ELSEVIER

Contraception xx (2016) xxx – xxx

Contraception

Original research article

Transcervical administration of polidocanol foam prevents pregnancy in female baboons☆,☆☆

Jeffrey T. Jensen[a,b,*], Carol Hanna[b], Shan Yao[b], Emily Thompson[b], Cassondra Bauer[c], Ov D. Slayden[a,b]

[a]Department of Obstetrics & Gynecology, Oregon Health & Science University (OHSU), Portland, OR
[b]Division of Reproductive and Developmental Sciences, Oregon National Primate Research Center, Beaverton, OR
[c]Southwest National Primate Research Center, San Antonio, TX

Received 6 March 2016; revised 6 July 2016; accepted 10 July 2016

Abstract

Background: Our objective was to conduct a pilot study to determine if transcervical administration of polidocanol foam (PF) with or without doxycycline or benzalkonium chloride (BZK) would prevent pregnancy in baboons.
Methods: In study phase 1, adult cycling baboons underwent a hysterosalpingogram to evaluate tubal patency prior to transcervical infusion of 20 mL of 5% PF followed by 1 mL of saline containing 100 mg doxycycline (5%/doxy; *n*=5), 3% PF plus doxycycline (3%/doxy; *n*=4), 3% PF with 0.01% BZK (3%/BZK; *n*=4) or no additional treatment (control; *n*=9). Immediately following treatment, animals received intramuscular depot medroxyprogesterone acetate (DMPA, 2 mg/kg) to suppress cyclicity during healing and were then socially housed with males of proven fertility. The primary outcome was pregnancy within six cycles of resumption of menses (efficacy phase 1). During study phase 2, PF-treated females from study phase 1 contributed additional cycles (6–8) of exposure (efficacy phase 2), and 5 control females who had recovered from medical abortion (after study phase 1 pregnancy) were subsequently treated with 5% PF (with DMPA) and exposed to breeding (efficacy phase 1; *n*=3 six cycles, *n*=2 five cycles).
Results: All females resumed normal menstrual cycles and mating activity after DMPA. During efficacy phase 1, 7/9 (78%) control females became pregnant. In contrast, fewer pregnancies occurred in PF-treated females: 5% PF 0/5 (0%), 5%/doxy 1/5 (20%), 3%/doxy 1/4 (25%) and 3%/BZK 1/4 (25%). During efficacy phase 2, only one additional pregnancy occurred (3%/BZK).
Conclusions: A single transcervical treatment with 5% PF prevented pregnancy in most baboons. Cotreatment with doxycycline or BZK did not improve results.
Implications: Transcervical intrauterine administration of PF resulted in a high rate of tubal occlusion with prevention of pregnancy; refinements are needed to increase the contraceptive rate following a single treatment to near 100%.

Keywords: Nonhuman primate; Sterilization; Nonsurgical; Female; Polidocanol; Permanent contraception

1. Introduction

Permanent methods of contraception are appropriate for women who have completed their desired family size and who wish never to become pregnant again. Although vasectomy also provides permanent contraception, around the world and in the United States, female procedures predominate [1–3]. Although the limited uptake of vasectomy may reflect poor acceptability by men, many women prefer female permanent contraception to protect themselves from undesired future pregnancies. While over 95% of vasectomized men in the United States report that they are currently or previously married, over 18% of sterilized

☆ Financial support: This research was supported by generous grants from the Bill & Melinda Gates Foundation (OPP1025233, OPP1060424). Core facilities at Oregon National Primate Research Center and Southwest National Primate Research Center are supported by National Institutes of HealthP51 OD011092 and P51 OD011133.
☆☆Conflicts of interest: None of the authors have financial conflicts of interest related to this research.
* Corresponding author. Tel.: +1 503 629 4058; fax: +1 503 494 3111.
E-mail address: jensenje@ohsu.edu (J.T. Jensen).

http://dx.doi.org/10.1016/j.contraception.2016.07.008

women have never been married [4]. Unfortunately, the availability of surgical permanent contraception for women varies widely in many regions, leading to unmet need for services [5,6]. The widespread use and preference for female methods support the development of nonsurgical options.

We have reported that transcervical administration of polidocanol (hydroxy-polyethoxy-dodecane) foam (PF) results in tubal occlusion in macaques and baboons [7,8]. In baboons, we observed a dose-dependent histological effect consistent with complete tubal occlusion (complete replacement of epithelium with collagen) confined to the intramural tubal segment in most animals treated with 5% PF [7]. Hormonal suppression with intramuscular depot medroxyprogesterone acetate (DMPA) may improve treatment results with PF; complete occlusion was seen in 4/4 females that received 5% PF followed by DMPA but in only 2/3 that received 5% PF without DMPA.

