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A healthy future: platinum in medical applications

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Introduction

Platinum group metals have contributed to many major advances in medical care since the mid twentieth century. Over the last four decades, alloys of platinum (often containing around 10% iridium) have been employed extensively in modern minimally- invasive treatments for coronary artery disease—such as angioplasty and stents—where inertness and visibility under X-ray are crucial. In the field of cardiac rhythm disorders, platinum's durability, inertness and electrical conductivity make it the ideal electrode material for devices such as pacemakers, implantable defibrillators, and electrophysiology catheters. More recently, its unique properties have been exploited in neuromodulation devices (including 'brain pacemakers', used to treat Parkinson's disease, and cochlear implants, to restore hearing), and in coils and catheters for the treatment of brain aneurysms.

However, perhaps platinum's most remarkable and unexpected quality is its ability, in certain chemical forms, to inhibit the division of living cells. The discovery of this property led to the development of platinum-based drugs, which are now used to treat a wide range of cancers.

Anti-cancer drugs

Although cancer remains one of the most feared diseases, its treatment has advanced rapidly in the last half century. Many types of cancer can now be treated very effectively using surgery, radiation and drug-based (chemo-) therapies. Chemotherapy drugs work by killing cells. They are designed to target cancer cells as specifically as possible, but inevitably cause damage to healthy cells as well, causing the side effects for which chemotherapy is notorious.

One of the most remarkable advances in the last few decades has been the improvement in the survival rate of patients with testicular cancer—it is estimated that 98% of men with testicular cancer will be alive 10 years after their diagnosis. The platinum anti-cancer drug cisplatin has played a vital role in making testicular cancer one of the most survivable cancers. This drug, along with its successor drug, carboplatin, is also widely used in the treatment of other common tumours, including ovarian, breast and lung cancer.

The discovery of cisplatin

Cisplatin is a relatively simple platinum compound which scientists first discovered in 1845. However, nothing was known about its anti-cancer properties until the 1960s. Like many important scientific advances, the discovery was made completely by accident. During 1962, Professor Barnett Rosenberg of Michigan State University was performing an experiment into the effects of electromagnetic fields on bacterial cell growth, using a piece of apparatus fitted with platinum electrodes. He noticed that the cells were failing to divide as they should, and after much research he concluded that this was caused by tiny quantities of platinum which had dissolved from the electrodes to form cisplatin.

Professor Rosenberg did not immediately realize that he had discovered a potential anti-cancer treatment, but by 1969 he was able to publish some initial anti-tumour screening results. Work at the National Cancer Institute in America and at the Royal Marsden Hospital in London led to the selection of the compound cisplatin for clinical trials.

Despite some early successes, many researchers doubted that cisplatin could ever become a realistic treatment for cancer. Its side effects seemed to be an insurmountable obstacle. Like many anti-cancer drugs, it led to severe nausea, but more troubling was the risk of kidney damage. Then, in 1977, a major breakthrough was made with the development of hydration techniques, which involve giving the patient large amounts of intravenous fluids before, during and after treatment in order to conserve kidney function.

Once these techniques became available, doctors could administer increased doses, and the full benefits of cisplatin quickly became apparent. This was most striking in the case of testicular cancer, which is particularly susceptible to treatment with platinum containing drugs, but there were also early successes with ovarian and head and neck cancers. Cisplatin was finally approved for sale in the late 1970s. It was licensed by Bristol-Myers Squibb and marketed under the trade name Platinol in the USA and Neoplatin in the UK.

Second generation platinum drugs

Meanwhile, work continued on the evaluation of other platinum complexes as potential chemotherapy drugs. Researchers at the Institute of Cancer Research and the Royal Marsden Hospital in London achieved a significant step forward when they identified a compound similar to cisplatin in terms of activity, but much less toxic. This drug, carboplatin, also licensed by Bristol-Myers Squibb, was first approved in 1986 and marketed as Paraplatin.

Since then, scientists have continued to seek to develop more active and less toxic platinum anti-cancer compounds. The drug oxaliplatin, first discovered in 1976, was first approved in 1996 and is marketed by Sanofi Aventis as Eloxatin. It is now widely used in the treatment of colorectal cancer. Other drugs are being subjected to clinical trials, including the compounds picoplatin and satraplatin.

