Pharmacology and Toxicology of Scandium Chloride

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The pharmacological and toxicological properties of scandium chloride have been investigated. The intraperitoneal and oral LD_{50}'s were 755 mg./Kg. and 4 Gm./Kg., respectively. Studies of chronic toxicity showed no body weight changes occurred in any group except the male rats on a 1% dietary level. The hemograms of all animals were within the normal range. Histopathological examination of the tissues revealed no damage related to the ingestion of scandium chloride. Transient ocular irritation was observed and the chemical produced extensive scar formation when applied to abraded skin. Pharmacological studies indicated that the chemical had a depressant action on all systems studied and produced lethality by respiratory paralysis coupled with cardiovascular collapse. The lethal effects could not be counteracted by atropinization or epinephrine administration.

In his review of the chemistry of the rare earths, Moeller (1) pointed out that these elements had certain properties which would eventually lead to their industrial usage. However, our knowledge of the biological effects of one of this series, scandium, is almost nonexistent. Mines (2) reported that scandium chloride decreased systole and stopped the perfused frog heart ventricle in diastole. Washing gradually restored its contractility. In this action, scandium was weaker than both erbium and lanthanum. Ishiwara (3) found that scandium exerted an inhibiting effect on mouse carcinoma. Chargaff and Green (4) showed that scandium exhibited an antithrombic effect but showed no antithromboplastic effect. Grant and Kern (5) found that scandium chloride had little or no effect on the intact rabbit eye but produced a permanent opacification of the corneal stroma when the epithelial layer of the cornea had been removed. In an effort to increase our knowledge of the biological actions of scandium chloride, we have investigated its pharmacological and toxicological effects.

EXPERIMENTAL METHODS

The intraperitoneal LD_{50} was obtained with 258 male CF-1 mice and the oral LD_{50} with 130 male CF-1 mice. Chronic toxic effects of scandium chloride were determined by including 0.01, 0.1, and 1.0% of the compound in the diet and feeding it over a period of 90 days to three groups of CRW rats. Each group contained six males and six females. Observations were made every 2 weeks of the following: total erythrocytes, total leukocytes, differential cell count, platelets, hemoglobin, hematocrit, and body weight. Upon completion of the study, histopathological examination was made of the heart, lung, liver, kidney, spleen, pancreas, adrenal, and small intestine. The method of Draize, *et al.* (6), was used to study ocular and skin irritation in rabbits and intradermal irritation in guinea pigs. Three rabbits were used in the ocular studies. Each rabbit had one eye exposed to 0.1 ml. of a 1:1 aqueous scandium chloride while the other eye served as the control. Rabbit skin irritation studies used six animals according to the design of Draize, *et al.* (6). Three guinea pigs were used in the intradermal studies; the concentrations of scandium chloride were: 1:10 to $1:10^6$. Effects of the chemical on isolated guinea pig ileal strips bathed in Locke-Ringers solution were studied in a thermostatically regulated 25-ml. bath using the Trendelenburg method (7). Studies were also made on the isolated rabbit ileum in the presence of 2.5 mcg. of acetylcholine. Ten cats of both sexes, weighing 2.72–3.90. Kg. were anesthetized with 0.5 ml./Kg. of Dial-urethane intraperitoneally. A six channel Offner Dynagraph with Statham transducers was used to record carotid arterial pressure, respiration, nictitating membrane contraction, ECG Lead II, femoral arterial pressure, and femoral arterial flow. The latter was obtained with a 25-ml. Shipley-Wilson flowmeter (8). Preganglionic stimulation of the cervical sympathetic fibers and the contralateral vagus fibers was accomplished with a Grass model S-4 stimulator at 8V/10 sec. Two hours were allowed to elapse prior to beginning drug administration. Intravenous doses of the drugs used were: scandium chloride 0.5 to 20 mg./Kg.; epinephrine 5 mcg./Kg.; acetylcholine 5 mcg./Kg.; histamine 2 mcg./Kg.; and atropine 2 mg./Kg. All injections were made at a constant volume of 1 ml. Where appropriate, the results were analyzed statistically by the Litchfield-Wilcoxon method (9) or standard errors were calculated.

RESULTS

Acute Toxicity.—The symptoms of acute toxicity were immediate defecation, abdominal stretching, depressed respiration, tremor of the hind legs, and sedation. The first deaths occurred within 24 hours but the peak was not reached until 96 hours.

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Throughout the entire 7-day period of observation the animals were unthrifty. The intraperitoneal LD_{50}/7 days for scandium chloride was 755(741.7–768.6) mg./Kg. with a slope value of 1.06(0.99–1.13). The oral LD_{50}/7 days was 4.0(3.96–4.04) Gm./Kg. with a slope value of 1.03(1.0–1.06).

