Associated
Pharmacologists &
Toxicologists

February 27, 1992

Dr. David Kessler
Commissioner
Food & Drug Administration
Rockville, MD

Dear Dr. Kessler:

We originally petitioned the FDA (copies enclosed) to halt the sale of the Today Contraceptive Sponge because we suspected it would be a frequent cause of vaginal irritation and an agent capable of increasing the user's risk of Toxic Shock Syndrome. Now there is an extended basis of user experience to support these concerns:

1. Data in the the Drug Experience Network as of 1/16/92 indicates that more than 47% of the complaints filed regarding the Today Sponge included either cervicitis or vaginitis.

These forms of irritation were predictable effects of the use of the Today Contraceptive Sponge because it contains more of the detergent/spermicide, nonoxynol 9, (1 gram/sponge) than any other OTC vaginal contraceptive, and the detergent is left in the vagina, with a polyurethane foreign body, longer than any other product. As was discussed in the petitions, the Today Contraceptive Sponge was formulated to contain the maximal feasible amount of N-9 in the sponge because the use of smaller quantities were grossly ineffective as contraceptives. It should also be noted that the complaints

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83P-0187 LET6

regarding the ineffectiveness of the Sponge (no drug effect, 102: pregnancy unintendec, 678) constitute 26% of all reports in the Drug Experience Network.

It is also important to note that the current package insert for the Sponge does not make it clear to the user that cervicitis and vaginitis are the most common complaints that have been associated with this contraceptive.

2. In 1986, Faich et al reported in the Journal of the American Medical Association (copy enclosed) that the use of the Today Sponge was associated with an increased incidence of Toxic Shock Syndrome.

This report lends further credence to the concerns originally brought before the FDA regarding the health risks associated with the Today Sponge.

An additional point raised in the petitions was the possibility that the continued use of the Sponge might increase the risk of vaginal or cervical neoplastic disease. This concern was based on the presence of the carcinogen, dioxane, in the spermicide, N-9, and the unknown risks that may be associated with the intravaginal use of a polyurethane. Clincal data on the possible carcinogenic effects of the Sponge are both unlikely and undesireable as a way to investigate this question. We would point out again that this matter has not been investigated adequately in the available animal models for studying vaginal carcinogens.

In the light of our continuing concerns regarding the possible carcinogenicity of the Sponge, and the reported adverse effects, which we cite above, we again request you review the safety and effectiveness of the Today Contraceptive Sponge. As we stated in our original petitions, we do not believe that this contraceptive product is safe and effective enough to be on the market.

Sincerely yours,

Armand Lione*
President,
Associated Pharmacologists &
Toxicologists

Judy Braiman-Lipson
President,
Empire State
Consumer Assoc.

Enclosures:

1. Petition, Empire State Consumer Association, Inc., #83P-0187/cp
2. Petition, Associated Pharmacologists & Toxicologists, #83P-0187/cp0002
3. Petition Supplement, (6/25/84), Associated Pharmacologists & Toxicologists, #83P-0187/cp0002
4. Summary, Drug Experience Network, Food & Drug Administration records for the Today Contraceptive Sponge, 1/16/92
5. Faich G et al: Toxic Shock Syndrome and the Vaginal Contraceptive Sponge. JAMA 255:216-8, 1986.

*to whom correspondence should be addressed.

FDA SPONTANEOUS REPORTING SYSTEM
CAUSE-EFFECT RELATIONSHIP BETWEEN EACH DRUG AND REACTION
CANNOT BE ESTABLISHED WITH CERTAINTY IN ALL CASES

TODAY

REPORT SOURCE	COSTART	TOTAL OCCURRENCES
DOMESTIC	ABDO ENLARGE	1
DOMESTIC	ABORTION	7
DOMESTIC	ABSCESS	1
DOMESTIC	ACIDOSIS DIABET	1
DOMESTIC	ALLERG REACT	125
DOMESTIC	ANURIA	1
DOMESTIC	APPLICAT SITE REACT	202
DOMESTIC	ARTHRALGIA	2
DOMESTIC	ARTHROSIS	2
DOMESTIC	ASTHENIA	11
DOMESTIC	ASTHMA	1
DOMESTIC	BALANITIS	14
DOMESTIC	BODY ODOR	1
DOMESTIC	BUN INC	1
DOMESTIC	CERVICITIS	16
DOMESTIC	CERVIX DIS	1062
DOMESTIC	CHILLS	4
DOMESTIC	CHILLS FEVER	15
DOMESTIC	CREATININE INC	2
DOMESTIC	CYST	2
DOMESTIC	CYSTITIS	47
DOMESTIC	DERM CONTACT	13
DOMESTIC	DERM EXFOL	13
DOMESTIC	DERM FUNG	1
DOMESTIC	DIARRHEA	28
DOMESTIC	DIARRHEA BLOODY	1
DOMESTIC	DIZZINESS	34
DOMESTIC	DYSMENORRHEA	1
DOMESTIC	DYSPAREUNIA	2
DOMESTIC	DYSPEPSIA	1
DOMESTIC	DYSPNEA	4
DOMESTIC	DYSURIA	27
DOMESTIC	EDEMA	8
DOMESTIC	EDEMA FACE	6
DOMESTIC	EDEMA LABIA	8
DOMESTIC	EDEMA PERIPH	1

