FERTILITY AND STERILITY®
VOL. 76, NO. 6, DECEMBER 2001

Published by Elsevier Science Inc.
Printed on acid-free paper in U.S.A.

Absorption and preferential vagina-to-uterus distribution after vaginal administration of ^{99m}Tc-pertechnetate in postmenopausal women

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Objective: To investigate in vivo and in humans the mechanisms and kinetics of vagina-to-uterus distribution.

Design: Controlled clinical study.

Setting: Volunteers in an academic research environment.

Patient(s): Six postmenopausal women undergoing transabdominal hysterectomy were selected.

Intervention(s): Women received 0.2 mL of ^{99m}Tc-pertechnetate vaginally. In three patients the cervical canal was previously sealed by means of surgical glue. Six postmenopausal women who had received ^{99m}Tc-pertechnetate intravenously for a thyroid scintigraphy were considered as a control.

Main Outcome Measure(s): Radioactivity was assessed every 30 minutes for 6 hours in the pelvis and in body regions where ^{99m}Tc-pertechnetate normally accumulates (thyroid, salivary glands, and stomach).

Result(s): Uterine activity appeared after 60 minutes and peaked between 120 to 210 minutes. These same times were observed in the patients who had a sealed cervix. Thyroid uptake appeared after 180 minutes and peaked between 210 and 330 minutes. Uterine uptake did not occur in any of the intravenous patients; their thyroid uptake was rapid, appearing after 30 minutes.

Conclusion(s): Preferential vagina-to-uterus distribution, at least in postmenopausal women, is not simply due an intracanalicular passage but is mediated by absorption of substances and probably by a countercurrent transfer mechanism. (Fertil Steril® 2001;76:1108–12. ©2001 by American Society for Reproductive Medicine.)

Key Words: Vaginal route, preferential distribution, uterine specificity, countercurrent transport

Received March 5, 2001; revised and accepted June 19, 2001.

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0015-0282/01/$20.00
PII S0015-0282(01)02905-3

In recent years the results of a number of experimental and clinical studies have supported the hypothesis that progesterone administered vaginally is selectively distributed to the uterus where tissue concentrations and effects exceed expectations drawn from peripheral levels achieved (1–3). This unexpected phenomenon, dubbed "first uterine pass effect" by analogy to hepatic findings after oral administration of hormones (4), has multiple clinical implications in gynecological endocrinology. Notably, the vaginal route now stands as the primary mode of progesterone administration (5). Moreover, a preferential distribution of drugs to the uterus, uncovered with vaginal progesterone, may serve for the administration of other substances and improve the treatment of disorders such as dysmenorrhea and other forms of uterine hypercontractility.

Yet the actual mechanisms by which vaginal administration results in unexpectedly high uterine concentrations despite low levels in systemic circulation remain obscure and puzzling to many gynecologists. Little is known about the actual mechanism or the kinetics that govern the direct transport of substances from the vagina to uterus. Theoretically, at least four different mechanisms may explain this phenomenon: [1] direct (passive) diffusion through tissues, [2] passage (aspiration) through the

cervical lumen from the vagina to the uterus, [3] transport by the venous or lymphatic circulatory systems, and/or [4] countercurrent vascular exchange with diffusion between uterovaginal veins and/or lymph vessels and arteries (6).

The aim of the present study was to investigate in vivo and in humans the mechanisms and kinetics of vagina-to-uterus distribution. For this purpose, we studied the distribution to the uterus of ^{99m}Tc-pertechnetate that was administered vaginally in postmenopausal women in whom the cervical canal had either been sealed or not. As control, we evaluated the uterine uptake of the same radionuclide administered intravenously in postmenopausal women who had undergone a thyroid scintigraphy.

MATERIALS AND METHODS

Six postmenopausal women in whom a transabdominal hysterectomy was indicated as part of surgical correction of urinary incontinence consented to participate in this pilot study, approved by our institutional review board. The patients were healthy, with a normal height and weight ratio (body mass index <25, weight/height^2; kg/m^2) and in spontaneous menopause for more than 1 but less than 5 years. The baseline serum FSH and estradiol (E_2) levels were within menopausal range (FSH $>$ 40 mIU/mL; E_2 <30 pg/mL). We excluded women with uterine prolapse, vaginal infections, myomas or genital cancer, or receiving other vaginal treatments.

