THE COCAINE CHARACTERISTICS

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Rezumat

În acest articol cocaina este prezentată sub aspectul proprietăţilor fizico-chimice, însuşirilor farmacologice şi toxicologice, biodisponibilităţii şi farmacocineticii. Această amplă caracterizare este absolut necesară pentru a distruge mitul acestui drog „miraculos" şi pentru a aduce la cunoştinţa tinerei generaţii, şi mai ales a copiilor, urmările consumului de cocaină.

Abriss

Das Werk stellt die physikalisch-chemische, pharmakologische sowie auch toxikologische Eigenschaften, die Biodisponibilität uns die Pharmakoskinetik der Kokain dar. Diese umgangreiche Darstellung ist notwendig für die Vernichtung dem Mythos dieser „Wunderdroge „ als Lehre für die junge Generation über die Nachwirkungen dem Kokaingebrauch.

Résumé

Dans cet article la cocaïne est présentée sans l'aspect des propriétés physico-chimiques, des traits pharmacologiques et toxicologiques, de la biodisponibilité et de la pharmacocinétique. Cette caractérisation ample est absolument nécessaire de détruire le mythe de cette drogue, « miraculeuse », et de porter á la connaissance de la jeune génération et surtout des enfants les conséquences de la consommation de cocaïne.

The drugs of different types were always consumed by the adults; from some decades now their use is associated with the young people negativism, that rebel against the established order and that tare looking for new experiences. This phenomenon generally implies a small number of persons or certain geographic areas, however in some regions it became almost an epidemic.

The average age of the drug addicted is reduced, and the poli drug addiction became ordinary. [St 03]

Cocaine history

Long time ago, the cocaine was extracted from the coca plant, and the leaves were masticated by the Amerindians from Peru and from other countries of Latin America.

The use of these leaves is anterior to the known historic time, so that all we know is entirely derived from the archaeological sources. The traces discovered on the clay pots from South America demonstrates the fact that the mastication of the coca leaves represented a cultural fact before the apparition of the Incas Empire, approximately the year 3.000 B.C. and that their effect on the state of mind and behaviour was highly appreciated by the Indians.

They considered the plant a gift from Gods and they used it during religious rituals, funerals and in other special situations. When the Spanish people appeared, in XV century, the Incas Empire was declining. In this period the coca leaves were used only by the leading class or only in ritual goals. At the beginning, the Spanish people tried to warn the Amerindians concerning their use, because they considered the coca leaves to be a barrier in the Christianity conversion way. Later, it became an aboriginal recompense modality for their work. In this way, they could oblige a big labour force to work under difficult conditions, at high altitudes, in the silver and gold mines. The coca leaves, together with the tea, coffee and tobacco were brought into Europe by the XVIth century exploiters, but unlike these, the coca leaves became unpopular even before the XIXth century. This fact could also happen because of the leaves' deterioration during the journey, and this reduced a lot their effect.

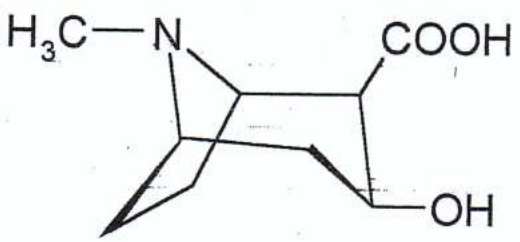
In 1862 Albert Niemann succeeds in extracting from a crystalline substance derived from the coca leaves a pure form of cocaine. The cocaine was highly appreciated in the eighth and ninth decades of the XIXth century and many prominent figures recommended the cocaine therapeutic use. Pope Leon the XII, Sigmund Freud, Jules Vernes and Thomas Edison approved in the year 1888 the cocaine use, the Coca – Cola drink that contained in naturally way cocaine and recommended itself as being "*the drink that alienates the tiredness*". (Meanwhile Coca-Cola substituted the cocaine content with caffeine content).

Before the year 1960, the cocaine was not largely used in the United States, but only by the bars animators and jazz players. The drug use was forbidden, both in medical field and in entertaining goal starting with the year 1914. The natives from the Andes still use the coca leaves for the stimulant effect. They often mix them with ash and lime and it is supposed that they can walk for days without being hungry or without feeling themselves tired.

However, the users have a hesitating walk, their teeth are covered by a greenish layer, and they suffer from incurable insomnias and a general apathy state. [Ti 03]

Physical – chemical properties structure

The cocaine is the only local natural anaesthetic that exists in 0,2-0,8% proportion in the *Erytroxylon coca* leaves, a shrub that grows in Peru and Bolivia.



the cocaine

the ecgonine

From the chemical point of view the cocaine is methyl-benzoil-ecgonine; and the ecgonine is an hidroxi-amino-acid.

