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Pulmonary complications related to heroin overdose and some changes in immune reactivity

Research Article

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Abstract: To examine the clinical spectrum of complications in pulmonary system and changes of some parameters of humoral and cell mediated immunity related to heroin overdose. The study includes 16 patients who are long-term heroin abusers with acute heroin and mixed with other psychoactive drugs intoxications with an average age of 21,5 ± 5.04 years (12 men and 4 woman). All patients were hospitalized in the Clinic of Toxicology, MHATEM "N.I.Pirogov", Sofia. We have used clinical, clinico-laboratory, immunological, chimicotoxicological, instrumental methods. In severe intoxications with heroin and other psychoactive drugs, we observed pulmonary system complications, i.e. pneumonia, aspiration of gastric contents, noncardiogenic pulmonary edema (NCPE) and acute respiratory distress syndrome (ARDS.). Of the 16 patients in our study, 3 patients died due to complications. Some changes in the immune reactivity observed in the study were (1) statistically significant lower mean levels of IgG and (2) tendency to lower mean levels of IgA, IgM and complement components – C3 in the studied patients in comparison with the values in healthy people. The changes were more demonstrative in the group with pulmonary complications compared to the group without pulmonary complications. We observed that the CD4 lymphocytes were significantly less in the studied patients; in addition, a lower level of CD56-bearing lymphocytes (natural killer /NK/ cells) was observed in comparison to healthy controls. The results show that the mixture of acute heroin with other psychoactive drugs leads to complications in the pulmonary system and changes of some parameters of cell-mediated and humoral immunity.

Keywords: *Intoxication • Heroin • Psychoactive drugs • Immune reactivity • Noncardiogenic pulmonary edema • Pneumonia • ARDS*

1. Introduction

Heroin is a member of a class of narcotic analgesic drugs called opioids. Heroin produces its effects known as *opiate intoxication syndrome* as an agonist on the mu, kappa, and delta receptors in the central nervous system. It is rapidly absorbed by all routes of administration. Most fatal and nonfatal heroin overdoses occur when the drug is administered intravenously.

Symptoms of a heroin overdose include, but are not limited to, muscle spasticity, slow and labored breathing, shallow breathing, stopped breathing (sometimes fatal within 2-4 hours), pinpoint pupils, dry mouth, cold and clammy skin, tongue discoloration, bluish colored fingernails and lips, spasms of the stomach and/or intestinal tract, constipation, weak pulse, low blood pressure, drowsiness, disorientation, delirium, and coma [4,15,20,22,24].

Complications resulting from drug abuse more frequently affect the lung than any other organ. The spectrum of pulmonary complications associated with drug abuse is wide. The current practice of using mixtures of drugs is mainly responsible for the increase in pulmonary complications. The chief complications observed in a series of drug abuse patients were aspiration pneumonitis, noncardiogenic pulmonary edema, ARDS, and pneumonia.

In approximately 1-3% of heroin overdose patients, develop, noncardiogenic pulmonary edema (NCPE) is observed, with 0.5-1.0% developing pneumonia [21].

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NCPE related to a heroin overdose usually presents as the combination of persistent hypoxia after resolution of opiate respiratory depression along with frothy, pink-tinged pulmonary secretions, and a characteristic radiograph pattern [18,23]. Histamine has been implicated as a possible mediator of NCPE related to heroin overdose. Human lungs are rich in histamine, and opiates have been shown to cause its systemic and local release [5,23,27]. Histamine has been shown to increase pulmonary lymph flow and capillary permeability. One study of fatal heroin overdose patients demonstrated a modest correlation with elevated tryptase levels (a post-mortem histamine surrogate) as compared to control subjects [5].

Acute respiratory distress syndrome (ARDS) is sudden, life-threatening lung failure. ARDS inflames the alveoli, thereby causing them to fill with liquid and collapse. Once the alveoli collapse, gas exchange ceases, thereby resulting in oxygen starvation. Alveolar damage is increased by the activity of immune system cells (neutrophils) that rush to the site of injury, ironically, to help out. The activity of these cells and the inflammation they cause create a cascade of further injury that may extend into the capillaries as well [13,16,17,19].

