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**M. A. Jakupec · P. Unfried · B. K. Keppler**

# Pharmacological properties of cerium compounds

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**Abstract** Cerium is a member of the lanthanide series or rare earth elements which exert diverse biological effects mainly by their resemblance to calcium. This similarity, which is particularly characteristic for the lighter members of the lanthanide series, enables these elements to replace calcium in biomolecules without necessarily substituting for it functionally. While the inhibitory effects on calcium-dependent physiological processes (such as those involved in the blood clotting cascade as well as in neuronal and muscular functions) are well-known, their relevance for the pharmacological properties of cerium are less clear. Historically, cerium oxalate was used as an antiemetic, especially in vomiting of pregnancy and kinetoses, although its mechanism of action has never been clarified. At present, cerium nitrate is available as an adjunct to silver sulfadiazine cream for the topical treatment of extensive burns not amenable to early wound excision. Apart from direct antiseptic effects, cerium helps to prevent postburn sepsis and systemic inflammatory response by fixing burn toxins. The antineoplastic potential of cerium compounds, which had fallen into oblivion, is currently being re-explored in experimental settings, though the mechanistic basis remains to be elucidated.

## Introductory remark

Cerium is a member of the lanthanides, lanthanoids, or rare earth elements. The definitions of these terms differ somewhat: while lanthanides (abbreviated Ln) is the historical name for the "d-element" lanthanum (La, atomic number: 57) and the following 14 "f-elements" from cerium (Ce, atomic number: 58) to lutetium (Lu, atomic number: 71), the term lanthanoids, created by the IUPAC in 1963, comprise only the "f-elements" from Ce to Lu, excluding La. Rare earth elements is the historical term still in use for the lanthanides plus yttrium (Y) and scandium (Sc), reflecting the fact that these two elements are associated with the lanthanides in their natural occurrence.

M. A. Jakupec · P. Unfried · B. K. Keppler (✉)
Institute of Inorganic Chemistry, University of Vienna,
Waehringer Strasse 42, 1090 Vienna, Austria
e-mail: bernhard.keppler@univie.ac.at · Tel.: +43-1-427752600 · Fax: +43-1-42772680

The discovery of the rare earth elements began in the year 1787, when Arrhenius identified a grayish-black and very heavy mineral which he named "ytterbite." This mineral turned out to be a real treasure, containing a lot of previously unknown elements and setting off an exciting quest for new elements (Kleber 1961; Moeller 1963, 1973; Trifonov 1963; Eyring 1964). First, subgroups were isolated, called "ceria," "terbia," "yttria," and "ytterbia," corresponding to mixtures of the light ("cerit-earth elements"), middle ("terbin-earth elements"), heavy ("ytter-earth elements"), and very heavy earths ("ytterbin-earth elements"). The similar chemical behavior of the components of these fractions made the first analyzers consider these mixtures as pure elements. In 1803, cerium became the first of the lanthanides to be isolated with high purity. Still, for most early applications purity was not important, and therefore one must be aware that the term cerium when used in older literature (up to the early twentieth century) does not always mean pure cerium.

## Chemical and biochemical aspects

To understand the chemical behavior of cerium and its unique position among the lanthanides, it is necessary to discuss some aspects of the chemistry of this family of very similar elements. In physiological solutions, most of the lanthanides are only stable in the trivalent form, the only exceptions being Ce(IV) and Eu(II) (Asprey and Cunningham 1960). The ionic radii of trivalent ions (in complexes with coordination number 6) steadily decrease with increasing atomic number within the small range from 1.03 Å to 0.86 Å, a phenomenon known as the lanthanide contraction. The small differences in ionic hardness result in slight differences of their distribution coefficients and the hydrolytic sensibility of their salts. Both effects are relevant for the purification of the individual elements. Ce(IV) (ionic radius: 0.89 Å) shows a hydrolytic behavior like a hypothetical "super-lutetium." Therefore, aqueous solutions of Ce(IV) salts (without complexation) are stable only if acidified to pH<3. Otherwise, hydrolysis takes place, together with formation of some turbidity or gel at higher concentrations. Since weakly bound ligands like biological buffers do not prevent hydrolysis, Ce(IV) salts have no biological relevance.

