LOCALIZATION OF ^{197}Hg CHLORMERODRIN AND SODIUM ^{131}I IN THE FEMALE REPRODUCTIVE TRACT

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Although he is cognizant of the advantages of radioisotopes, the physician in nuclear medicine is continually mindful of possible remote harm to his patient from these agents. Such harmful effects might require years before becoming apparent through genetic alterations. Although some target tissues receive amounts of radiation measurable in rads, diagnostic doses of radioisotopic agents generally expose the patient's cells to low (millirad) and probably "safe" levels of radiation. No effects have been demonstrated from millirad amounts of radiation to human reproductive cells. More significantly, x-ray treatment to women with 100–225 roentgens to the pelvis for anovulatory and other gynecologic problems has not discernibly altered the children born subsequently (*1*).

Radioactive mercury chlormerodrin is regularly used diagnostically in comparatively large doses (*2*). This compound is administered intravenously and rapidly becomes attached to serum protein (*3*). Subsequently chlormerodrin appears in protein-rich transudatory fluids whenever they are present in the body. This property may account, at least in part, for the tendency of chlormerodrin to localize in and around tumors and hematomas (*4,5*).

Our study was designed to determine whether the human cervix, uterus, ovary or ovarian cyst fluid contains increased amounts of radioactivity over the concentration in the blood following the intravenous administration of 1 mc of ^{197}Hg chlormerodrin. In addition, we measured the radioactivity in ovarian cyst fluid in other patients following the oral administration of 100 μc sodium ^{131}I.

MATERIAL AND METHODS

Studies were made on 27 women divided into three groups. All were of reproductive age and were scheduled for pelvic surgery. The first group of six patients had brain scanning included in their clinical work-up. 1 mc of ^{197}Hg chlormerodrin was administered intravenously the day before surgery, and the brain scan was performed. At the time of surgery, weighed portions of excised tissue as well as measured amounts of blood, peritoneal fluid, gastric juice and, when it was present, ovarian cyst fluid were assayed for radioactivity using a well-type scintillation counter.

A Model 410A spectrometer (Packard Instrument Co.) was used for these determinations. This instrument incorporates a fixed base line so that 100 volts corresponds to 1 Mev. Calibration is undertaken with the probe voltage set at 700 volts and both discriminators set at zero. A ^{137}Cs source is placed in the well detector with the lower discrimination set at 657 kev and the upper at 667 kev. This constitutes a 1-volt or 10-kev window. The probe voltage is then adjusted until a maximum counting peak has been obtained.

The specific activity for each type of tissue and fluid was determined. Microscopic sections from each tissue specimen were examined to determine the tissue type.

A second group of 13 patients was studied to determine the radioactivity in the contents of a variety of ovarian cysts following 1 mc of intravenous ^{197}Hg chlormerodrin. Comparisons were made with specific activities of blood, gastric juice and peritoneal fluid. (Patient #13 was given 700 μc of ^{203}Hg chlormerodrin rather than 1 mc of ^{197}Hg chlormerodrin.) The time from isotope administration to surgery varied in this group.

Finally, a third group of eight patients was given 100 μc of sodium ^{131}I orally before gynecological surgery. In each of these, the radioactivity content was determined for cyst fluid, blood, gastric juice and portions from selected cyst walls. All counts were

Received Sept. 19, 1966; revision accepted July 26, 1967.

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TABLE 1. RADIOACTIVITY* 24 HR AFTER INTRAVENOUS ^{197}Hg CHLORMERODRIN (GROUP 1 PATIENTS)

	Patients						Mean
	1	2	3	4	5	6	± 1s.d.
Tissue or fluid							
Cervix	3.3	—	—	3.8	4.4	3.2	3.4 ± 0.5
	2.9				3.8	2.7	
Uterus	3.1	—	—	3.3	5.3	2.4	3.5 ± 1.1
	3.0				5.2	2.4	
Ovary	—	3.7	2.3	4.3	5.3	—	4.1 ± 1.0
		3.9			5.2		
Blood	3.0	2.4	2.7	3.8	3.0	3.0	3.0 ± 0.4
Cyst fluid	—	10.0	0.4†	6.2	—	9.6	8.8 ± 1.4
				8.3		10.0	
Diagnosis	Myomata	Breast ca.	R. ovarian cyst	Breast ca.	Endomet. ca.	Breast ca.	

