

## NATURAL AND PARTIALLY SYNTHETIC ANALGESICS

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Humans have a long history of stimulating and mind-altering substances use. Depressive drugs, including morphine and other narcotics, barbiturates and ethanol, are strongly addictive for susceptible individuals. The phenomenon is most striking in the case of opiates.

Morphine is an alkaloid of opium. Named after the Roman god of dreams, Morpheus, the compound has potent analgesic properties toward all types of pain. By substitution of two hydroxylic groups of morphine many natural and semisynthetic derivatives with different pharmacological activity and analgesic action are obtained.

Determinations and quantifications of narcotic analgesics in drug addicts are important in forensic medicine and clinical toxicology. With development of highly sensitive chromatography technique (HPLC-GC, GH-MS), more and more substances are determined, including opioid drugs: morphine, codeine, dihydrocodeine, and heroin and 6-monoacetyl morphine. Hair analysis by HPLC/MS spectroscopy is an effective forensic tool for determining the use of abused drugs. The "fingerprint" for heroin in the mixture with the other substances (1-10 components) is determined by 1D-TOCSY NMR. *Acta Medica Medianae* 2005;44(4): 67 – 73.

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### Introduction

There is an old proverb saying: "Sedare dolorem, divinum opus est", (Divine is curing the pain). The tendency of humans to relieve the pain has existed since the beginning of mankind. For that purpose, people have organized religious rituals, used some secret recipes and other methods of getting free from the pain.

Analgesics relieve the pain without blocking the nerve impulses and significant change of sensoric functions. According to the mode of action, there are two types of analgesics. Opioid drugs (opiates and semisynthetic analgesics) act upon brain receptors blocking the nerve impulse of pain. They may be used for the short-term or long-time relief from pain. Antipyretic analgesics are considerably less potent in their action compared to opioid analgesics, and may be used for relieving the pain of minor intensity (headaches, toothache).

The narcotic and analgesic effects of opium – dried juice of opium poppy, have been known for over 6000 years as the source from which the princi-

pal alkaloid morphine was first isolated (Derosne and Sertürner, 1803). Morphine constitutes up to 10% of the dried weight of opium. Some minor quantities of other alkaloids such as codeine, thebaine and papaverine are also present.

Morphine and codeine served as models for preparing semisynthetic and synthetic drugs with a selective analgesic activity and minor undesirable side effects. Since 1938, over one thousand potential analgesics have been synthesized (1).

### Natural and partially synthetic analgesics of morphine group

**Morphine** (3, 6 $\alpha$ -dihydroxy-N-methyl-4,5  $\alpha$ -epoxy-7-morphinene) occurs as levorotatory, odorless, white, needlelike crystals with bitter taste. It is almost insoluble in water (1: 5000. ili 1:1100 at boiling point), ether (1:6250), or chloroform (1:1220). Morphine is monoacidic base and readily forms water soluble salts with most acids<sup>1</sup>. For this reason, in pharmaceutical practice sulphate and hydrochloride water-soluble salts of the drug are used more frequently (2).

By substitution of phenolic and alcoholic hydroxyl groups of morphine, many of their derivatives are

<sup>1</sup> Morphine was discovered by Friedrich Wilhelm Adam Sertürner (1783-1841), an obscure, uneducated, 21-year-old pharmacist's assistant with little equipment but loads of curiosity. Gulland and Robinson were given actual formula, and total synthesis of morphine is done by Gates and Tschudi (1952)

obtained (Table 1). Activity of morphine is increased by catalitical reduction, methylation, oxidation and elimination of hydroxyl group at position C<sub>6</sub>, incorporation of hydroxyl group at position C<sub>14</sub> or methyl group at position C<sub>5</sub> or substitution of N-methyl group with another group, such as N-CH<sub>2</sub>-CH<sub>2</sub>-C<sub>6</sub>H<sub>5</sub>. The activity of morphine decreases by methylation of phenolic group, quaternaryation of the azote atom and opening of 4,5-oxygen bridge (3).

