Associated Pharmacologists & Toxicologists

April 24, 2000

Dr. Jane E. Henney
Commissioner of the Food & Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Henney,

Enclosed you will find three copies of our Citizen's Petition requesting that FDA approval of the Today Contraceptive Sponge be withdrawn.

Please contact me if you would like additional information on any of the topics discussed in the Petition.

Sincerely yours,

Armand Lione, Ph.D.
President,
APT
202.244.1384

83P-0187

CP 3

Associated
Pharmacologists &
Toxicologists

April 24, 2000

Dr. Jane E. Henney
Commissioner of the Food & Drug Administration
5600 Fishers Lane
Rockville, MD 20857

CITIZEN PETITION

The undersigned submits this petition under 21 CFR 15 10.25 of the Federal Food, Drug and Cosmetic Act to request that you, Dr. Henney, the Commissioner of the US Food and Drug Administration, withdraw FDA approval for the marketing of the Today Contraceptive Sponge because this product cannot be used as recommended without frequently causing damage to genital tissues that increases the users risk of toxic shock syndrome (TSS) and infection with the Human Immunodeficiency Virus (HIV).

Summary

1. The spermicide in the Today Contraceptive Sponge can promote the survival of pathogenic organisms in the vagina.
2. The use of the Today Sponge as currently recommended is likely to cause vaginal irritation and tissue damage more frequently than any other non-prescription contraceptive.
3. When used as recommended, the Today Contraceptive Sponge can damage the vaginal and cervical epithelium and increase the risk of TSS and HIV infection.

4007 Connecticut Ave., Washington, DC 20008 202.244.1384

Statement of Grounds

The Today Contraceptive Sponge, when used as directed, is likely to cause damage to vaginal and cervical tissue more frequently than any other non-prescription contraceptive. Clinical reports on the use of this product have shown that it increases the risk of toxic shock syndrome, and, when used repeatedly, it may alter the vaginal environment and harm the surface tissues of the vagina and cervix, thereby increasing susceptibility to various infections, including infection with the AIDS virus. Because of serious defects in the design, composition and recommended use of this product, the Today Contraceptive Sponge should not be sold as an over-the-counter contraceptive.

Detailed Statement of Grounds

The Today Contraceptive Sponge is a round piece of polyurethane foam that contains 1 gram of the detergent/spermicide, Nonoxynol-9 (N-9). In our previous petition (and supplements)(APT Petition, 1983,1984,1992), we cited research showing that this product was inadequately tested in animals before being sold for human use, and the limited data from clinical tests suggested that the Today Contraceptive Sponge would be a frequent cause of vaginal and cervical irritation when used as directed. Also in our original petition, we speculated that this irritation could be a factor in increasing a woman's risk of developing toxic shock syndrome. Since that petition, reports by members of the FDA and the Centers For Disease Control & Prevention have confirmed that this product does increase the risk of TSS (Faich et al, 1986; Schwartz et al, 1989).

Additional data on the irritating properties of this product and other products containing N-9 have grown out of research into the possible role N-9 and the Today Contraceptive Sponge might play as a means of controlling the spread of infection with Human Immunodeficiency Virus (HIV), the causative agent for AIDS. This research has clearly demonstrated that N-9 is not a suitable agent to deter infection with the AIDS virus. Rather, available reports now show that in adequate doses and with frequent use, N-9 alters the vaginal flora to increase the likelihood that pathogens will survive, and with repeated exposure this spermicide can erode the tissues lining the vagina and cervix, facilitating the entrance of the AIDS virus.

Most of the data available on these matters has been generated in studies that used N-9-containing products other than the Today Contraceptive Sponge. However, all of the concerns that have been raised in tests using other products are likely to be most severely manifested in association with the use of the Today Contraceptive Sponge, since it contains more N-9 (1 gram) than any other OTC contraceptive and it is recommended to be left in place longer (30 hours) than any other non-prescription contraceptive.

Harmful Alterations in the Vaginal Environment Caused by N-9.

Since the early 1990s, there has been a growing body of evidence that some of the normal bacteria that colonize the vagina, ie., the lactobacilli, can inhibit the growth of a number of pathogenic organisms, including the AIDS virus (Ongradi et al, 1990; Klebanoff & Coombs, 1991; O'Conner et al, 1995). The mechanism by which the lactobacilli restrict the growth of pathogenic organisms is believed

to involve the production of peroxide and lactic acid, which are toxic to many pathogens (Klebanoff & Coombs, 1991).

