JOURNAL OF Pharmaceutical Sciences

May 1965 volume 54, number 5

Review Article

Pharmacology and Toxicology of the Rare Earth Elements

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CONTENTS

INTRODUCTION

A Pandora's box was opened by the discovery of a black mineral specimen at Ytterby by Arrhenius in 1789. From that time to the present, many of the most famous names in chemistry spent at least part of their lifetimes in attempting to unravel the secrets of the chemical composition of yttria and ceria. Many controversies flowered as a result, and almost 100 years passed before elements 21, 39, and 57–71 were separated in a reasonable degree of purity, and their chemical and physical properties determined. The difficulties encountered in the separation of the rare earths were the result of the ground-state electronic configuration of their atoms and their almost identical chemical reactivity. A detailed review of the subject has been presented by Moeller (1). Other facets may be obtained by reference to the monograph by Spedding and Daane (2). The high purity of the rare earths now available resulted from the application of ion exchange techniques, such as those described by Ketelle and Boyd (3) and Spedding *et al.* (4). Such methods were required because the rare earths were a by-product of the fission of uranium, and useful applications were being sought for all such radionuclides. Prior to the Atomic Age, the greatest use of the rare earths was in Welsbach mantels for increasing the brightness of the gas light and the Coleman lantern. Modern applications include incorporation of some of these elements in the control rods used to regulate atomic reactors. Ransohoff (5) has discussed the economics of the large cross-section capture values for neutrons shown by dysprosium, erbium, europium, and gadolinium compared to cadmium and concluded that

Received from the Laboratory of Nuclear Medicine and Radiation Biology, Department of Biophysics and Nuclear Medicine, School of Medicine, University of California, Los Angeles.

These studies were supported by contract AT(04-1)GEN-12 from the U. S. Atomic Energy Commission, Washington, D. C.

TABLE I.—THE LANTHANONS

Name	Symbol	At. Wt.	At. No.	Abundance, Gm./metric ton
Scandium	Sc	44.956	21	5
Yttrium	Y	88.905	39	28.1
Lanthanum	La	138.910	57	18.3
Cerium	Ce	140.120	58	46.1
Praseodymium	Pr	140.907	59	5.53
Neodymium	Nd	144.240	60	23.9
Promethium	Pm	147.000	61	About 0
Samarium	Sm	150.350	62	6.47
Europium	Eu	151.960	63	1.06
Gadolinium	Gd	157.250	64	6.36
Terbium	Tb	158.924	65	0.91
Dysprosium	Dy	162.500	66	4.47
Holmium	Ho	164.930	67	1.15
Erbium	Er	167.260	68	2.47
Thulium	Tm	168.934	69	0.2
Ytterbium	Yb	173.040	70	2.66
Lutetium	Lu	174.970	71	0.75

combinations of these elements were more desirable than the use of a single element because of cost. Spiller (6) pointed out the use of cerium in increasing the life of nickel–chrome resistance wire and the application of radiothulium for portable roentgenographic equipment. Savitskiy (7) has reviewed the Russian industrial applications of the rare earths in the production of new types of alloys. Spedding and Gschneidner (8) recently pointed out that the rare earths are now being used in microwave devices, lasers, masers, phosphors, insulators, capacitors, semiconductors, ferroelectrics, and last but not least, in color television, where a europium phosphor gives a better red color. There are many other industrial applications, and when the cost of individual elements is reduced, many more will be found. With continuing industrial usage, it became necessary to obtain more modern and detailed information on the toxicology and pharmacology of the rare earth elements to forestall any possible deleterious effects occasioned by their use. This review seeks to present the information available at this time. Table I lists the elements to be discussed.

TOXICITY

Acute Toxicity.—Upon the basis of toxicity classification (32), these elements can be considered only slightly toxic. Early studies which reported MLD (minimum lethal dose) are included in Table II, but it must be borne in mind that the work was done prior to the development of biometrics. The symptoms of toxicity for all of these elements include writhing, ataxia, labored respiration, walking on the toes with arched back, and sedation. There is a delayed lethality with the peak death rate not occurring for 48 to 96 hr. There is also a sex difference, with the female being more susceptible than the male. In animals surviving 30 days, there was generalized peritonitis, adhesions, and hemorrhagic ascitic fluid (19) and also true granulomatous peritonitis and focal hepatic necrosis (33). The use of citrate or other chelation agents tends to obscure the lethal effects of the elements by either decreasing the rate of release of the element or by increasing the lethability through removal of another essential element, such as calcium. The effect of atomic weight on lethality is difficult to determine, but the transition elements (terbium group) appear to be less toxic than those above or below them in the periodic table. The low oral toxicity is undoubtedly related to poor intestinal absorption, as has been shown by chronic feeding experiments.