Table 1. Natural and semisynthetic analgesics of morphine group

N <sup>o</sup>	Compound Generic name	Principal Use
1.	Morphine	Analgesic
2.	Codeine	Analgesic, depresses cough reflex
3.	Diacetylmorphine-hydrochloride, heroin	Causes strong addiction, analgesic, depresses cough reflex
4	Ethilmorphine Dionin	Ophthalmology
5.	Normorphine	Morphine abstinence syndrome in drugs addicts

**Codeine** (3-methoxy-6 $\alpha$ -hydroxy-N-methyl-4,5 $\alpha$ -epoxy-7-morphinene) naturally occurs in opium, but in the amount to small to be of commercial importance. Consequently, the most commercial codeine is prepared by methylation of phenolic hydroxyl group of morphine. In the process of methylation, reagents such as diazomethane, dimethyl sulfate, and methyl iodide are used. Newer methods are based on its synthesis from thebaine, which makes it possible to use *Papaver bracteatum* as a natural source (2).

Codeine occurs as levorotatory, colorless, refruorescent crystals or a white crystalline light-sensitive powder. Codeine is slightly soluble in water (1:120), freely soluble in alcohol (1:2) and very soluble in chloroform (1:0.5). Codeine is monoacidic base and readily forms salts with acids (mostly sulfate and phosphate salts) (2).

Codeine may be administrated orally as an analgesic, antitussive and antidiarrheal drug in a dose of 10 to 60 mg. It is available in the form of salts, codeine-phosphate. Codeine is known as an antitussive drug, depressing the cough center (2). Analgesic activity of codeine is only 15 to 25% of morphine activity, and most of other properties of codeine are tenfold less potent compared to morphine (4). Codeine is the less effective when administrated orally when compared to parenteral administration. It can cause many undesirable side effects and induce the habit-forming codeinomania.

Codeine is metabolised by liver to morphine. If codeine is applicated directly into the brain, it will not produced analgesic activity because of inability of hydrolytic dividing of ether bonds in the brain. Methylation of phenolic group of morphine increases basicity

(pKa codeine =8,2; pKa morphine =8,0), lipophility and stability of molecule (1).

**Ethylmorphine hydrochloride** (3 $\alpha$ -etoxy-6 $\alpha$ -hydroxy-N-methyl-4,5 $\alpha$ -epoxy-7-morphinene hydrochloride, Dionin) is ethyl ether of morphine. It may be prepared by treating an alkaline alcoholic solution of morphine with diethyl sulfate. The hydrochloride salts is obtained from the free base by neutralisation with diluted hydrochloric acid (2).

Ethylmorphine has analgesic and antitussive properties. As a depressant of the cough reflex, it is as effective as codeine and, consequently, is found in some commercial cough medications. The chief use of this compound is in ophthalmology where it dilates blood vessels, by which it stimulates the vascular and lymphatic circulation of the eye (2).

**Diacetylmorphine-hydrochloride** (heroin) (3,6 $\alpha$ -diacetoxy-N-methyl-4,5 $\alpha$ -epoxy-7-morphinene-hydrochloride) is semisynthetic derivative of morphine. Heroin was first synthesized in 1874 from morphine by English chemist C. R. Wright (1874) who named it heroin. Although its analgesic action is 2 to 3 times stronger than that of morphine, it is not used in therapy, because it causes strong habit-forming and addiction stronger than morphine (5).

The International Commission for Drugs has recommended to the members of the World Health Organization (WHO) to prohibit the use of heroin and ban its production. More than 50 countries have adopted this recommendation, including the United States (6). The use of heroin for medical purposes is still allowed in Great Britain (5).

Completely pure heroin is white powder of bitter taste, water-soluble. But, street heroin ("horse"-street term), is in most of the cases dark brown, and contains only 7 to 10 % of diacetylmorphine. For commercial purposes, the street heroin is often mixed with substances such as sugar, starch, milk powder, baby powder, strychnine, kinin etc.(5).

Heroin can be sniffed, (quickly absorbed by nasal epithelium), smoked (warming of heroin and inhalation of vapor) or injected (intravenously or subcutaneously). Initial effects, immediately after consumption, are of great intensity. It is an euphoric state followed by the feeling of calmness and warmth, safety, absence of pain, anxiety and tension. Besides high doses of heroin, a great risk may be the combination of heroin and alcohol, then heroin after alcohol and sedatives or its use after the great exhaustion of the body. These combinations slow down breathing and cardiac function, and due to oxygen deficiency lead to giddiness and, consequently, death (5).

