-2 receptor. Naloxonazine administered *in vivo* represses the analgetic effect of morphine while its depressant



action in the respiratory system remains unchanged. It is also known that specific mu-2 agonist metkephamid evokes respiratory depression.

All these findings indicate that stimulation of mu-1 receptors leads to analgesia and mu-2 receptors mediate respiratory depression.

Delta receptors

Studies of the role of delta receptor in the ventilatory control were conducted using its agonists tyr-D-ser-gly-phe-leu-thr (DSLET) and tyr-D-ala-gly-phe-D-leu (DADLE). Unfortunately, these peptides has also an agonist propriety for mu-2 receptor but DSLET has a 22-fold selectivity for delta receptor (14) and DADLE has only a 2-fold selectivity for delta over mu receptors (22). Both DSLET and DADLE induce respiratory depression, but because of their nonselectivity, the role of delta receptors could be elucidated with the aid of the specific delta and mu receptor antagonists. Administration of the selective mu receptor antagonist beta-funaltrexamine (beta-FNA) does not lead to blocking of a depressive effect of DADLE (47), thus one can suppose that, at least, a part of the opiate respiratory depressant activity was connected with delta receptor. This supposition was confirmed by Ward and Holaday who has shown that delta receptor antagonist ICI 154, 129 shifted the morphine respiratory depression dose-response curve to the right what is characteristic for the competitive antagonism (46). Beta-FNA also shifts this curve to the right which suggests that morphine acts through both mu and delta receptors provoking respiratory depression.

Kappa receptors

In general, kappa receptor agonists have little or null depressive effect on respiratory system despite their relative lack of full selectivity in receptor binding assays (22,26). MR 2034, an agonist which has equal binding ability for mu and kappa receptors and a 10-fold less preference for delta, has no effects on ventilatory parameters (36). Ethylketocyclazocine (EKC) having a 2-fold preference for kappa over mu receptors and a 10-fold for kappa over delta, evokes only minimal amount of respiratory depression (48). U50-488, the most specific kappa agonist (1300-fold preference for kappa over mu and 12 000-fold preference for kappa over delta), produces analgesia but does not induce ventilatory depression (11) and even in high doses provokes an increase in respiratory rate.

All these findings show that the kappa receptors are not involved in respiratory depression.

Sigma receptors

The role of this receptor in the ventilation control is not so clear. SKF 10,047 (N-allylnormetazocine), sigma receptor agonist, stimulates respiratory rate (27). On the other hand, it is known that there are two isomers of the SKF 10,047 and one of them is a mu receptor antagonist and the other is a sigma receptor agonist (28). It is not clear which receptor is responsible for the respiratory stimulation.

There are not convincing data about the role of sigma receptor, but reports mentioned above suggest that sigma and mu receptors may mediate opposite effects on the respiratory system.



To sum up, mu and delta receptors have depressing effects on ventilation but the latter ones act less intensively. Stimulation of kappa receptors leads to small respiratory depression and sigma receptors may stimulate ventilation, although full explanation of their role in the respiratory control requires further investigations.

Mast cells

Mast cells isolated from different sites of organism vary in some morphological and physiological features, among them in the response to secretory stimulators (2,4,5,24,34,35,40) such as morphine and other opiates. In rodents, cells arising in connective tissue and in peritoneal cavity are similar and differ from those present in the bone marrow and intestinal mucosa. In humans, Irani et al. (21) have identified two distinct populations of mast cells varying in contents of neutral proteases – tryptase and chymotryptase. Most cells obtained from the skin contains both these enzymes (TC cells), whereas lung and intestinal mast cells contain only tryptase (T cells).

It is suggested that all mast cells origin from common precursor cells which enter into the target anatomical sites where their further determination and proliferation depends on microenvironmental conditions (25).

The main role of lung and intestinal mast cells is to defense the organism against the external stimuli usually during infections (23). Their maturation is dependent on colony stimulating factors i.e. interleukin-3 derived from T-lymphocytes activated in the course of infection (20).

Skin mast cells develop without any contact with the external environment and their maturation is independent of interleukin-3 which suggests rather homeostatic than defensive role. Only this subpopulation degranules and releases histamine during stimulation by opiates.