On the day before surgery, the women received a single vaginal administration of 0.2 mL of ^{99m}Tc-pertechnetate (corresponding to 15 MBq) with the use of a 1-mL syringe connected to an atraumatic 16-gauge caliber Teflon cannula introduced in the vaginal posterior fornix without the aid of a speculum. In the last three patients enrolled in the study, 5 minutes before administering the radionuclide, the cervical canal was sealed by injecting 2 mL of surgical glue into the canal. After administration of the diagnostic product, a tampon was inserted in the lower third of the vagina to avoid any leakage of the radioactive liquid.

All administrations were made at 8:00 A.M. with patients in supine position, lying on a scanning table synchronized with a wide-field-of-view gamma camera. For the first 30 minutes after the administration, the patients were asked to maintain a supine position while a continuous anterior view recording of radioactivity was performed (dynamic data acquisition). Subsequently, the women were allowed to walk and additional scans from the anterior and right lateral view were obtained every 30 minutes for 6 hours after the initial administration. Each time, the uptake of radionuclide was assessed in the area of administration and in the body regions where ^{99m}Tc-pertechnetate normally accumulates (the thyroid, salivary glands, and stomach).

All of the evaluations, performed by one investigator (G.R.), consisted of morphologic and quantitative analyses of the radioactivity in the designated areas. Uterine activity was considered to have occurred when an oval-shaped area of radioactivity appeared above the injection area. In all cases, at the moment of the first appearance of the uterus on the gamma scintigraphy, a transabdominal ultrasound scanning was performed to confirm the correspondence between the area highlighted by the radionuclide on the gamma camera and the uterus. Quantitative analysis of the uptake was performed retrospectively on the serial recordings by means of an arbitrary scale from 0 (no uptake) to 3 (maximum uptake).

After surgery the uteri were opened with a frontal cut and the cavities were examined to rule out the presence of any abnormality and to confirm the presence of glue sealing the cervical canal in the cases when it was used.

As a control, we investigated the uterine uptake in six postmenopausal women in whom 50 MBq of ^{99m}Tc-pertechnetate was administered intravenously for a thyroid scintigraphy. Hormone replacement therapy, vaginal hormonal treatments, uterine myomas, or cancer were considered exclusion criteria.

The uptake score values of the uterus and thyroid at different times are reported as median and variation range. For statistical evaluation, the Wilcoxon rank-sum test was employed; $P < .05$ was considered statistically significant.

RESULTS

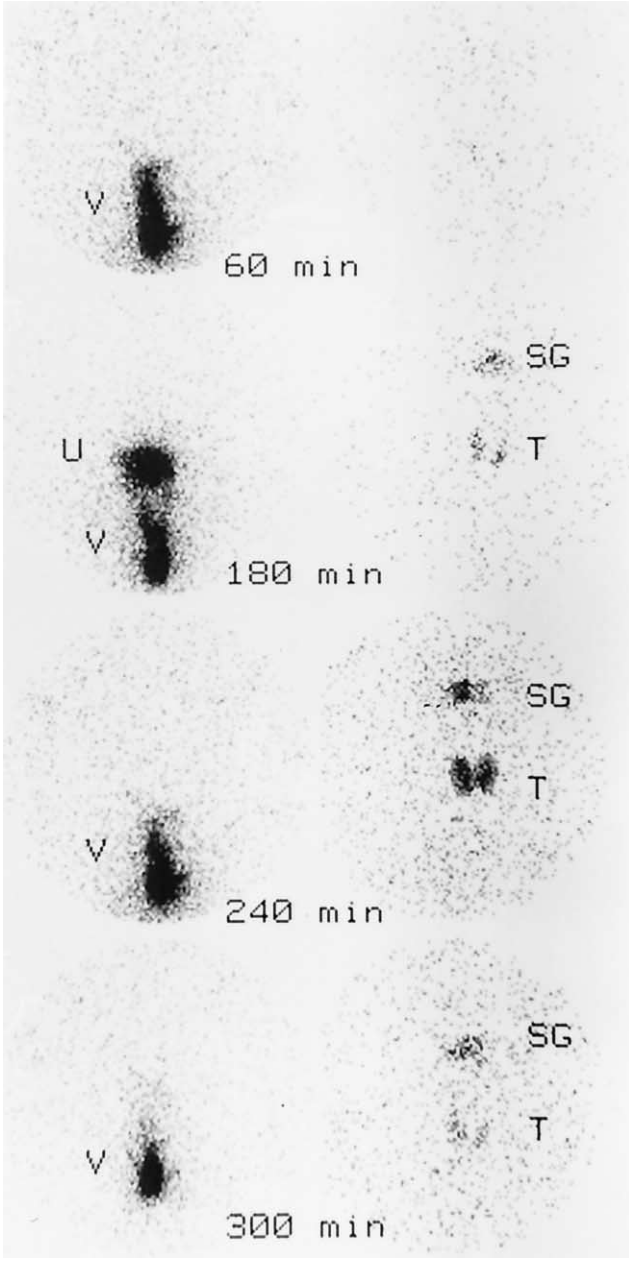
After vaginal administration in all patients, clear visualizations of the uterus, thyroid, and salivary glands were obtained. Figure 1 shows the uptake of ^{99m}Tc-pertechnetate in different organs of a patient whose cervical canal was not sealed. The uptake scores of the uterus and thyroid in parallel evaluations were significantly different (Fig. 2). Before 60 minutes, radioactivity was found only at the injection site. From 60 minutes onward, uterine activity began to appear, gradually reaching the maximum at 2 hours after administration of the tracer. The concentration of the radionuclide was maximal from 180 to 210 minutes, but decreased progressively afterward. The uterine image disappeared by 330 minutes. In patient 1, the appearance and the subsequent disappearance of uterine activity were delayed by about 60 minutes.