The speed and the power of heroin activity is the result of good dissolving in fat, which contributes to higher speed of crossing the blood-brain barrier.

**Normorphine** (3 $\alpha$ ,6-dihydroxy-4,5 $\alpha$ -epoxy-7-morphinene) is prepared by N-demethylation of morphine. It has analgesic effects, it is four times less active than morphine. Side-effects are less marked (2).

Many synthetic narcotics have also been produced, such as: Meprobamate (Demerol), Levorphanol (Levo-Dromoran), Methadon (Dolophine), Fentanyl (Sublimaze), Propoxyphen (Darvon, Dolen) (7).

**Pharmacokinetics** As many other opioid analgesics, morphine is well resorbed from subcutaneous tissue, muscles, through nasal epithelium and gastrointestinal tract. Absorption from the gut is good, but the serum morphine concentration is variable due to the first passing of drugs through the liver. All metabolites are excreted by kidneys. Only a small part of glucuronide conjugates of opiates are excreted by bile (3).

Metabolism of opioids is closely related to their own chemical structure. In the first phase of metabolic reactions, they are subjected to: O-dealkylation, N-dealkylation, ketoreduction or deacetylation. By glucuronidation or sulfation, phase-II metabolites are formed. Some metabolites of opioids, are active and contribute to the effects of the parent compounds. When in human organism, a part of codeine (methylmorphine) transforms into morphine, and probably, a part of its effects are the result of morphine realising. After administration, heroin is subjected to enzyme hydrolysis (of the tissue esterases) to 6-acetyl morphine, and then slowly hydralised to morphine. 6-acetyl morphine is less polar than morphine and easily passes through the blood-brain barrier. The half-life in the blood plasma for heroin is 2 to 8 minutes, so the initial compound is only a weak agonist of  $\mu$ -opioid receptors, which is the case with codeine.

The morphine is further metabolised in the liver and also in the small intestine to normorphine and codeine. With morphine, the active metabolite morphine-6-glucuronide exerts important clinical opioid effects, when it accumulates in the plasma of patients with renal failure. In case of normal renal functions, the importance of morphine-6-glucuronide is probably less compared to morphine.

The morphine forms 3-0 and 6-0 glucuronide, both of which are active compared to opiate receptors in the body. The overall analgesic effect of morphine is a combination of both active glucuronides' effects and is, as a result, very complex (8).

Several factors may influence the level of analgesics' biotransformations, and those are: psychological status of the patient, genetic predisposition, coadministered drugs leading to toxic and subtherapeutic concentrations of the drugs. Therefore, 35 % analgesics are metabolised by the reaction of phase II-glucuronidation (9) (Table 1, 2).

### Semisynthetic analgesics of dihydromorphine group

**Hydromorphone**, (dihydromorphinone) (3 $\alpha$ -hydroxy-N-methyl-4, 5 $\alpha$ -epoxy-6-oxomorphine) is obtained by catalytic hydrogenation and dehydrogenation of morphine in acidic condition, using large amounts of platinum and palladium. Hydromorphone as the free base has similar properties to those of morphine, being slightly soluble in water, well soluble in alcohol, and very soluble in chloroform.

Analgesics effect of hydromorphone is five times stronger compared to morphine, but it has the same dependence properties, and has short duration of actions. It is potent antitussive and is often used for coughing difficult to control (2).

**Hydrocodone**, (dihydrocodeinone) (3 $\alpha$ -methoxy-methyl-4, 5 $\alpha$ -epoxy-6-oxomorphine) is prepared by the catalytic rearrangements of codeine or by hydrolysis of dihydro-thebaine. It appears as fine, white crystals or as white crystalline powder, soluble in water (1:16), slightly soluble in alcohol, and insoluble in ether. The hydrochloride salts is also available (2).

According to its action, hydrocodone is between codeine and morphine. Hydrocodone does not cause many undesirable side effects. It is more effective than codeine, and, as antitussive, it is contained in many cough medications, as well as in tablets and parental forms (2).