Platinum in anti-cancer drugs

We estimate that over 25 000 oz of platinum are now used annually in anti-cancer drugs, contributing to the treatment of many thousands of patients. Most of this platinum is used in carboplatin, the most widely-used platinum anti-cancer drug; it has a slightly lower platinum content than cisplatin, but is generally used in higher doses. Oxaliplatin is the second largest contributor to platinum demand, with cisplatin in third place.

Cisplatin and carboplatin are off-patent, and generic versions of these drugs are now manufactured and sold around the world. Oxaliplatin is still partly protected by patents, but is increasingly sold in its generic form. Use of all three compounds is expected to rise in future, mainly because more cases of cancer will be diagnosed: according to the World Health Organization, new cases of cancer will increase from 11.3 million in 2007 to 15.5 million in 2030. This is largely due to rising incidence of cancer in the developing world, reflecting longer life expectancies, the adoption of Western diets, and the widespread use of tobacco. This is leading to much higher rates of lung, breast, and colorectal cancers in particular—cancers that are commonly treated with platinum-based drugs.

Platinum in biomedical components

Platinum is an important constituent of modern medical devices such as pacemakers and catheters. As a metal, it can be fabricated into very tiny, complex shapes, while it has some important properties not shared by base metals. It is inert, so it does not corrode inside the body; also the allergic reactions to metals which sometimes occur such as nickel and copper are extremely rare in response to platinum. Modern, minimally- invasive medical techniques often use electricity to diagnose and treat patients' illnesses, and platinum's conductivity makes it an ideal electrode material. It is also radiopaque, so it is clearly visible in X-ray images, enabling doctors to monitor the position of the device during treatment.

Devices for cardiac rhythm management

Abnormalities of the heart's rhythm are common, often debilitating, and sometimes fatal. For example, bradycardia is a condition in which the heart's 'natural pacemaker' is set too slow, resulting in fatigue, dizziness and fainting. Other patients may be at risk of sudden cardiac death, a condition in which the heart's lower chambers (the ventricles) 'fibrillate', or pulse in a rapid and uncoordinated manner. This prevents the heart from pumping blood and leads rapidly to death unless the victim receives cardioversion (a strong electric shock to the heart, which restores normal rhythm).

These and other cardiac rhythm disorders can now be managed very successfully using implanted devices such as artificial pacemakers and implantable cardioverter defibrillators (ICDs). These consist of a 'pulse generator', a small box containing a battery and an electronic control system which is implanted in the chest wall, and one or more leads which run through a large vein into the heart itself. The electrodes on these leads deliver electrical impulses to the heart muscle—in the case of a pacemaker, these ensure that the heart beats regularly and at an appropriate pace, whereas in the case of an ICD, a much stronger electrical shock is delivered as soon as the device detects a dangerously irregular heartbeat. Each lead typically has two or more electrodes made of platinum-iridium alloy, and platinum components are also used to connect the pulse generator to the lead.

In the developed world, the majority of patients who are suitable for treatment by a pacemaker now receive one, and as a result, growth in implantation rates is relatively modest (typically less than 5% a year). However, there remains much potential for growth in the developing world. In the USA and many European countries, the rate of pacemaker implantation is over 1 000 devices per million people—in most developing countries, the rate is no higher than 50 per million and often much lower. As GDP increases and medical coverage improves, this figure is likely to grow substantially over time.

The market for ICDs is much less well developed than that for pacemakers: there has been rapid uptake of these devices in the USA and in some European countries, but even so, only a fraction of potentially eligible patients receive a device. Elsewhere, few patients are fitted with an ICD. There is therefore significant scope for growth going forward, particularly in the developing world, where uptake of ICDs is currently negligible.

Catheters and stents

Catheters are flexible tubes which are introduced into the body to help diagnose or treat illnesses such as heart disease. The doctor can perform delicate procedures without requiring the patient to undergo invasive surgical treatment, improving recovery time and minimizing the risk of complications. Many catheters incorporate platinum components: marker bands and guidewires, which help the surgeon guide the catheter to the treatment site, or electrodes, which are used to diagnose and treat some cardiac rhythm disorders (arrhythmias).