As 5% PF is higher than the concentration currently FDA approved for vein sclerotherapy (1%), we have performed pilot investigations of adjunctive agents to improve the effectiveness of lower concentrations. We previously reported that the addition of dilute (0.01%) benzalkonium chloride (BZK) (a common preservative) to polidocanol improves the stability of the resulting foam [9]. While unproven, we hypothesize that duration of foam exposure may be associated with greater tissue effects.

Doxycycline is another venous sclerosing agent [10]. While the effects of coadministration of PF and doxycycline are unknown, we further hypothesized that combining these agents could improve the rate of tubal occlusion.

Herein, we conducted a pilot fertility study in baboons to determine whether a single transcervical treatment with PF would prevent pregnancy. We evaluated two concentrations of PF and tested whether the administration of intrauterine doxycycline as a co-sclerosant or BZK would improve the contraceptive outcome. We also evaluated the histologic features induced by these treatments.

2. Materials and methods

2.1. Animal care

All study procedures were approved by the Southwest National Primate Research Center (SNPRC) Institutional Animal Care and Use Committee. Twenty-two adult female and two adult male baboons (*Papio anubis, Papio anubis/hamadryus* hybrids) of proven fertility were used in this study. Animal husbandry provided by SNPRC is in accord with the National Institutes of Health Guidelines for Care and Use of Laboratory Animals [11]. Menstrual cyclicity was monitored by evaluation of sex skin tumescence and confirmed by measurement of serum estradiol and progesterone as previously described [7]. Observation of a semen plug was considered to be evidence of mating. A blood sample for complete blood count and chemistry panel was obtained prior to treatment and at the end of study.

In an effort to standardize our evaluation of animals, all females not expected to be in the follicular phase on the day of evaluation were pretreated with a combined oral contraceptive (30 mcg ethinyl estradiol/150 mcg levonorgestrel) for 15–21 days and then allowed to have a 6–7-day hormone-free interval prior to treatment to induce a withdrawal bleed.

2.2. Clinical evaluation of tubal patency

Females underwent a hysterosalpingogram (HSG) procedure to confirm tubal patency as previously described [7]. Briefly, under transabdominal ultrasound guidance, we passed a small silicone HSG balloon catheter (model J-CHSG-503000; Cook, Bloomington, IN, USA) through the cervix into the uterine cavity. A series of digital radiographs was obtained to evaluate tubal patency (unilateral patent, bilateral patent, bilateral nonpatent) following the infusion of small aliquots (1–3 mL) of radiopaque contrast (Isovue®, iopamidol injection; Bracco Diagnostics, Monroe Township, NJ, USA). At the end of the study, tubal patency was assessed ex vivo by introducing an HSG catheter transcervically and then infusing an indigo carmine saline solution into the uterine cavity under mild pressure observing for spill of dye from the tubal fimbria.

2.3. Polidocanol foam and adjunctive treatments

Polidocanol 3% and 5% solutions were prepared by mixing polidocanol stock (Sigma P9641) with sterile physiologic buffered saline. To prepare polidocanol solution containing 0.01% BZK, we added BZK (Sigma-Aldrich 234427) to 3% stock polidocanol solution mixing overnight [9].

We prepared PF using a ratio of 1 mL solution to 4 mL air to generate 5 mL foam [7]. For all PF treatment groups, a total of 20 mL of foam was instilled via the HSG catheter into the uterine cavity over 2–4 min.

Some females received doxycycline (100 mg/mL), prepared by diluting pharmaceutical-grade doxycycline powder (Novaplus, Irving, TX, USA) in sterile saline, as a 1-mL bolus via the HSG catheter following the foam treatment.

All control and PF-treated females received a single dose of DMPA (2.0 mg/kg, im; Pharma & Upjohn [Pfizer], New York, NY, USA) immediately following the HSG examination.

2.4. Contraceptive experiment

The overall design of the contraceptive experiment is illustrated in Fig. 1. In study phase 1, the initial treatment groups were 5% PF followed by doxycycline (5%/doxy), 3% PF plus doxycycline (3%/doxy), 3% PF with 0.01% BZK (3%/BZK) and untreated controls. We defined the first six ovulatory cycles of exposure to the male as efficacy phase 1. Study phase 2 began after completion of this initial efficacy phase. Nonpregnant PF-treated animals remained in the