Studies of Oka et al. indicated that skin contained significant concentration of opioid which, in contrast to the central nervous system, are alkaloids similar to morphine (30). Then skin mast cell-mediator release has a physiologic rather than immunologic mechanism. Intradermal injection of morphine leads to wheal-and-flare response (10) through activation of skin mast cells. That was confirmed by antihistamine pretreatment effect on this reaction. The evidence of opioid receptor on mast cells surface has not yet been confirmed but it is known that naloxone, inhibitor of mu receptors, inhibits the effect of opiates on histamine release (45).

Therefore, only skin mast cells are responsible for the increase in histamine level observed during opiates challenge. It is calculated that release of only 20% of skin mast cells population's histamine may lead to about an 80-fold growth of plasma histamine level, from 0.7–0.9 ng/ml (normal value) to 57 ng/ml (13) what is about a 10-fold greater value than that observed during morphine infusion (37,38).

LUNG FUNCTION AFTER OCCUPATIONAL EXPOSURE TO OPIATES

In 1988 a study on the effect of opiates on lung function in occupationally exposed pharmaceutical industry workers was conducted in the USA (8):

- 26% of examined workers reported bronchial asthma confirmed by their physicians and in all of these cases asthmatic symptoms occurred just after contact with opiates. In 40% of asthmatic subjects disease developed within one year of exposure;



– 62% of workers had, at least, episodes of wheezing since the beginning of their employment at the factory; 85% of this group reported episodes of work-related wheezing within a month preceding the examination. In 81% of them wheezing occurred with shortness of breath, in 67% chest tightness and in 71% coughing; 29% reported that the episode had lasted less than 1 hour. The subjects also reported itchy, runny nose (49%), stuffy nose (57%) and itching eyes (56%). Besides, 41% reported rash on hands, face, neck and forearms;

– 82% of workers completed an 8 day-testing of daily maximum-minus-minimum changes in peak expiratory flow rate $PEFR_{\max-\min}$ – $PEFR$ variability ratio = $(PEFR_{\max} - PEFR_{\min}/PEFR_{\max}) \cdot 100$; 26% of them demonstrated over 20% single-day increases in $PEFR_{\max-\min}$. When changes in $PEFR_{\max-\min}$ were evaluated for all workers, there was statistically significant reduction of this parameter from Monday through Thursday when compared to combined results for free weekend (Fig. 2).

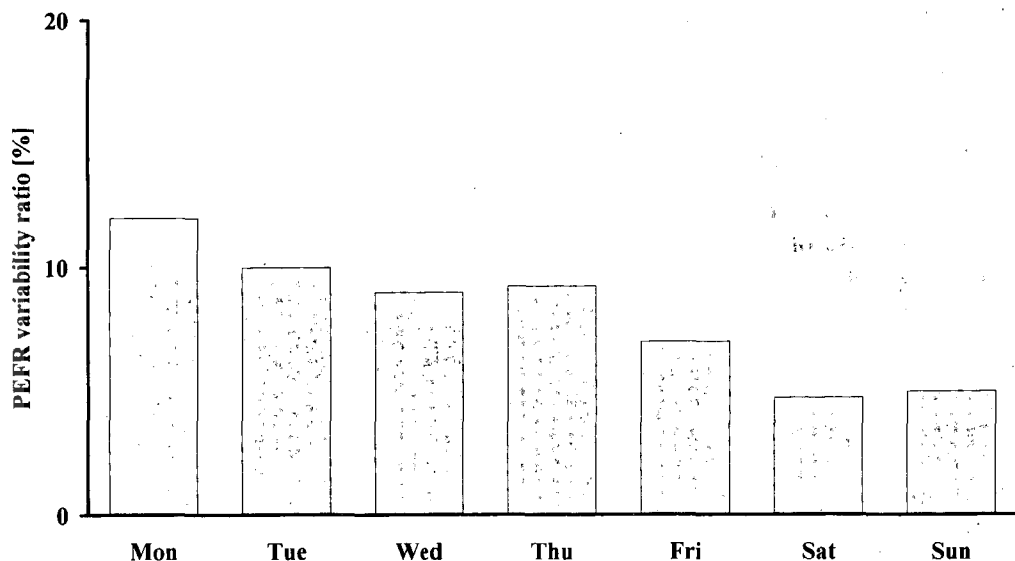


Fig. 2. PEFR variability ratio in opiate exposed workers during workweek and free from exposure weekend.