One of the most common coronary complaints in the developed world is atherosclerosis, the furring up of the artery walls with fatty deposits, which can lead to angina and heart attack. It is estimated by the American Heart Association (AHA) that some 17.6 million Americans suffer from coronary heart disease[1], which can lead to myocardial infarction ('heart attack'), angina and stroke. Blockages in the coronary arteries are often treated using a procedure called 'percutaneous transluminal coronary angioplasty' (PTCA, also known as balloon angioplasty). This treatment uses a catheter with a tiny balloon attached to its end, which is guided to the treatment site then inflated, crushing the fatty deposits and clearing the artery. Afterwards, a small tubular device called a stent is usually inserted in order to keep the newly cleared artery open. The AHA estimates that 1.3 million patients underwent percutaneous coronary intervention procedures in 2006[1].

Platinum's role in PTCA is to help ensure that the balloon is correctly located. First, the surgeon uses a guidewire to direct the balloon to the treatment site. This guidewire is made of base metal for most of its length, but has a coiled platinum-tungsten wire at its tip, which makes it easier to steer and ensures that it is visible under X-ray. Platinum is also used in marker bands, tiny metal rings which are placed either side of the balloon in order to keep track of its position in the body.

Stents are usually made of base metals (typically stainless steel or cobalt-chromium). However, in 2009, the American device manufacturer Boston Scientific introduced a cardiac stent made of a platinum chromium alloy. This stent has been approved in Europe, and the company is currently seeking approval from the US Food & Drugs

Administration (FDA). If successful, it could generate substantial platinum demand in future.

The first balloon angioplasty procedure was performed less than 35 years ago, in 1977. Since that time it has become a very widely used procedure: we estimate that some 2 million angioplasty procedures are undertaken in the USA and Europe every year. With the ageing of the population and rising rates of obesity, these numbers are likely to grow. At the same time, PTCA is becoming a more widely used treatment in many developing nations—for example, it is estimated that the number of procedures undertaken in China is growing by more than 25% annually.

Catheters containing platinum components are also used to detect and treat some types of cardiac arrhythmia. Devices called electrophysiology catheters, which contain platinum electrodes, are used to map the electrical pathways of the heart so that the appropriate treatment—such as a pacemaker—can be prescribed.

Other catheters with platinum electrodes are used for a minimally invasive heart treatment known as radio-frequency (RF) ablation. Arrthymias are often caused by abnormalities in the conduction of electricity within the heart, and it is often possible to cauterize part of the heart muscle in order to restore normal heart rhythm. For example, ablation is increasingly used to treat a very common heart problem called atrial fibrillation, in which the upper chamber of the heart (the atrium) quivers rapidly and erratically. Using a catheter equipped with platinum-iridium electrodes, the surgeon ‘ablates’ or makes small burns to the heart tissue, causing scarring, which in turn blocks the superfluous electrical impulses which trigger the fibrillation. The success of this procedure is currently contributing to strong growth in demand for platinum in ablation catheters, with treatment rates estimated to be rising by over 25% annually.

Neuromodulation devices

One new and rapidly expanding application for platinum is in the neuromodulation or neurostimulation sector. Neuromodulation devices deliver electrical impulses to nerves and even directly to the brain, treating disorders as varied as deafness, incontinence, chronic pain and Parkinson’s disease. Many of these devices are based on an extension of heart pacemaker technology, and they are sometimes referred to as ‘brain pacemakers’. Like heart pacemakers, they have platinum-iridium electrodes and may also incorporate platinum components in the pulse generator.

There are a number of different types of neurostimulation, depending on the condition that is being treated. Spinal cord stimulation (the commonest neuromodulation therapy) is used to treat severe chronic pain, often in patients who have already had spinal surgery. Small platinum electrodes are placed in the epidural space (the outer part of the spinal canal) and connected to an implanted pulse generator. The patient can turn the stimulation off and on, and adjust its intensity.

