*Brit. J. Pharmacol.* (1961), 17, 526–532.

# TOXICOLOGICAL AND PHARMACOLOGICAL EFFECTS OF GADOLINIUM AND SAMARIUM CHLORIDES

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(*Received September* 13, 1961)

A study has been made of the toxicology and pharmacology of gadolinium and samarium chlorides. The symptoms of acute toxicity following intraperitoneal injection are described. The chronic oral ingestion of both chemicals for 12 weeks produced no effects on growth or the blood picture, and only the male rats receiving gadolinium chloride showed liver damage. The pharmacological responses to both chemicals were mainly depressant on all systems studied, and death was associated with cardiovascular collapse coupled with respiratory paralysis. The greatest damage seen was on abraded skin, where non-healing ulcers were produced by both chemicals, whereas irritation of intact skin and ocular tissues was only transient in nature.

In the past many of the rare earth lanthanons were difficult to obtain, because methods were not available for their economical extraction from ores. Recent technological advances have remedied this situation, and many of the elements in this group are now produced in quantity (Spiller, 1960). However, little is known of their biological effects. Niccolini (1931) investigated the pharmacological effects of samarium on several systems. Durbin, Williams, Gee, Newman & Hamilton (1956) reported on the metabolism of the various lanthanons including $Sm^{153}$ and $Gd^{159}$. They found that both of these elements concentrated in the liver and kidney and eventually were laid down in the skeleton although not to the same extent as the heavier members of the lanthanium group. The minimal lethal dose of $SmCl_3$ for rats was 2 g/kg by subcutaneous injection (Steidle & Durr, 1929; Niccolini, 1931) and for guinea-pigs 0.75 to 1.0 g/kg (Niccolini, 1931) or about 0.5 g/kg (Steidle & Durr, 1929). Kyker & Cress (1957) found gadolinium non-toxic in doses of 3.5 to 60 mg/kg of Gd by intravenous injection. Snyder, Cress & Kyker (1959) showed that samarium but not gadolinium produced fatty infiltration of the liver of rats receiving one intravenous injection of the chemical. In view of the fact that even the above information was not complete and because the purity of the salts used was not known, we have reinvestigated the toxicology and pharmacology of gadolinium and samarium with salts of known purity.

## METHODS

The purity of the salts used was gadolinium chloride, 98%, and samarium chloride, 99%. The intraperitoneal LD50 figures were determined on 240 male CF1 mice. The chronic toxicities of gadolinium and samarium chlorides were determined by including 0.01, 0.1 and 1% of either

compound in the diet and feeding it over a period of 12 weeks to 3 groups of rats for each compound. Each group contained 6 males and 6 females. Observations were made of the following: total erythrocytes, total leucocytes, differential cell count, haemoglobin, haematocrit and body weight. At the conclusion of the study the following tissues were examined histologically: heart, lung, liver, kidney, pancreas, spleen, adrenal and small intestine. The method of Draize, Woodward & Calvery (1944) was used to study ocular and skin irritation in rabbits and intradermal irritation in guinea-pigs. Three rabbits were used for each compound in the ocular studies; each rabbit had one eye exposed to 1 mg of crystals of gadolinium chloride or samarium chloride, while the other eye served as a control. In the rabbit skin irritation tests 6 animals were employed. Five guinea-pigs were used for each compound in the intradermal studies, and the concentrations of the chlorides were 1:10 to $1:10^6$.

Effects of gadolinium and samarium chlorides on isolated strips of guinea-pig ileum bathed in Locke solution were observed in a thermostatically regulated 25 ml. bath using the Trendelenburg method (1917). Experiments were also made on the isolated rabbit ileum in the presence of 0.5 $\mu$g of nicotine or 2.5 $\mu$g of acetylcholine.