Chronic Toxicity.—Various salts of the rare earths injected intravenously in rabbits caused liver and spleen degeneration with yellow atrophy and central lobe necrosis as prominent features of the former (34). Single or repeated injections of the chlorides of La, Ce, Pr, and Nd into rabbits caused considerable change in hemoglobin, leukocyte count, erythrocyte count, and differential count, whereas oral administration was without effect (35). Intraperitoneal administration of yttrium chloride for more than 5 months produced only intestinal adhesions and no effect on growth (19). With the exception of gadolinium, terbium, thulium, and ytterbium, which produced perinuclear vacuolization in the liver, all of the other rare earths caused no internal organ damage when fed at levels of 0.01, 0.1, and 1% of the diet for 90 days. None of the rare earths had an effect on growth or on the hemogram. The liver damage appeared to be sex-linked because it was more prominent in males than in females (9, 23, 25, 27–29, 31). Similar results were obtained by Vincke and Oelkers (36) regarding accumulation of rare earths in the internal organs of mice and rabbits; only the Kupfer cells of the liver and the spleen pulp cells contained any rare earths.

Inhalation of rare earth fluoride or oxide mixtures by guinea pigs resulted in progressive lung retention, depending upon the duration of total exposure. No pneumoconiotic fibrosis was observed (37). Further work with rare earth oxide mixtures showed fatal delayed chemical hyperemia and cellular eosinophilia. An isolated cellular vascular granulomata occurred after 1 year in the animals surviving the initial insult (38). When a mixture with a high fluoride con-

TABLE II.—ACUTE LETHAL DOSES OF THE RARE EARTHS

Chemical	Species and Sex	LD_{50}, mg./Kg.	Adm. Rt.[b]	Ref.
Scandium chloride	Mouse ♂	755(741.7–768.6)	i.p.	(9)
	Mouse ♂	4000(3960–4040)	P.O.	(9)
Yttrium chloride	Mouse	88(67.7–114.4)	i.p.	(10)
	Rat	450	i.p.	(11)
	Rat	45(41.1–49.3)	i.p.	(10)
nitrate	Frog	350[a]	s.c.	(12)
	Mouse	1660	s.c.	(12)
	Rat	20–30[a]	i.v.	(13)
	Rat	350	i.p.	(11)
	Rabbit	500	i.v.	(12)
oxide	Rat	500	i.p.	(11)
Lanthanum acetate	Rat	10,000	P.O.	(11)
	Rat	475	i.p.	(11)
ammonium nitrate	Rat	3400	P.O.	(11)
	Rat	625	i.p.	(11)
citrate chloride	Mouse	78.2(70.0–100.3)	i.p.	(16)
	Guinea pig	60.7(17.7–207.0)	i.p.	(16)
chloride	Frog	about 1000[a]	s.c.	(14)
	Mouse	3500[a]	s.c.	(14)
	Mouse	3500[a]	s.c.	(15)
	Mouse	372.4(323.6–428.5)	i.p.	(16)
	Mouse	>500[a]	s.c.	(17)
	Mouse	>160[a]	i.p.	(18)
	Rat	106(91.4–123)	i.p.	(10)
	Rat	350	i.p.	(11)
	Guinea pig	129.7(105.4–159.6)	i.p.	(16)
	Rat	4200	P.O.	(11)
	Rabbit	200–250[a]	i.v.	(11)
nitrate	Rat	4500	P.O.	(11)
	Rat	450	i.p.	(11)
	Mouse ♀	410(353–475)	i.p.	(19)
oxide	Rat	>10,000	P.O.	(11)
sulfate	Rat	>5000	P.O.	(11)
	Rat	275	i.p.	(11)
Cerium chloride	Frog	about 300[a]	s.c.	(20)
	Mouse	5000–10,000[a]	s.c.	(21)
	Mouse	353.2(296.5–420.7)	i.p.	(16)
	Rat	2000–4000[a]	s.c.	(21)
	Rat	50–60[a]	i.v.	(13)
	Guinea pig	55.7(40.1–77.4)	i.p.	(16)
citrate chloride	Rat	146.6(128.6–167.1)	i.p.	(16)
	Guinea pig	103.5(73.1–146.5)	i.p.	(16)
nitrate	Mouse ♀	470(435–508)	i.p.	(19)
	Rat ♀	290(238–354)	i.p.	(19)
	Rat ♀	4200(3684–4788)	P.O.	(19)
	Rat ♀	4.3(3.4–5.6)	i.v.	(19)
	Rat ♂	49.6(32.8–74.4)	i.v.	(19)
Praseodymium chloride	Frog	about 1000–1500[a]	s.c.	(22)
	Mouse	2500[a]	s.c.	(15)
	Mouse	358.9(297.2–433.5)	i.p.	(16)
	Mouse	900–1500[a]	s.c.	(22)
	Mouse ♂	600(552–652)	i.p.	(23)
	Mouse ♂	4500(4054–4995)	P.O.	(23)
	Rat	<2000	i.p.	(22)
	Guinea pig	125(78.2–200)	i.p.	(16)
	Rabbit	200–250	s.c.	(15)
citrate chloride	Mouse	140.6(126.2–156.7)	i.p.	(16)
	Guinea pig	53(29.9–70.3)	i.p.	(16)
nitrate	Mouse ♀	290(259–325)	i.p.	(19)
	Rat ♀	245(209–287)	i.p.	(19)
	Rat ♀	3500(3017–4060)	P.O.	(19)
	Rat ♀	7.4(5.1–10.8)	i.v.	(19)
	Rat ♂	77.2(49.7–119.8)	i.v.	(19)
	Rat	10.8–13.9[a]	i.v.	(13)
Neodymium chloride	Frog	250[a]	s.c.	(24)
	Mouse	4000[a]	s.c.	(15)
	Mouse ♂	600(562.0–640)	i.p.	(23)
	Mouse ♂	5250(4730–5830)	P.O.	(23)
	Mouse	348.3(297.2–408.3)	i.p.	(16)
	Rat	150–250[a]	i.p.	(24)
	Guinea pig	70[a]	i.v.	(24)
	Guinea pig	139.6(99.3–196.3)	i.p.	(16)
	Rabbit	200–250[a]	i.v.	(15)

