

SOME PATHOGENICALLY ASPECTS OF THE SKIN-DYSTROPHIC SYNDROME IN ACUTE INTOXICATIONS

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SUMMARY:

The pathogenesis of the skin lesions in acute intoxications is still not clear and the strict mechanism is not defined. Our 10 year investigation reveals considerable relationship between skin lesions appearance and frequency of coma status ($RR = 25.59 \pm 2.53$) and other clinical and laboratory factors connected with the coma. We discussed some mechanisms that may be important to form the skin lesions: 1. Neurotoxicants interacted with neuromediators in CNS and their trophic function to skin cells is disturbed. 2. Neurotoxicants interacted with the skin microcirculation (permeability and motility) by three ways: direct toxic interaction; through neuromediators and through vessel's obstructions when there is pressure or fixation. 3. Through other trophic metabolites (CO_2 , ATP, lactate, cADP, cAMP) in cells and interstitial space. 4. We discuss some hypothesis connected with the direct toxic mechanism of skin cell damage: through xenobiotics microsomal oxidation with cytochrome P450 and forming free oxygen species and in consequence - damage of the cells membrane; through excretion by sweat glands and hair follicles.

Key words: xenobiotics, neurotoxins, coma, CNS, poison, skin bullae lesions.

INTRODUCTION:

The bibliographic data shows that approximately 6 % of the patients with acute drug intoxications develop skin and soft tissue lesions under the shape of erythema spots, bullae, necrosis, haematoma and decubitus (1, 6, 8, 12). There are not decided problems for a decade discussion concerning this phenomenon: 1. Clinical characteristic with description of the time of appearance, localization, kind of lesion, clinical dynamics; 2. Histogenesis and pathogenesis. The authors discuss the pathogenic significance of the direct toxic effect of barbiturates on skin (1, 6, 8, 14); coma status "per ce" (3, 4, 9), local pressure, followed by total hypoxic and

dystrophic effect on the tissues (8). Our aim is to discuss some pathogenically aspects of the skin syndrome in acute intoxications after our 10 years investigation of this problem.

MATERIAL AND METHODS:

We have performed a 10 year study (retrospective and prospective) over a 5381 acutely poisoned patients. 297 of them were comatose and 76 of them presented with different types of skin lesions. A control group of 97 comatose patients without skin lesions have been used for comparison. There have been registered following indications: kind of noxis, degree of intoxication, macroscopic characteristic of lesions, time of appearance, clinical dynamics; laboratory factors. There have been taken 13 skin biopsies from both of the skin lesions - non traumatised skin areas and traumatic places, colored with hematoxylin- eosin. To detect toxic noxes we have made mass-chrom spectrometric analysis of the blood at 44 patients and examination of bullae fluid, contained in 11 patients. We performed investigation of toxic substances in sweat secret of 5 patients with toxic coma by methods of pilocarpin iontophoresis for sweat stimulation. We have made immunological investigation of the tissue biopsies of bullous skin lesion, bullae fluid and blood serum by two patients. We conducted statistical analysis of the obtained data.

RESULTS AND DISCUSSION:

Skin lesions (SL) are 1.58 ± 0.17 % ($p < 0.05$) of all acute intoxications. The SL frequency in exotoxic comas is high - 25.59 ± 2.53 % ($p < 0.05$). Most often they could be met by barbiturates, glutethimid, tardyl, neuroleptics, anticonvulsives, antidepressants, benzodiazepines, baclofen, rimicid, organic phosphate compounds, heroin, ethanol, methanol, CO. The risk of developing skin lesions is twice higher in comatose conditions, caused by several types of toxic agents in comparison with the risk for developing skin lesions in

comatose conditions, caused by one single toxic agent. In 76 of the comatose patients we observed 161 with different types of skin lesions. We have seen, that most commonly appear the bullae and necroses, followed by erythemas, ulcers, erosions and soft tissue infiltrates. 30% of them are observed on non-traumatic places (fig. 1) and 70% - on traumatic places (fig. 2). The SL appearance has been established at least 12 hours after ingestion and maximum 48-72 hours after it. Their frequency is in significant dependence of the acute phase of the intoxication. The earliest skin eruptions are irregular, nonblanchable erythema spots and plaque. Their evolution is different, including development of vesiculae and bullae under erythema. Bullous lesions are the most specific eruptions in acute intoxications. The bullae have thick walls, clear or hemorrhagic contents surrounded by erythema, but without inflammatory reaction. Most frequently they localize in lower extremities: knees, medial area, where they touch, buttocks-lateral and medial aspects, lateral and medial aspects of ankles, dorsal aspects of fingers, foot, heels. In arm area they localize on the shoulder, forearm, arm, dorsal wrist, fingers. In the body- lateral back, chest, scapulae, sacrum, gluteus.