Twenty cats of both sexes, weighing 1.79 to 4.08 kg, were anaesthetized 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, electrocardiogram lead II, femoral arterial pressure and femoral arterial flow. The arterial flow was measured with a 25 ml. Shipley–Wilson flowmeter (1951). Preganglionic stimulation of the cervical sympathetic fibres and the contralateral vagus fibres was carried out with a Grass model S-4 stimulator at 8 V/10 sec. Two hours were allowed to elapse before drug administration. Intravenous doses of the drugs used were: gadolinium chloride 0.5 to 50 mg/kg; samarium chloride 0.5 to 40 mg/kg; epinephrine 5 $\mu$g/kg; acetylcholine 5 $\mu$g/kg; histamine 0.5 $\mu$g/kg; and atropine 2 mg/kg. The gadolinium and samarium chlorides were injected at a constant volume of 1 ml./dose. Where appropriate, the results were analysed statistically by the Litchfield–Wilcoxon method (1949) or standard errors were determined.

## RESULTS

*Acute toxicity.* The symptoms of acute toxicity for both gadolinium and samarium chloride were decreased respiration, lethargy, abdominal cramps and diarrhoea. The abdominal irritation forced the animals to crawl on their abdomens in order to move about the cage. Samarium also produced muscular spasms. The first deaths did not occur until 24 hr after injection. The peak mortality was reached between the fourth and fifth day. The intraperitoneal LD50/7 days was gadolinium chloride 550 (495.5 to 610.5) mg/kg and samarium chloride 585 (508.7 to 672.7) mg/kg and the respective slope values were 1.35 (1.08 to 1.69) and 1.36 (1.08 to 1.71). Oral administration of doses up to 2 g/kg produced no lethality, and as it was impossible to obtain more concentrated solutions further any evaluation of oral toxicity was not possible.

*Chronic toxicity.* Neither gadolinium nor samarium chloride had any apparent influence on the growth of rats of either sex throughout the feeding period of 12 weeks. Fig. 1 shows the growth curves for gadolinium chloride, and those for samarium are almost identical. Furthermore, both substances produced no significant effects on the haematology of the animals (see Table 1). The increases in the cells and haemoglobin between the beginning and the end of the experiment were probably related to normal growth pattern of the animals and not to any influence of the chemicals, because the control group did not differ significantly from the medicated groups. It should alsc be noted that all of the values in Table 1

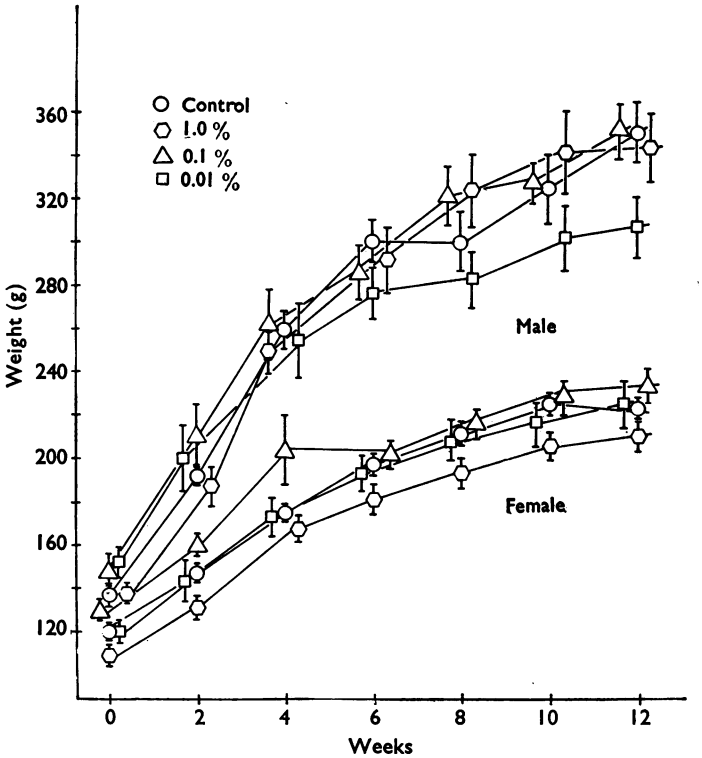


Fig. 1. Effects of various concentrations in the diet (0.01 to 1.0% w/w) of gadolinium chloride on growth in rats. The vertical lines represent the standard errors.

