

DETERMINATION OF TOXIC SUBSTANCES IN SWEAT SECRET OF SEVERE FORMS OF POISONING - TOXIC COMA. CLINICAL MEANING.

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SUMMARY:

The aim is to investigation of toxic substances in sweat secret, blood and urine of patients with toxic coma. Study includes 4 patients in toxic coma, caused by: amitriptyline, diazepam, carbamazepine, amitriptyline and clomipramine. The concentration of the drugs substances is determined in sweat samples, collected after stimulation of eccrine sweat glands, using the pilocarpin iontophoresis - a modified method by Gibson and Cooc (1959), and in blood and urine, taken at the same time with the first sweat sample. The analytical procedure includes a separation of the drugs from the sample with organic solvent, concentrating the extract, followed by analysis of the extract with GC 5890-series II, equipped with MSD-5971 and LC 1090-series II, Hewlett Packard. We have proved that in all sweat samples drugs exist (amitriptyline, diazepam, carbamazepine, amitriptyline and clomipramine). The drug concentration in sweat, compared to blood and urine, is less in all samples..

Key words: amitriptyline, diazepam, carbamazepine, amitriptyline and clomipramine; sweat glands; toxic coma

INTRODUCTION:

The determination of toxic substances in sweat secret is not a commonly used method. It is an alternative of the analytical methods using blood, urine, hair, nails, stomach secret to prove xenobiotics. Our knowledge about the information that this method may give us is exceptionally small. Very few laboratories in the world have been using it because of its labor-consumption and lack of information. In the clinical practice this method was used by sweat extract analysis of drug abusers for proving drug presence, long time after taking off cocaine (1). The sweat glands excrete many drugs and toxic substances: it is proved for barbiturates (9), broom and Jodi (6, 10), selen, talium, arsen (7) cocaine (1), alcohol, acetone, phenol, chalogenic carbohydrates (7). It is accepted that drug sweat excretion has small pathogenic meaning for forming excreting dermatoses - bromoderma and jododerma (6). According to Al. Monov (10) the process of sweat elimination (drug and toxic excretion) has formed skin topical damages. The aim

of study is to determination of toxic substances in sweat secret of patients with severe form of poisoning- toxic coma. Clinical meaning.

MATERIAL AND METHODS:

The analysis includes 4 patients (P) in toxic coma after poisoning with amitriptylin (P№1), amitriptylin and clomipramin (P№2), diazepam (P№3), carbamazepin (P№4). Samples of sweat are taken at the 12-th,16-th,18-th,24-th hour after swallowing the drug, caused the poisoning. Samples of sweat are taken from non-affected skin in forearm area. Simultaneously with the first sweat sample is taken blood serum and urine. Pilocarpin iontophoresis for sweat stimulation: This is Gibson and Cooc (1959) modified method (5). After washing and drying the inside and outside area at the right forearm, a tampon is put with 0.2% pilocarpin (inside) and 0.6% NaH₂CO₃ (outside). The anode is connected with the pilocarpin's tampon and the cathode is connected with sodium bicarbonate tampon. Sweat secret is stimulated with 5 mA electricity for 15 minutes. After the stimulation the electrodes must be removed, the inside and outside area of forearm - washed and dried. Preliminary the filter paper (5891, Schleicher&Schnell, Germany) is weighted. The filter paper is placed in sweat's area and covered with parafilm. After 30 minutes the filter paper is removed. It is soaked up with sweat and again is weighted for measuring sweat quantity. Then the filter paper is cut in 2 mm stripes, which are left incubating for 24 hours in room temperature with 2 ml. Ethyl acetate. Hromato-massspectrometric analysis and fluid-fluid hromatographia have been used for detection of toxic substances.

RESULTS AND DISCUSSION:

For patient №1 presence of Amitriptylin is proved in sweat, blood and urine. For patient №2 presence of Amitriptylin and Clomipramine (Anafranyl) is proved in sweat, blood and urine. For patient №3 presence of Diazepam in blood and urine is proved quantitatively, while in sweat - qualitatively. For patient №4 presence of Carbamazepin is proved in sweat, blood and urine (tabl.1) .