In deep brain stimulation (DBS), the electrodes are placed in the brain itself. As well as pain, DBS may be used to treat movement disorders such as Parkinson’s disease, and it is being investigated as a potential treatment for a wide range of other illnesses, including epilepsy and depression. Currently, some epileptic patients are treated using a vagus nerve stimulation device (the vagus nerve is situated in the neck).

A cochlear implant is used to restore hearing to people with moderate to profound hearing loss (many patients receive two implants, one in each ear). A typical device consists of a speech processor and coil, which are worn externally behind the ear, an implanted device just under the skin behind the ear, and a platinum electrode array which is positioned in the cochlea (the sense organ which converts sound into nerve impulses to the brain). The speech processor captures sound and converts it to digital information, which is transmitted via the coil to the implant. This in turn converts the digital signal into electrical impulses which are sent to the electrode array in the cochlea, where they simulate the hearing nerve. These impulses are interpreted by the brain as sound. It is believed that around 200 000 people worldwide have received one or more cochlear implants.

At present, neuromodulation is expensive and is only available in a small number of specialist centres; even in developed countries only a small proportion of potentially eligible patients receive this treatment. However, neuromodulation can be used to help patients with common and sometimes difficult to treat conditions (such as chronic pain, epilepsy and migraine), and we therefore believe that this market has very substantial potential for expansion.

Other implants

Platinum’s biocompatibility makes it ideal for temporary and permanent implantation in the body, a quality which is exploited in a variety of treatments in addition to the heart implants already discussed. Irradiated iridium wire sheathed in platinum can be implanted into the body to deliver doses of radiation for cancer therapy. This treatment takes advantage of platinum’s radiopacity to shield healthy tissues from the radiation, while the exposed iridium tip of the wire irradiates the tumour. Although this procedure is gradually being replaced by other forms of radio- and chemotherapy, it remains a useful weapon in the battle against cancer.

A more recent development is the use of coils made of platinum wire to treat aneurysms, balloonings in blood vessels caused by weaknesses in the vessel walls. If the blood pressure rises, the vessel may rupture, causing a haemorrhage. Although this can occur anywhere in the body, platinum is mainly used to treat aneurysms in the brain, where surgery is difficult and fraught with risk. Platinum is used because it is inert, easy to shape, and radiopaque.

This treatment was first introduced about 20 years ago. In the late 1980s, a doctor and inventor, Guido Guglielmi, developed a detachable platinum coil which could be used to treat brain aneurysms. Coils are delivered to the site of the aneurysm by microcatheter, then detached using an electrolytic detachment process; once in place, the coils help to coagulate the blood around the weak vessel wall, forming a permanent seal. The coils, numbering between one and around thirty depending on the size of the aneurysm, are left inside the patient indefinitely. The Guglielmi Detachable Coil (GDC® Coil) device was approved in Europe in 1992 and in the USA in 1995, and by 2009 this and subsequent generations of platinum coil technology were being used in an estimated 30–40% of US patients treated for brain aneurysms. To date, we estimate that at least 200 000 patients have received platinum coils, and further growth is likely as this treatment becomes standard.

Demand for platinum in biomedical devices

In Johnson Matthey's most recent review of the platinum market[2], it was estimated that consumption of platinum in medical applications totalled 250 000 oz in 2009 (this includes demand from the dental industry, which is not discussed in this paper). This makes the medical industry the fifth largest demand sector, ahead of traditional consumers such as the glass, petroleum and electronics industries.

Of this total, some 140 000 oz was consumed in platinum components for medical devices. Approximately 80% of this is taken by guidewires (for PTCA and other catheter-based interventions), along with electrodes and other components for cardiac rhythm management devices such as pacemakers. Demand from the remaining sectors is relatively small at present—for example, we estimate that neuromodulation devices and stents each require around 5 000 oz of platinum annually. However, it is in these sectors that the largest potential for growth exists. We believe that total demand for platinum in biomedical devices will increase by around 50% by the end of the decade, but this figure could prove conservative should neuromodulation devices become as extensively used in future as pacemakers are at present.

References

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