were within the ranges given for the rat by Gardner (1947). The data on the differential counts are not given in Table 1, because there was no significant difference between the medicated and control groups. At autopsy the internal organs of all groups of rats appeared normal and there were no outward signs of damage from ingestion of either gadolinium or samarium chlorides for 12 weeks. Gadolinium chloride produced perinuclear vacuolization of the parenchymal cells of the liver and a coarse granularity of their cytoplasm. Although these effects were not regularly observed at the 0.01 and 0.1% levels in the diet, all 6 male rats showed these changes at the 1% level. These histological effects were absent in the females at all levels. No changes were observed in the other tissues studied. Samarium chloride at all the concentrations used in the diet produced no histopathological changes in any of the organs studied.

*Ocular irritation.* The introduction of 1 mg of either gadolinium or samarium chlorides into the conjunctival sac of the eyes of rabbits resulted in an immediate increase in the rate of blinking and a redness of the palpebral conjunctiva within 1 hr. After 24 hr there was no evidence of corneal or iris damage, conjunctival irritation, chemosis or increased lacrimal discharge. Apparently the natural buffering capacity of the lacrimal fluid was sufficient to counteract the nascent hydrochloric acid released when the gadolinium or samarium chlorides dissolved in the tears.

TABLE 1

HAEMATOLOGICAL EFFECTS OF GADOLINIUM AND SAMARIUM CHLORIDES IN THE RAT

| | | | Erythrocytes ($mm^3 \times 10^6$) | | Leucocytes ($mm^3 \times 10^3$) | | Haematocrit (vol. %) | | Haemoglobin (g %) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Weeks: | 0 | 12 | 0 | 12 | 0 | 12 | 0 | 12 |
| Control | Male | Mean±s.e. | 6·20±0·25 | 10·38±0·31 | 15·00±0·47 | 11·60±1·39 | 47±1·79 | 52±1·02 | 12·4±0·41 | 15·2±0·25 |
| | | Range | 5·40–6·95 | 9·59–11·29 | 10·2–19·45 | 7·25–16·05 | 40–53 | 47–54 | 11·6–14·3 | 14·4–15·9 |
| | Female | Mean±s.e. | 6·51±0·32 | 8·99±0·38 | 13·20±0·58 | 18·20±2·02 | 47±1·07 | 50±0·80 | 12·6±0·25 | 13·9±0·24 |
| | | Range | 5·08–8·35 | 7·67–11·00 | 7·00–18·60 | 10·6–30·80 | 43–54 | 47–54 | 11·3–13·6 | 12·5–15·2 |
| Gadolinium 0·01% | Male | Mean±s.e. | 6·12±0·18 | 9·89±0·52 | 13·70±2·01 | 13·70±2·56 | 43±1·03 | 51±1·65 | 12·5±0·18 | 15·0±0·53 |
| | | Range | 5·60–6·70 | 7·87–11·70 | 8·25–14·85 | 12·60–24·00 | 39–46 | 45–57 | 11·8–13·0 | 13·5–16·6 |
