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Review Article

Codeine Structure, Metabolism and Drug Design

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Abstract

A prodrug or prodrug is a drug that is metabolized to a pharmacologically active form only after it is administered to the body. These types of drugs are usually used due to their superior mode of absorption, distribution, metabolism and excretion. Promedications are designed in such a way that they have a superior bioavailability compared to the pharmacologically active forms, being, for example, better absorbed at the intestinal level than these. Prodrugs are synthesized to achieve a specific goal. Such objectives can be a reduction of drug toxicity, improvement of bioavailability, taste, achieving specificity at the site of action, etc. To reduce the toxicity of active drugs with unwanted side effects, prodrugs have been created that are better tolerated by patients due to the gradual metabolic transformation of the prodrug into the active principle. Codeine is a natural alkaloid from the morphine subgroup, being the most commonly used opioid in the world. It is found in opium in a concentration of 0.3%, but most of the marketed codeine is obtained by synthesis from morphine, through a methylation process).

Key words: codeine; natural alkaloid; morphine subgroup; opioid; therapeutic indications

Introduction

Alkaloids are natural substances, usually basic and of vegetable origin, but not necessarily. The name of this class derives from the basic character, quite important for organic researchers. They are found in several organs of the plant. Alkaloid-producing plants are quite widespread. These plants are usually dicotyledonous and rarely monocotyledonous. An alkaloid that is found in a certain plant can also be found in plants similar in species and also accompanied by chemically similar substances [1].

Codeine - is also an alkaloid obtained from opium, in the extract of which it is present in a proportion of 0.7-2.5%. Codeine is also known as methylmorphine. It is also an analgesic, but weaker than morphine. It is used in antitussive and antidiarrheal medicinal preparations [2].

The biotransformation occurs at the level of the liver, being inactivated by conjugation with glucuronic acid, resulting in 6-glucuronide-codeine (ca. 80% inactivation by glucuronoid conjugation). Codeine was also obtained through laboratory synthesis (later and industrially) through O-methylation of morphine [3].

The presence of various alkaloids with attributes of biologically active substances in vegetable products (and sometimes in animal products) is of interest for the effects induced on the body when they enter food, but especially when they are used in pharmacology. Although they are found in small quantities in natural products, alkaloids are important for their physiological/pharmacological role and, in limited situations, for their toxicological effects. These considerations were the basis for including alkaloids in the group of biologically-active substances, being considered physiologically-active, when they accompany nutrients from food, or pharmacologically-active, when they are used therapeutically, but also toxicologically-active in accidental circumstances [4].

In general, it is known that in the initially isolated forms, alkaloid molecules exhibit high toxicity. In low doses, however, it exhibits physiological, pharmacological (acute or chronic) activity with some delayed effects, or even toxicological activity (with some delayed effects). Thus, the use of small amounts of caffeine from coffee, cocaine from coca leaves, nicotine from tobacco is mentioned, they were accepted in various human cultures, often very old in time [5].

It was difficult to assess the reason for the various effects, e.g. stimulants, tonics, psychotropics, psychoactives, emetics, sedatives, analgesics, etc. It is now known that alkaloid molecules in their pure state are often very toxic, e.g. strychnine, atropine, aconitine, cocaine, etc. In certain, controlled doses, they lend themselves to therapeutic use, for example: morphine and codeine are used in therapeutic protocols with anesthetic purpose; quinine is considered an agent with antimalarial (antimalarial) effects; vinblastine and vincristine are used as anticancer agents, etc. [6].

The investigations undertaken on the chemical compounds present in plants, in general, and in medicinal plants in particular, led to the isolation of a significant number of nitrogenous compounds, among them proteins, amines, amides, some vitamins and antibiotics, as well as numerous alkaloids. . From a biochemical point of view, alkaloids, as they have been

presented, are organic substances with nitrogen content in the molecule, mainly of vegetable origin but also of animal origin. Usually there is a main alkaloid and a number of secondary alkaloids that are structurally related [7].

For example, Opium contains morphine, thebaine, codeine, as related substances, originating from the morphinan nucleus.

The practical importance of studying drug metabolism lies in the possibility of clarifying the following issues:

• the ability of the drug to participate in biotransformation in the body;

• the chemical structure of the metabolites and the sequence of their mutual transformation;

• body systems responsible for drug metabolism;

• metabolites with therapeutic activity and/or toxicity;

• interaction of the metabolite with other drugs and their metabolites used in therapy [8].

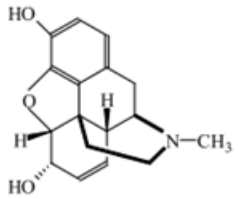
High-resolution physicochemical methods for the study of substances, especially the combination of chromatography and spectroscopy, make it possible not only to establish the structures of metabolites, but also to evaluate the subtle features of their functioning in living systems. The pathways of drug metabolism in the body are determined by the chemical structure, and their study is a complex and at the same time extremely fascinating problem chemically, biologically, pharmaceutically and medically.

