Toxicology of the Iodophor, Imidecyl Iodine

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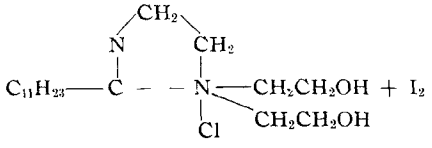
The iodophor imidecyl iodine is relatively nontoxic in rats, guinea pigs, rabbits, and dogs. In rats, calculated oral LD_{50} for males was 14.0 ± 2.1 mg./Kg., and for females 11.0 ± 1.5 mg./Kg. Dermal, eye, skin, and chronic toxicity studies were essentially negative. Urinary bladder studies in rabbits terminated fatally in two animals given undiluted and 1:2 dilutions in water. Dilutions of from 1:10 to 1:64 were progressively decreasing local irritants. Microscopic lesions in LD_{50} studies included pulmonary emphysema, ascites, distended stomach, hyperemia, and parenchymal damage in the liver and kidneys. Lesions in rabbits were compatible with shock. Lesions in chronic studies were mainly mild kidney damage. Three dogs fed imidecyl iodine for 3 to 5 months were unaffected.

FOR MANY YEARS, iodine has been used as a topical germicide and antiseptic. Although it is highly effective against fungi, bacteria, and viruses, it also has some detrimental attributes in the elemental form (1). It is irritating to body tissues and has objectionable odor and staining properties, and thus has given way to other antiseptics with less offensive side effects.

The combination of iodine with certain detergents greatly reduces objectionable side effects while retaining most of the desirable qualities of iodine (2). One such preparation, the iodophor imidecyl iodine[1] is a germicidally effective combination of iodine with an amphoteric detergent possessing the approximate structural formula:



There appears to be a positive chemical interaction between the detergent and the elemental iodine which results in a nearly complete loss of the caustic, corrosive, staining, and physically unstable properties of the halogen. The toxicity of this compound, however, has not been completely investigated.

This paper deals with the toxicological properties of imidecyl iodine and its effect upon various tissues in several species under various conditions and routes of administration. Specifically the studies involve determination of the LD_{50} in rats, dermal toxicity in rats, intradermal sensitivity reactions in guinea pigs, toxicity to ocular tissues of adult and newborn rabbits, toxicity when instilled into the urinary bladder of adult rabbits, and chronic toxicity feeding trials in dogs.

METHODS

LD_{50} in Rats—The oral LD_{50} was determined for each sex of adult Wistar rats in good physical condition. The animals were starved for 24 hr. and then given graduated solutions of imidecyl iodine *via* stomach tube. One hour after receiving the drug, the animals were allowed food and water *ad libitum*. Controls were run with each group and surviving animals closely observed for 14 days. LD_{50} values were calculated by the method of Reed and Muench (3). Fatalities were examined postmortem and outstanding lesions were noted. Results are shown in Table I.

TABLE I—ORAL LD_{50} OF IMIDECYL IODINE

Species and Sex	Dose, ml./Kg.	Observed Deaths	Calcd. LD_{50}, ml./Kg.
Rat, male	4.0	0/5	14.0 ± 2.1
	10.0	1/5	
	12.5	2/5	
	15.0	3/5	
	25.0	5/5	
Rat, female	4.0	0/5	11.0 ± 1.5
	10.0	2/5	
	15.0	4/5	
	25.0	5/5	

Acute Dermal Toxicity—The abdomens and backs of five Wistar rats of both sexes were shaved and the skin abraded. Specially fitted rubber sleeves were placed over the lesions to prevent the loss of material from the skin areas being tested. Five milliliters of imidecyl iodine in various concentrations, *e.g.*, undiluted, 1:5, and 1:10, was placed under the sleeves, and 5 ml. of saline applied in the same manner served as the control. The animals were observed at 1, 4, 24, and 48-hr. intervals after the application for signs of edema, erythema, vesiculation, and other signs of irritation.

Guinea Pig Sensitization—Five adult female guinea pigs were used to determine sensitivity. Concentrations of undiluted, 1:10, and 1:15 of imidecyl iodine in distilled water were injected intradermally. One animal was kept as control. Each animal received 0.05 ml. of imidecyl iodine intradermally as the first dose, followed by a dose of 0.125 ml. daily for 10 days. The sensitizing injection (0.05 ml.) was given 10 days after the last dose.

Eye Toxicity—*Adult Rabbits*—Twelve adult male domestic rabbits were used to determine if local eye irritation was produced by imidecyl iodine. Four strengths of the drug were employed, *e.g.*, undiluted, 1:10, 1:15, 1:25. One instillation of 0.3 ml. was made in the left eye; the right eye received 0.3 ml. of normal saline and served as control. The corneas, irises, and conjunctivae of each animal were observed for erythema, vesiculation, edema, or other signs of irritation at 1 hr., 24 hr., 96 hr., and 168 hr. after instillation. The degree of toxicity was evaluated by the method of Draize *et al.* (4).