The preferred coordination number of all lanthanides is 8–9, but complexes from 6–12 could be prepared as well. In aqueous solution, the hydration shell includes 9–12 water molecules—a controversy about these values is still going on. The ionic character of complexes of trivalent lanthanide ions is very high, with a typical order in strength of bonding to O<N<S. The interaction with nitrogen in complexes such as those with o-phenanthroline (Sinha 1966) is very weak, and ligands containing only N-donor atoms do not complex with rare earth ions under physiological conditions. The predominant donor in aqueous solutions is the oxygen atom. Sugars, nucleosides, and ligands with carboxyl groups are preferential complexing groups, and chelating is the predominant form of complexation (Komiyama and Sumaoka 2001).

The redox potential $\epsilon^{o}$ of the system $Ce^{3+}/Ce^{4+}$ is 1.70 V (in 1 M $HClO_4$). In comparison with the standard potential of the redox system $H_2O/O_2$ (1.299 V) and the possible formation of Ce(III) and $O_2$, the meta-stable character of aqueous Ce(IV) solutions can be understood. Ce(IV) is a powerful oxidant without biological relevance (Nash and Sullivan 1991), but it has been studied as a catalyst of phosphate ester and nucleic acid hydrolysis (Sumaoka et al. 1998; Takarada et al. 2000; Shigekawa et al. 1999). On the other hand, Ce(III) is very resistant to oxidation and reacts only with very strong oxidants.

Calcium in the bivalent state (ionic radius: 1.00 Å) is very similar to trivalent cerium (ionic radius: 1.01 Å) in terms of size, bonding, and preferences to donor atoms. Hence, it is not surprising that trivalent cerium behaves chemically similar to calcium. One of the most characteristic differences between Ln(III) and Ca(II) is the higher charge-to-volume-ratio of the former, resulting in a stronger binding to water molecules, an increased stability of analogous complexes, and a preference for higher coordination numbers. The similarity of cerium and calcium reflects in their natural occurrence, where cerium is always found together with calcium (e.g., in apatite). In the biological context, the tendency to precipitate together with calcium is reflected in the affinity of cerium to the mineral bone matrix (Jowsey et al. 1958; Ewaldsson and Magnusson 1964; Schmautz 1964) and in the induction of local soft-tissue calcification (Gabbiani et al. 1966; McClure 1980; Garrett and McClure 1981). The mechanism of this calcergic action is not exactly known, but it has been hypothesized that cerium precipitates with pyrophosphate, resulting in the loss of the calcification-inhibitory function of pyrophosphate, and that these precipitates form crystallization nuclei on which calcium and phosphate accumulate to form apatite (Boeckx et al. 1992).

Because of their similar ionic radius, $Ce^{3+}$ and other lanthanide ions are able to replace calcium in many biomolecules, without necessarily substituting for it functionally. For example, they interfere with calcium-dependent reactions involved in the blood clotting cascade such as the activation of prothrombin (Furie et al. 1976) and factor XIII (Achyuthan et al. 1989). This behavior probably accounts for the long-known anticoagulant effects of the lanthanides, which prior to the widespread availability of heparin raised temporary interest in using them as antithrombotic drugs (Vincke and Oelkers1937; Vincke and Schmidt 1942; Beaser et al. 1942; Vincke 1944).