continued overleaf

TABLE II.—CONTINUED

Chemical	Species and Sex	LD_{50}, mg./Kg.	Adm. Rt.[b]	Ref.
citrate chloride	Mouse	138(94.4–201.8)	i.p.	(16)
	Guinea pig	40.5(4.7–348)	i.p.	(16)
nitrate	Mouse ♀	270(221–329)	i.p.	(19)
	Rat ♀	270(231–316)	i.p.	(19)
	Rat ♀	2750(1896–3988)	P.O.	(19)
	Rat ♀	6.4(5.5–7.3)	i.v.	(19)
	Rat ♂	66.8(53.5–83.6)	i.v.	(19)
Samarium chloride	Frog	about 150[a]	s.c.	(22)
	Mouse ♂	585(508.7–672.7)	i.p.	(25)
	Mouse ♂	>2000	P.O.	(25)
	Rat	>2000[a]	s.c.	(22)
	Guinea pig	750–1000[a]	s.c.	(22)
nitrate	Frog	1600[a]	s.c.	(26)
	Mouse ♀	315(258–384)	i.p.	(19)
	Rat ♀	285(254–319)	i.p.	(19)
	Rat ♀	2900(2660–3161)	P.O.	(19)
	Rat ♀	8.9(6.8–11.8)	i.v.	(19)
	Rat ♂	59.1(40.5–86.3)	i.v.	(19)
	Guinea pig	about 500[a]	s.c.	(26)
Europium chloride	Mouse ♂	550(515.5–586.9)	i.p.	(27)
	Mouse ♂	5000(4505–5500)	i.p.	(27)
nitrate	Mouse ♀	320(294–349)	i.p.	(19)
	Rat ♀	210(172–256)	i.p.	(19)
	Rat ♀	>5000	P.O.	(19)
Gadolinium chloride	Mouse ♂	550(495.5–610.5)	i.p.	(25)
	Mouse ♂	>2000	P.O.	(25)
nitrate	Mouse ♀	300(261–345)	i.p.	(19)
	Rat ♀	230(204–260)	i.p.	(19)
	Rat ♀	>5000	P.O.	(19)
Terbium chloride	Mouse ♂	550(521.3–580.3)	i.p.	(28)
	Mouse ♂	5100(5049.5–5151)	P.O.	(28)
nitrate	Mouse ♀	480(444–518)	i.p.	(19)
	Rat ♀	260(232–291)	i.p.	(19)
	Rat ♀	>5000	P.O.	(19)
Dysprosium chloride	Mouse ♂	585(552–620)	i.p.	(29)
	Mouse ♂	7650(7150–8186)	P.O.	(29)
nitrate	Mouse ♀	310(261–369)	i.p.	(19)
	Rat ♀	295(236–369)	i.p.	(19)
	Rat ♀	3100(2870–3348)	P.O.	(19)
Holmium chloride	Mouse ♂	560(541–580)	i.p.	(29)
	Mouse ♂	7200(6667–7776)	P.O.	(29)
nitrate	Mouse ♀	320(302–339)	i.p.	(19)
	Rat ♀	270(237–308)	i.p.	(19)
	Rat ♀	3000(2804–3210)	P.O.	(19)
Erbium chloride	Frog	300–400[a]	s.c.	(30)
	Mouse ♂	535(509–562)	i.p.	(29)
	Mouse ♂	6200(5390–7140)	P.O.	(29)
nitrate	Mouse ♀	225(194–261)	i.p.	(19)
	Rat	82.8–96.6[a]	i.v.	(13)
	Rat ♀	230(195–271)	i.p.	(19)
	Rat ♀	35.8(27.8–49.9)	i.v.	(19)
	Rat ♂	52.4(37.0–74.5)	i.v.	(19)
Thulium chloride	Mouse ♂	485(466.3–504.4)	i.p.	(28)
	Mouse ♂	6250(5430–7190)	P.O.	(28)
nitrate	Mouse ♀	255(226–288)	i.p.	(19)
	Rat ♀	285(252–322)	i.p.	(19)
Ytterbium chloride	Mouse ♂	395(375–416.7)	i.p.	(28)
	Mouse ♂	6700(6374.9–7041.7)	P.O.	(28)
nitrate	Mouse ♀	250(185–338)	i.p.	(19)
	Rat ♀	255(220–296)	i.p.	(19)
	Rat ♀	3100(2924–3286)	P.O.	(19)
Lutetium chloride	Mouse ♂	315(267–372)	i.p.	(31)
	Mouse ♂	7100(6630–7590)	P.O.	(31)
nitrate	Mouse ♀	290(259–325)	i.p.	(19)
	Rat ♀	325(294–382)	i.p.	(19)