Codeine [$C_{18}H_{21}NO_3$] is contained in opium like morphine, of which it is the mono-methyl ether. Small crystals. It is used as a substitute for morphine, as a sedative [9].

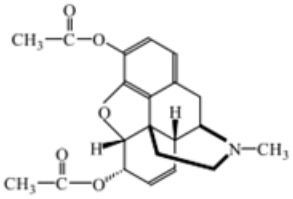
Codeine, also called methylmorphine, is a natural opium alkaloid. Its concentration in opium extract (meconate) varies between 0.7% and 2.5%. Codeine belongs to a class of drugs called opioid analgesics, which relieve pain through their action. It can be used alone or in combination with other analgesics, such as paracetamol [10].

Morphine is the first alkaloid (Seturner 1806) isolated in a pure state from plants. It features a tertiary amine with a methyl group attached to the nitrogen atom. It is used in the form of hydrochloride (very active), but it also has a narcotic effect. Repeated administration causes addiction called morphism (from Morpheus, the winged god of dreams in Greek mythology). The diacetate derivative of morphine, heroin, is a more active narcotic than morphine [11].

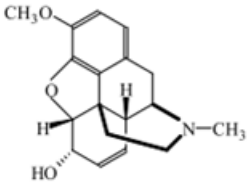
Codeine, the methyl ether of morphine with the participation of phenolic hydroxyl, is a weak narcotic used against cough, but it can cause addiction:



Morfină



Heroină



Codeină

The study of the pathways of metabolic transformation of drugs provides the key to understanding the mechanism of their direct and secondary effects and serves as a scientific basis for the creation of new drugs with desired pharmacological properties and greater safety. Promedical products are also designed to prolong the action of a drug released by slow biotransformation from the original compound. Slow release and duration of action are often achieved by hydrolysis of an amide or ester bond in the precursor structure. At the same time, it is possible to simultaneously increase the exposure time of the drug in the body for several hours or even weeks [12].

Mode of action

Codeine is well absorbed after oral administration, the bioavailability being 60-70%. Codeine is considered a prodrug, being metabolized in vivo into its active compounds - morphine and codeine-6-glucuronide. The percentage of non-biotransformed codeine excreted in the urine within 24 hours is approximately 6-8% of the total amount and can increase to 10% in conditions of low urinary pH. The conversion of codeine into morphine takes place in the liver and is catalyzed by the cytochrome P450 enzyme CYP2D6. Some drugs can inhibit or even block this enzyme, thus blocking the conversion of codeine into morphine [13].

Other drugs such as rifampicin or dexamethasone, on the other hand, stimulate the activity of cytochrome P450, thus increasing the conversion of codeine into morphine. Thus, if the metabolism of codeine is increased, higher doses are needed to maintain an effective plasma concentration from an analgesic point of view. On the other hand, in the case of a slow metabolism of codeine, the plasma concentrations of the metabolites tend to increase, causing toxicity. The main therapeutic indication of codeine is antitussive, the low risk of addiction making possible its wide use for this purpose. In therapeutic doses, codeine has an antitussive effect and causes reduced respiratory depression compared to morphine. Codeine is a relatively weak analgesic, being much less potent than morphine (a dose of 120 mg of codeine being equivalent to a dose of 10 mg of morphine) [14].

The depression of the cough center is stronger than in the case of morphine (the antitussive action is superior to morphine). Codeine is less toxic than morphine, but the blocking of the phenolic group by the methyl radical increases the convulsive effect, children being very sensitive (the toxic dose is only 2 mg) [15].

Codeine is transformed into morphine by an enzyme in the liver. Morphine is a substance that causes pain relief. Certain people have a different version of this enzyme, and this fact can affect them in different ways. In some people, no morphine is produced or it is produced in very small amounts and there will not be sufficient pain relief. Other people are more prone to the occurrence of serious adverse reactions, because a very large amount of morphine is produced [16].

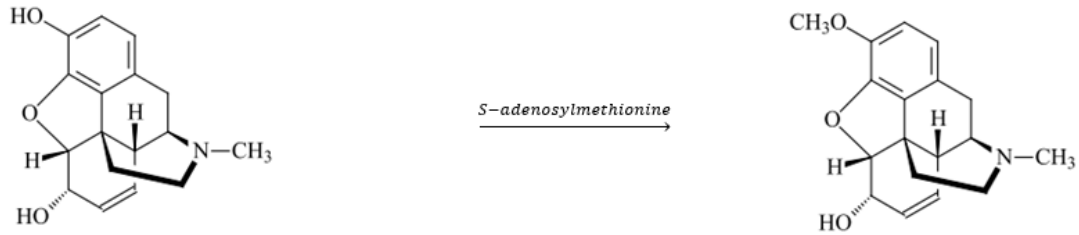
Codeine reduces intestinal peristalsis. Analgesic opioids should be used with caution in patients with intestinal obstructive disorders. The use of codeine is not recommended for patients with ulcerative colitis (it can cause toxic dilation of the colon). It should also be avoided in case of recent surgical interventions on the gastrointestinal tract.