$Ce^{3+}$ is capable of binding to the $Ca^{2+}/Mg^{2+}$-ATPase of sarcoplasmic reticulum of skeletal muscle (Yamada and Tonomura 1972) and of inhibiting the active transport of calcium through mitochondrial membranes (Mela 1969; Crompton et al. 1979). Moreover, $Ce^{3+}$ is a potent blocker of neuronal low voltage-activated (T-type) calcium channels (Mlinar and Enyeart 1993; Beedle et al. 2002) and of high voltage-activated calcium channels of presynaptic nerve terminals (Nachshen 1984) and skeletal muscle cells (Lansman 1990). Thereby, its interactions with ion channels are not exhausted: A-type potassium channels of adrenal cortical cells are inhibited by binding of $Ce^{3+}$ to sites which are not specific for calcium (Enyeart et al. 1998), whereas currents through type A $\gamma$-aminobutyric acid (GABA)-activated chloride channels of rat dorsal root ganglion neurons are enhanced (Ma and Narahashi 1993; Narahashi et al. 1994). $Ce^{3+}$ is also capable of binding to the calcium-binding sites of the N-terminal domain of calmodulin (CaM), which mediates intracellular responses to calcium fluxes, in a cooperative manner (Bentrop et al. 1997) and of substituting for calcium in the regulation of calcium/CaM-dependent enzymes such as phosphorylase kinase (Sotiroudis 1986).

The strong interrelation between these two ions is further illustrated by the fact that cerium(III) chloride administered intravenously to rats induces an increase of serum calcium levels over a certain dose range, with high doses being ineffective (Johansson et al. 1968). The reason for this phenomenon is unknown, but it has to be kept in mind that a variety of biological actions of the lanthanides do not follow simple monotonic dose-response relationships, but may turn from enhancing to inhibiting, depending on the dose (Evans 1990; Wang et al. 2003).

## Antiemetic properties

The first documented medical use of cerium dates back to the mid nineteenth century when the obstetrician James Y. Simpson reported on satisfactory therapeutic results obtained with cerium nitrate for the relief of vomiting (Simpson 1854). Especially in vomiting of pregnancy, oral administration of cerium(III) oxalate has been widely practiced during the following decades. Its use has also been proposed for other forms of vomiting such as in cases of sea-sickness, for other gastrointestinal disorders such as chronic diarrhea, and even in neurological disorders such as epilepsy and chorea. The medicinal preparations used until the early twentieth century contained substantial and varying amounts of other lanthanides, however, supposedly without altering its therapeutic effects (Böhm 1915; Wilcox 1916).

As controversial as the opinions regarding the therapeutic value of cerium(III) oxalate were the tentative explanations for its effects, ranging from sedative effects on the cerebral vomiting center or on the pneumogastric nerve and a lowering effect on the reflex excitability of the gastrointestinal tract to astringent properties or the mere formation of a protective coating on the wall of the stomach (Baehr and Wessler 1908; Hara 1923; Umezawa 1925). Objections to this apparently nontoxic drug mainly arose from the facts that it is nearly insoluble in water, except for strongly acidic solutions, and that it is not absorbed from the gastrointestinal tract to any meaningful extent, making pharmacological actions other than locally gastric rather unlikely (Wilcox 1916). The basis for its use was seriously challenged by studies in dogs, which indicated marked effects on vomiting caused by local irritation of the stomach, but either no or only a weak inhibitory effect on vomiting of central nervous origin as induced by apomorphine (Baehr and Wessler 1908; Umezawa 1925). Since some soluble cerium(III) salts are actually capable of preventing apomorphine-induced vomiting when given intravenously, the modest effects of oral cerium(III) oxalate observed in these studies can easily be explained by its poor intestinal absorption (Umezawa 1925).

The low bioavailability and the apparently unreliable therapeutic properties soon led to the development of various soluble cerium preparations with the aim of overcoming these limitations (Böhm 1915). A formulation described as colloidal cerium(III) oxalate (Lange 1933) was available until the 1950s, with vomiting of pregnancy and all forms of motion sickness as primary indications, but it was later blended with (and eventually replaced by) the antihistaminic meclizine (Gigglberger and Höhn 1958). Unfortunately, the efficacy of cerium(III) oxalate has never been objectivized by clinical studies, and interest in elucidating its mode of action ceased after its use had been abandoned.