Chronic Toxicity.—Throughout the 12-week period of feeding the various levels of scandium chloride in the diet, the test animals did not appear to differ in general appearance from the controls. The growth curves (Fig. 1) indicate that, at the dietary levels of scandium chloride studied, there was no significant effect on growth except at the 1% level in male rats. However, at the conclusion of the experimental period even these animals were beginning to approach the control animals in growth. The hemogram of all the animals (Table I) indicated that the chemical had no significant effects on the hematological response of the animals. The changes in the various cells and hemoglobin were probably related to the normal growth pattern of the rats because they were within the ranges given for the rat by Gardner (10). Data on differential counts are not included in Table I because there were no significant differences between the control and treated groups and the data were equivalent to the normal distribution given by Gardner (10). At autopsy, the internal organs of all groups appeared normal; there were no outward signs of damage attributable to the ingestion of scandium chloride for 12 weeks. Furthermore, histopathological examination of the heart, lung, liver, kidney, spleen, pancreas, adrenal, and small intestine revealed no changes which could be related to the ingestion of scandium chloride at the dietary levels studied.

Ocular Irritation.—Direct application of 0.1 ml. of 1:1 scandium chloride solution to the eyes of three rabbits produced a slight translucency in-

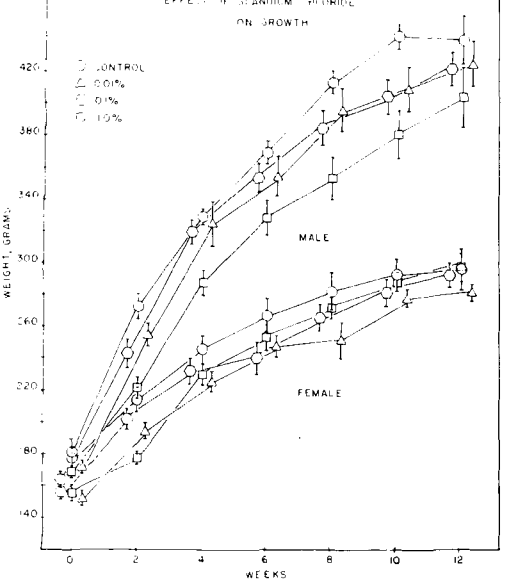

Fig. 1.—Response of male and female CRW rats to feeding various levels of scandium chloride in the diet for 90 days. Bars signify the standard errors. Each group contained six animals for each dosage level.