In recent tests, investigators have evaluated how various doses of N-9 in the vagina may affect the normal growth and activity of lactobacilli (McGroarty et al, 1990; Rosenstein et al 1997; Stafford et al, 1998). For example, McGroarty et al (1990) studied the possible effect of N-9 on lactobacilli and pathogenic bacteria in vitro. Their data showed that most lactobacilli were either inhibited in growth or killed by concentrations of N-9 equal or greater that 1% (McGroarty et al, 1990). Pathogenic bacteria, such as E. coli and Staphylococcus aureus (the causative agent of toxic shock syndrome) were shown in this study (and elsewhere (Kramer & Nickerson (1984)) to be far more resistant to detergent effects than were the lactobacilli, suggesting that the presence of the detergent/spermicide, N-9, may facilitate the survival of some pathogens in the vagina.

In one clinical study, Rosenstein et al (1997) found that 100 mg doses of N-9 on four consecutive nights decreased vaginal lactobacilli and significantly increased the likelihood of vaginal colonization with abnormal bacilli. They concluded that the continuous use of N-9 could increase susceptibility to urinary and gynecological infections (Rosenstein et al, 1997). Stafford et al. (1998) performed a clinical study in which women used a daily dose of 100 mg N-9 for seven days. The researchers found that this use of N-9 was associated with a reduction in numbers of vaginal lactobacilli. They also reported on the signs of vaginal irritation and tissue disruption that were associated with the daily use of N-9.

N-9 Irritation and Erosions of the Vaginal Epithelium

The preceding article by Stafford et al. (1988) is only one of several recent articles on the vaginal irritation caused by N-9 (Niruthisard et al, 1991; Roddy et al, 1993; Patton et al, 1999). Although this detergent/spermicide has been in commercial use for nearly 60 years, details on its adverse effects on the vaginal environment and vaginal tissues have largely been reported in the last decade. Attention was particularly focussed on this topic after the publication of a 1992 article by Kreiss et al (1992) that reported an increased incidence of HIV infections in Nairobi prostitutes who used the Today Contraceptive Sponge. Although subsequent observations did not implicate the use of the Today Sponge as the clear culprit in the increased incidence of genital ulcers and HIV infections in the sex workers (the placebo used in this study may have been a superior lubricant and actively decreased the likelihood of vaginal irritation), this article did bring needed attention to the possible role N-9-containing contraceptives may play in vaginal pathology and the acquisition of an HIV infection.

The study by Stafford et al (1988) on the vaginal irritation caused by N-9 involved two groups of 20 women, in which one group used 100 mg N-9 for 7 days. The second group used a placebo gel. Genital irritation was reported by 10 women using N-9 and 5 women in the placebo group; colposcopy showed erythema in 9 of the N-9

Older Irritation Data

The absence of clinical data on the safety of repeated use of the Today Sponge was cited in the original petition as one of the reasons it was not safe enough to be sold as an OTC contraceptive. The limited data available at the time of its first approval (in 1983), showed that in 15 women studied by the manufacturer, one-third of them developed vaginal irritation after using the sponge for seven consecutive days (FDA, 1983a).

group and 2 of the placebo group; tissue inflammation was found in 7 of the N-9 group and 2 of the placebo group. Based on the tissue reactions they observed, these investigators concluded that a daily 100 mg dose of N-9 is unsuitable as a microbicide.

The Amount of N-9 Released by the Today Sponge.

The manufacturer has adopted a convenient fiction that the Today Sponge releases only 125 mg of N-9 during each use. Since each Sponge contains a reservoir of 1,000 mg of N-9, the suggestion of a single number for the amount of N-9 released is immediately suspect. As was pointed out by Dr. William J McCann, in his Medical Officers Review of the Today Sponge for the FDA (FDA, 1983b): "there is substantial variation in the amount of N-9 eluted from the sponge over time in the individual patient, due in great part to the variation in the amount of vaginal fluids absorbed, seminal fluid absorption, menstrual blood absorbed, numbers of coital episodes and the measure of wetting of the sponge prior to insertion." Despite the broad array of factors that contribute to "substantial variation" in the amount of N-9 released, the FDA has left unchallenged the assertion that 125 mg of N-9 represents the typical N-9 exposure associated with the use of a Today Sponge. It would seem inherently more credible if the amount released was represented by an upper and lower range of values for a typical user. 125 mg of N-9 is far too small to represent the center of the typical range of exposures derived from the Sponge.