[a] Minimum lethal dose. [b] s.c., subcutaneous; P.O., oral; i.p., intraperitoneal; i.v., intravenous.

tent was used, the following occurred: acute transient chemical pneumonitis, subacute bronchitis and bronchiolitis, focal hypertropic emphysema, and regional bronchiolar stricturing but no granulomatosis (39). Roshchin (40) obtained similar results with inhalation of the rare earth fluorides. Intratracheal administration of the oxides of yttrium, neodymium, and cerium to rats resulted in the production of granulomas after 8 months (41). Inhalation of $Ce^{144}O_2$ by dogs resulted in a typical radiation effect rather than the usual chemical damage seen with stable cerium (42). Human exposure to vapors of rare earths caused sensitivity to heat, itching, and a sharper sense of odor and taste (43).

BIOCHEMISTRY

Both cerium chloride and cerium ammonium nitrate stimulate gastric secretion in low doses and suppress it in high doses (44). Hyperglycemia has been produced in rabbits by intravenous injection of cerium, lanthanum, neodymium, and praseodymium salts (45). Vincke (46) studied the effects of an organic neodymium salt on human serum α-amylase, lactic acid dehydrogenase, sorbitol dehydrogenase, and acid and alkaline phosphatase in relation to blood sugar and bilirubin. All were affected 2 hr. after drug administration but returned to normal in 24 hr. Further investigation indicated that the neodymium salt also influenced erythrocyte glucose-6-phosphate dehydrogenase activity (47). Succinic dehydrogenase can be activated by lanthanum and inhibited by yttrium chlorides. These two salts also inhibit adenosine triphosphatase (11). The mitochondria from fatty livers of animals poisoned with praseodymium gave evidence of uncoupling of oxidative phosphorylation (48, 49). However, the toxic effects of lanthanum, praseodymium, neodymium, and samarium on the liver do not appear to be related to the synthesis or breakdown of ATP in the mitochondria (50). The over-all effects of the rare earths as enzyme catalysts and inhibitors have been reviewed by Bamann and Trapman (51). The most prominent biochemical effect of injected rare earths is the production of a fatty liver. This condition is not seen after oral administration and occurs only with the elements lanthanum through samarium. The fatty liver reaches a maximum at 48 hr. and is characterized by an increase in neutral fat esters. The effect is more consistent in females and castrated males. Testosterone reduces the fatty infiltration in both intact and ovariectomized females. Adrenalectomy was effective in males, and hypophysectomy was effective in both sexes. Neither choline nor methionine was able to prevent the condition (52). The rare earth-induced fatty liver is not seen in guinea pigs, chickens, or dogs; only occasionally in rabbits; and always in rats, mice, and hamsters (53). Cerium also decreases blood glucose while increasing plasma free fatty acids prior to producing the fatty liver (54). The total liver lipids become similar to adipose tissue prior to detection of massive accumulation of fat in hepatic cells (55).

METABOLISM OF THE RARE EARTHS

Very small amounts of stable rare earths are absorbed by the oral route (56, 57). Subcutaneous injection gives greater absorption with very slow excretion, mostly *via* the intestinal route (22). The greatest difficulty encountered in assessing absorption and excretion of the stable rare earths lies in the lack of a specific analytical method. On the other hand, the radionuclides of these elements can be determined readily, and modern knowledge of their absorption, fate, and excretion has been obtained by radioactive techniques. Scott *et al.* (58) reported that $Sc^{46, 47, 48}$, when administered intravenously, had the highest concentration in the liver and reticuloendothelial system and the lowest in the skeletal system. Only 25% was excreted in 4 days. Intramuscular injection resulted in retention of 76.6% at the site of injection, with the remainder distributed in the skeleton, liver, kidney, and spleen. With Tm^{170}, 16.2% was found at the site of injection 8 months later. Of the absorbed material, the skeleton had 44.7%, and 49% was excreted in urine and feces. A more detailed metabolic study was undertaken by Durbin *et al.* (59). Absorption from parenteral injection in rats was complete in 4 days. The elements lanthanum through samarium deposited 50% in the liver and 25% in the skeleton. Elimination from the liver *via* the bile had a half-time of 15 days. After 8 months, the skeleton still retained two-thirds of its initial amount. Europium and gadolinium gave a more equal distribution in the liver and skeleton. Elimination was both fecal and urinary. Terbium through lutetium deposited 50 to 60% of the dose in the skeleton and had a slow elimination half-time, 2.5 years. The extra-skeleton burden was excreted in the urine within 2 weeks. Magnusson (60) made an even more extensive investigation of the metabolism of the rare earths, confirming previous reports and adding new information. Fecal excretion occurs partially *via* the bile and partially by direct secretion