It has long been known that $Ce^{3+}$ reduces the contractility of the heart (Mines 1910) and skeletal muscles by inhibiting neuromuscular transmission (Hara 1923). It also affects excitation-contraction coupling in intestinal smooth muscle, where it inhibits both the phasic and tonic components of the response to a muscarinic agonist (Triggle and Triggle 1976). Since $Ce^{3+}$ generally interferes with basic muscular and neuronal functions mainly due to its calcium-antagonistic actions, it is tempting to assume a connection between this behavior and its antiemetic properties.

## Antiseptic and immunomodulatory properties with special reference to the treatment of burns

The bacteriostatic effects of cerium(III) nitrate and other cerium compounds had already been recognized near the end of the nineteenth century (Drossbach 1897), soon leading to their use as topical antiseptics in human and veterinary medicine. Apart from "dymal," a mixture of rare earth salicylates, several preparations were marketed under the common name "ceolat," namely cerium(III) acetate solutions as well as powders and ointments containing cerium(III) stearate. These remedies have been beneficial in the treatment of wounds, including burns, weeping eczema, intertrigo and decubitus, skin gangrene, impetigo contagiosa, and other skin diseases (Böhm 1915). The idea that the oxidizing properties of cerium(IV) might add to the bacteriostatic effects led to the use of cerium(IV) potassium sulfate, which was applied as an antiseptic powder under the name "ceriform" (Böhm 1915).

Systematic investigations later confirmed the bacteriostatic and bactericidal activity of cerium(III) chloride, cerium(III) nitrate, and cerium(IV) sulfate in a wide variety of bacteria (Burkes and McCleskey 1947) and showed that gram-negative bacteria tend to be somewhat more susceptible than gram-positive bacteria (Muroma 1958). These findings formed the basis for the clinical evaluation of topical cerium(III) nitrate (applied as a cream or in saline solution) in the treatment of extensive, life-threatening burns, with the encouraging result of a nearly 50% reduction in the death rate as compared to the mortality anticipated if the patients had been treated with silver nitrate (Monafo et al. 1976).

Because the flora recovered from treated wounds tended to be dominated by gram-positive bacteria, combination with the complementary acting silver sulfadiazine has been recommended (Monafo et al. 1976). Death from sepsis in patients surviving the original hemodynamic and pulmonary insults from near-total burns could be effectively prevented with the use of this combination (Fox et al. 1977; Monafo et al. 1977, 1978), and halving of the mortality rate as compared to prediction was confirmed (Monafo 1983). Although results of in vitro studies concerning the synergism or antagonism of these drugs have been conflicting (Rosenkranz 1979; Heggers et al. 1979; Saffer et al. 1980; Holder 1982; Marone et al. 1998) and the first prospective, randomized studies comparing silver sulfadiazine plus cerium nitrate to silver sulfadiazine alone failed to demonstrate any advantage of the combination in adults (Munster et al. 1980) and children (Bowser et al. 1981), a more recent trial confirmed the greater efficacy of the combination in terms of faster re-epithelialization, earlier readiness for autologous skin grafting, and reduced duration of hospitalization and even suggests a reduced mortality (de Gracia 2001).

Further beneficial aspects of the cerium nitrate adjunct have been emphasized: a reduced number of highly colonized wound sites (Hermans 1984) and the formation of a dry, adherent eschar which allows an excellent take of graft after excision (Ross et al. 1993) and postponing of skin grafting (Wassermann et al. 1989; Hadjiiski and Lesseva 1999). The characteristic leathery consistency of these eschars, which form upon contact of dermal collagen with cerium, at least in part results from superficial calcification induced by the calcergic action of cerium and constitutes an additional, physical barrier that insulates the dermis from germ contamination (Boeckx et al. 1992). Penetration through the eschar and skin is low (Boeckx et al. 1992; Herruzo-Cabrera et al. 1992), and no cerium could be detected in blood and urine even after treatment of large wounds for several weeks (Monafo et al. 1976).