Niruthisard et al. (1991) performed a clinical study to determine the effects of frequent insertion of a 150 mg dose of N-9 over a 14 day period. The frequency studied here was four insertions per day. In a group of 19 women, 14 used N-9 containing products, and 5 used placebos. The investigators found that six of the 14 women who used the N-9 inserts (43%) had vaginal and/or cervical epithelial disruptions, which included blood loss. It should be noted that none of these women experienced symptoms that prompted them to discontinue the study. The investigators concluded "...as with any medication or device, N-9 may be appropriate at one frequency and dosage but inappropriate at a higher level."

The study by Niruthisard et al. (1991) was followed by a phase II dosing study to determine the signs and symptoms of genital irritation produced by different frequencies of N-9 use (Roddy et al., 1993). Using suppositories like those used by Niruthisard et al. (1991), containing 150 mg N-9, 5 groups of 35 women applied the suppositories at the following frequencies: once every other day; once a day; twice a day; four times a day; and placebo four times a day. The women agreed to refrain from sexual intercourse during the study. The investigators found that women using N-9 every other day had an incidence of epithelial disruption comparable to that in the women who used the placebo product. Use of N-9 once or twice daily produced epithelial disruption more than twice as much as the use of placebo. N-9 use 4 times a day increased the rate of epithelial disruption to about 5 times that associated with placebo use. The investigators focussed attention on the incidence of epithelial disruption because it had been defined as a critical factor for increasing the risk of HIV transmission.

In this study, as well as in the preceding study by Niruthisard et al. (1991), no relationship was found between reports of symptoms by women and the presence of vaginal and cervical epithelial disruption. The authors pointed out that this fact "makes it difficult to obtain reliable information from simple interview surveys among women to determine the prevalence of important signs of irritation, such as epithelial disruption."

More recently, Patton et al. (1999), working in the pigtailed macaque (monkey), applied intravaginal doses of 60 mg of N-9 for 3 days, then left the animals untreated for 2 days, and again treated the animals with the same N-9 dose for 3 additional days. This exposure schedule resulted in vaginal and cervical erythema in all

four N-9 treated animals, cervical papillae in 3 of the four, and cervical petechial hemorrhage in one animal. The investigators concluded that their data "confirm that the repeated use of N-9 is detrimental to epithelial tissues in the lower reproductive tract."

N-9, Tissue Disruption and Increased Risk of HIV Infection.

In an article published in December of 1999, a small study done in sex workers produced data that indicated the absence of vaginal lactobacilli was associated with an increased risk of HIV infection and gonorrhea (Martin et al, 1999).

Even more provocative findings were reported by Rustomjee et al. (1999) who found that women with genital lesions were much more likely to have vaginal HIV-RNA (an indicator of vaginal shedding of the AIDS virus) than were women without genital lesions. Although preliminary, these data suggest that when used by women previously infected with the AIDS virus, the Today Contraceptive Sponge may increase the viral exposure of the sex partners of HIV infected women.

General Concerns

Cumulative experience with the previous sale of the Today Contraceptive Sponge has shown that removal problems are among the most commonly reported (APT Petition 1992). In the course of removing this product, prolonged exposure of the vagina to spermicide and additional vaginal damage may occur as a women attempts to probe her vagina to remove the Sponge.

Observations by investigators such as Niruthisard et al (1991) and Roddy et al (1993) indicate that the typical user of this product may not be aware of the tissue damage that has been done to her vagina or cervix. Thus, consumer complaints from users of this product only

represent a small fraction of the women who may have experienced harm. It must also be kept in mind that an OTC product such as the Today Sponge may be purchased and used by young people who do not wish to publicly acknowledge their contraceptive practices. Therefore, complaint reports from users may often be stifled by fears of public embarrassment and compromised privacy regarding sexual activity.

Conclusion

The predictable irritation and vaginal damage caused by the Today Contraceptive Sponge, when used as currently recommended, is likely to be far greater that that caused by any other OTC contraceptive. Because this damage increases the risk of life-threatening infections due to toxic shock syndrome and the AIDS virus, this product should not be approved for sale as an over-the-counter contraceptive.

Certification

The undersigned certifiers, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information know to the petitioner which are unfavorable to the petition.

