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PERMEATION OF IODINE THROUGH HUMAN EPIDERMIS

by

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ABSTRACT

In vitro measurements of the apparent permeability of human epidermis to iodine vapor were made using iodine traced with radioactive iodine-131. Separated epidermis was used for these measurements since the epidermal layer appears to be the site of the skin's barrier function. The measurements show that the epidermis is significantly permeable to iodine activity and suggest that the permeating iodine species is ionic or water soluble. The permeation is a complex process and does not follow a simple diffusion model. Iodine is sorbed on the epidermis during an exposure forming a reservoir of iodine for later permeation. After 30 minutes exposure to iodine vapor, apparent vapor permeabilities of from 0.08 to 17.8 cm/min were found for several samples of human epidermis.

SUMMARY

Measurements of the rate at which iodine permeates through human epidermis show that the mechanism involved is not simple diffusion. The apparent vapor permeability is far too large and is a function of the exposure period.

These measurements show that the human epidermis will pass significant amounts of radioiodine. The apparent vapor permeability constants, measured after an initial 30 minute exposure, range from 0.08 to 17.8 cm/min.

The measurements show that a reservoir of iodine is created in the skin during an exposure to iodine vapor. Unless removed, it serves as a source for continued iodine permeation even after the vapor exposure is stopped.

The chemical species of iodine which actually penetrates the epidermis is water soluble and not appreciably volatile. This rules out species such as elemental iodine or methyl iodide. The permeating species is probably ionic and its permeation through human skin the result of a three-step process. These steps are: first, sorption of elemental iodine at the skin surface; second, a chemical conversion of iodine to the ionic species; and third, aqueous diffusion of the ionic species through the epidermis to the circulating fluids of the dermal layer.

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PERMEATION OF IODINE THROUGH THE HUMAN EPIDERMIS

INTRODUCTION

This report describes the first phase of a program intended ultimately to evaluate the hazards caused by the permeation of radioactive iodine or radioactive iodine compounds through human skin. The principal goals of the program are procedures for making accurate predictions of the thyroid dose that would result from an accidental exposure of the skin to iodine activity. These procedures are needed by health physicists and workers in the fields of Environmental Safety and Reactor Safety Analysis. Other goals of the program are to establish the mechanisms involved in the permeation of iodine and iodine compounds through the skin, to select iodine impermeable materials for protective clothing, and to develop improved decontamination procedures.

Past measurements^[1,2] of the iodine permeability of skin have been difficult to apply to accident situations because of the iodine concentrations used. In most of these measurements, the skin was exposed to solid iodine, high concentrations of iodine vapor, or high concentrations of iodine in solution. In high concentrations, iodine has an irritant effect on the skin and produces a breakdown of the protective properties. In reactor accident situations, the radioactive iodine will be present as a very low concentration of vapor in air and the skin is not likely to be exposed to solid iodine or to solutions of iodine. To simulate reactor accident conditions, the concentrations of iodine used in these measurements were kept at low values.

The skin's natural permeation barrier appears to be located in the skin's outer layer, the epidermis (see Figure 1). The inner layer, the dermis, has a rich blood supply and is not an effective barrier. Experiments have shown

FIG. 1 CROSS SECTION OF SKIN.

that the actual permeation barrier is the outermost layer of the epidermis, the stratum corneum[3]. This layer of flat, horny, dead cells forms the thin, elastic membrane that gives the skin its remarkable protective properties.

The stratum corneum, along with the rest of the epidermis, can be separated from the remainder of the skin by heat or chemical irritants and used for permeation measurements. Because it is composed of dead cells, it can be frozen and subjected to extremes of heat, humidity, and various fluids without substantially altering its barrier properties[4]. Because of this property, in vitro permeation measurements made with separated epidermis produce the same results as in vivo measurements[5,6]. The iodine vapor permeation measurements described in this report were made using separated human epidermis since it permitted the measurements to be made faster, more accurately, and with a wider range of iodine concentrations and activities than corresponding measurements made with human volunteers.

This report covers the effects of the elemental iodine concentration and exposure time on the apparent permeability of the separated epidermis. To verify these measurements, some limited in vivo measurements will be made with human volunteers.

EXPERIMENTAL

APPARATUS AND PROCEDURE

The iodine permeability of the epidermis is measured by exposing a known area of epidermis to an airstream containing a constant concentration of radioactive iodine vapor for a known time and measuring the amount of iodine that passes through it.