In general, decrease of spirometric parameters might be explained by stimulation of adequate opioid receptors in the brain stem, what, as has been said, leads to ventilatory depression, but this mechanism is not sufficient to explain the variability of these parameters during workweek. A stable fall of $PEFR_{\max-\min}$ observed from Monday to Friday suggested that mast cells are involved in this process. Mast cells stimulated by opiates release histamine and other mediators and, during long lasting stimulation depletion of mediators could be observed, which may explain the lack of spirometric changes at the end of the workweek.

But it is not the only explanation of asthmatic symptoms in opiate exposed subjects.



The possibility of immunologic reactions due to the contact with opiates both in humans (43) and animals (6,41) was postulated in the early 70's. The presence of specific antibodies of IgG (7) and IgM (15) classes in workers of the pharmaceutical industry and drug users has been postulated recently. Changes in the distribution of T-lymphocyte subpopulations in opiate abusers (12,29) and in occupationally exposed workers (19) suggest a possible role of immunologic mechanisms in the development of opiate hypersensitivity. There was no evidence that IgE or IgG4 (42) class antibodies were present in sera obtained from these groups of subjects, although in several cases opiate-related adverse health effects such as chest tightness or skin rashes compatible with allergic (IgE-mediated) or short term sensitizing (IgG-mediated) reactions were reported. It is possible that anti-opiate IgE antibodies, if present, are cell-bound or opiates are weak allergens which may occur in conditions different from exposure observed in the reported studies. Specific anti-morphine IgE antibodies were detected in serum of the subject with anaphylactic reaction after administration of scopolamine (18). Studies on hapten inhibition with morphine and its analogues demonstrated that morphine and codeine are the most potent inhibitors of IgE binding to the solid phase. These findings suggest that opiates may contribute, in some cases, to the production of specific IgE.

DIAGNOSIS OF OPIATE-INDUCED ASTHMA

This procedure does not differ from others used in diagnostics of occupational asthma. Because of lack of specific IgE antibodies, exposure test in the workplace and provocation challenge with proper opiates can play the main diagnostic role. Skin-prick tests are generally useless because both exposed and unexposed subjects react to opiates with wheal-and-flare response, although the reaction of the latter ones is stronger and demands lower concentration of challenging agent than the former ones. The best method for determining the etiology of possible opiate induced asthma is bronchial or nasal provocation challenge estimated on the basis of cellular contents and the protein level in bronchial or nasal lavage fluid. The nasal provocation is more simple and less challenging for patients and is suggested as a method of choice in diagnosis of occupational asthma.

Nasal provocation method, together with the estimation of the number of cells and biochemical examination of lavage fluid allows to differentiate between allergic and irritant effects of various substances on the respiratory system. Increase in the number of granulocytes and the total protein level in nasal lavage fluid can be observed in the case of irritant-type reaction (33). It is, however, short-lasting and does not cause changes either in the relative number of eosinophils and basophils (3,9) or in the relative concentration of albumin (39). An increase in the number of granulocytes together with an increase in the number of eosinophils and basophils, and growth of relative albumin level suggest a specific type of reaction and confirm occupational etiology of asthma.

Immunologic study such as the determination of specific IgG and IgM antibodies in sera is rather an evidence of an exposure than a relationship between asthma and exposure to opiates.

No epidemiological studies of this problem have been carried out in Poland or in any other country, except the USA, but the percentage of bronchial asthma and



respiratory disorders in studies presented above suggests an important role of exposure to opiates in the etiology of bronchial asthma in pharmaceutical industry workers and in opiate abusers. Single reports on asthmatic symptoms in this group of patients have already been published but this problem requires further investigations particularly in view of a growing number of exposed persons followed by a rapid growth of the number of morphine and heroine abusers. So this problem lies not only within a field of interest of occupational medicine.

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