through the intestinal wall. Liver uptake involved the cell nuclei, the mitochondria, and the microsomes. Acute liver damage causes an elevation of ornithine-carbamyl-transferase as well as fatty liver (cerium) or intralobular necrosis (yttrium, terbium, holmium, and ytterbium). There is also damage of the endoplasmic reticulum. Ekman *et al.* (61) have shown that Y^{91}, Ce^{144}, Pm^{147}, and Yb^{169} rapidly combine with serum albumin and low molecular weight ultraviolet absorbing complexes of the serum. This mechanism for rapid distribution to organ systems could explain the localization not only in the liver cells but also in the nongrowing inorganic fraction of bone (62). Whole-body autoradiography of mice given Ce^{144} or Pm^{147} prior to birth further confirms the rapid distribution of the materials in the liver and skeleton. A high uptake of Ce^{144} occurs in the kidneys, spleen, cartilage, and adrenal cortex and of Pm^{147} in the kidneys and cartilage (63). Tb^{180} and Yb^{169} distribute similarly to Ce^{144}, while Ho^{166} follows the pattern of Pm^{147} (64).

PHARMACODYNAMIC EFFECTS

Ocular Effects.—All of the rare earths produce a high degree of irritation of the conjunctiva but not the cornea or iris. Conjunctival ulcers requiring 1 to 3 weeks for healing also are seen after topical application of strong solutions or crystals of these compounds (9, 23, 25, 27–29, 31). When the cornea is denuded, the rare earths cause opacification but only after a latent period of several hours or days. Although the mechanism involved is obscure, it concerns deposition of excess calcium in the injured area (65).

Skin Irritation.—Damage of the skin from physical contact is always a problem for industrial medicine. The rare earths cause no damage or irritation to intact skin but extensive injury to abraded skin, resulting in epilation and scar formation. Such injuries do not appear to be related entirely to the acidic portion of the molecule but are related in part to the rare earths combining with tissue constituents, *e.g.*, proteins, phosphate, etc. (9, 23, 25, 27–29, 31). Of greater importance, in so far as skin lesions are concerned, is the production of granulomas from intradermal injection of the rare earths at doses of 0.05 to 0.5 mcg. in guinea pigs (66). Shelley *et al.* (67) also found lesions in human skin after injection of rare earths in patients with sarcoidosis and anthracosilicosis.

Smooth Muscle Effects.—Bernardi (68) reported decreased tonus and finally loss of contractility of the isolated ileum and uterus of rabbits, cats, and dogs exposed to lanthanum nitrate. Neodymium, praseodymium, and samarium have similar effects (22, 24). Haley *et al.* (9, 23, 25, 27–29, 31), after a more extensive investigation of the rare earths, obtained similar results and showed that all of these chemicals had a nonspecific antispasmodic effect against acetylcholine and increased intraluminal pressure. Moreover, continuous washing would not restore contractility.

Effects on Isolated Heart.—Mines (69) demonstrated the cardiac toxicity of the rare earths on the isolated frog heart. In all cases, the heart stopped in diastole. Similar results were obtained on the isolated rabbit heart and the heart-lung preparation of the cat. There has been ample confirmation of this work (12, 20, 22, 24, 26, 70–72, 74). The rare earths produce a negative inotropic effect prior to paralysis of the isolated hearts of rats, guinea pigs, and rabbits (22, 24, 70, 73, 74).

Effects on Striated Muscle.—Chistoni (73) reported that cerium nitrate had a curariform effect on frog striated muscle, while Brunton and Cash (75) found that the decreased contractility of such muscles depended upon the particular rare earth being studied. Others (12, 20, 26, 76) have reported similar results.

GENERAL PHARMACOLOGY

All of the rare earths produce a decreased blood pressure when administered intravenously to animals (12, 20, 22, 24, 45, 70, 74). A more recent detailed series of studies have shown that all of the rare earths produce hypotension in cats and death by cardiovascular collapse coupled with respiratory paralysis. ECG records showed slowed conduction time, increased height of the P-wave, decreased height of the entire complex, inverted then increased height of the T-wave, transient ventricular fibrillation, and 2:1 to 4:1 heart block. Autonomic drugs would not counteract these lethal effects (9, 23, 25, 27–29, 31). Similar effects have been reported for dogs; and when citrate was used for complexing, the hypotension was more pronounced. EDTA complexing did not cause such effects (77).

Miscellaneous Effects.—Maxwell and Bischoff (13) reported that cerium, erbium, yttrium, and praseodymium salts had no effect on rat sarcoma or Hyde rat carcinoma. The rare earths have been used also as antibacterial agents and antiemetic agents; but in both instances more modern and effective drugs have supplanted them.