Drug addiction influences many physiological functions including reactions of the immune system. Heroin addicts are reported to have numerous immunological abnormalities [14].

The higher occurence of infectious and other diseases in drug addicts has been explained by the depression of immunity due to the harmful effects of the drug [11,28].

The objective of the study is to examine the clinical spectrum of complications in pulmonary system and the changes of some parameters of humoral and cell mediated immunity related to heroin overdose.

2. Material and Methods

The study includes 16 patients with an average age of 21,5 ± 5.04 years (12 men and 4 woman), hospitalized in the Clinic of Toxicology, MHATEM "N.I.Pirogov", Sofia. All patients have taken heroin mixed with other psychoactive drugs intoxications. The heroin is combined with benzodiazepines, amphetamines, alcohol, phenobarbital, glutetimide or cocaine.

We have used clinical, clinico-laboratory (hemogramma, biochemical investigations), chimicotoxicological, instrumental (electrocardiographia - ECG, electroencephalographia - EEG, reography, computer tomography - CT) and immunological methods.

Table 1. Pulmonary complications.

Pulmonary complications	Number of patients
Pneumonia	7
Aspiration of gastric contents	5
NCPE	3
ARDS	1

The level of IgG, IgA, IgM antibodies, C4, alfa-2 macroglobulin and haptoglobin were determined in patient serum by Manchini's radial diffusion test in agar/agarose gel, using immunoplates by "Immunotest", Sofia.

By laser flow cytometry, CD markers of the basic lymphocyte population and subpopulation were determined *via* the use of monoclonal antibodies.The results of studied patients were compared with the data of healthy controls persons at the same ages.

Three groups were separated:

- Group I - Helthy controls – 10 persons
- Group II - 8 persons – without pulmonary complications;
- Group III - 8 persons – with pulmonary complications

Statistical analysis of data was accomplish by program SPSS 11.00.

3. Results and Discussion

In Table 1, the main pulmonary complications in patients included in Group III are summarized.

All studied patients includes in Group III admitted into the emergency room in a comatose state; none responded to painful stimuli. The physical examination findings of a patient substantially decreased respirations. Seven of the observed patients required artificial ventilation and were hypoxic on arrival into the emergency room. Five patients regained consciousness, while three of them died.

We observed clinical, clinico-laboratory and radiographic data for pneumonia in 7 patients, noncardiogenic pulmonary edema in 3 patients, aspiration of gastric contents in 5, associated with ARDS in one person.

Pulmonary complications, including various types of pneumonia, may result from the poor health condition of the patients,as well as from heroin's depressing effects on respiration.

Heroin-related NCPE was defined as the syndrome in which the studied patients developed significant hypoxia (room air saturation < 90% with a respiratory rate > 12/min) within 24 hours of a clinically apparent

Table 2. Changes of the studied humoral immunity parameters.

IgG	**mean**	**SD**
Norm: 6.4 – 15.8		
Gr. I Helthy controls	11,1*	6,64
Gr. II (A)	10,71*	4,95
Gr. III (B)	10,85*	2,80
IgA	**mean**	**SD**
Norm: 0.8 – 2.85		
Gr. I Helthy controls	1,82*	1,44
Gr. II (A)	1,62*	0,66
Gr. III (B)	1,90	0,69
IgM	**mean**	**SD**
Norm: M: 0.46 – 2. 36		
Gr. I Helthy controls	1,41*	1,34
Gr. II (A)	1,07*	0,60
Gr. III (B)	1,38	0,45
C3	**mean**	**SD**
Norm: 0.5 – 2.0		
Gr. I Helthy controls	1,25	1,06
Gr. II (A)	0,93*	0,61
Gr. III (B)	1,03	0,25
C4	**mean**	**SD**
Norm: 0.2 – 0.5		
Gr. I Helthy controls	0,21	0,21
Gr. II (A)	0,26	0,13
Gr. III (B)	0,21	-

*Legend: * - p level < 0,05*

Table 3. Study of the lymphocyte receptor markers.