Newborn Rabbits—Three drops of 1:64 dilution of

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[1] Amphodyne (pat. pend.), Kapson Laboratories, Newport, Oreg.

TABLE II—ADULT RABBIT EYE TOXICITY

Concn. of Imidecyl Iodine	Area of the Eye	Rabbit 1					Rabbit 2					Rabbit 3				
		Hr. After Imidecyl Iodine Application														
		1	24	48	96	168	1	24	48	96	168	1	24	48	96	168
Undiluted	Cornea	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Iris	5	2	0	0	0	5	1	0	0	0	4	3	0	0	0
	Conjunctiva	4	3	1	0	0	4	3	1	0	0	5	5	1	0	0
1:10	Cornea	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Iris	5	2	0	0	0	5	1	0	0	0	3	3	1	0	0
	Conjunctiva	2	1	0	0	0	2	0	0	0	0	5	5	5	0	0
1:15	Cornea	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Iris	0	0	0	0	0	3	2	0	0	0	1	1	0	0	0
	Conjunctiva	2	0	0	0	0	5	5	2	0	0	4	3	0	0	0
1:25	Cornea	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Iris	0	0	0	0	0	1	2	0	0	0	2	2	0	0	0
	Conjunctiva	0	1	0	0	0	4	4	0	0	0	4	4	1	0	0

imidecyl iodine was instilled in the left eye of five newborn rabbits (7–10 days old) four times daily for 5 days. The right eye served as a control. The corneas, irises, and conjunctivae were observed for erythema, vesiculation, edema, and other signs of irritation during the days of administration and daily thereafter for 2 months. The degree of toxicity was evaluated by the method of Draize *et al.* (4).

Rabbit Bladder Toxicity—Fifteen milliliter solutions of the following strengths of imidecyl iodine, *e.g.*, undiluted, 1:2, 1:10, 1:20, and 1:40 were each used in two animals and a dilution of 1:64 was used in four animals and of 1:128 in two animals. In each case the solutions were placed in an empty bladder of male and female adult domestic rabbits through a urethral catheter. The solutions were kept in the bladder for 30 min., after which the bladder was evacuated by catheter if urination was not spontaneous. Three animals given equal volumes of saline were used as controls. Each animal received three treatments at intervals of 24 hr., and 24 hr. after the last treatment, was killed and examined grossly and microscopically for abnormalities.

Chronic Toxicity—A group of three mature male dogs maintained on a basic diet of Purina laboratory chow (Ralston-Purina, St. Louis, Mo.) were given 1:15 dilutions of imidecyl iodine four times weekly. Dosage level was based on extrapolation of the calculated LD_{50} for rats. During the course of this experiment, the animals were examined daily for appearance, behavior, weight gain, and food consumption (5). After 90 days, one animal was sacrificed. At autopsy the entire carcass was examined grossly and the heart, lung, liver, kidney, spleen, and brain were removed and weighed, and portions of these organs were prepared for histological examination. The two other animals were sacrificed and examined in the same way at the end of 5 months.

RESULTS

The median lethality (LD_{50}) of imidecyl iodine for rats is given in Table I. The deaths were usually very rapid; nearly all fatalities were found within 18 hr. after dosage. No deaths occurred in treated animals after the ninth day. Prior to death, the rats showed depression, piloerection, and a crouched attitude indicative of abdominal pain. Immediately prior to death, each animal went into mild convulsions and regurgitated a small amount of brownish material. The survivors were lethargic for periods of 1 to 3 days after administration of the drug.

On postmortem the viscera contained a fairly uniform pattern of lesions which included mild thoracic and abdominal ascites, pulmonary emphysema, and petchiation, and grossly distended stomachs filled with a mixture of gas, food, and a dark greenish-brown fluid. Other lesions included gassy distention of the intestines, cloudy swelling and congestion of the liver, engorgement of the myocardial vessels, hyperemia, and tubule damage in the kidneys. Scattered and insignificant damage was found in other organs. The pattern of lesions was indicative of a toxic reaction affecting the vascular system. Death probably occurred from a combination of pulmonary lesions and distention of the abdominal viscera resulting in respiratory collapse and suffocation, perhaps partly due to the large volumes used.

The administration of such a large (10 ml.) quantity of solution *via* stomach tube apparently caused pylorospasm since no drug was found in the intestinal tract. Regurgitation, which is not a normal phenomenon in rats, occurred immediately prior to death. This was probably the result of gas pressure in the stomach overcoming the resistance of the distal esophagus to dilation in the moribund animals.