CLINICAL APPLICATIONS

Harper *et al.* (78) used implanted Yt^{90} pellets in the hypophysis for treatment of metastatic carcinoma. The results were very encouraging. Spode (79) pointed out the usefulness of Ho^{166} and Lu^{177} in interstitial radiotherapy with particular emphasis on Ho^{166}. Perfusion therapy of brain tumors with Sc^{49} and Dy^{165} appears to offer promise because of the high tumor-to-normal brain ratio. These nuclides were more effective in the chelate form. Other applications are being developed for the clinical use of the rare earth radionuclides.

It has long been known that the rare earths act as anticoagulants (80). Dyckerhoff and Goossens (81) pointed out that a neodymium preparation, Auer 144, appeared to act like heparin on the blood coagulation process. However, Vincke (82) believes the rare earths act as antiprothrombins. Rare earth compounds were tried in 1943 and recommended for thrombosis and embolism prophylaxis (83). At the same time, it was discovered that such compounds also were antagonists of thrombokinase (84). Moreover, vitamin K compounds could correct the blood incoagulability produced by rare earth salts (85). Vincke (86) developed neodymium nicotinate as a more active less toxic anticoagulant, because prior work had shown that the rare earth chlorides produced some very unpleasant side effects (87). The nicotinate has a less pronounced early effect on blood coagulation, but it is effective for a longer period of time (88, 89). Soulier and Weilland (90), after a more thorough investigation of the anticoagulant properties of the neodymium salt of sulfoisonicotinic acid, concluded that it acts as an anticoagulant by interfering with proconvertin, thus suppressing thromboplastin formation, and also it interferes with prothrombin. Several reviews have pointed out the widespread use of this product in Europe (91–94); but recently Hunter and Walker (95) called attention to the production of hemoglobinuria after intravenous administration of the compound. They felt that great caution should be exercised in clinical application of the compound. Vincke (96) did not think this reaction was unusual but considering the availability of highly purified heparin, there does not appear to be a real reason for using a compound which might cause damage to the patient.

CONCLUSIONS

The pharmacology, toxicology, and clinical application of the stable and radioactive rare earths have been reviewed. These elements have a low to moderate acute toxicity rating and cause very little change in animals when fed for several months. The most striking effects produced by these compounds are the induction of both skin and lung granulomas after local injection or inhalation. Further work should be undertaken to find antidotes. The fatty liver produced by intravenous or intraperitoneal injection, while serious, is a self-limiting condition which is reversible without therapy.

