Chemistry Chat -Focusing on the Elements-

Elements in Pharmaceutical Drugs

Kentaro Sato

If you were asked to list chemical elements in the order of abundance in human body, could you answer it right away? In terms of the number of atoms, the most physiologically abundant element is hydrogen, followed by oxygen, carbon, nitrogen, phosphorus, and sulfur. Minerals like calcium and other minutely present elements such as iron and copper play essential roles, but they constitute only about 1 percent altogether. Clearly, the sextet of C, H, O, N, S, and P owns an important place in physiology.

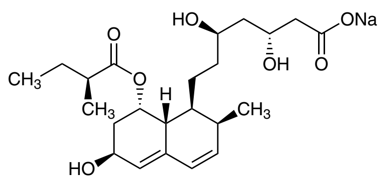
Most pharmaceutical drugs that we take are also made up of these six elements. Drug molecules enter human systems and produce medicinal effects, so it is natural that their compositions resemble to that of human body. However, there are always interesting exceptions in which you can find unusual elements. The previous article focused on anticancer drugs, so this time let us look at other drug types featuring metallic elements.

Group I Elements

A survey of drug compositions would find many examples containing sodium and potassium. However, most of these drugs are the salts of sodium or potassium, meaning that the metals are used as "counterions" to simply increase the solubility of the parent acidic drug. For example, a famous hyperlipidemia drug pravastatin is isolated as a lactone from its natural source, but is hydrolyzed into the sodium salt of carboxylic acid in order to increase the solubility.

A well-known example in which an alkali metal itself has a medicinal property is lithium. Salts of lithium such as lithium carbonate play an essential role in the treatment of bipolar disorder, a mental illness that typically involves alternating states of mania and depression.

The effect of lithium was discovered by sheer serendipity. Around the late 1940's, an Australian psychiatrist John Cade decided to inject urea to lab animals based on his hypothesis that the dysfunction of the urea metabolism was causing bipolar disorder. Since free urea was poorly soluble in water, he used it in lithium salt form,



Pravastatin Sodium

which led to the observation of a dramatic therapeutic effect. Cade carefully investigated into the results, and concluded that it was not the urea but the lithium ion from the salt that was responsible. The effect of lithium was eventually proven in human clinical trials and lithium became an important medicine in psychiatric therapy.

Despite the widespread use of lithium around the world since the discovery, its mechanism of action is still unknown. One theory suggests that lithium helps regulating the internal clock system, while another theory states that it affects the interneuron signal transmission process. The actual mechanism is probably a combination of multiple functions. Nevertheless, this kind of drug is perhaps most unlikely to come out from today's systematic drug discovery approach.

Group II Elements

Beryllium, the lightest element among the Group II elements, has no medicinal application because of its low natural abundance and high toxicity. In contrast, magnesium (a row below beryllium in the periodic table) is known to be less toxic. Magnesium oxide is an ingredient of stomach medicines as acid neutralizer and also used as a safe laxative. In addition, the deficiency of magnesium has been reported to be linked with the risks of diabetes and depression. Though not always recognized, magnesium is surely an important element for our body.

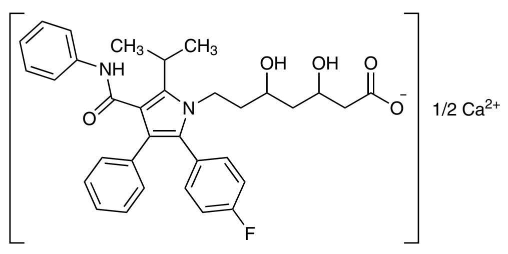
Calcium is not only an important constituent of bones, but also an essential player in intercellular signal transduction. Calcium deficiency causes a serious medical condition known as hypocalcemia and there are many supplementary medications for it. In other applications, calcium can be found as the counterion of a number of drugs including the biggest blockbuster of all time, Lipitor®, which is technically called the calcium salt of atorvastatin.

Strontium (atomic number 38) shows very similar chemical properties to calcium. Therefore, when people are exposed to radioactive strontium by a nuclear experiment or a nuclear plant accident, it can cause long-term damages by accumulating in the bones.

Interestingly, there is actually a drug that makes use of this troublesome property of strontium. Strontium-89 is a radioactive isotope that emits a beta ray with the half-life of 50.5 days, and it can be used as a medicine that alleviates the severe pains associated with metastatic bone cancer. It is strange that a radioactive isotope of strontium has both cancer-inducing and pain-relieving properties, but this is an example of the complex relationships between human body and radioactivity, and between human body and drugs.

Barium is below strontium in the periodic table and is well-known as the radiocontrast agent used in X-ray imaging of the digestive system. Despite the unpopularity because of its unpleasant taste and stressful aftercare, there are good reasons why it is used.