**Oxymorphone**, (14-hydroxydihydromorphinone) (3 $\alpha$ ,14-dihydroxy-N-methyl-4,5 $\alpha$ -epoxy-6-oxomorphine) is prepared by cleavage of the corresponding codeine derivative. It is used as the hydrochloride salt, which appears as white crystalline powder, well soluble in water and scarcely soluble in alcohol (2).

Pharmacological action of oxymorphone is much stronger than morphine. The action is faster and with less undesirable side effects (2).

**Oxycodone**, (14-hydroxyhydrocodeinone), (3 $\alpha$ -methoxy-14-hydroxy-N-methyl-4,5 $\alpha$ -epoxy-6-oxomorphine) is prepared by the catalytic reduction of 14-hydroxycodeinone. This derivatives of morphine occurs as white water and alcohol soluble crystalline powder (1:10). Aqueous solutions may be sterilized by boiling. This drug is almost as likely to cause addiction as morphine. It is used as the sedative, analgesic and narcotic (Table 2) (2).

Table 2. Semisynthetic analgesics of dihydromorphine group

N <sup>o</sup>	Compound Generic name	Principal Use
1.	Hydrocodone (dihydrocodeinone)	Analgesic, depresses cough reflex
2.	Oxymorphone (14-hydroxydihydromorphinone)	Analgesic
3.	Oxycodone (14-hydroxyhydrocodeinone)	Analgesic, depresses cough reflex, sedative
4.	Dihydrocodeine	Depresses cough reflex

**Dihydrocodeine**, (3 $\alpha$ -methoxy-6-hydroxy-N-methyl-4, 5 $\alpha$ -epoxy morphine) is produced by reduction of codeine. The bitartrate salt appears as white crystals that are soluble in water (1:4.5), and only slightly soluble in alcohol (2).

**Apomorphine**, (6 $\alpha$ - $\beta$ -aporphine-10,11-diole) is produced by the action of hydrochloride acid on morphine at temperature of 150<sup>o</sup>C. It has emetic action, and is administered parenterally. Apomorphine is characterized by weak narcotic effects (6).

**Dihydromorphine**, (Paramorphan) (2-Hydroxy--N-methyl-1,11-epoxy-morphinan) results from catalytic hydrogenation of the double bond of morphine in the presence of colloidal palladium. It is used more frequently than morphine, from which it is obtained by

substitution. There are some authors who claim that dihydromorphine is characterized by stronger analgesic effect (compared to morphine), but weaker convulsive and toxic effect. It is not widely used. In USA, it is not used at all, and is hardly used in Europe (10).

**Methyldihydromorphinone**, (Metopon) (11,N-Dimethyl-2-hydroxy-12-oxo-1,11-epoxy-morphinan). The structure of this compound has not been established yet. Most probably, it is the first reaction induced by the effect of methyl-magnesium halide on dihydrothebaine, which is difficult to interpret (Table 4).

It can be observed that the first aforementioned reaction actually produces two isomers, the formation and constitution of which are still hard to explain. Metopon has been studied clinically only in cases of inoperable cancer. It is administered orally and has been found to possess few undesirable side-effects (10).

The addiction to which it gives rise is less marked than that caused by morphine. Despite these promising results, it is too early to make any final judgement.

### Effects of clinically used opioids

The effects of morphine and their derivatives on CNS of patients and also healthy persons, are very complex. The most important effects of morphine are registered at the level of CNS and GIT (11).

The most important pharmacological action of morphine, when used in therapy, is analgesic one. Morphine acts on the CNS, so that even in very small doses (5 to 10 mg), decreases the sensibility of stimuli, reducing unpleasant and painful sensations. Morphine increases the level of the pain perception, changing the way of emotional reaction towards pain. It also has sedative effects (3). Morphine has strong analgesic characteristics (50 times stronger than aspirine) and it is used only in cases of very strong pain. In higher doses, it has narcotic properties (12).

Morphine is used to relieve the most severe kinds of pain, such as: burn, fracture pain, myocardial infarction, shock and cancer pain. The pain caused by biliary and renal colic may be relieved by administration of combination of morphine or some other opiates with spasmolytic drugs. Doses of morphine are 10 to 15 mg, administered subcutaneously per 4 to 6 hours (3).

Pain and morphine are antagonists: with increasing of pain, it is necessary to administer higher doses of morphine to relieve the pain, and it is impossible to induce pain sensation in person to whom morphine has been administered (3).

