CASE REPORT

Distribution of a spermicide containing Nonoxynol-9 in the vaginal canal and the upper female reproductive tract

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Topical, intravaginal microbicides and spermicides are greatly needed to prevent transmission of sexually transmitted diseases and/or unwanted pregnancies. The development of such compounds is a high research priority. The presumed method of action of existing, or novel, microbicides/spermicides is to provide a chemical barrier to the vaginal epithelium preventing exposure to micro-organisms. Other intravaginal products are used to treat vaginal bacteria of fungal infections. Little is known, however, about the actual or optimal initial distribution and subsequent spread of medications placed in the vagina. We describe a sensitive new technique to quantify the spread of a gel placed in the vagina using magnetic resonance imaging (MRI). Five millilitres of an over-the-counter spermicide containing Nonoxynol-9 was mixed with Gadolinium. MRI was used to quantify spread of the mixture 10 min after insertion with a standard applicator. We demonstrated contiguous spread of gel throughout the vagina. The coverage of material was thicker in the upper vagina than in the lower vagina. We also demonstrated, for the first time, that spermicidal compounds may migrate from the vaginal canal into the endocervix within 10 min of insertion. This finding suggests that topical microbicides/spermicides may act both in the vaginal canal and in the upper female genital tract.

Key words: microbicide/MRI/Nonoxynol-9/spermicide/vagina

Introduction

As sexually transmitted infections such as chlamydia, gonorrhoea and HIV are among the most common causes of illness in the world (Gerbase et al., 1998), the development of prophylactic intravaginal microbicides and viricides is a high research priority (Elias and Coggins, 1996; Hitchcock and Fransen, 2000). To date, only Nonoxynol-9 has been shown to offer some protective benefit against transmission of some of these pathogens (Cook and Rosenberg, 1998; Louv et al., 1998; Niruthisard et al., 1992) but its effect on HIV is yet to be demonstrated (Weir et al., 1995; Roddy et al., 1998). New microbicides, which may be used as prophylactics to prevent the spread of sexually transmitted infections, especially HIV, are currently under development (Elias and Coggins, 1996; Hitchcock, 2000).

Little is known about the optimal distribution of a vaginally placed gel used for sexually transmitted diseases (STD) prophylaxis and protection from unwanted pregnancy. The in-vivo mechanism of action of topical spermicide/microbicide is not known, but it has been presumed to act locally in the vaginal canal. A spermicide may act at, or near, the exocervix to kill spermatozoa before they enter the upper female genital tract. The sites of HIV infection within the female reproductive tract are not known. There is evidence to suggest that macrophages and Langerhans’ cells, located throughout the vaginal epithelium, are likely targets (Spira et al., 1996; Miller, 1998; Sodora et al., 1998). Thus, a topical anti-HIV preparation would optimally cover the entire vaginal epithelium to prevent transmission of the virus. It is possible, however, that the cells of the upper genital tract such as the endocervical, endometrial or tubal mucosa may also be target sites of infection. Currently it is unknown if a topical microbicide migrates, or is transported, into the upper genital tract. If so, does such migration serve any function?

Magnetic resonance imaging (MRI) has been successfully used to image the female pelvis and detect vaginal or other Mullerian anomalies with high sensitivity (Siegelman et al., 1997; Barnhart et al., 2001). This investigation was performed to establish if MRI could be used to determine the intravaginal distribution of an over-the-counter vaginal product in a human subject and determine if any of the gel could be detected outside the vaginal canal.
Figure 1. T1-weighted fat saturated gradient echo MR images obtained 5 min following contraceptive gel insertion demonstrates high contrast between the gadolinium enhanced gel and the unenhanced pelvic structures. (A) Sagittal image allows quantification of gel thickness by measuring the gel in the anterior-posterior dimension. The gel is thickest just below the cervix, but gel is visualized in the posterior vaginal fornix and in the distal vaginal canal. Gel is visualized in the cervical canal and gel is demonstrated in the entire vaginal canal form the posterior vaginal fornix to the introitus. (B) Axial image allows quantification of the gel transversely in the cervical canal and vaginal fornix. (C) Sagittal image demonstrates gel in the entire vaginal canal and spillage of gel from the introitus.

Materials and methods

After obtaining institutional approval to perform this experiment on human subjects, a single nulliparous volunteer with normal menstrual cycles and no gynaecological pathology was recruited. This subject underwent a MRI scan of the pelvis following the insertion of 5 ml of Gynol-II® (Advanced Care Products, North Brunswick, NJ, USA) mixed with a previously determined concentration of 1:100 of Gadolinium-based MR contrast material [gadolinium chelate magnivist (gadopentate dimeglumine; Berlex Laboratories, Wayne, NJ, USA)] (Barnhart et al., 2001). The mixture was self-inserted using a standard clinical applicator. The subject then ambulated to the MRI table. MR images were obtained 10 min after insertion. The MRI was performed in the mid-follicular phase of the menstrual cycle (day 8 from last normal menstrual period). Images were obtained using a fat-saturated, T1-weighted gradient echo using a GE 1.5T Sigma scanner (GE Medical Systems, Milwaukee, WI, USA) with the assistance of a phased array surface coil centred on the pelvis as previously described (Barnhart et al., 2001).