* %/gm or ml × 10^{-4} of administered dose.
† Mucinous cystodenoma not included with physiologic cyst fluids.

standardized to a woman 62 in. tall and weighing 121 lb (55 kg).

RESULTS

In the first group of patients, the average 24-hr radioactivity concentrations were 3.4 × 10^{-3} μc/gm of cervix; 3.5 × 10^{-3} μc/gm of uterus; 4.1 × 10^{-3} μc/gm of ovary; 2.7 × 10^{-3} μc/ml of blood; and 8.8 × 10^{-3} μc/ml of ovarian cyst fluid. Table 1 lists the individual tissue and fluid values for these six patients as percent of the administered dose. While no statistical difference was seen among the amounts of radioactivity contained in blood, cervical, uterine and ovarian tissue, the activity of the fluid of physiological ovarian follicular cysts was significantly greater (Fig. 1). The lowest concentration of radioactivity was present in the fluid of an ovarian mucinous cystadenoma (patient #3), a cyst which does not contain transudatory fluid.

Table 2 lists the results from the second group of patients. Corpus luteum cysts generally contained the greatest concentration of ^{197}Hg chlormerodrin. The mucinous cystadenoma and cystadenocarcinoma contained the lowest amounts of radioactivity.

The third group of patients was studied following the oral administration of 100 μc of ^{131}I. Figure 2 shows the comparative levels of radioactivity in ovarian cyst fluid, blood, gastric juice and peritoneal fluid. Generally little difference was found among the specific radioactivity levels of ovarian cyst fluid, blood and peritoneal fluid. When differences occurred, the blood level was usually higher than the ovarian or peritoneal fluid levels. Gastric juice contained comparatively high amounts of ^{131}I. The ovarian cyst-wall specimens did not differ from blood in radioactivity content.

RADIATION DOSE TO OVARY

Radiation dose to the ovary from 1 mc of ^{197}Hg chlormerodrin was calculated separately for the radioactivity in the circulating blood and for the radioactivity in the ovarian follicle. Since the half-value layer in tissue for the photon from ^{197}Hg is approximately 3.8 cm and the distance from the kidney to the ovary is about 12.5 cm, that source of radiation is negligible for the ovary and does not need to be considered (half-value layer = $1n\ 2/\mu = 0.693/0.18 = 3.8$ cm).

The average whole-blood volume for the "standard" 55-kg woman was determined to be 4,000 ml. The blood concentration could be no greater than 0.25 μc/ml when 1 mc of ^{197}Hg chlormerodrin was diluted in 4,000 ml of blood. This concentration fell rapidly and at 24 hr was 0.003 μc/ml of blood. At that point the radioactivity concentration for the

TABLE 2. SPECIFIC RADIOACTIVITY IN OVARIAN CYST FLUID* AFTER INTRAVENOUS ^{197}Hg CHLORMERODRIN (1 MC/PATIENT)

Patient	Ovarian cyst type	Time after dose (hr)	% dose/ml × 10^{-4}	Mean ± 1s.d.
4	Follicular	24	6.2	
6	Follicular	24	9.6	
9	Follicular	24	7.3	7.4 ± 2.7
12	Follicular	24	6.4	
13	Follicular ^{203}Hg	24	16.0	16.0
2	Corpus Luteum	24	10.0	
4	Corpus Luteum	24	8.3	9.4 ± 1.4
6	Corpus Luteum	24	10.0	
8	Corpus Luteum	48	3.6	3.6
10	Corpus Luteum	48	36.0	36.0
9	Dermoid	24	8.2	8.2
13	Dermoid	24	6.0	
	Dermoid ^{203}Hg	24	4.2	5.1 ± 1.3
7	Abscess	24	2.8	2.8
14	Abscess, sterile	24	14.0	14.0
3	Mucinous cystadenoma	24	0.4	0.4
12	Serous cystadenocarcinoma	24	1.4	1.4
11	Endometrioma	6	10.0	10.0

* % of dose/ml × 10^{-4}.

follicular-cyst fluid averaged 0.0088 μc/ml. While the blood would continue to decrease with an effective half-life of 5¼ hr (0.22 days) (*14*), the radioactivity in the ovarian follicle (*8*) would probably decrease at a rate approaching the physical half-life of 2.7 days.