Apart from direct antibacterial effects, immunomodulatory properties have been recognized as a major mechanism by which cerium helps prevent sepsis in burn patients. In mice, cerium nitrate protects from postburn immunosuppression, as indicated by the preservation of hypersensitivity reactions following antigen challenge of previously sensitized animals (Hansbrough et al. 1984; Peterson et al. 1985), reduced alterations of the splenic helper to suppressor lymphocyte ratio (Zapata-Sirvent and Hansbrough 1985), and improved survival following septic challenge (Zapata-Sirvent et al. 1986). In humans, it seems to preserve normal T-cell functions such as the production of interleukin 2 (IL-2) and IL-2 receptor expression (Sparkes 1993; Allgöwer et al. 1995). This effect probably results from the neutralizing action on the immunosuppressive burn toxins formed at the wound site. In particular, cerium irreversibly denaturizes the toxic lipid-protein complex (LPC), thereby probably fixing it in the eschar and preventing its entry into the circulation (Allgöwer et al. 1995). Additionally, it inhibits the calcium-dependent hemolytic activity of a low molecular weight lipid-peptide complex termed SAP isolated from the serum of burn patients (Ninnemann et al. 1985). A study in mice receiving skin autografts, which were burned and treated or not with cerium nitrate in vitro, demonstrated the protective effect against the mortality induced by grafting burned skin. Because the observed survival rate was nearly identical to that of burned animals after necrotomy and subsequent skin grafting, the effect of cerium nitrate was considered a chemical equivalent to surgical wound excision and recommended in cases not allowing early surgical intervention (Kistler et al. 1990). An impressive reduction of the anticipated death rate following treatment of patients with a single early bathing in aqueous cerium nitrate solution supports this opinion (Scheidegger et al. 1992).

Since it has been recognized that, apart from sepsis, a systemic inflammatory response characterized by a chaotic cytokine cascade, which is responsible for an eventual multiple organ dysfunction syndrome, is another major cause of “late” mortality in burn patients, new aspects of the neutralizing action of cerium on LPC have become evident (Allgöwer et al. 1995; Sparkes 1997). Recent experimental studies focus on the protective effect against the processes involved in the systemic inflammatory response (Deveci et al. 2000; Eski et al. 2001).[1]

Apart from these indirect effects specific for the burn setting, cerium also possesses direct immunomodulatory properties. Injections of cerium(III) salts in rats inhibit edematous inflammation caused by inflammatory agents (Jancsó and Jancsó-Gábor 1960) and inhibit reticuloendothelial system functions, in particular the phagocytotic activity of Kupffer cells (Lazar 1973). Cerium(III) chloride is capable of interfering with epidermal Langerhans cell functions by inhibiting their $Ca^{2+}/Mg^{2+}$-dependent ATPase (Gruner et al. 1991) and of inhibiting histamine release from basophil granulocytes (Gruner et al. 1992). Because of the pathogenetic role of both histamine-releasing mast cells and Langerhans cells in atopic eczema, therapeutic use of lanthanides has been proposed.

[1] The cerium nitrate–silver sulfadiazine cream marketed under the name “flammacerium” in several European countries and much advocated by clinicians (Lansdown et al. 2003), but classified as an orphan drug in the USA, was subject to an accelerated approval prior to the termination of a clinical phase III trial to respond to the urgent need resulting from the terror attacks of Sept. 11, 2001.

## Antineoplastic properties

Dating back to the pioneering era of cancer chemotherapy, two clinical reports on the use of "introcid," i.e., a solution of cerium(III) iodide for intravenous administration, in the treatment of patients with lymphogranulomatosis (M. Hodgkin) or inoperable solid tumors deserve mentioning. This experimental drug has been explored for its antineoplastic properties among other compounds of iodine which were expected to accumulate in tumor tissue. According to the clinical reports, cerium(III) iodide has been applied with remarkable benefit, as indicated by tumor shrinkage and improved quality of life in several cases of locally advanced or metastatic tumors of different origin (Lewin 1924; Cohn 1925). The authors judged the therapeutic effects as superior to those of other compounds of iodine and therefore considered cerium either the active component or an activator for iodine. Animal experiments using Kato's rabbit sarcoma confirmed the superiority to other compounds of iodine, in particular potassium iodide and calcium iodide which lack any appreciable activity in this tumor model (Ito 1937).