CD3+ %	**mean**	**SD**
67-76		
Gr. I Helthy controls	71,5*	6,36
Gr. II	66,12*	9,04
Gr. III	69,37*	9,84
CD+ DR+ %	**mean**	**SD**
8-15		
Gr. I Helthy controls	11,5	4,94
Gr. II	4,03	1,41
Gr. III	6,62	2,66
CD3+ CD4+ %	**mean**	**SD**
38-46		
Gr. I Helthy controls	42*	5,65
Gr. II	35,87*	5,16
Gr. III	40,87*	5,76
CD3+ CD8+ %	**mean**	**SD**
22-31		
Gr. I Helthy controls	26,5*	6,36
Gr. II	25,0*	7,81
Gr. III	24,50*	5,20
CD4/CD8 %	**mean**	**SD**
1,0 – 1,5		
Gr. I Helthy controls	1,59	0,35
Gr. II	1,43*	0,32
Gr. III	1,66*	0,34
CD19+ %	**mean**	**SD**
11-16		
Gr. I Helthy controls	13,5	3,53
Gr. II	23,5	9,42
Gr. III	10,75	2,05
CD3- CD56+ %	**mean**	**SD**
10-19		
Gr. I Helthy controls	14,5*	6,36
Gr. II	7,5*	4,17
Gr. III	14,75	4,83

*Legend: * - p level < 0,05*

heroin overdose. This was accompanied by radiographic evidence of diffuse pulmonary infiltrates not attributable to other causes, such as cardiac dysfunction, pneumonia, pulmonary embolism, or bronchospasm, and which resolve clinically and radiographically within 48 hours.

ARDS is a syndrome, not a specific disease. A variety of underlying conditions, from blood-borne infections to major trauma, can cause the characteristic inflammation and accumulation of fluid (edema) in the alveoli.The alveolar epithelial cells normally form a very tight barrier around the alveolar space, thus preventing any fluid from entering and disrupting gas exchange. In ARDS, the alveolar epithelial barrier breaks, thereby allowing flooding of the alveolar space and making it difficult or impossible for oxygen to diffuse into the capillaries. ARDS also can affect the “type II alveolar cells”, whose main function is to produce surfactant, which plays an essential role in preventing the alveoli from collapsing.

The symptoms of ARDS in our patients were sudden in occurrence and included dyspnea or tachypnea, severe hypoxaemia, pulmonary hypertension, cyanosis as a result of above mentioned damages in the lung.

Table 2 shows the changes of the studied humoral immunity parameters in the included in the study patients - drug abusers. We observed statistically significant lower mean levels of IgG, and a tendency of a decrease of IgA, IgM and the level of complement component C3 in the studied patients in comparison with the values in healthy people. The changes were more expressive in the group with pulmonary complications as compared to the group without pulmonary complications.

These data may lead to the conclusion that chronic abuse with heroin impairs the synthesis of the major classes of immunoglobulins as well as of the complement

component – C3. All they play an essential, protective role in the immune response in a variety of bacterial and viral infections. It may explain to some extent the higher incidence of infections, especially with respect to respiratory infections in in drug abusers.

Table 3 summarizes the results of laser flow cytometry study of lymphocyte markers/receptors. We observed that the CD4 lymphocytes were significantly less in the studied patients. A lower level of CD56-bearing lymphocytes (natural killer /NK/ cells) was observed in comparison to healthy controls. That reveals a tendency for cell-mediated immunity suppression in the studied heroin addicts.The results also showed a statistically significant lower level of CD4 and CD8 lymphocytes in heroin abusers with pulmonary complications.

These results confirm those from our investigations on groups of heroin abusers with mild or moderate degree of intoxication. The analysis showed a high rate of suppressed cell-mediated immunity, as determined by intradermal tests with a battery of bacterial and fungal antigens [29].

4. Conclusion

In the course of severe intoxications with heroin and other psychoactive drugs, we observed complications in the pulmonary system, i.e. pneumonia, aspiration of gastric contents, pulmonary edema, and ARDS. They substantially aggravated the condition of the patients and thereby required a special attention.

From an immunotoxicology viewpoint, our results from this pilot study show that the mixture of acute heroin with other psychoactive drugs intoxication leads to unfavorable changes in humoral and cell mediated immunity. It was more intense in drug abusers with pulmonary complications.

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