Acute Dermal Toxicity—The different concentrations of imidecyl iodine failed to cause any significant dermal reactions with the exception of reddening which disappeared shortly after removal of the agent.

Guinea Pig Sensitization—The challenging dose of imidecyl iodine failed to cause any abnormal or unique reactions at the time of injection or afterward.

Eye Toxicity—*Adult Rabbits*—The results of instillation of imidecyl iodine in the eyes of adult rabbits are reported in Table II. With all dilutions, the eyes were back to normal by 96 hr. after each instillation of the maximum concentration. There were no signs of damage in the corneas of any of the animals. Sixty days after the tests, the eyes of these animals were still normal.

Newborn Rabbits—Imidecyl iodine concentration of 1:64 failed to produce any clinical evidence of ocular irritation during treatment or within the 2-month period following treatment.

Rabbit Bladder Toxicity—Gross and microscopic examination of the urinary bladders and viscera of rabbits treated with various concentrations of imidecyl iodine indicated that dilutions up to and including 1:64 were tissue irritants. Dilutions stronger than 1:64 were accompanied by effects ranging from mild toxicosis to sudden death. The deaths occurred in the animals given undiluted and 1:2 dilutions of imidecyl iodine in water. At a dilution of 1:128 there were no gross or microscopic lesions that could be attributed to the iodophor. Dilutions of 1:10 or greater produced local lesions in the bladder. The lungs of the animals receiving up to 1:64 dilutions of imidecyl iodine contained congested areas and small areas of emphysema and consolidation. The extent and severity of the lesions dropped markedly between 1:40 and 1:64 dilutions. However, there was no correlation between dosage levels and extent and severity of lesions in the 1:10 through 1:40 dilutions. In the kidneys, glomerular and tubular damage compatible with toxicosis, *e.g.*, nonsupportive nephritis, epithelial and glomerular swelling, and edema were seen in a majority of the animals receiving dilution through 1:64 of the iodophor. Other accompanying lesions ranged through a wide spectrum that had no uniformity and were more compatible with naturally occurring lesions in conventional animals than with iodophor toxicity.

In dilutions up to 1:10, death occurred shortly after injection. The lungs were congested, but the lesions were not sufficient to account for the collapse of the animals. Death was probably the result of shock.

Dilutions of 1:10 through 1:40 produced urinary bladder lesions consisting mainly of edema and local hemorrhage. In these animals, the bladder was empty at the time of examination. There were no other significant lesions except in the lungs, and these could be attributed to the manner in which the animals were killed (*e.g.*, Na pentobarbital intracardially) rather than to the imidecyl iodine. Dilutions of 1:40 were, at least as far as postmortem evidence is concerned, on the borderline toxic level.

Two rabbits receiving the 1:64 dilution were killed by pentobarbital intracardially, and the remaining two by concussion. The two killed by pentobarbital had appreciable pulmonary congestion; one of the other two had inflammatory lesions and the second had minimal congestion. The bladders of all animals were slightly edematous, but the lesions were minimal.

Dilutions of 1:128 produced no visible lesions in the urinary bladder, nor any lesions elsewhere in the body which could be attributed to imidecyl iodine toxicity. At this dilution the drug exercised no observable effect upon the viscera. Lesions present were evaluated as conditions existing prior to the experiment and were not apparently related to the iodophor.

Chronic Toxicity—There was no clinical evidence of adverse effects in the dogs continuously fed imidecyl iodine. Gross and microscopic postmortem examination showed no lesions which could be attributed to imidecyl iodine. All organs and structures were examined grossly. Organs examined microscopically were the heart, lungs, liver, kidneys, and urinary bladder.

SUMMARY

The LD_{50} potential toxic effects of sublethal doses of imidecyl iodine were investigated. Oral lethal dosage in rats, skin sensitization, and dermal reaction in guinea pigs, corneal, and urinary bladder reaction in rabbits, and the effect of chronic sublethal dosage in dogs were studied. LD_{50} values measured by oral administration to male and female Wistar rats were, respectively, 14.0 ± 2.1 and 11.0 ± 1.5 ml./Kg. Corneal reactions, skin sensitization, and dermal reactions were transient or negative.

Dilutions of 1:64 infused into the urinary bladder of rabbits produced edema of the bladder musculature. Dilutions of 1:40 and below were accompanied by lung and kidney damage in addition to the bladder lesions. Full strength and 1:2 dilution produced collapse and death, probably from shock. Dogs fed diets containing imidecyl iodine over a period of 5 months exhibited no toxic lesions or symptoms

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