Erythema spots and bullae reveal 12-24 hours after ingestion of toxic substances, but the most frequent time of appearance is between the 48th and the 72th hour. They may be detected by administration or after comatose state. Mass-spectrometric analysis of the blood and of the contents of the bullous lesions show toxic substances in both of them. We performed investigation of toxic substances in sweat secret and established amitriptylin, clomipramin, diazepam, phenobarbital and carbamazepin. Our investigation revealed considerable relationship between skin lesions and frequency of coma status ($RR = 25.59 \pm 2.53$) and other clinical and laboratory factors connected with toxic coma: degree of toxic coma, prolonged coma 24-48 h., the period before hospitalising 12-24h., fatal dose, mixed poisoning, hypoproteinemia, metabolic acidosis, insufficiency of ventilation, high level of blood enzymes concentration-ASAT, ALAT, LDH, CPK, urea. We detected higher enzymes concentration - ASAT, LDH, CPK in content of bullous lesions. Hystomorphological analysis shows unspecific degenerative damages in all skin structures, the most affected being the epidermis, followed by the exocrine sweat glands, hair follicles, derma, muscle fibres, changes in the wall of the vessels, as well as mild to moderate inflammatory infiltrate, correlating with the severity of skin lesion. DIF has showed no immunocomplexes, put off in tissue at two of the

patients. In blood serum, investigated later (on the 3rd day after poisoning) has been established high level of IgG and IgM and low level of C₃. This result show that there are no evidence, that bullous lesion in drug induced coma are formed after immunological process.

We discussed some mechanisms that may be important to form the skin lesions:

The first important mechanism is the neurodystrophic mechanism: We think that skin lesions have dystrophic characteristic and in our opinion we may give a name "skin-dystrophic syndrome": 1. The SL frequency in exotoxic comas is high - 25.60 %. SL show significant frequency by intoxications induced by drugs with heavy neurotoxicity. The main factors with significant statistic risk to form SL are: toxic coma, long time before hospitalization and fatal drug concentration in blood. In our opinion neurotoxicants interacted with neuromediators in CNS and their trophic function to skin cells is disturbed. 2. Neurotoxicants interacted with the skin microcirculation (permeability and motility) by three ways: direct toxic interaction; through neuromediators and through vessel's obstructions when there is pressure or fixation. 3. Through other trophic metabolites (CO₂, ATP, lactat, cADP, cAMP) in cells and interstitial space. The second important mechanism is the direct toxic mechanism of skin cell damage: 1. Toxic substances present in bullae and sometimes their concentration is bigger then in the blood. 2. The bigger concentration of enzymes (ASAT, LDH, CPK) in bullae contents we link with direct damage to skin cells by toxic substances. 3. The skin excretes by sweat many toxic substances (Amitriptylin, Anafranyl, Diazepam, Phenobarbital, Carbamazepin). 4. We have build a hypothesis about direct toxic skin's cell damage through xenobiotic microsomal oxidation with cytochrome P450 and forming free oxygen species and in consequence damaging the cells' membrane. This hypothesis is a possibility, because this mechanism of cell's damage is known about liver and other tissue. Some authors investigated cytochrome p450 in the skin structure. They found that in the epidermis, sweat glands and hair follicles exists cytochrome p450 and its activity is much better then in the liver (2, 5, 7, 10, 11, 13). The third important mechanism is trauma. In our opinion trauma is inevitable in patients in coma status. On skin areas which are not traumatically affected we observed only erythema spots and bullae. We think that in non-traumatic places the pathological process causes only epidermal cells' damage. But on the places with pressure a local anoxia presents obligatory and the skin is damaged with early deep necrosis.



Fig. 1. - erythematous spots, vesiculae and bullae on non-traumatic places.



Fig. 2. - erythema, erosion and ulceration on traumatic places (capillitium).

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