REFERENCES

(1) Moeller, T., "The Chemistry of the Lanthanides," Reinhold Publishing Corp., New York, N. Y., 1963, p. 117.
(2) Spedding, F. H., and Daane, A. H., "The Rare Earths," John Wiley & Sons, Inc., New York and London, 1961, p. 639.
(3) Ketelle, B. H., and Boyd, G. E., *J. Am. Chem. Soc.*, **69**, 2800(1947).
(4) Spedding, F. H., *et al.*, *ibid.*, **69**, 2812(1947).
(5) Ransohoff, J. A., *Nucleonics*, **17** (No. 7), 80(1959).
(6) Spiller, R., *Atom Industry*, **9**, 13(1960).
(7) Savitskiy, Y. M., *Vestn. Akad. Nauk SSSR*, **6**, 81 (1960).
(8) Spedding, F. H., and Gschneidner, K. A., Jr., *Ind. Res.*, **6**, 20(1964).
(9) Haley, T. J., *et al.*, *J. Pharm. Sci.*, **51**, 1043(1962).
(10) Kyker, G. C., and Cress, E. A., *A.M.A. Arch. Ind. Health*, **16**, 475(1957).
(11) Cochran, K. W., *et al.*, *Arch. Ind. Hyg. Occ. Med.*, **1**, 637(1950).
(12) Steidle, H., and Ding, M., *Arch. Exptl. Pathol. Pharmakol.*, **141**, 276(1929).
(13) Maxwell, L. C., and Bischoff, F., *J. Pharmacol. Exptl. Therap.*, **43**, 61(1931).
(14) Ajazzi-Mancini, M., *Arch. Fisol.*, **24**, 162(1926).
(15) Vincke, E., *Arch. Exptl. Pathol. Pharmakol.*, **188**, 465 (1938).
(16) Graca, J. G., Garst, E. L., and Lowry, W., *A.M.A. Arch. Ind. Health*, **15**, 9(1957).
(17) Laszlo, D., *et al.*, *J. Natl. Cancer Inst.*, **13**, 559(1952).
(18) MacDonald, N. S., *et al.*, *J. Biol. Chem.*, **195**, 837 (1952).
(19) Bruce, D. W., Hietbrink, B. E., and DuBois, K. P., *Toxicol. Appl. Pharmacol.*, **5**, 750(1963).
(20) Hara, S., *Arch. Exptl. Pathol. Pharmakol.*, **100**, 230 (1923).
(21) *Ibid.*, **100**, 217(1923).
(22) Niccolini, P., *Arch. Intern. Pharmacodyn.*, **37**, 199 (1930); **40**, 260(1931).
(23) Haley, T. J., *et al.*, *Toxicol. Appl. Pharmacol.*, **6**, 614 (1964).
(24) Guida, G., *Arch. Intern. Pharmacodyn.*, **37**, 305 (1930).
(25) Haley, T. J., *et al.*, *Brit. J. Pharmacol.*, **17**, 526(1961).
(26) Steidle, H., and Durr, H., *Arch. Exptl. Pathol. Pharmakol.*, **145**, 19(1929).
(27) Haley, T. J., *et al.*, *J. Pharm. Sci.*, **54**, 643(1965).
(28) Haley, T. J., *et al.*, *Toxicol. Appl. Pharmacol.*, **5**, 427 (1963).
(29) Haley, T. J., *et al.*, *ibid.*, to be published.
(30) Steidle, H., Kohl, H., and Schonefeld, H., quoted by Heffter, A., "Handuch der Experimentellen Pharmakologie," vol. 3.4, Julius Springer Verlag, Berlin, 1935, p. 2197.
(31) Haley, T. J., *et al.*, *J. Pharm. Sci.*, **53**, 1186(1964).
(32) Hodge, H. C., and Sterner, J. H., *Am. Ind. Hyg. Assoc. Quart.*, **10**, 93(1943).
(33) Steffee, C. H., *A.M.A. Arch. Ind. Health*, **20**, 414 (1959).
(34) Fischer, F., and Roeckl, K. W., *Arch. Exptl. Pathol. Pharmakol.*, **189**, 4(1938).
(35) Oelkers, H. A., and Vincke, E., *ibid.*, **188**, 53(1938).
(36) Vincke, E., and Oelkers, H. A., *ibid.*, **188**, 465(1938).
(37) Schepers, G. W. H., Delahant, A. B., and Redlin, A. J., *A.M.A. Arch. Ind. Health*, **12**, 297(1955).
(38) Schepers, G. W. H., *ibid.*, **12**, 301(1955).
(39) *Ibid.*, **12**, 306(1955).
(40) Roshchin, I. V., *Gigiena Truda i Prof. Zabolevaniga*, **7**, 41(1961).
(41) Mogilevskaya, O. Ya., and Raikhlin, N. T., in "Toxicology of Rare Metals," Israelson, Z. I., ed., Gosudarstvennoe Izdatel'stvo Meditsinskoi Literatury, Moscow, 1963, pp. 195–208.
(42) Stuart, B. O., Casey, H. W., and Bair, W. J., Hanford Symposium, Health Physics, vol. 10, 1964.
(43) Gehrcke, E., Lau, E., and Meinhardt, O., *Z. Ges. Naturwissenschaften*, **5**, 106(1939).
(44) Oda, S., *Z. Ges. Exptl. Med.*, **80**, 6(1932).
(45) Mori, I., *Japan. J. Pharmacol.*, **5**, 13(1931).
(46) Vincke, E., *Therapie der Gegenwart*, **100**, 605(1961).
(47) *Ibid.*, **101**, 276(1962).
(48) Neubert, D., and Hoffmeister, I., *Arch. Exptl. Pathol. Pharmakol.*, **237**, 519(1960).