RADIATION TO THE OVARIAN TISSUE AT 24 HR POST-DOSE FROM 1 MC ^{197}Hg CHLORMERODRIN

$D = CT\,(73.8\bar{E}_B + 0.0346\bar{g}\Gamma)$
$C = 0.004$ μc/gm of body tissue (as measured in ovary)
$T = 0.22$ days (*14*)
$\bar{E}_B = 0.0773$ Mev
$\bar{g}$ = whole body = 122 (for 55-kg, 150-cm woman)
$\Gamma = 0.35$
73.8 = beta dose constant
0.0346 = gamma dose constant
$D = 6.3$ mrad

RADIATION TO THE FOLLICLE AT 24-HR POST-DOSE FROM 1 MC ^{197}Hg CHLORMERODRIN

$C = 0.009$ μc/ml of cyst fluid
2 ml = contents of mature follicular cyst
$\bar{g} = 4.5$ $\quad 3\pi r = 4.5$
$T = 2.7$ days (cyst 1.0 cm in dia)
$D = 140$ mrad

DISCUSSION

While much has been written about ovarian physiology, little of this information has been obtained from human studies. Since there are marked species differences in reproductive physiology, extrapolations to the human from experimental animal studies must be regarded as speculative (*6*). Von Kaulla, Aikawa and others have determined that the human uterine cervix excretes ^{131}I, ^{131}I-tagged serum albumin, L-thyroxine and ^{35}S thiocyanate in concentrations grossly similar to the salivary concentrations of the same substances. The ^{131}I was higher in concentration in the cervix than in the uterus. Two incidentally encountered ovarian cysts contained very little radioactivity (*7*). Mancini *et al* used fluorescent dyes as well as autoradiographic techniques to demonstrate the presence of circulating labeled serum proteins in the follicle of the rat ovary without attempting to quantitate the amounts transferred to the follicle (*8*).

Von Kaulla *et al* studied the transfer of other radioactive tracers and drugs to ovarian follicular fluid from the blood in humans (*9,10*). ^{131}I was noted to be present in the follicle in less concentration than in serum up to 7 hr after administration. ^{203}Hg mercaptomerin was found in follicular fluid in greater-than-serum levels at 11–12 hr. ^{131}I human gamma globulin, ^{14}C meprobamate, penicillin and pyridium were noted to penetrate into but probably not concentrate in the follicular fluid (*10*).

After sodium ^{131}I administration, Dor (*11*) and Weijer (*12*), in humans, and Martinenghi (*13*), in

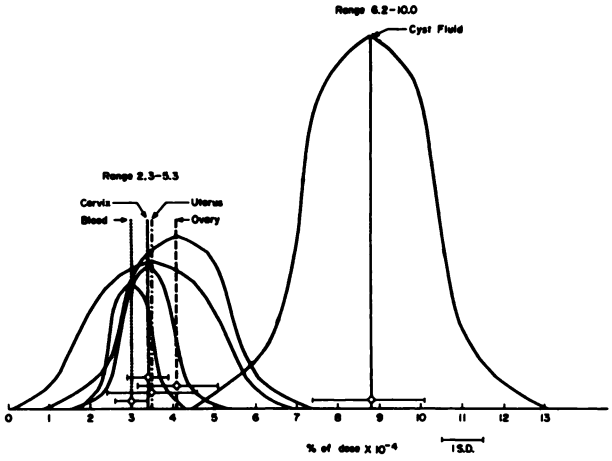

FIG. 1. Radioactivity (%/gm or ml of administered dose) 24 hr following intravenous ^{197}Hg chlormerodrin in Group 1 patients. Radioactivity in uterus and ovary approximates that of blood background. Follicular cyst fluid, however, contained significantly higher amounts.