| | Female | Mean±s.e. | 6·27±0·31 | 9·46±0·55 | 10·35±0·82 | 13·40±1·22 | 48±1·06 | 51±1·40 | 13·5±0·40 | 15·4±0·34 |
| | | Range | 4·92–7·12 | 7·15–10·55 | 7·70–12·95 | 9·65–17·25 | 43–50 | 44–53 | 12·8–15·3 | 14·6–16·6 |
| Gadolinium 0.1% | Male | Mean±s.e. | 4·99±0·36 | 10·41±0·46 | 10·70±1·33 | 15·05±3·30 | 42±0·89 | 53±0·87 | 11·6±0·38 | 16·0±0·28 |
| | | Range | 3·20–5·52 | 9·16–11·63 | 5·80–14·60 | 7·60–26·00 | 39–45 | 50–55 | 10·4–13·2 | 15·1–16·7 |
| | Female | Mean±s.e. | 5·79±0·19 | 8·67±0·34 | 8·90±0·74 | 13·30±1·28 | 46±1·28 | 49±0·88 | 13·0±0·16 | 15·1±0·35 |
| | | Range | 5·00–6·40 | 7·59–10·05 | 7·05–11·20 | 9·45–18·80 | 42–49 | 46–50 | 12·6–13·5 | 13·4–15·7 |
| Gadolinium 1.0% | Male | Mean±s.e. | 6·45±0·51 | 10·61±0·48 | 10·10±0·75 | 13·20±1·19 | 46±1·66 | 54±0·71 | 12·4±0·40 | 15·8±0·25 |
| | | Range | 5·08–7·95 | 9·22–11·95 | 8·40–12·60 | 9·80–16·80 | 40–50 | 51–55 | 10·8–13·7 | 14·6–16·2 |
| | Female | Mean±s.e. | 5·41±0·22 | 9·51±0·45 | 13·25±2·80 | 19·30±2·25 | 47±1·21 | 52±1·06 | 12·6±0·43 | 15·3±0·29 |
| | | Range | 4·80–6·32 | 8·45–11·17 | 4·20–19·70 | 12·40–26·45 | 42–50 | 48–55 | 10·7–13·7 | 14·0–16·0 |
| Samarium 0.01% | Male | Mean±s.e. | 6·89±0·18 | 11·03±0·30 | 9·70±1·40 | 9·80±1·01 | 45±0·77 | 56±1·47 | 13·0±0·14 | 17·1±0·37 |
| | | Range | 6·20–7·45 | 10·23–12·08 | 5·00–13·80 | 6·25–13·00 | 43–47 | 53–63 | 12·7–13·6 | 16·0–18·6 |
| | Female | Mean±s.e. | 6·80±0·23 | 9·55±0·28 | 11·05±0·57 | 11·30±0·92 | 49±1·90 | 50±0·80 | 13·2±0·31 | 15·0±0·33 |
| | | Range | 6·25–7·80 | 8·39–10·19 | 8·65–12·40 | 9·00–14·15 | 45–58 | 47–53 | 12·5–14·2 | 13·9–16·2 |
| Samarium 0.1% | Male | Mean±s.e. | 6·53±0·29 | 9·89±0·17 | 13·20±1·18 | 10·60±1·25 | 47±1·00 | 51±0·48 | 12·8±0·25 | 14·7±0·20 |
| | | Range | 5·90–7·75 | 9·35–10·48 | 10·10–16·75 | 7·40–15·0 | 43–49 | 49–52 | 12·2–13·9 | 14·3–15·6 |
| | Female | Mean±s.e. | 7·06±0·29 | 9·21±0·30 | 12·90±0·62 | 15·30±2·43 | 47±1·49 | 50±0·84 | 12·4±0·95 | 14·7±0·30 |
| | | Range | 5·75–7·80 | 8·59–10·22 | 10·80–14·85 | 7·40–23·0 | 41–52 | 46–52 | 9·2–14·9 | 13·5–15·6 |
| Samarium 1.0% | Male | Mean±s.e. | 7·58±0·76 | 10·79±0·39 | 10·50±1·17 | 12·60±0·71 | 45±0·86 | 54±2·21 | 11·8±0·41 | 15·7±0·73 |
| | | Range | 5·95–10·90 | 9·57–12·21 | 6·05–13·05 | 9·80–14·65 | 43–48 | 47–60 | 10·5–13·1 | 12·9–18·0 |
| | Female | Mean±s.e. | 6·47±0·45 | 10·13±1·23 | 9·90±1·47 | 12·50±1·46 | 47±1·03 | 50±1·54 | 12·4±0·31 | 14·5±0·41 |
| | | Range | 5·45–8·05 | 9·08–16·59 | 7·45–16·10 | 7·65–17·80 | 44–51 | 47–57 | 11·0–13·0 | 13·5–16·4 |