The ecgonine is a tropan derivate, bicyclical system that contains a pyrolidinie nucleus, condensed with a piperidine one.

The base cocaine is a crystalline substance, white, little water soluble, but soluble in ether, alcohol and chloroform. It easily discomposes itself at hot temperature, because it hydrolyses. Cocaine chlorinehydrate looks like white crystals, bitter, very soluble in water and ethanol. The natural cocaine is levogyrate. A dextrogyrate isomer, pseudococaine (the delchayne, the psychaine) isn't active and does not cause drug addiction.

Intoxications' etiology

The cocaine toxicological implications mean acute and chronic intoxications, as well as a series of adverse reactions.

The acute intoxications happen accidentally at the cocaine administration as anaesthesic, by confusion as well as by overdose. The voluntary intoxications (suicide attempts, crimes) are very rare.

The chronic intoxications, that is the cocaine addiction, is a major drug addiction, representing the usage, a strong psychic dependence, with a tolerance increase. The interruption of the cocaine administration determines the apparition of the absence syndrome, very serious. [Pr 00]

Toxicokinetics

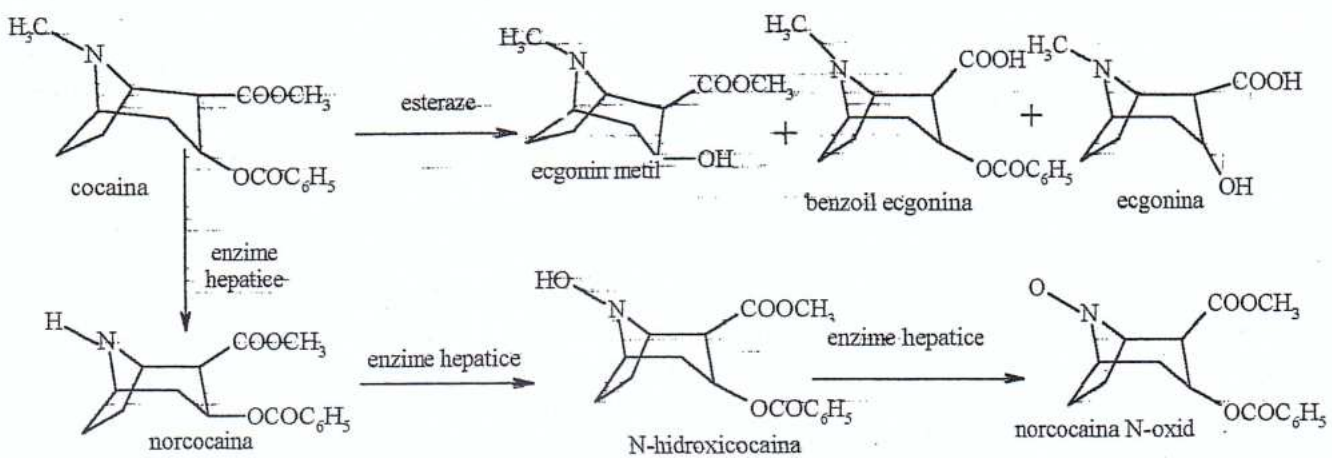
The cocaine is rapidly absorbed from the application place and goes to the general circulation. The absorption takes place from all the application places, even from the bladder, if there is an inflammation.

Campell and Adriani showed that the cocaine rapid absorption from the superior respiratory tract level takes place after a few minutes since its application, and the maxim absorption is realised by the bronchial and tracheal mucous membrane. The maxim plasmatic level appeared proportionally to the dose.

The cocaine bioavailability intranasally administrated is estimated to be 46 times smaller than the plasmatic concentration after the intravenously administration of the same dose (0,140 – 2,0 mg/kg). Due to the strong vasoconstriction that it produces, the cocaine can limit its own absorption. One can notice that even if it has a late absorption, the orally administrated cocaine produces plasmatic levels similar to those produced by the application on the nasal mucous membrane.

By oral administration, the cocaine hydrolyses at the gastrointestinal tract level and becomes inefficient.

The major way of cocaine metabolisation into the organism is by hydrolyses. In the plasma, the cocaine is *hydrolysed* at *methylated ester* and *the ecgonine* under the influence of *cholinesterase*. The hydrolyse at *benzoil-ecgonine* seems to be spontaneous, because the serum esterase's don't give this compound leaving from the cocaine.



The cocaine biotransformation

The ulterior split, in *benzoic acid* and *ecgonine* is realised by enzymatic way, under the action of the *tropinesterase*. A secondary way of cocaine metabolisation is by *N-demethylation*, obtaining the *norcocaine*, which forms the *hydroxynorcocaine* by hydroxylation; this, by oxidation, forms the *norcocaine* N-oxide. [Dă 96]

The cocaine deposits itself at the liver level, kidneys' level, mucous membranes level, bile and saliva level. The *norcocaine* is the only cocaine metabolite which presents significant pharmacological activity. It was detected in the monkey brain, where it appeared to have the same concentration with the cocaine used for the inhibition of the nervous supra-solicitation with norepinephrine. It was noticed that the foetus or newly born children have the cocaine metabolism modified.