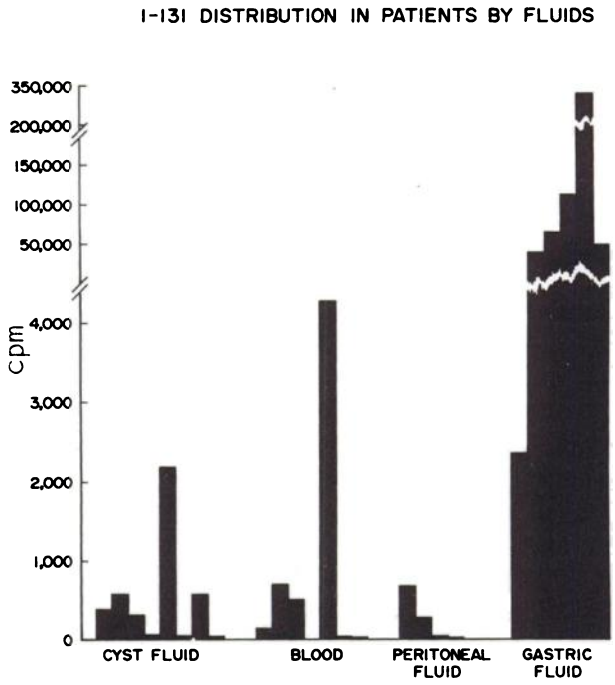

FIG. 2. Radioactivity in cyst fluid (F), blood (B), peritoneal fluid (P) and gastric fluid (G) 24 hr after 100 μc of ^{131}I by mouth. All fluids except gastric approximate blood concentration.

rats, demonstrated a low concentration of ^{131}I in the ovarian follicle. Bengtsson *et al* (*14*) used autoradiography to demonstrate increased concentration of ^{131}I in the walls of large Graafian follicles at 4 hr and in the follicular fluid at 24 hr. However, the radioactivity in the ovaries did not exceed that in the blood. Weijer (*12*) calculated the average beta-radiation levels to the ovary in normal, premenopausal women to be 9.4 mr/100 μc of administered ^{131}I. This was about equal to the beta radiation in the whole blood.

The present study confirms the low radioactivity levels present in ovarian cysts following oral administration of sodium ^{131}I. It also demonstrates the tendency of ^{197}Hg chlormerodrin, a mercurial diuretic similar to the ^{203}Hg mercaptomerin used by von Kaulla, to concentrate in follicular fluid in amounts in excess of its concentration in blood.

One day after the intravenous administration of a 1-mc dose of ^{197}Hg chlormerodrin, its concentration in the ovarian follicular fluid is significantly higher than that in the ovarian stroma or in the other female reproductive tissues. This isotopic concentration can provide a maximum of 140 mrad to the follicle with its growing ovum. The radioisotope contained in ovarian tissue provides 6.3 mrad to that organ. The kidneys with their concentration of ^{197}Hg chlormerodrin are usually distant enough from the ovaries so that they need not be considered as a source of radiation to the germ-plasm.

Even though it is probably justifiable to consider any amount of radiation as "bad," it must be emphasized that these amounts of radioactivity are quite small. The female genital organs contain minute amounts of activity 24 hr after a brain scan using 1 mc of ^{197}Hg chlormerodrin. Although the ovarian follicle contains more radioactive mercury, the total amount of radiation delivered to the developing ovum is approximately 150 mrad. This amount of radiation is not likely to damage an ovum sufficiently to result in detectably altered offspring; however, it could possibly induce genetic changes.

SUMMARY

Three groups of women were studied to determine the radioactivity in the ovary and in the uterus after the intravenous administration of ^{197}Hg chlormerodrin in two groups, and the oral administration of ^{131}I in the third group. The majority of the genital tissues studied contained radioactivity equal to or less than blood background with both isotopic agents. However, the maturing Graafian follicles contained significantly higher amounts of ^{197}Hg chlormerodrin. ^{131}I, on the other hand, did not concentrate in the ovary nor in the follicles to a degree higher than that found in the blood. Although radioactive mercury chlormerodrin was not concentrated by the stomach, ^{131}I was present in gastric secretions in large amounts. Bathing the maturing ovum in follicular fluid which contains even these low levels of radioactivity may have some genetic significance.

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