Regarding this drug, the tolerance increases easily, leading to the need for increasing doses, and addiction comes from physical and psychological dependence when cramps, vomiting, muscular spasm, and dysphoria appear.

Table 3. Characteristics of natural, semisynthetic and synthetic analgesics of morphine group

Chemical Name	Trade Name	Dose (mg)	Time of Action (h)	Symptoms
Morphine		10	4-5	Sleepiness, analgesic, change of behavior and psychological status
Heroin		3	3-4	Similar to morphine
Codeine		10-30	4-6	Analgesic, depresses cough reflex
Levorphanol	Levo-Dromoran	2-3	4-5	Similar to morphine
Methadone	Dolophine	8-10	3-5	Similar to morphine

Table 4. Characteristic of semisynthetic and synthetic analgesics of dihydromorphine group

Chemical Name	Trade Name	Dose (mg)	Time of Action (h)	Symptoms
Hydromorphine	Dilandid	1,5	4-5	Similar to morphine
Oxymorphone	Numorphan	1,0-1,5	4-5	Similar to morphine
Hydrocodone	Hycodan	5-10	4-8	Similar to morphine and codeine
Dihydrocodeine	Paracodin	60	4-5	Similar to morphine and codeine
Oxycodone	Percodan	10-15	4-5	Similar to morphine

Morphine, as all other opiates, induces good mood (euphoria). Parallely with euphoria, morphine causes sleepiness, depression, decreasing of physical activity and lethargy (Table 3). However, in healthy persons – persons not suffering from pain, morphine may cause dysphoria (unpleasant mood) (Table 4).

Tolerance and physical dependence in repeated taking of drugs, as well as psychological dependence on morphine, are the main limiting factors for their administration, even for the medical purposes. The role of neurotransmitters in appearance of tolerance, induced by administration of opiates, is very complex, and often depends on the way of taking it and psychological status of opiate addicts (13).

Heroin, diacetyl derivate of morphine, is more potent analgesic and causes stronger addiction compared to morphine, since it passes through the brain, where it is hydrolysed to morphine.

Physical dependence is characterized by abstinence crises occurring 24 to 48 hours after the last consumption. Psychic dependence is harder to control, and it is associated with needs for every day consumption, which is not possible to control (14). Codeine, a monomethyl derivate of morphine, is about one tenth as potent as an analgesic, but it is less addictive and is used in a synergic combination with aspirin (15). This effects may be inhibited by narcotic antagonists and with some derivatives of phenothiazine, which block dopamine activity.

Morphine and the other opiates release histamine, whose role in the occurrence of hypotension is very important. Only partly, hypotension can be blocked by antihistamine drugs. (Eckenhoff i Oech, 1960) (13).

Morphine reduces sensibility of respiratory centre to carbon dioxide (CO<sub>2</sub>) and in that way depresses respiration. The level of breathing depression depends of quantity of administration doses. All opiates are strong inhibitors of the cough reflex. Respiratory function depression is very prominent, and even in very small doses, it increases progressively along with increasing of the opiate doses taken into the organism.

Therapeutical doses influence decreasing of all phases of respiratory activity: speed, minimal volume, the interval between inhalation and exhalation, unequal rhythm of breathing, and also increasing of the CO<sub>2</sub> content in blood. Maximal respiratory depression occurs 7 minutes after administration of morphine in the body (13).

Morphine significantly increases the common intrabiliary pressure, inducing contraction of the smooth muscles of bile ducts.

By slowing down tonus of the small intestine, morphine can cause persistent constipation. Besides morphine, methadone, levorphanol, codeine, dihydrocodeine and levallorphan have also decreased gastric motility (11).

Central action of morphine causes *myosis* even in the dark (13).

Contraindication of morphine administration are: increased intracranial pressure, bronchial asthma, acute poisoning with ethanol, convulsive disorders, hypothyroidism, Addison's diseases, emphysema of the lungs (3).

### Mechanisms and sites of action of opioid-induced analgesia

Opioids exert their therapeutic effects by mimicking the action of endogenous opioid peptides in opioid receptors. These receptors are found in various cortical and subcortical region of the brain. Endogenous opioid peptide endorphine, responsible for the regulation of pain, nausea, breathing, hormonal activity, also contributes to good mood.