The apparatus used is shown in Figure 2. The radioactive iodine vapor produced in an iodine generation apparatus is flushed into the mixing chamber with a small flow of helium. There it is mixed with a 240 cc/min flow of filtered air and passed either through the skin exposure chamber to the sampling chamber or directly into the sampling chamber. The exit stream of the sampling chamber passes through two charcoal traps to remove the radioactive iodine and into the house vacuum system. The mixing chamber, the three-way valve, and the sampling chamber are wrapped with heat tape to prevent condensation that would trap iodine.

FIG. 2 SKIN PERMEATION APPARATUS.

The concentration of iodine vapor in the air stream is checked periodically during a measurement to verify its stability. At intervals of 30 or 60 minutes, a large syringe is used to pull 100-cc volumes of the iodine vapor-air mixture through glass tubes containing beds of selective iodine adsorbents. Since the specific activity of the iodine is determined by the amounts of inactive and radioactive iodine used in the generation step, the amount and purity of the iodine can be established by counting the iodine activity trapped in the adsorbent beds.

The epidermal membranes taken from the skin samples are mounted on the end of the exposure chamber with an O-ring. This provides a defined exposure area of 1.28 cm². The exposure chamber and the attached collection bottle are immersed in a thermostatically controlled water bath at body temperature (37°C).

The separated epidermal membranes are held in contact with an iodine adsorbing solution. This simulates the normal condition for intact skin in which the epidermis is in contact with the fluids of the dermal layer. Physiological saline was used as the adsorbing solution for a few experiments until it was replaced by 0.1 molar sodium thiosulfate. The thiosulfate solution was used because of its ability to reduce elemental iodine to iodide ion, a non-volatile form. Either solution appeared to give the same results. The solution and the collection bottle are changed at intervals, usually 30 minutes, and are counted to find the amount of iodine that has passed the epidermal membrane. The bottles are fitted with a serum stopper so that the pressure on the membrane can be relieved by the insertion of a hypodermic needle when bottles are removed or replaced.

The iodine activity in the airstream leaving the system is removed by the two large safety traps so that the vacuum system is not contaminated. The traps are loaded with beds of activated charcoal impregnated with potassium iodide. This charcoal will retain organic iodides as well as elemental iodine. These traps are changed periodically or when there is evidence that iodine activity has penetrated to the second trap.

PREPARATION OF SKIN

Fresh human skin is obtained through an arrangement with several area hospitals. The skin comes from amputated limbs or from operations requiring skin removal. As new specimens are received, they are washed, the fat is removed, and the skin is cut into approximately 100-cm² sections. These sections are sealed in polyethylene bags and kept frozen until needed.

When needed, a section of skin is removed from its bag, allowed to thaw and then placed in water at 60°C for 20 to 30 seconds [7]. The epidermis can then be separated from the rest of the skin by careful peeling. Hair follicles usually come off with the epidermis. The separated epidermis is then placed on a piece of paper, noting the outer side, and refrigerated in another sealed polyethylene bag with a drop or so of water to keep the tissue moist.

Before each experimental run, the epidermis is removed from the refrigerator, back-lighted, and inspected under a magnifying glass. A 3-cm square section free from holes, lesions, or skin abnormalities is cut for a measurement.

IODINE GENERATION TECHNIQUES

Two methods were used in the program to provide the continuous stream of radioactive iodine vapor. For the first method, a small amount of solid radioactive iodine is prepared by the reaction between molten potassium dichromate and iodine-131 labeled potassium iodide and sublimed into a cooled U-tube. When radioactive iodine vapor is needed for a measurement, it is stripped out of the U-tube with a stream of helium. The rate of stripping is adjusted by controlling the helium flow or the U-tube temperature.

In the second method, iodine is continuously generated in solution by the oxidation of iodide ion with iodate. As it is formed, the iodine is swept out of the solution into the measurement apparatus by a constant flow of helium bubbled through the solution. The generation apparatus is shown, in place, in Figure 2. This second method of generation is rapid, convenient, and better suited for producing low iodine vapor concentrations.

The iodine produced by either of the two generation methods was reasonably pure. The results from the iodine samplers indicated that less than 1% of the iodine activity was in a form other than elemental iodine.

IODINE SAMPLERS

These samplers contain selective iodine adsorbers and are used to determine both the concentration and purity of the iodine vapor pulled through them. One of these samplers is shown in place in Figure 2. They are 6.5-mm diameter glass tubes containing three 1 to 2 cm beds of adsorbing materials separated by glass wool plugs. The first bed traps only iodine. The second bed, containing a general iodine adsorber, traps the remaining (organic) forms of iodine. The third bed, a charcoal backup trap, collects any species passing the first two traps. The amount of iodine in each bed, and consequently the purity of the iodine, is found by counting the beds separately.

The adsorbing materials in the first two beds were recently developed by Idaho Nuclear Corporation research workers[8]. A short description of preparation procedures for these materials is in order since they are not generally available.