*Skin irritation.* Direct application of gadolinium and samarium chloride crystals to intact rabbit skin produced no irritation within 24 hr and no delayed reaction after 72 hr. There was a very severe reaction to both chemicals by abraded skin resulting in the maximum irritation index of 8 within 24 hr. No change was observed within 72 hr, and within 7 days perforating ulcers 25 to 30 mm in diameter developed with penetration through the skin to the underlying muscle layers. Inasmuch as healing did not occur, the animals were killed at 14 days. The differences in response between intact and abraded skin may be related to the liberation of nascent hydrochloric acid by tissue fluids. Intradermal administration of gadolinium or samarium chlorides in guinea-pigs at concentrations of $1 \times 10^4$ to $1 \times 10^6$ gave 24 hr erythema indices of 1 (Draize *et al.*, 1944) and complete healing without scar formation within 7 days. Erythema, oedema and necrosis were observed 1 hr after injection of a 1 : 10 concentration of either chemical. The 24 hr irritation indices, erythema plus oedema formation, for concentrations of 1 : 10, 1 : 100 and 1 : 1,000 of both gadolinium and samarium chlorides were 8, 6 and 4. The three concentrations produced eschars whose diameters were 14, 10 and 6 mm for gadolinium and 12, 10 and 7 mm for samarium. Epilation of the area and scar formation occurred at 7 days with the 1 : 1,000 concentration of either chemical. At concentrations of 1 : 10 and 1 : 100, similar effects were observed after 14 days, but complete healing required 4 weeks. Such effects are probably related to the acidic nature of both compounds.

*Effects on isolated intestine.* An increasing depression of tonus and contractility of the rabbit ileum was produced by both gadolinium and samarium chlorides throughout the dosage range of 25 to 400 mg. When paralysis occurred at the highest dose, contractility of the intestine could not be restored by repeated washing. The spasmogenic effects of acetylcholine and nicotine were counteracted by the depressant action of both the rare earth elements. The antispasmodic ED50 figures for gadolinium and samarium chlorides against acetylcholine were 157 (74.8 to 329.7) mg and 187 (85 to 411.4) mg respectively and against nicotine were 360 (326.8 to 396.5) mg and 248 (138.6 to 443.9) mg. Similar depressant effects were observed with the Trendelenburg guinea-pig preparation where the ED50 figures for blocking both the circular and longitudinal muscular contractions respectively were: gadolinium 3.9 (2.17 to 7.02) mg and 5.8 (3.31 to 10.15) mg ; samarium 2.4 (1.21 to 4.75) mg and 2.7 (1.56 to 4.51) mg. Because the muscular contractions of this preparation are induced by pressure stimulation of the enteric ganglia, it would appear that both gadolinium and samarium may produce intestinal depression by ganglionic blockade. However, experiments with the superior ganglion preparation of the cat indicated that this was unlikely.

*Pharmacological effects.* No observable pharmacological effects were produced in the anaesthetized cat by the injection of 5 to 10 mg/kg of gadolinium chloride or 5 to 15 mg/kg of samarium chloride. Administration of 20 to 25 mg/kg of either chemical produced transient hypotension of 15 to 60 mm Hg in both the carotid and femoral blood pressure, coupled with a decrease in femoral blood flow ; the respiratory rate was unaffected. The dosage causing complete cardiovascular collapse was variable ; gadolinium 30 to 50 mg/kg and samarium 35 to 40 mg/kg.

The terminal electrocardiographic changes included a transient increase in the height of the P-wave until it equalled the QRS complex, decreased height of the P-wave coupled with an increased T-wave, absence of the P-wave and QRS complex, inverted T-wave, notched T-wave, high take-off of the T-wave, 2 to 1 or 3 to 1 heart block and finally ventricular fibrillation. Within the dosage ranges studied, neither gadolinium nor samarium chlorides had an effect on the physiological responses to acetylcholine, epinephrine, histamine or vagal stimulation. Furthermore, neither chemical had any effect on transmission in the superior cervical ganglion or on contraction of the nictitating membrane. The cardiovascular effects of gadolinium and samarium chlorides could not be counteracted by epinephrine or atropine.