Tabl. 1. Comparison of drug concentration in blood, urine and sweat secret.

Drug	Blood (mg/ml)	Urine (mg/ml)	Sweat (mg/ml)
Amitriptylin (P№1)	0.42mg/ml	1.050mg/ml	0.200mg/ml
Amitriptylin(P№2)	1.5mg/ml	6.250mg/ml	0.078mg/ml
Clomipramine (P№2)	0.43mg/ml	0.970mg/ml	0.280mg/ml
Diazepam (P№3)	2.94mg/ml	0.174mg/ml	(+)
Carbamazepin (P№4)	12.35mg/ml	4.200mg/ml	3.267mg/ml

Our results demonstrate that in non-affected skin area sweat glands are functioning well. They excrete toxic substances (amitriptylin, clomipramin, diazepam, carbamazepin) in first sweat portion. Drugs get into gland's cells from surrounding blood vessels or from the interstitium by process of simple diffusion. Skin lesion complicates severe acute drug poisoning with approximately 5-6%. Their clinical manifestation are erythema spots in irregular form, vesicles and bullae, soft tissue infiltration and necrosis. They appear 12 hours after the drug swallowing and localize on different body parts, often, but not obligated to spots with trauma and pressure. U.W Laevell (8) proposes the hypothesis about possibility drugs to be excreted by the sweat glands following their necrosis (by toxic mechanism) and forming skin lesion and developing patient's hypertermia. G.W Beveridge (2), S. Mandy and A.B.Ackerman (9) decline this hypothesis, because they establish normal sweat glands in spots of non-affected skin and normal temperature by patient with skin lesions. Except from barbiturate intoxications, skin lesions can be developed from CO; glutethimid; benzodiazepines: tranxen, lorazepam, flunitrazepam; meprobamat; chlorprotixen; heroin, methadon; alcohols and organophosphate compounds. The histological findings of erythema and bullae show intra- and subepidermal bullae, necrosis of skin appendix (sweat glands, hair follicles, fat glands). The pathogenesis of skin lesion in drug intoxication is still unclear. The regulation of sweat

secretion is accomplished by Autonomic Nerves System through spinal cords, hypothalamus and cerebral cortex. It is a proven fact, that by denervation through axon - reflex way without participation of the central regulating mechanism, sweat glands have being stimulated much more. We established this fact, because the sweat glands of patients with coma (when Central Nerves System is excluded) excrete significant quantities sweat, gradually decreasing after stimulating. Our findings of drugs in the early hours after the intoxication show us toxicokinetic behavior of drugs in acute intoxication. They have been distributed in peripheral tissue including skin. Is local affection of sweat glands possible through localized there drugs or other toxic substances (excreting mechanism)? Are skin lesions in drug induced coma an excreting dermatoses? We made analog with bromoderma, jododerma and other dermatoses, formed after sweat excretion (talium, arsenicum, selenium). Excreting mechanism is suggested about all this drugs, but not about Amitriptylin and Diasepam. We haven't found data about direct cytotoxic effects of these drugs. According to data oxidases with mixed function (OMF) present in skin cells epidermis, sweat glands and hair follicles (11,12,15). OMF participate in drug metabolism. P.Noonan and D. Paul show that skin oxidizes are 80-240 more active than hepatic oxidizes with mixed function(12,13). We propose a hypothesis about the possibility the local toxic skin effect to be caused by common cytotoxic mechanism trough forming free radicals in the metabolic process (3,4,11,15). According to Beveridge, late Mandy and Ackerman, the toxic mechanism theory is not acceptable because in non-affected skin area sweat glands are normal (2, 9). Our examination establishes good functioning of the sweat glands in normal skin area. Our clinical observation and other authors show that many factors may influence forming, localization and progress of skin damage. The pathogenesis is not cleared yet. We believe that our examinations will contribute to most fully and rightly understanding of skin lesion's forming mechanism in acute intoxication.

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Journal of IMAB - Annual Proceeding (Scientific Papers) 2007, book 1

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, lactat, 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 pathogenic 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