1st Section: Iodide-loaded hydrous zirconium oxide. The basic material, an inorganic anion exchanger[a], was obtained commercially.

[a] Bio-Rad HZO-1 ion exchange crystals, 50 to 100 mesh, Bio-Rad Laboratories, 32nd and Griffin, Richmond, California.

The zirconium oxide was shaken in contact with a solution containing an amount of KI or HI in excess of its exchange capacity. The material is then filtered, air dried, and stored in a dark bottle. The material is photosensitive and decomposes when heated near 100°C.

2nd Section: Silver loaded Molecular Sieve. - Linde 13X Molecular Sieve, 20 to 60 mesh, is loaded with silver ion by passing strong silver nitrate solution through a column of the material. Loading is complete when silver ion breaks through the column. The Molecular Sieve is then washed with water, dried, and stored in a dark bottle.

RESULTS AND DISCUSSION

A number of permeability measurements were made using different skin samples and a wide range of iodine vapor concentrations. Fourteen measurement runs, during which there was no indication of leaks or of water permeation, were used for the permeability calculations.

Four different epidermal thicknesses ranging from 33 to 100 μ were used. However, the data did not permit any conclusions about the relationship between epidermal thickness and iodine permeability. The limited number of skin specimens also made it impossible to relate the permeabilities to the skin texture, color, or to the part of the body from which they came.

The permeability values given in this study are calculated using the following steady state form of the diffusion equation:

$$P(\text{cm/min}) = \frac{\text{iodine flux through the membrane } (\mu\text{g/cm}^2\text{-min})}{\text{iodine vapor concentration } (\mu\text{g/cm}^3)}$$

This equation is valid only when permeation is simply diffusion controlled, the iodine vapor concentration is constant, and when enough time has passed following the start of exposure so that the permeation equilibrium has been established across the membrane. Unfortunately, the process involved in the permeation of iodine activity from the radioactive iodine vapor through the epidermis is complex, so that this steady state equation is not strictly applicable. However, after an exposure period of about 30 minutes, the process approximates a simple diffusion controlled permeation. The steady state equation can then be used to calculate the "apparent" permeation values given in this report.

Average "apparent" permeabilities were obtained by a graphical method. The total weight of iodine permeating through the epidermis was plotted against exposure time and a best fit line was drawn through points obtained after 30 minutes. The slope of this line is the average "apparent" permeability.

PERMEABILITY AS A FUNCTION OF IODINE VAPOR CONCENTRATION

Table I lists the average "apparent" permeabilities for the 14 selected measurement runs and their corresponding average iodine vapor concentrations. These concentrations were between 10^{-2} and 10^{-9} $\mu\text{g/cm}^3$. All but two of the permeability values are between 0.08 and 2.6 cm/min. These two values, 5.14 and 17.8 cm/min, were obtained with a very thin (approximately 33 μ) epidermal layer.

Two conclusions can be drawn from these permeability values. First, the iodine permeability of the epidermis is almost independent of the concentration of iodine vapor. Second, the measured permeabilities are far too large for simple diffusion. They are 10^5 to 10^6 times larger than skin permeabilities measured for other gases or for aqueous solutes. Such high values

TABLE I

PERMEABILITY AS A FUNCTION OF CONCENTRATION

CONCENTRATION	RUN #	PERMEABILITY
$\mu\text{g}/\text{cm}^3$		cm/min.
4.60×10^{-2}	27	0.54
3.87×10^{-2}	24	1.30
3.55×10^{-2}	28	0.48
3.18×10^{-2}	40	0.28
2.88×10^{-2}	25	0.97
2.42×10^{-2}	35	0.39
2.11×10^{-2}	31	0.32
1.52×10^{-2}	38	5.14 *
1.32×10^{-2}	36	0.72
6.40×10^{-6}	37	17.82 *
5.40×10^{-6}	39	2.61
8.10×10^{-8}	34	0.14
3.49×10^{-8}	33	0.08
4.58×10^{-9}	41	1.07

* 33 μ Skin

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suggest that the permeation mechanism includes a step that produces a large increase in the effective iodine concentration.

If, as expected, these permeabilities are representative of intact skin, the iodine dose received through the skin in an accidental iodine exposure may be as important as the inhalation dose. For comparative calculations of the thyroid dose received by these two routes in hypothetical exposure, assume (a) a specific activity of iodine of 10^{-6} $\mu\text{C}/\text{cc}$, (b) an exposure period of 60 minutes, (c) a skin area of 1.2×10^4 cm^2 , (d) a breathing rate of 20/min and a tidal volume of 1.0 liter, and (e) a permeability constant of 1.0 cm/min. Using these values, the calculated iodine doses to the thyroid via the skin and the lungs are 0.9 and 1.5 rem.