## DISCUSSION

The present investigation of the toxicology and pharmacology of gadolinium and samarium confirms previous reports (Steidle & Durr, 1929 ; Niccolini, 1931 ; Kyker & Cress, 1957) and extends our knowledge of the biological effects of these chemicals. The failure to observe fatty infiltration of the liver following prolonged ingestion of samarium may have been related to rapid conversion of the chloride to the hydroxide and/or oxide and a failure of absorption of samarium in this form. Such an explanation appears likely because both Durbin *et al.* (1956) and Snyder *et al.* (1959) gave the chemicals by injection, thus by-passing the gastrointestinal tract. In both instances the substances were able to reach the liver and be excreted by the kidneys. The situation with gadolinium was different ; Snyder *et al.* (1959) reported no fatty infiltration of the liver, whereas we observed perinuclear vacuolization of the parenchymal cells and a coarse granularity of their cytoplasm. Although this histological change did not appear to affect the health of the animals since their growth and haematology were unimpaired, it is possible that more prolonged exposure to gadolinium chloride might cause detrimental changes. It is of interest that the CFN strain of rats used by Snyder *et al.* (1959) and also by us showed two different responses which appeared to be sex-linked, fatty livers being more consistent in females and parenchymal cell damage more consistent in males. The local effects on abraded skin present the greatest hazard in handling these chemicals, but such effects can be prevented by good industrial hygiene practice.

These studies were supported by Contract AT(04-1)GEN-12 between the Atomic Energy Commission and the University of California.

## REFERENCES

DRAIZE, J. H., WOODWARD, G. & CALVERY, H. O. (1944). Methods for the study of irritation and toxicity of substances applied topically to the skin and mucous membranes. *J. Pharmacol. exp. Ther.*, **82**, 377–390.

DURBIN, P. W., WILLIAMS, M. H., GEE, M., NEWMAN, R. H. & HAMILTON, J. G. (1956). Metabolism of the lanthanons in the rat. *Proc. Soc. exp. Biol. (N.Y.)*, **91**, 78–85.

GARDNER, M. V. (1947). The blood picture of normal laboratory animals. A review of the literature 1936–1946. *J. Franklin Inst.*, **243**, 77–86.

KYKER, G. C. & CRESS, E. A. (1957). Acute toxicity of yttrium, lanthanum, and other rare earths. *A.M.A. Arch. Ind. Health*, **16**, 475–479.

LITCHFIELD, J. T., JR. & WILCOXON, F. (1949). A simplified method of evaluating dose-effect experiments. *J. Pharmacol. exp. Ther.*, **96**, 99–113.

NICCOLINI, P. (1931). Contributo allo studio farmacologico delle terre rare-il samario. *Arch. int. Pharmacodyn.*, **40**, 247–291.

SHIPLEY, R. E. & WILSON, C. (1951). An improved recording rotameter. *Proc. Soc. exp. Biol. (N.Y.)*, **78**, 724–728.

SNYDER, F., CRESS, E. A. & KYKER, G. C. (1959). Liver lipid response to intravenous rare earths in rats. *J. Lipid Research*, **1**, 125–131.

SPILLER, R. (1960). The uses of rare earth metals. *Atom Industry*, **9**, 13.

STEIDLE, H. & DURR, H. (1929). Beitrage zur Pharmakologie der seltenen Erdmetalle. III, Über das Samarium. *Arch. exp. Path. Pharmak.*, **145**, 19–23.

TRENDELENBURG, P. (1917). Physiologische und pharmakologische Versuche über die Dunndarm-peristaltik. *Arch. exp. Path. Pharmak.*, **81**, 55–129.