In the three patients in whom the cervical canal had been sealed, the appearance of uterine activity occurred at the same time as in the patients with unobstructed cervical canals. One patient (patient 5) showed a 1-cm oval-shaped area of hyperactivity in the area of uterine uptake with characteristically regular borders.

Extrapelvic uptake (in the thyroid, stomach, and salivary glands) was also detected in all patients, but with a delay of 30 minutes compared to the uterine uptake. Specifically, the thyroid uptake started to appear at 180 minutes and reached

FIGURE 1

Uptake of ^{99m}Tc-pertechnetate in pelvic and extrapelvic areas of a patient whose cervical canal was not sealed, at different times after vaginal administration of the radionuclide. (V = vagina; U = uterus; T = thyroid; SG = salivary glands.)

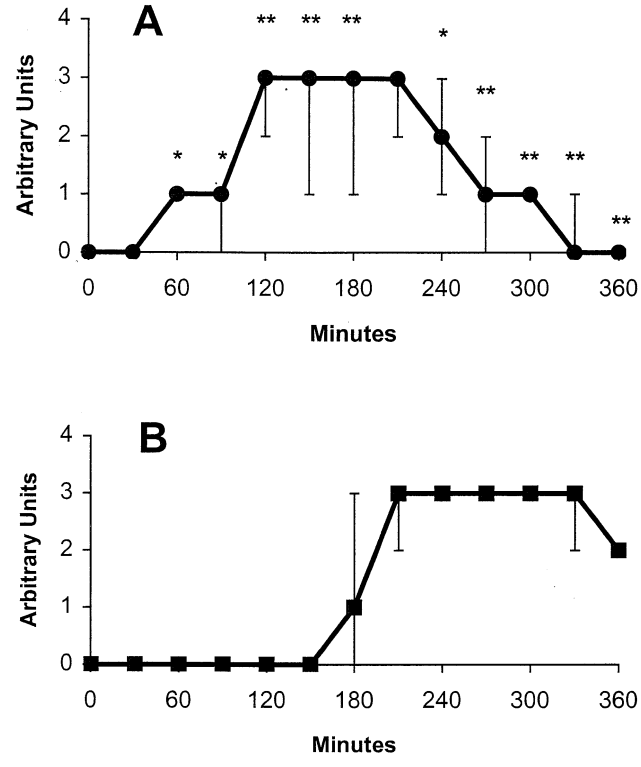


Cicinelli. Preferential vagina-to-uterus transport. Fertil Steril 2001.

a maximum in all patients (except one) at 210 minutes. In patient 1, the thyroid uptake was delayed, reaching the peak value at 240 minutes. Direct inspections of uterine cavities was negative, except in patient 5, in whom an endometrial polyp was detected.

FIGURE 2

Temporal patterns of (**A**) uterine and (**B**) thyroid ^{99m}Tc-pertechnetate uptake scores in six postmenopausal women who received a single vaginal administration of the radionuclide. Data are displayed as median and variation range. (*$P<.05$; **$P<.005$.)



Cicinelli. Preferential vagina-to-uterus transport. Fertil Steril 2001.

Among the control patients who received the radionuclide intravenously, no uterine visualization was observed before 360 minutes, whereas the thyroid uptake was rapid and already massive after 30 minutes.