In an actual skin exposure to radioactive elemental iodine vapor, the dose received via the skin would probably be reduced by clothing or prompt decontamination of the skin. It appears, however, that the amount of iodine entering through the skin could be significant.

PERMEABILITY AS A FUNCTION OF EXPOSURE TIME

Data taken during a measurement run can be used to calculate apparent permeabilities for several different times during the run as well as the single smoothed value given in Table I. When plotted against the exposure times, Figure 3, these values show that the apparent permeability of the epidermis changes during the measurement. The apparent permeabilities rise to a peak at about 30 minutes, drop to a "trough", and then rise again. This "permeability change" occurs in almost every measurement run. As Figure 3 shows, the higher the iodine vapor concentration, the shallower the "trough" that follows the peak. At high iodine concentrations, the "trough" almost disappears.

FIG. 3 TIME DEPENDENCE OF THE APPARENT PERMEABILITY.

The initial rise of the permeability curves in Figure 3 probably represents the time needed to establish diffusion equilibrium rather than a genuine rise in permeability. The subsequent drop and rise represent a real drop and rise in either the permeability of the epidermis or in the concentration of the permeating species.

RESERVOIR EFFECT

In two measurements made during these studies, radioactive iodine in the air stream was cut off after several minutes. All other conditions were similar to the usual measurement. At the time of the cutoff, direct reading radiation instruments showed the epidermal membrane to be reading approximately 200 mrem/hr at 3 cm. This indicated the deposition of a considerable amount of iodine. After the cutoff, as Figure 4 indicates, iodine continued to permeate through the epidermal membrane at nearly the same rate observed before the cutoff. In fact the "permeability change" effect occurred much as if the permeation mechanism were time-reversible. When the iodine stopped permeating through the epidermal membrane, it was no longer detectable on the membrane surface.

FIG. 4 PERMEATION FROM A "RESERVOIR".

These measurements indicated that iodine was sorbed on the epidermis, much of it reversibly bound, and that the sorbed iodine served as a source or reservoir for continued iodine permeation. This reservoir character of skin was noted by Vickers[9] and Tregar[6], who indicated that the storage site was the outer layer of the epidermis, the stratum corneum.

THE PERMEATION MECHANISM

To throw some light on the mechanism of iodine permeation, two measurements were run with an air gap between the thiosulfate solution in the collection bottles and the inner surface of the epidermal membrane. The first measurement ran for two hours without finding radioiodine in the thiosulfate solution. When contact between the solution and the inner surface of the membrane was restored, iodine collection began immediately. When the thiosulfate solution was replaced with iodine impregnated charcoal, an efficient collector for both iodine and methyl iodide, no radioactive iodine was found in the charcoal. Apparently, direct aqueous contact is essential for the permeation of iodine activity. This is, of course, the normal situation for intact skin.

In the second experiment, the epidermal membrane was replaced by a 2-mil membrane of a material known to be iodine permeable, polyvinyl chloride. In this experiment, the radioactive iodine entered the thiosulfate solution with or without the air gap. The air gap is apparently not an effective barrier to elemental iodine.

These observations suggest that the iodine species penetrating the epidermal membranes is water soluble, not appreciably volatile, and probably ionic. This suggestion, the existence of the "iodine reservoir" in the epidermis and the high apparent permeabilities, is the basis for postulating a three-step process for the permeation of iodine activity through the epidermal membranes. The three steps are: first, a weak sorption of the elemental iodine on the surface of the skin; second, a chemical conversion of the iodine to new ionic or water soluble species; and third, aqueous diffusion of the new species through the epidermal layer into the circulating fluids of the dermal layer.

Some additional work is needed to test this hypothesis. The permeating iodine species should be identified and their permeation rates measured separately. The permeation path, or paths (transcellular, transfollicular, or interstitial), and the mechanism responsible for the "permeability change" effect should be identified. Appropriate work is planned.

CONCLUSIONS

The initial iodine permeation studies described in this report lead to four conclusions. These are: first, the epidermis will adsorb elemental iodine vapor to form a surface concentration or reservoir which serves as a source for iodine permeation; second, the permeating iodine species is probably ionic, not elemental iodine; third, if the apparent iodine permeation rates observed for separated epidermis are valid for intact skin, the thyroid dose received through the skin in an accident involving total immersion in an iodine-containing atmosphere could be comparable to the inhalation dose; and fourth, the mechanism for permeation of iodine activity is not simple diffusion. The experimental observations are consistent with, but do not prove, a hypothetical three-step mechanism involving sorption on the skin, chemical conversion, and diffusion through the epidermis.

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