The cocaine hydrolyses into the plasma can be reduced in hepatic diseases, gravidity, malnutrition and anticholinesterasic medication.

It is experimentally determined that the liver can metabolise a minim lethal cocaine dose in 60 minutes.

The cocaine elimination is generally made by renal way under the form of metabolites, and 1-5% non-metabolised. The two main cocaine metabolites: ecgonine's methylated ester and the benzoil-ecgonine present a 4-6 hours halving time. The cocaine is also eliminated by saliva and by the bile.

Cocaine effects on human body

The cocaine has effect on the central and peripherical nervous system, but it also works as local anaesthesic, its general effect being the C.N.S. stimulation.

At the present the cocaine is used as topic anaesthesic in E.N.T. surgery. It isn't used in ophthalmology, because of the cornea lesion risk. *It isn't injected* because the strong local vasoconstriction determines ischemic phenomena, and the systemic toxicity is bigger.

The main cocaine ***adverse reactions*** manifest at:

- *the central nervous system level*, which is stimulated from top to bottom. The first action is on the cerebral cortex and concretises at the humans by: logorrhea, anxiety and excitation. Sometimes the intellectual functions are intensified. It may appear an increase of the muscular work capacity, explained by the reduction of the tiredness sensation. At cocaine small doses the motor action is coordinated, yet at big doses trembling and convulsions appear. The cocaine affects the bulb, by an increase of the respiratory rhythm, with a rapid and superficial breathing. The puke and vasomotor centres are influenced, so that frequent pukes appear. After the central nervous stimulation the inhibition appears and death is determined by a respiratory insufficiency.
- *the cardiovascular system level.* Experimental data show that at small cocaine doses the cardiac beats rhythm is reduced as a result of the vague central stimulation. After moderate doses the rhythm is accentuated, and at big doses by intravenous administration immediate death takes place by cardiac insufficiency due to a direct toxic action on the myocardium. If the cocaine is locally applied, it produces a direct vasoconstriction.
- *the striped muscle level.* There aren't proofs that demonstrate that the cocaine would increase the contraction power of the voluntary muscle, so that its possibility of tiredness suppression results from the central stimulation.
- *the sympathetic nervous system level.* The cocaine behaves as an indirect sympathomimetic because it prevents the returning at the neuron of a noradrenaline part normally issued and reintegrated. The cocaine intensifies the organs reactions with sympathetic intervention, towards the adrenaline, noradrenaline and towards the sympathetic nervous stimulation. All these have as effects: vasoconstriction (unlike the majority of the local anaesthesics), high blood pressure, tachycardia, midriasis, intestinal inhibition.
- *on the body temperature.* The cocaine has a strong pyrogen action due to the following factors: increased muscular activity, vasoconstriction as direct action on the thermo-regulators centres.

- *the eye level.* The cocaine produces midriasis (by simpatico-mimetic), cyclopics (weaker than the atropine) and cornea lesion (ulcerations, dryness).

The addiction appears rapidly, up to some centigram per day. The *psychic dependence* is pronounced, while the physic dependence is little accentuated, because the abstinence syndrome is not significant.

The toxic dose depends on: the solution concentration (so that 1% from the solutions are toxic); the administration way (the cocaine is less toxic by digestive way); individual sensitivity, addiction.

It is considered to be lethal dose 1 – 2 g by oral administration and 0,2 – 0,3 g subcutaneous administration. There are survival cases with 5 g ingestion and deaths by subdural injection of 0,01 – 0,03 g of cocaine.

Manifestations in case of intoxications

Acute intoxications have two forms:

- *the easy form*, that is physic and psychic hyperexcitation, euphoria, tachycardia, "dance fury" increased physical exercises and a pronounced sensuality increase, especially at women;
- *the severe* form, that is a sympathic, strong excitation, that leads to midriasis, tachycardia, face congestion, transpiration, hyper-thermia, hypertension and hands' trembling. The nervous excitation can determine epileptic convulsions, muscular hypertonia and hallucinations, the speech gradually becomes heavy, the breathing ample and irregular, and then the loss of consciousness appears. In the favourable evolution cases can appear aftereffects such as: intense cephalitis, anxious states, insomnia and sometimes pukes.
- *the cocaine shock* can appear at hypersensitive persons even at very small doses (30-50 mg). The symptom pathology is characterised by a sudden anxiety state followed by an agitation state and serious shock signs with extreme pallor, cold transpirations, intense dyspnoea, very rare pulse, tachycardia, the blood pressure diminishes and appears a profound coma state from which the patients cannot be saved, even after the adequate treatment.