The amount and spread of gel were quantified. Measurements were obtained using electronic callipers of digitally stored images at the following anatomical structures: (i) at the posterior vaginal fornix (measurements taken in the anterior and posterior (AP) and longitudinal plane (craniocaudal)]; (ii) 1 cm below the cervix (measurement taken in the AP and transverse plane); (iii) at the flexure of the vagina as it passes through the pelvic diaphragm (AP and transverse); (iv) at the mid–lower vagina, 3 cm above the introitus (AP and transverse); and (v) just above (1 cm) the introitus (AP and transverse).

Results

Quantification of spread of gel in the vaginal canal

After 10 min the gel spread within the vaginal canal providing a contiguous covering of the epithelium of variable thickness. Gel thickness and transverse spread were quantified in demarcated sites in the vagina (Figure 1A). The majority of gel was visualized in the upper vagina as demonstrated by an increase in the thickness of the gel (AP measurements) at or above the pelvic diaphragm. In the posterior vaginal fornix there was 2 mm of gel noted in the AP dimension and 31 mm noted in the longitudinal dimension. One cm below the cervix there was 7 mm of gel in the AP and 41 mm in the transverse dimension. At the flexure of the vagina, as it passed through the pelvic diaphragm, there was 4 mm of gel in the AP and...
36 mm in the transverse dimension. Three centimetres above the introitus there was 1 mm of gel in the AP and 20 mm in the transverse dimension. One centimetre above the introitus there was 3 mm of gel in the AP and 29 mm in the transverse dimension.

**Visualization of gel outside the vaginal canal**

The majority of the gel was located in the vaginal canal. However, spread of material into the cervical canal is clearly demonstrated in Figure 1A and 1B. Additionally, some leakage of material from the introitus was noted (Figure 1C).

**Discussion**

Our data demonstrate that a vaginally-placed product spreads contiguously throughout the vagina. Some of the material is lost as discharge from the introitus and importantly some is visualized in the upper female genital tract. These images depict for the first time the identification of a labelled contraceptive preparation in the endocervix as soon as 10 min after vaginal administration. While this finding is based on only a single patient, it strongly suggests that vaginal products are transported into the upper genital tract of at least some women.

It has been assumed that, to provide contraception, a spermicidal compound should kill spermatozoa before they enter the upper genital tract (Sangi-Haghpeykar et al., 1996; Mauck et al., 1997a,b). However, spermatozoa are located in the cervical mucus almost immediately after coitus (Sobero and McLeod, 1962). Additionally, spermatozoa are transported to the oviduct and peritoneal cavity almost immediately after insemination in rabbits (Overstreet and Cooper, 1978) and are located in the human Fallopian tube within 5 min (Settlage et al., 1973). The speed of passage far exceeds the swimming velocity of spermatozoa. In fact, artificial insemination with dead spermatozoa results in rapid transport into the upper genital tract (Drobnis and Overstreet, 1993). There is evidence that rapid sperm transport through the female genital tract is provided by uterine contractions (Kunz et al., 1996). Imaging with hysterosalpingoscintigraphy has demonstrated that there is immediate ascension of macrospheres (the size of spermatozoa) into the Fallopian tubes following deposition at the external os of the cervix (Kunz et al., 1996). This process is thought to be mediated by uterine peristalsis controlled by endocrine and possibly paracrine events (Kunz et al., 1998). Thus, it is not surprising that there may be transport of vaginal topical medications into the upper tract by similar mechanisms.

The initial bolus of gel was delivered into the upper portion of the vagina, above the urogenital diaphragm. This is determined by the design and dimensions of the applicator. Thereafter, the bolus of gel is spread into the vaginal fornices and ‘flattened’ to cover the lateral aspects of the vagina. Without ambulation, the majority of this early spread was confined to the upper vagina. With ambulation and longer elapsed time, there was further spread of gel in the upper vagina, as well as spread into the lower vagina and a concomitant significant increase in overall vaginal surface coverage (Barnhart et al., 2001). The amount of material and the confined dimensions of the vagina allow reproducible quantification of gel thickness to 1 mm. The amount of material transported to the upper tract cannot be easily quantified. Small amounts of gel are likely to be taken up into the upper tract. The material is diluted as it moves from the vagina, to the endocervical canal, into the endometrial cavity and possibly into the Fallopian tubes.

It is critical to describe and quantify the distribution of intravaginal products in order to optimize their formulation (e.g. volume, viscosity, bioadhesive properties). The demonstration of transport of topical vaginal medications into the upper genital tract has important clinical implications. Transport into the cervix, uterus and tubes may represent an important unrecognized contraceptive or microbicidal mechanism of action of these compounds. The vaginal mucosa is relatively inert compared with that of the endocervix or endometrium (Barnhart and Shalaby, 1998). Gonorrhoea in women usually involves the endocervix and may result in pelvic inflammatory disease. Primarily, gonococcal infection of the vagina is rare (Sweet and Gibbs, 1995). *Chlamydia trachomatis* has been implicated in endocervicitis, endometritis and pelvic inflammatory disease. It does not cause vaginitis or appear to grow in vaginal squamous epithelium (Sweet and Gibbs, 1985). The site of HIV transmission in the female genital tract has yet to be definitively determined, but the portal of entry may be via endocervical or other upper genital tract mucosa. Thus, spread of a compound prophylactic against sexually transmitted infection to the upper tract, where infection may be more likely to take place, may be advantageous or even optimal. Conversely, since topically placed compounds may enter the upper tract, or be absorbed systemically, their safety should be demonstrated.

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**References**


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