TABLE I.—HEMATOLOGICAL EFFECTS OF SCANDIUM CHLORIDE

Week		Erythrocytes, mm.^{3} × 10^6 0	Erythrocytes, mm.^{3} × 10^6 12	Leukocytes, mm.^{3} × 10^3 0	Leukocytes, mm.^{3} × 10^3 12	Hematocrit, Vol. % 0	Hematocrit, Vol. % 12	Hemoglobin, Gm. % 0	Hemoglobin, Gm. % 12	Platelets, mm.^{3} × 10^5 0	Platelets, mm.^{3} × 10^5 12
Control	♂ M ± SE[a]	6.38 ± 0.33	9.41 ± 0.20	16.88 ± 0.82	17.73 ± 1.92	41 ± 0.89	50 ± 1.00	12.1 ± 0.31	15.3 ± 0.35	7.35 ± 0.92	6.55 ± 0.37
	Range	4.72 – 7.92	8.70 – 10.50	12.9 – 20.0	11.2 – 26.7	39 – 46	47 – 56	11.3 – 13.5	13.7 – 16.9	4.96 – 11.20	5.52 – 8.88
	♀ M ± SE	7.10 ± 0.46	7.39 ± 0.43	15.44 ± 1.44	15.44 ± 1.69	43 ± 1.26	48 ± 0.71	12.7 ± 0.28	14.0 ± 0.26	6.99 ± 0.67	5.98 ± 0.35
	Range	5.92 – 9.46	5.35 – 8.75	10.2 – 20.5	8.5 – 21.9	38 – 50	45 – 51	11.4 – 13.8	12.8 – 15.1	4.84 – 9.68	4.88 – 7.44
Scandium	♂ M ± SE	6.71 ± 0.31	9.44 ± 0.38	15.42 ± 1.72	15.72 ± 1.97	41 ± 0.80	51 ± 0.56	12.5 ± 0.40	15.1 ± 0.15	7.37 ± 0.62	6.92 ± 0.44
0.01%	Range	6.04 – 7.78	8.29 – 10.42	11.5 – 22.4	10.2 – 22.6	39 – 44	49 – 53	11.4 – 14.1	14.5 – 15.6	5.20 – 9.28	6.16 – 9.04
	♀ M ± SE	6.69 ± 0.16	8.31 ± 0.44	16.23 ± 2.38	17.02 ± 3.06	44 ± 0.79	48 ± 1.17	12.0 ± 0.20	14.5 ± 0.38	8.12 ± 0.55	7.21 ± 0.39
	Range	6.22 – 7.14	6.97 – 9.72	8.9 – 24.8	9.1 – 28.3	41 – 46	45 – 53	11.4 – 12.5	13.5 – 16.1	6.28 – 9.44	5.36 – 8.0
Scandium	♂ M ± SE	6.27 ± 0.38	8.52 ± 0.38	12.15 ± 1.65	16.57 ± 0.74	41 ± 0.72	49 ± 0.67	11.2 ± 0.32	14.7 ± 0.34	7.34 ± 0.82	7.33 ± 0.41
0.1%	Range	5.18 – 7.78	7.50 – 10.0	7.7 – 18.7	14.3 – 19.5	38 – 43	47 – 51	10.2 – 12.1	13.7 – 16.1	4.84 – 10.52	6.40 – 8.88
	♀ M ± SE	6.41 ± 0.49	8.0 ± 0.30	15.67 ± 2.36	12.30 ± 0.97	42 ± 0.67	49 ± 0.31	12.0 ± 0.21	14.9 ± 0.24	8.70 ± 1.09	7.53 ± 0.31
	Range	4.76 – 8.02	6.96 – 8.93	10.2 – 24.1	8.9 – 14.7	40 – 44	48 – 50	11.5 – 13.0	14.2 – 15.6	5.92 – 12.04	6.56 – 8.40
Scandium	♂ M ± SE	5.14 ± 0.29	9.61 ± 0.55	15.68 ± 1.63	14.60 ± 0.82	41 ± 1.21	50 ± 0.62	11.4 ± 0.44	14.5 ± 0.35	8.20 ± 0.74	7.49 ± 0.19
1.0%	Range	4.26 – 6.22	7.15 – 11.05	11.1 – 21.1	12.0 – 16.9	38 – 45	48 – 52	10.0 – 12.7	13.6 – 15.7	6.44 – 11.40	6.96 – 8.16
	♀ M ± SE	6.14 ± 0.51	8.10 ± 0.24	14.23 ± 1.50	12.10 ± 1.19	41 ± 0.75	49 ± 1.03	11.4 ± 0.22	14.2 ± 0.24	7.49 ± 0.59	7.60 ± 0.16
	Range	4.22 – 7.78	7.60 – 9.21	9.4 – 19.6	7.5 – 15.0	39 – 44	46 – 51	10.7 – 12.3	13.7 – 15.3	5.56 – 9.0	7.12 – 8.24

[a] M ± SE = mean ± standard error—based upon six animals per group per dosage level. Based on determinations done every two weeks.

volving less than half of the cornea with a loss of reaction to light by the iris. This corneal reaction completely cleared up within 48 hours and no residual damage was observed. The 24-hour irritation indices for the cornea and iris were 20 and 5, respectively, indicating a transient medium degree of irritation to these structures. Within 1 hour, the conjunctiva was a diffuse beefy red, chemosis had produced a swelling of the eyelids which kept them more than half closed, and there was a discharge which moistened the lids and a considerable area around the eyes. The irritation index reached the maximum score of 20 and small ulcers appeared on the conjunctiva within 24 hours. Healing progressed satisfactorily. All evidence of damage was absent after 96 hours.

Skin Irritation.—Direct application of 0.5 Gm. of crystalline scandium chloride to intact rabbit skin produced no reaction throughout the entire 14-day observation period. There was a very severe reaction on abraded rabbit skin with a maximum irritation index of 8 at 24 hours. No changes in irritation index occurred up to 14 days. However, healing with scar formation was observed at 45 days. The scars were 25 to 30 mm. in diameter. Intradermal injection of scandium chloride at concentrations of 1:10 and 1:100 produced necrosis within 1 hour and an irritation index (erythema plus edema) of 8 which persisted for 7 days. Healing occurred at 14 days with epilation and scar formation in the injected area. At the concentration of 1:1000, the only difference in response was the absence of the early necrosis. The concentrations of $1:10^4$ to $1:10^6$ gave an irritation index of 2 at 24 hours, and complete healing w.thout scar formation occurred at 72 hours.