DISCUSSION

The results of the present study show that ^{99m}Tc-pertechnetate administered vaginally in postmenopausal women concentrated in the uterus but also in extrapelvic sites such as the thyroid, stomach, and salivary glands. This means that the radionuclide was absorbed through the vaginal mucosa and reached the blood circulation. However, the appearance of uterus activity occurred much earlier than activity in the extrapelvic sites. Specifically, uterine activity was detectable approximately 2 hours after vaginal administration; extrapelvic uptake did not occur until at least 30 minutes later. In contrast, when the radionuclide was administered intravenously, this order of distribution was reversed. These find-

ings strongly suggest the existence of a preferential distribution of radionuclide from the vagina to the uterus.

In recent years, the existence of preferential vagina-to-uterus distribution of substances administered vaginally has been repeatedly suggested by many experimental and clinical studies. For example, after vaginal administration of progesterone, secretive endometrial modifications and endometrial hormone levels far exceed those expected based on the relatively modest systemic serum levels achieved (1, 3, 4, 7). Theoretically, at least four different mechanisms could explain this unexpected phenomenon: [1] direct (passive) diffusion through tissues, [2] passage (aspiration) through the cervical lumen from the vagina to the uterus, [3] the venous or lymphatic circulatory systems, [4] countercurrent vascular exchange with diffusion between uterovaginal veins and/or lymph vessels and arteries (6). The same exact mechanisms could also explain the direct transport of ^{99m}Tc-pertechnetate to the uterus that we found in our study.

Direct-through-tissue diffusion of the radiotracer from the cervix to the uterine corpus can be excluded, because in none of the scans obtained did we visualize any form of gradual diffusion from the cervical area to the upper portion of the uterus. Our results also permit us to rule out direct transfer ("aspiration") of the radionuclide through the cervical canal. In the three women whose cervical canal was sealed, the time course and intensity of the diffusion of radioactivity to the uterus was similar to that seen in the other women. Moreover, no evidence of intracavitary distribution of the radiotracer was observed in the women whose cervical canal remained open.

Transvaginal absorption of radionuclide into the interstitial space, ultimately reaching the lymph and/or venous blood, and distribution through the general circulation cannot explain the fast uptake of radionuclide in the uterus as compared to the thyroid, the primary target organ for ^{99m}Tc-pertechnetate. After conventional distribution by the circulatory system, ^{99m}Tc-pertechnetate has higher tropism for the thyroid and salivary glands than for the uterus, where no uptake is seen after intravenous administration (as verified in our intravenous patients).

In nuclear medicine literature, uterine uptake of ^{99m}Tc-pertechnetate has been sporadically described in premenopausal women (8–11), in association with large uterine fibroids (12), and in relation to carcinomas (13), all exclusion criteria in our study. Hence, the early and relevant uterine uptake observed after vaginal administration in our postmenopausal women confirms a preferential concentration of the radionuclide in this organ entirely specific to the route of administration, resulting in a large fraction of the total dose administered transiting through the uterus before reaching the general circulation.

The results of the study speak for the occurrence of a countercurrent vascular exchange occurring between the vagina and the uterus. Countercurrent transport is a physiological exchange mechanism known to take place between fluids flowing in opposite directions in nearby vessels. This can particularly occur between two fluid-filled tubes such as blood vessels that share a common (or very close) surface with flow in opposite directions (14). When this situation exists, exchanges can occur if substances are in higher concentrations in venous blood/lymphatic vessels than in the nearby artery. As normal substances transported in the circulatory system travel from artery to vein, transport in opposite direction from vein to artery is logically referred to as countercurrent transport. Hence, through this system, local arterial concentration of substances that diffused from the vein to the artery will become progressively higher than in arteries supplying other organs. The higher progesterone concentrations found in uterine arterial blood as compared to peripheral circulation (radial artery) after vaginal administration of progesterone strongly supports the latter mechanism (15). Numerous other examples of countercurrent exchange exist in the body. This includes in the kidney (Henle's loop), and for heat exchange in the sinus cavernous between the carotid and venous flow draining the nasopharyngeal area (6, 7).

Our hypothesis is that radiotracer is absorbed through vaginal mucosa, raising its concentration in the paravaginal spaces, and lymph and vaginal venous vessels, and reaching ultimately the systemic circulation. However, at the same time, in the arterial blood of the uterine artery the concentration of radiotracer reaches levels higher than in systemic circulation, allowing the uterus to be visualized earlier than extrapelvic organs on scans.

This study provides an in vivo human demonstration of the existence of a preferential distribution of substances from the vagina to the uterus and provides insight into the mechanisms underlying this phenomenon. It can be stated that, at least in postmenopausal women, preferential vagina-to-uterus distribution is not simply due to an intracanalicular passage but rather is mediated by absorption of substances and by a subsequent countercurrent transfer mechanism.

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