Opiates exert their influence on various neurotransmitters, directly or indirectly. Opiates from peripheral and central cholinergic neurones increase the level of acetylcholine in the brain (Harris i Dewey, 1973). Numerous investigations' results show that opiates may induce analgesia and euphoria by central noradrenergic activity (13).

The binding sites for morphine are the endorphine, dynorphin, and enkephalin receptors, ( $\mu$ ,  $\kappa$ ,  $\delta$ ).  $\mu$  receptors bind morphine most tightly.

The sigma receptors do not belong to analgesic receptors, but can be activated by some opioid analgesics. Activation of this receptor may generate hallucination effects. The results of numerous investigations shown that opiates can induce analgesia and euphoria by general noradrenergic mechanism. There are two subtypes of delta 1 and delta 2 receptors, whose functional importance has not been determined yet. The receptor subtypes differ in physiological and pharmacological effects caused by different agonists, in potency of naloxone to antagonise their effects, in differences in the way of binding to receptors in vitro and in the power to influence adenylat-cyclase (1).

Majority of narcotic receptors are polycyclic in nature. The flexible methadone molecules bind to the same receptors.

The activity of morphine and the other opioid agonists is closely connected with the changes of metabolism of cellular Ca<sup>2+</sup>. Thus, decreasing of concentration of Ca<sup>2+</sup> emphasizes the effects of opioid agonists, and increasing of Ca<sup>2+</sup> concentration may antagonise their activity.

Na<sup>+</sup> ion can be important for the process of binding of opioid analgesics to receptors, in the way that it increases binding of antagonists and decreases binding of agonists.

There is a close connection between modifications of the chemical structure of the morphine molecule (or some the others opioids) and pharmacological activity, that is, the affinity of binding to receptors. Aromatic ring and free electron pair of nitrogen are the most responsible for the opioid activity of analgesics, and represent the necessary components for  $\mu$  agonist action. Phenolic group, as a part of natural, semisynthetic and synthetic analgesics increase the affinity of binding to opioids receptors, but it is not necessary for their action (1).

Very discreet changes in the structure of natural opiates can significantly change pharmacological characteristics of their action and transform them into almost pure competitive antagonists (naloxone and naltrexone) or substances with complex pharmacological characteristics (mixture agoniste-antagoniste).

Comparing the efficiency of morphine, 6-acetyl morphine and heroin (diamorphine), it was shown that 6-acetylmorphine is the most toxic. 6-acetyl morphine is less polar and this is the reason for easier crossing the blood-brain barrier. Phenolic group is free and can react with the receptor. Heroin has two protected polar groups, and it crosses the blood-brain barrier most easily, but it can not react with the receptor, until the brain esterases deacetylate the phenolic group.

### Acute opioid toxicity

During administration of high doses of morphine (15 to 20 mg) subjective effects become less marked. In normal persons, euphoria is associated with respiratory depression and sensory disorders of touch, vibration, vision and hearing.

Heroin has sedative effects on respiratory system, which is the reason why it is used for sedation of obstinate cough, when the other drugs are not useful. Therapeutic doses of heroin are almost equal to toxic doses, which makes it very dangerous for use. In doses of 1 to 2 mg, it has analgesic effects, while doses of 5 mg of heroin may be toxic.

A long-term administration of heroin is very harmful for emotional, physical, psychological and social aspects of one's personality. Also, the person loses interests in anything but taking drugs. Sniffing heroin is harmful to nasal epithelium. For example, it may cause poisoning (strychnine), problems with blood coagulation, blockage of small capillaries if the particles are not completely water-soluble (5). The effects of heroin use can also cause arthritis and other rheumatic problems and infection of blood borne pathogens such as HIV/AIDS and hepatitis B and C (which are transmitted by sharing syringes and other injection paraphernalia).

### Estimation of narcotic analgesics

Determination and quantification of narcotic analgesics in drug addicts is important in forensic medicine and clinical toxicology. With development of highly sensitive chromatographic technique (HPLC-GC, GH-MS), more and more substances are determined, including opioid drugs: heroin, 6-monoacetyl morphine, morphine, codeine and dihydrocodeine (16).