Chronic intoxication (cocaine addiction)

The cocaine addiction is a major drug addiction. The junkies use:

- Coca leaves used in masticated natural state, fumed or transformed into paste;
- Cocaine chlorinehydrate (by sniffing, unguents application, lotions);
- Crack (free base) obtained by power cocaine warming up with ammoniac or sodium bicarbonate and it is fumed;
- Cocaine with heroin (speedball).

The individual gets used rapidly and the individual can stand toxic cocaine doses even if it is lethal for an ordinary person; so the cocaine "need" is continuously increasing. After a long time of cocaine use (36 weeks and even months) chronic intoxication can appear which is characterised by three phases:

- *the initial phase* or "*cocaine drunkenness*", with the following symptoms: psychomotor agitation, euphoria, irritability, digestive and sensorial disturbances, weight loss, behaviour modification. In the sniffing case can appear, as a characteristic sign, the nasal septum perforation, due to the prolonged vasoconstriction, as well as to local irritant actions.
- *the hallucination phase* is characterised by itches, insects sensation "on" or "under" the teguments (Ekbom syndrome), visual and hearing disturbances (baked like smell), delirium, escape tendency, memory, will and affectivity diminishing. The persons become dangerous for the society, have an aggressive attitude, being able to commit antisocial acts. Many

junkies become paranoid, suffer from persecution and believe that other people read their thoughts. At women the cocaine addiction has erotic character and determines harmful effects on the descendents, giving birth to abnormal children.

- *the cachectic phase* is characterised by complete physic, moral and intellectual degradation and it becomes complete after 5 – 10 years of cocaine abuse.

The *abstinence syndrome*, in the junkies' case, is less relevant and the cocaine use interruption is less difficult that for the morphine addicted persons, the created dependence being more psychic than physic. [Pr. 00]

Toxicological analysis

1. Isolation

The biologic products (urine, blood, gastric liquids) alkalise at 8 - 9 pH with sodium bicarbonate and it is extracted with solvent agents.

2. Identification

- Precipitation reactions

The cocaine produces precipitates with precipitation general reagents of alkaloids (Hager, Bouchardat, Mayer).

The residue treated with potassium permanganate solution in acid medium produces violet precipitates.

- Colour precipitates

▫ *Pesez reaction* (Vitali reaction variant) with the apparition of a dark violet – red ring;

▫ *Ferreira de Silva reaction*: with the apparition of the ethyl benzoate smell (and at strong concentration also appears a purple – red coloration);

▫ *Guerbert reaction*: with the formation of a precipitate or red – orange coloration;

3. Chromatography on thin layer

Stationary phase – G. Merck silicagel chromateplates activity at 110° C for one hour.

Mobile phase – chloroform: methanol (9:1 v/v)

Test – basic chloroform extract

Revelation – potassium of iodoplatinate.

Standard – cocaine in chloroform

R_F value = 0,60.

4. Spectrophotometry in U.V. and I.R.

Maxim **U.V.**:

- ❖ Cocaine base in ethanol (230, 270, 281 nm);
- ❖ Cocaine chlorinehydrate in water (233, 274 nm).

I.R. (in KBr):

- ❖ cocaine base: A (1275); B (1700); C (1106, 1728). [Pr 00] [*** 98]

5. Physiologic test

If ones put cocaine on his tongue it produces anaesthesia. Instilated in the cat or rabbit's eye, it produces midriasis (the other eye serving as witness). [Mu 95]

Conclusions

Considered by the users as excitant and provoking or as a last and only solution of the existing problems, the cocaine is a dangerous drug against which we can fight only knowing its physical chemical properties, its pharmacological and toxicological features, as well as bioavailability and pharmacokinetics.

The consequences of the cocaine use and of other coca-based products affect the physic and psychic health:

o physic and psychic dependence;

o cardio – vascular problems with irregular pulse, palpitations, crises and cardio – vascular diseases;
o neurological problems, cerebral accidents, haemorrhage in the tissues from the brain vicinity, cerebral mycosis.
o pulmonary problems such as: accumulation of liquids into the lungs, aggravation of the existent pulmonary affections or respiratory affections, that can lead to respiratory insufficiency;
o psychic disturbances that include the paranoid state, depression, anxiety and hallucinations, reality inadequate perception,
o violent or criminal behaviour;
o other effects such as: somnolence, sexual disturbances, smell reduction, perforation of the nasal septum, nausea and cephalea;
o the effects on the foetus are: placenta detachment, spontaneous abortion, premature birth, underweight newly born, the cranium circumference smaller, seeing disturbances, mental retardation, genital urination infections and reduced immunology;
o for the users of injected cocaine there is the risk of infections with: HIV virus, C hepatitis virus and endocarditis;

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