Similar to other symptomatic antidiarrheals, codeine administered to patients with diarrhea reduces the loss of fluids and electrolytes and may delay the elimination of microorganisms in infectious diarrhea. Symptomatic treatment of diarrhea with codeine is not recommended in the acute phase because it can mask the symptoms and signs of an infection with possible severe consequences [17].

Codeine is not recommended as an antidiarrheal in children, because it can cause severe hydroelectrolyte imbalance. Among all opioid receptors,

codeine has the highest affinity for μ (miu) receptors, μ2 subtype (responsible for the antitussive effect). Binding to the slightly weaker μ1 subtype is responsible for the analgesic effects. It is metabolized in the liver to 6-glucuronide-codeine by conjugation with 80% glucuronic acid. The rest passes into norcodeine (2%), morphine (0.5%), 2-glucuronide-morphine (2%), 6-glucuronide-morphine (0.8%) and normorphine (2.5%) [16]. The transformation into morphine and implicitly into 6-glucuronide-morphine, the most active metabolite, is an O-dealchylation (O-demethylation) reaction catalyzed by the cytochrome P450 enzyme CYP2D6. In a segment of the white population of about 6-10%, the CYP2D6 enzyme is either poorly translated or deficient, so that codeine is almost devoid of analgesic effects. All this phenomenon is the basis of the reduction of the analgesic effect of codeine by substances that inhibit this enzyme, such as the antidepressants fluoxentin and citalopram. There are also genetic variations of CYP2D6 which, through intense metabolism, produce at "antitussive" doses of codeine 3-12 times greater amounts of morphine.[8] One case has been reported that presented with respiratory arrest due to this [19].

The methylation reaction is a detoxification process, as most methylated metabolites have a reduced pharmacological activity compared to the original xenobiotic. An activity-modifying exception is found in the methylation of morphine (opioid analgesic) with the formation of codeine, which has much weaker analgesic properties than morphine, but is more advantageous than it in terms of antitussive action:



Morfină Codeină

Methylation is a common but minor pathway of biotransformation of xenobiotic compounds, catalyzed by enzymes called transferases [20]. Methylation differs from most of the phase II reactions because it generally decreases the water solubility of xenobiotic compounds and masks functional groups that can be conjugated by other phase II enzymes. An exception to this rule is N-methylation of compounds that produce quaternary ammonium ions, which are soluble in water and rapidly excreted.

Medicinal substances administered in the body are metabolized by special enzyme systems, located in the cells of organs such as the liver, kidneys, lungs. In subsequent series of metabolic reactions, lipid-soluble drugs are transformed into more polar, hydrophilic products, which facilitate their excretion from the body [21]. The metabolite can intervene in normal and pathological processes, providing a favorable or unfavorable effect on the human and animal body. The speed and direction of biotransformation of drugs depend on the duration of their circulation in the body and on the pharmacological properties, a fact that influences the final therapeutic effect and must be taken into account when developing strategies for their use.

Conclusion

One of the interesting aspects, based on the knowledge of the pathways of metabolic transformations, is the design of drugs with specific properties. The design of such drugs is aimed at achieving certain goals - increasing the bioavailability of drugs when administered, increasing (or, on the contrary, reducing) the duration of action and effectiveness, reducing toxic side effects, eliminating unpleasant taste, etc. To increase the duration of the drug's action, the structure must be modified in such a way as to replace the reactive groups with less reactive groups and thus reduce the metabolic rate. N-dealkylation is most easily accomplished when a methyl group is attached to the nitrogen atom. Replacing a methyl group with a tert-butyl group can completely prevent this biotransformation pathway. Oxidative hydroxylation of an aromatic ring can be significantly reduced or even prevented by replacing electron-donating groups attached to the ring with electron-withdrawing groups. Ester groups, easily hydrolyzable, in the structure of the drug can be replaced by amide groups more resistant to hydrolysis. However, such a modification can lead to a change in the pharmacological action. A well-known example of such a change is the anesthetic novocaine and the antiarrhythmic drug novocainamide. An increase in the rate of metabolic processes can also be achieved by introducing metabolically labile groups (for example, ester groups) into the structure of the medicinal substance. The use of biologically active compounds that metabolize intensively is one of the ways to create non-toxic drugs. The advantage of these drugs is their short half-life, which is especially important for drugs used for anesthesia. Altering metabolic pathways can be used to design drug analogs that do not have unwanted side effects.

Conflict of interests

The authors declare no conflicts of financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employments, gifts, and honoraria.

This article is a review and vegetal products have not been administered to men or animals.

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