For determination of morphine, colorimetric determination is used. Colorimetric method for morphine estimation is based on transformation of morphine into apomorphine (Denigès).

In a live organism, morphine decomposes quickly, so that the quantities which should be isolated

from organs of persons poisoned with this alkaloid, is usually too small and difficult to detect (6).

Codeine differs from morphine in the following reactions: iron (III) chloride and iodate acid do not react with codeine, because codeine does not have the free phenolic group. For identification of codeine, when it is not mixed with morphine, the most suitable reagent is Lafon's one, which colors in emerald green when reacting with codeine. A lot of heroin reactions are identical with reactions of morphine (as Fröhde and Marquis), but as hydrogen of phenolic group is substituted with acetyl group, heroin will not induce reactions typical of free phenolic group (iron (III) chloride and iodate acid) (6).

Hair analysis by HPLC-MS is a standard forensic method for the analysis of addictive opiate content. Changes in the chemical structure of morphine and codeine in the presence of hydrogen-peroxide, the major components of hair dye, were examined with quoted spectroscopy. The investigation showed that cosmetic treatments, such as hair dyeing and bleaching, affected stability of morphine, codeine and cocaine. It should be considered when the contents of these substances in the hair are analyzed (17).

Extreme instability of heroin limits the possibility to be identified in detection of addicts. Therefore, as a method for routine testing of addicts, 6-acetyl morphine (6-AM) is considered the best marker of heroin, because: it is not a natural source, it is not the codeine metabolite, and it is more stable when compared to heroin (18).

The mixture of street doses of heroin is very complex, including alkaloid opiates (narcotine, papaverine, morphine and codeine), impurities coming from acylation of opioid alkaloids during the production of raw morphine (acetyl-codeine, O<sub>3</sub>-acetyl morphine), degradation products of heroin and other opiate alkaloids (O<sub>6</sub>-acetyl morphine) and some other different additional substances (caffeine, paracetamol, procaine) (19). This mixture is analyzed in forensic laboratories.

### Conclusion

The first thing noticed about drugs was that they caused euphoric states. Cross-tolerance occurs between drugs with the same mechanism of action. Reported drugs' use may also lead to psychological, physical and cross-dependence (between drugs with the same mechanism of action). In desire to enjoy drugs, a dopaminergic pathway in the CNS may be involved. In the case of opioids, people made great efforts to discover an opioid that would relieve pain, but not result in tolerance. In addition, their activities were directed towards development of numerous opioid components.

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## PRIRODNI I PARCIJALNO-SINTETIČKI ANALGETICI

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Čovečanstvo ima dugačku istoriju upotrebe stimulišućih supstanci koje menjaju stanje svesti. Depresivni farmaceutski preparati, uključujući morfin i druge narkotike, barbiturate i etanol, izazivaju jaku zavisnost kod pojedinih osoba. Fenomen je još izraženiji u slučaju opijata.

Morfin je alkaloid opijuma. Nazvana po rimskom bogu sna Morpheusu, ova komponenta ima potentnu analgetičku aktivnost prema svim vrstama bola. Supstitucijom dve hidroksilne grupe molekula morfina dobijaju se njegovi mnogobrojni prirodni i polusintetski derivati, koji pored drugih farmakoloških delovanja deluju i analgetički.

Određivanje i kvantifikacija narkotičkih analgetika kod zavisnika ima značaj kako u sudskoj medicini, tako i kliničkoj toksikologiji. Sa razvojem visoko senzitivnih hromatografskih metoda (HPLC-GH, GH-MS) sve se više supstanci određuje uključujući i opijate: morfin, kodein, dihidrokodein, heroin, 6-monoacetilmorfin. Za određivanje morfina koristi se i kolorimetrijsko određivanje. Analiza vlasi kose HPLC/MS spektroskopijom je uobičajena sudska metodologija za određivanje sadržaja droga koje izazivaju zavisnost. "Fingerprint" za heroin u smesi sa drugim supstancama (1-10 komponenti) određuje se jednodimenzionalnim 1D-TOCSY NMR. *Acta Medica Medianae* 2005;44(4): 67 – 73.

**Ključne reči:** antitusisci, kodein, heroin, morfin, opioidni analgetici