(49) Dianzani, M. U., *Biochem. Biophys. Acta*, **14**, 514 (1954).
(50) Neubert, D., *ibid.*, **69**, 399(1963).
(51) Bamann, E., and Trapman, H., "Advances in Enzymology," vol. 21, Interscience Publishers, Inc., New York, N. Y., 1959, p. 169.
(52) Snyder, F., Cress, E. A., and Kyker, G. C., *J. Lipid Res.*, **1**, 125(1959).
(53) Snyder, F., Cress, E. A., and Kyker, G. C., *Nature*, **185**, 480(1960).
(54) Snyder, F., and Stephens, N., *Proc. Soc. Exptl. Biol. Med.*, **106**, 202(1961).
(55) Snyder, F., and Kyker, G. C., *ibid.*, **116**, 890(1964).
(56) Bachem, C., *Arch. Intern. Pharmacodyn.*, **17**, 381 (1907).
(57) Baehr, G., and Wessler, H., *Arch. Intern. Med.*, **2**, 517(1908).
(58) Scott, K. G., Crowley, J., and Wallace, P., UCRL Rept. 1561, Sept. 1951.
(59) Durbin, P. W., *et al.*, *Proc. Soc. Exptl. Biol. Med.*, **91**, 78(1956).
(60) Magnusson, G., *Acta Pharmacol. Toxicol. Suppl. 2*, **20**, 95(1963).
(61) Ekman, L., Valmet, E., and Aberg, B., *Intern. J. Appl. Radiation Isotopes*, **12**, 32(1961).
(62) Jowsey, J., Rowland, R. E., and Marshall, J. H., *Radiation Res.*, **8**, 490(1958).
(63) Ewaldsson, B., and Magnusson, G., *Acta Radiol.*, **2**, 65(1964).
(64) *Ibid.*, **2**, 121(1964).
(65) Grant, W. M., and Kern, H. L., "Rare Earths in Biochemical and Medical Research," Kyker, G. C., and Anderson, E. B., eds., ORINS-12, Sept. 1956, pp. 346–351.
(66) Haley, T. J., and Upham, H. C., *Nature*, **200**, 271 (1963).
(67) Shelley, W. B., *et al.*, *J. Invest. Dermatol.*, **31**, 301 (1958).
(68) Bernardi, O. M., *Boll. Soc. Ital. Biol. Sper.*, **1**, 246 (1926); **4**, 493(1929).
(69) Mines, G. R., *J. Physiol.*, **42**, 809(1911).
(70) Ajazzi-Mancini, M., *Arch. Fisol.*, **25**, 43(1927).
(71) Iwao, T., *Japan. J. Pharmacol.*, **5**, 13(1931).
(72) Mori, L., *ibid.*, **4**, 39(1930).
(73) Chistoni, A., *Arch. Soc. Biol.*, **5**, 78(1923).
(74) Oelkers, H. A., *Arch. Exptl. Pathol. Pharmakol.*, **194**, 477(1940).
(75) Bruton, T. L., and Cash, J., *Proc. Roy. Soc. London*, **35**, 324(1883).
(76) Hober, R., and Spaeth, R. A., *Pfluger Arch. Ges. Physiol.*, **159**, 433(1914).
(77) Graca, J. G., Davison, F. C., and Feavel, J. B., *Arch. Eviron. Health*, **8**, 555(1964).
(78) Harper, P. V., *et al.*, "Rare Earths in Biochemical and Medical Research," Kyker, G. C., and Anderson, E. B., eds., ORINS-12, Sept. 1956, pp. 388–391.
(79) Spode, E., *Strahlentherapie*, **108**, 296(1959).
(80) Vincke, E., and Oelkers, H. A., *Arch. Expil. Pathol. Pharmakol.*, **187**, 594(1937).
(81) Dyckerhoff, H., and Goossens, N., *Z. Ges. Exptl. Med.*, **106**, 181(1939).
(82) Vincke, E., *Hoppe-Seyler Z. Physiol. Chem.*, **272**, 65(1941).
(83) Schneider, E., and Kickelhayn, R., *Deut. Z. Chirurgie*, **257**, 221(1943).
(84) Dyckerhoff, H., and Grunewald, O., *Biochem. Z.*, **314–315**, 124(1943).
(85) Vincke, E., *Z. Naturforsch.*, **1**, 458(1946).
(86) Vincke, E., *Arch. Exptl. Pathol. Pharmakol.*, **204**, 497(1947).
(87) Beaser, S. B., Segel, A., and Vandam, L., *J. Clin. Invest.*, **21**, 447(1942).
(88) Vincke, E., and Sucker, E., *Klin. Wochschr.*, **28**, 74 (1950).
(89) Vincke, E., "Thrombose und Embolie," I. Internationale Tagung, Basel, 1954, B. Schwabe and Co., Basel, 1955, pp. 319–327.
(90) Soulier, J. P., and Weilland, C., *Rev. Hematol.*, 11 265(1956).
(91) Jancso, N., *J. Pharm. Pharmacol.*, **13**, 577(1961).
(92) Vincke, E., *Therapie der Gegenwart*, **99**, 509(1960).
(93) Schalk, K. E., *Chirurg.*, **33**, 1(1962).
(94) Flack, K., *Arzneimittel-Forsch.*, **13**, 377(1963).
(95) Hunter, R. B., and Walker, W., *Brit. Med. J.*, **I**, 227(1957).
(96) Vincke, E., *ibid.*, **I**, 882(1957).

Research Articles

Dissolution Kinetics of Certain Crystalline Forms of Prednisolone

By DALE E. WURSTER and PALMER W. TAYLOR, JR.

The activity, dissolution rate, and crystal behavior of three crystalline forms of prednisolone, each exhibiting distinctly different properties, have been investigated. By determining the relative dissolution rates of the crystal forms under different agitation conditions, it was found that dissolution could be described by consecutive processes involving a reaction at the interface and transport away from the interface. The data suggested that these processes pose a double barrier to dissolution under the experimental conditions.

RECENTLY, a number of studies (1–3) have investigated the influence of solid phase characteristics on the dissolution rate of pharmaceutical compounds. Studies of such a nature are especially important in the case of steroids since they exhibit a low water solubility and a variety of crystalline states. A knowledge of dissolution rates, solubility, and physical stability of crystalline forms of pharmaceuticals is pertinent to ascertain the limits of their physiological availability.

One of the above studies (1) also pointed out that under certain agitation conditions the relative dissolution rates of different crystalline forms may not reflect their relative rates under *in vivo* conditions. Since under different condi-

Received August 26, 1964, from the School of Pharmacy, University of Wisconsin, Madison.
Accepted for publication December 4, 1964.
Presented to the Scientific Section, A.PH.A., New York City meeting, August 1964.
Based on a dissertation submitted by Palmer W. Taylor, Jr., to the Graduate School, University of Wisconsin, Madison, in partial fulfillment of Doctor of Philosophy degree requirements.
The authors express their appreciation to The Upjohn Co., Kalamazoo, Mich., for supplying some of the prednisolone used in these studies.