Effects on Isolated Ileum.—Scandium chloride, dosage range of 10 to 30 mg., produced an increasing depression of intestinal tonus and contractility terminating in complete paralysis of the rabbit ileum. Repeated washing of the five ileal strips did not restore contractility. This depressant effect counteracted the spasmogenic action of acetylcholine. The antispasmodic ED_{50} of scandium chloride was 15.5(8.0–30.2) mg. with a slope value of 2.15(0.65–7.1). Such depressant action also occurred with the Trendelenburg guinea pig preparation where the ED_{50} figures for blocking both the circular and longitudinal muscular contractions, respectively, were: 11.7(8.8–15.3) mg. and 5.6(2.8–11.2) mg. The muscular contractions of this preparation are related to pressure stimulation of the enteric ganglia, thus it would seem that scandium has ganglionic blocking properties. However, experiments with the superior cervical ganglion preparation of the cat indicated that this was unlikely.

Pharmacological Effect.—Within the dosage range of 0.5 to 2 mg./Kg., scandium chloride produced no observable pharmacological effects in the cat. At a dose of 5 mg./Kg. there was a transient loss of blood pressure varying from 15 to 70 mm. Hg and a permanent loss of 10 to 20 mm. Hg from the predrug level. A similar reaction occurred with femoral arterial pressure and blood flow decreased slightly. At this dose the electrocardiogram showed a decrease in the height of the entire complex followed by a high takeoff of the P-wave and a return to normal rhythm and size. In four of the five animals, complete cardiovascular collapse occurred at 10 mg./Kg. and was followed by respiratory paralysis. A similar effect was observed in the other animal at 20 mg./Kg. Prior to exitus, the respiratory rate was not affected. The terminal electrocardiographic changes included a decrease in the entire complex, P-wave absent, T-wave inverted, transient ventricular fibrillation, increased interval between the QRS and the T-wave, a 2 to 1 heart block, inverted QRS complex, and an increased T-wave. Within the dosage range investigated, scandium chloride did not affect the pharmacological responses to acetylcholine, epinephrine, histamine, or vagal stimulation. Furthermore, it had no effect on transmission in the superior cervical ganglion or on contraction of the nictitating membrane. None of the effects of scandium chloride could be counteracted or modified by atropine and the cardiovascular collapse could not be counteracted by epinephrine.

DISCUSSION

From a toxicological viewpoint scandium chloride is less toxic acutely or chronically than gadolinium or samarium (11) or niobium (12) or hafnium (13). However, its detrimental effects on ocular tissues and skin are only exceeded by niobium and hafnium (12, 13). The depressant effects observed by Mines (2) on the isolated frog heart appear to be quite similar to those we observed on the cat heart *in situ*. In general the overall pharmacological effects of scandium chloride on the various body systems studied were of a depressant nature. The mode of death, respiratory paralysis coupled with cardiovascular collapse, was almost identical with what has been observed for the other chemicals in the rare earth series (11–13). Upon the basis of the present investigation, it would appear that scandium chloride exerts its greatest toxicity locally, and proper application of good industrial hygiene practices; respirators, protective clothing, etc.; would prevent acute or chronic exposure.

REFERENCES

(1) Moeller, T., in "Rare Earths in Biochemical and Medical Research," edited by G. C. Kyker and E. R. Anderson, Oak Ridge Institute of Nuclear Studies, No. 12, pp. 1–11 (1956).
(2) Mines, G. R., *J. Physiol.*, **42**, 309(1911).
(3) Ishiwara, F., *Ber. Ges. Physiol. Exptl. Pharmakol.*, **49**, 615(1928).
(4) Chargaff, E., and Green, C., *J. Biol. Chem.*, **173**, 263 (1948).
(5) Grant, W. M., and Kern, H. L., "Rare Earths in Biochemical and Medical Research," edited by G. C. Kyker and E. R. Anderson, Oak Ridge Institute of Nuclear Studies, No. 12, pp. 346–355 (1956).
(6) Draize, J. H., Woodward, G., and Calvery, H. O., *J. Pharmacol. Exptl. Therap.*, **82**, 377(1944).
(7) Trendelenburg, P., *Arch. Exptl. Pathol. Pharmakol.*, **81**, 55(1917).
(8) Shipley, R. E., and Wilson, C., *Proc. Soc. Exptl. Biol. Med.*, **78**, 724(1951).
(9) Litchfield, J. T., Jr., and Wilcoxon, F., *J. Pharmacol. Exptl. Therap.*, **96**, 99(1949).
(10) Gardner, M. V., *J. Franklin Inst.*, **243**, 77(1947).
(11) Haley, T. J., Raymond, K., Komesu, N., and Upham, H. C., *Brit. J. Pharmacol.*, **17**, 526(1961).
(12) Haley, T. J., Komesu, N., and Raymond, K., *Toxicol. Appl. Pharmacol.*, in press (1962).
(13) Haley, T. J., Raymond, K., Komesu, N., and Upham, H. C., *ibid.*, **4**, 238(1962).