The X-ray radiocontrast agent is barium sulfate, which is insoluble in water thus not absorbed by the digestive system and non-toxic. And because barium is a large element with atomic number 56 it effectively scatters X-ray, providing the visualization of the stomach and the intestines in white color after drinking the chalky liquid. Because it is also inexpensive, barium will likely continue to be used for years to come. However, its user-friendliness has been improved in recent years by reducing the dose and improving the taste. The experience of undergoing a medical examination is therefore getting less painful.



Atorvastatin Calcium

Transition Metal Elements

As mentioned in the beginning, the six elements C, H, O, N, S, and P constitute the core of human body. But supporting life requires contributions from not just these six elements but also various metal elements. The biologically essential metal elements include chromium, manganese, cobalt, nickel, copper, and molybdenum, some of which might be unexpected.

Many transition metal elements are toxic, however, when overdosed. Therefore, there are only a few examples of them being used for pharmaceutical purposes. For instance, certain mercury compounds were once used widely as antiseptics but are no longer used today because of the toxicity concerns.

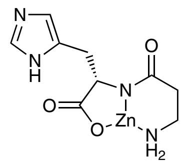
Like the proverb "fight poison with poison," there are heavy metal based drugs that can protect us against the toxicity of another heavy metal. An example is zinc acetate used as the treatment of Wilson's disease, which involves the accumulation of inorganic coppers in the body. Zinc acetate is thought to hinder the absorption of copper in the digestive system.

Zinc is also utilized in stomach medicines. A zinc complex called polaprezinc functions to repair gastric mucosal injury. Additionally, ointments containing zinc oxide has been used traditionally as a safe medicine to treat various skin problems. Zinc is probably the most frequently used transition metal element in pharmaceutical drugs.

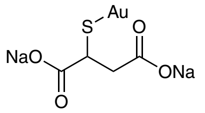
Gold complexes such as sodium aurothiomalate and auranofin are great examples of pharmaceutically used organometallic complexes. In auranofin, the thiosugar and the phosphine bind to the gold atom, making the molecule look like a catalyst of chemical reaction. These complexes are used as a medication of rheumatoid arthritis and the mechanism of action is considered to involve accumulation in the joint fluids, preventing collagen decomposition, and binding and neutralizing inflammation causing substances.

Recently, lanthanum carbonate has been approved as the drug for hyperphosphatemia. In the patients suffering from kidney disease, the serum concentration of phosphate ions becomes abnormally high due to inefficient removal of the ions. The phosphates react with the calciums in the serum and causes serious conditions such as muscle weakness and calcification of organ tissues and blood vessels. Because most foods contain phosphates, an effective way to remove them becomes necessary.

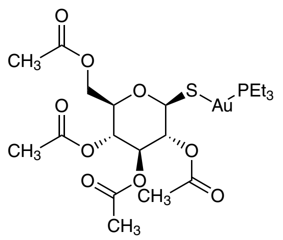
When a patient takes lanthanum carbonate after meals, the lanthanum ions bind strongly to the phosphate ions, alleviating aforementioned symptoms. In the past, patients



Polaprezinc



Sodium Aurothiomalate



Auranofin

used to have to avoid having tasty foods that are also high in phosphates. Lanthanum is a relatively anonymous element to general public, but let us hope it becomes a savior for thousands of patients.

Another transition metal element with a promising medicinal potential would be vanadium. Vanadium is used as an additive in steel industry and is categorized as one of the rare metals. It has so far been considered an unrelated element to human health even though certain types of mushroom and sea skirt are known to selectively ingest vanadium, which implies some sort of biological functions.

Recent studies are showing that vanadium may be effective in treating diabetes. It has been reported that the daily administration of 150mg of vanadyl sulfate ($VOSO_4$) to diabetic patients resulted in lowered blood sugar levels. It is quite interesting that a simple metal salt shows a similar medicinal effect to that of peptidic insulin composed of 51 amino acids. If the absorption could be further improved (by organometallic complexation, for example) and the toxicity problem could be solved, practical use would become realistic. Since peptidic insulin can be taken only by injection, the development of an orally administered antidiabetic drug would be significant.

As you have seen, there are surprisingly large numbers of metal-containing pharmaceutical drugs. These compounds have been generally overlooked by medicinal scientists because of the preconceived impression about toxicity. However, it seems there are more drug seeds waiting to be discovered and there should be ways to explore. With unbiased research, this field could become pharmaceutical gold mine.

Introduction of the author :

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[Brief career history] He was born in Ibaraki, Japan, in 1970. 1995 M. Sc. Graduate School of Science and Engineering, Tokyo Institute of Technology. 1995-2007 Researcher in a pharmaceutical company. 2007-Present Freelance science writer. 2009-2012 Project assinstant professor of the graduate school of Science, the University of Tokyo.
[Specialty] Organic chemistry
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