These observations are in peculiar contrast to the poor results obtained with cerium(III) chloride in experimental tumor models. While this compound is completely devoid of activity in two transplantable rat tumors (Maxwell and Bischoff 1931), it exerts moderate inhibitory effects on the proliferation of malignant cells in vitro, requiring high micromolar or even millimolar concentrations. The antiproliferative effects have been reported to be associated with morphological changes (polyhedral spreading) and cell cycle arrest in the $G_0/G_1$ phase in melanoma cells (Sato et al. 1998), decreased calmodulin levels in leukemia cells, upregulation of p53 and p21 tumor suppressor gene expression in gastric cancer cells (Ji et al. 2000), and apoptosis in leukemia cells (Dai et al. 2002).

Cerium(III) complexes of coumarin derivatives with known antibacterial, anticoagulant, and cytotoxic properties have been synthesized and explored for their cytotoxicity in malignant cells. In particular, $Ce(HL)_3 \cdot 5\ H_2O$ with L=4-hydroxy-3-[1-(4-chlorophenyl)-3-oxobutyl]-2H-1-benzopyran-2-one (coumachlor) (Kostova et al. 1999), $Ce(HL)_3 \cdot 4\ H_2O$ with L=4-hydroxy-3-[1-(4-nitrophenyl)-3-oxobutyl]-2H-1-benzopyran-2-one (niffcoumar) (Manolov et al. 1999), and $Ce(HL)_2(OH) \cdot 5\ H_2O$ with L=4-methyl-7-hydroxy-2H-1-benzopyran-2-one (mendiaxon) (Kostova et al. 2001) exert moderate cytotoxic effects in lymphoma and leukemia cells, while $Ce(HL)_3 \cdot 4\ H_2O$ with L=4-hydroxy-3-(3-oxo-1-phenylbutyl)-2H-1-benzopyran-2-one (warfarin) is devoid of cytoxicity in relevant concentrations (Kostova et al. 1999).

Cerium(III) complexes with 2,2′-bipyridine, 1,10-phenthroline and related ligands have been synthesized and evaluated in vitro. Among these complexes, those with 1,10-phenanthroline appear most promising. In particular, *trans*-[aquachlorobis(1,10-phenanthroline)cerium(III)] dichloride (KP776) exerts strong cytotoxic effects in cancer cells, with $IC_{50}$ values mainly in the low micromolar range. Experiments in cell models, each comprised of a parental cell line and a doxorubicin-selected subline overexpressing either P-glycoprotein or MRP1, revealed that KP776 is substrate to none of these two multidrug resistance-conferring transport proteins, but that the multidrug-resistant sublines show an unexpected collateral sensitivity to this compound (Jakupec et al. 2002). Moreover, all attempts to induce resistance to KP776 in cancer cell lines by prolonged exposure to minimally cytotoxic concentrations of the compound failed (P. Heffeter and W. Berger, personal communication). KP776 has a much lower DNA interstrand cross-linking efficiency than cisplatin and induces neither strand breaks nor alterations of the secondary structure

of plasmids (Jakupec et al. 2002). Thus, the mechanisms by which KP776 and related compounds exert their effects on malignant cells remain to be elucidated. Given the pivotal role of calcium signaling in controlling cell cycle and proliferation (Short et al. 1993; Takuwa et al. 1995; Munaron et al. 2004) as well as malignant progression and angiogenesis (Kamrava et al. 2002), it seems reasonable to hypothesize a connection between the capability of cerium to interfere with calcium-dependent processes and its antineoplastic potential.

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