Judith Braiman
Empire State Consumer Assoc.
50 Landsdowne Lane
Rochester, NY 14618

Armand Lione, Ph.D.*
President,
APT
Washington, DC
202.244.1384

*Please address all correspondence to Dr. Lione.

References

APT Petition: "A citizen's petition on the safety evaluation of the Contraceptive Sponge," submitted to the U.S. Food & Drug Administration, June 21, 1983. Docket no. 83P-0187/CP0002.

APT Petition Supplement: "Clinical reports on vaginal irritation and toxic shock syndrome associated with the use of the Today Contraceptive Sponge," Supplement to Citizen Petition 83P-0187/CP0002. U.S. Food & Drug Administration, Rockville, MD, June 25, 1984.

APT Petition Supplement 2: "Drug Experience Network Data on the Safety of the Today Contraceptive Sponge." Petition Supplement, submitted to the U.S.Food and Drug Administration, March 1992.

Faich G, Pearson K, Fleming D, Sobel S, Anello C: Toxic shock syndrome and the vaginal contraceptive sponge. JAMA 255:216-8, 1986.

FDA's Approval of the Today Contraceptive Sponge." Hearing before a Subcommittee of the Committee on Government Operations, 98th Congress, 1st Session; July 13, 1983. Government Printing Office, Washington,DC.

a. VLI Technical Review, p. 508.

b. Dr. McMann's letter pp. 350-1.

Klebanoff SJ, Coombs RW: Virucidal effect of Lactobacillus acidophillus on human immunodeficiency virus types: possible role of heterosexual transmission. J Exp Med 1991; 174:289-92.

Kramer VC, Nickerson KW: A transport-dependent energy burden imposed by growth of Enterbacter cloacae in the presence of 10% sodium dodecyl sulphate. Can J Microbiol 30:699-702, 1984.

Kreiss J, Ngugi E, Holmes K et al: Efficacy of nonoxynol 9 contraceptive sponge use in preventing heterosexual acquisition of HIV in Nairobi prostitutes. JAMA 1992;268:477-82.

Martin HL, Richardson BA, Nyange PM et al.: Vaginal lactobacilli, microbial flora, and risk of human immunodeficiency virus type 1 and sexually transmitted disease acquisition. J Infect Dis 1999;180:1863-8

McGroarty JA, Chung S, Reid G, Bruce AW: Influence of the spermicidal compound nonoxynol-9 on the growth and adhesion of urogenital bacteria in vitro. Curr Microbiol 1990;21:219-23.

Niruthisard S, Roddy RE, Chutivongse S: The effects of frequent nonoxynol-9 use on the vaginal and cervical mucosa. Sex Transm Dis 1991;18:176-9.

O'Connor T, Kichington D, Kangro H, et al: The activity of candidate virucidal agents, low pH and genital secretions against HIV 1 in vitro. Int J STD AIDS 1995;6:267-72.

Ongradi J, Cecchevirus-Nelli L, Pistell M et al: Acid sensitivity of cell-free and cell-associated HIV-1: clinical implications. AIDS Res Human Retrovirus 1990; 6:1433-6.

Patton DL, Ganzle Kidder G, Cosgrove Sweeney Y, Rabe LK, Hillier SL: Effects of multiple application of benzalkonium chloride and nonoxynol 9 on the vaginal epithelim in the pigtailed macaque. Am J Obstet Gynecol 1999;180:1080-7.

Roddy RE, COrdero M, Cordero C, Fortney JA: A dosing study of nonoxynol-9 and genital irritation. Int J STD AIDS 7:165-70, 1993.

Rosenstein IJ et al: Effect on normal vaginal flora of three intravaginal microbicidal agents potentially active against human immunodeficiency virus type 1. J Infect Dis 1998; 177:1386-90.

Rustomjee R, Abdool Karim Q, Abdool Karim SS, Laga M, Stein Z. Phase 1 trial of nonoxynol-9 film among sex workers in South Africa. AIDS. 1999;13:1511-5.

Schwartz B, Gaventa S, Broome CV et al: Nonmenstrual toxic shock syndrome associated with barrier contraceptive: report of a case-control study. Rev Infect Diseases II(supp 1):S43-8, 1989.

Stafford MK, Ward H, Flanagan A, Rosenstein IJ, Taylor-Robinson D, Smith JR, Weber J, Kitchen VS: Safety study of nonoxynol-9 as a vaginal microbicide: evidence of adverse effects. J Acquir Immune Defic Syndr Hum Retrovirol 1998;17:327-31.