FDA SPONTANEOUS REPORTING SYSTEM
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TODAY

REPORT SOURCE	COSTART	TOTAL OCCURRENCES
DOMESTIC	ENDO DIS	1
DOMESTIC	ENDOMETR DIS	3
DOMESTIC	ENZYME ABNORM	2
DOMESTIC	EYE DIS	1
DOMESTIC	FEVER	88
DOMESTIC	FLATUL	2
DOMESTIC	FLU SYND	15
DOMESTIC	GAIT ABNORM	1
DOMESTIC	GLOSSITIS	1
DOMESTIC	HEADACHE	10
DOMESTIC	HEM	11
DOMESTIC	HEM VAGINAL	77
DOMESTIC	HEMATURIA	4
DOMESTIC	HYPERTENS	2
DOMESTIC	HYPERTONIA	2
DOMESTIC	HYPESTHESIA	1
DOMESTIC	HYPOTENS	21
DOMESTIC	HYPOTENS POST	2
DOMESTIC	INFECT	197
DOMESTIC	INFECT URIN TRACT	25
DOMESTIC	JAUNDICE	1
DOMESTIC	KIDNEY FAIL	2
DOMESTIC	LARYNGISMUS	1
DOMESTIC	LDH INC	2
DOMESTIC	LEUKOCYTOSIS	2
DOMESTIC	LEUKORRHEA	68
DOMESTIC	LIVER FUNC ABNORM	1
DOMESTIC	LYMPHADENO	1
DOMESTIC	MALAISE	2
DOMESTIC	MENORRHAGIA	1
DOMESTIC	MENS DIS	2
DOMESTIC	METRORRHAGIA	3
DOMESTIC	MONILIA	6
DOMESTIC	MONILIA VAGINA	86
DOMESTIC	MYALGIA	23
DOMESTIC	NAUSEA	41

FDA SPONTANEOUS REPORTING SYSTEM
CAUSE-EFFECT RELATIONSHIP BETWEEN EACH DRUG AND REACTION
CANNOT BE ESTABLISHED WITH CERTAINTY IN ALL CASES

TODAY

REPORT SOURCE	COSTART	TOTAL OCCURRENCES
DOMESTIC	NAUSEA VOMIT	13
DOMESTIC	NAUSEA VOMIT DIAR	17
DOMESTIC	NEOPL SKIN	1
DOMESTIC	NEPHRITIS	1
DOMESTIC	NO DRUG EFFECT	102
DOMESTIC	OVAR DIS	1
DOMESTIC	PAIN	38
DOMESTIC	PAIN ABDO	61
DOMESTIC	PAIN BACK	5
DOMESTIC	PAIN PELVIC	12
DOMESTIC	PAIN URETHRA	1
DOMESTIC	PALPITAT	2
DOMESTIC	PAP SMEAR SUSP	1
DOMESTIC	PARESTHESIA	6
DOMESTIC	PAROTID ENLARGE	1
DOMESTIC	PENIS DIS	8
DOMESTIC	PHARYNGITIS	5
DOMESTIC	PHOTOSENSITIVITY	1
DOMESTIC	PREGN DIS	6
DOMESTIC	PREGN UNINTEND	678
DOMESTIC	PRURITUS	32
DOMESTIC	PSYCHOSIS	1
DOMESTIC	RASH	61
DOMESTIC	RASH MAC PAP	6
DOMESTIC	RASH POST	1
DOMESTIC	RASH VESIC BULL	6
DOMESTIC	REACT AGGRAV	2
DOMESTIC	REACT UNEVAL	82
DOMESTIC	SALPINGITIS	26
DOMESTIC	SEPSIS	1
DOMESTIC	SERUM SICK	1
DOMESTIC	SGOT INC	1
DOMESTIC	SHOCK	4
DOMESTIC	SKIN DIS	1
DOMESTIC	SKIN DRY	1
DOMESTIC	STUPOR	1

FDA SPONTANEOUS REPORTING SYSTEM
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CANNOT BE ESTABLISHED WITH CERTAINTY IN ALL CASES

TODAY

REPORT SOURCE	COSTART	TOTAL OCCURRENCES
DOMESTIC	SWEAT	1
DOMESTIC	SYNCOPE	7
DOMESTIC	THINKING ABNORM	1
DOMESTIC	THROMBOCYTOPENIA	1
DOMESTIC	TINNITUS	1
DOMESTIC	TREMOR	3
DOMESTIC	URETHRITIS	9
DOMESTIC	URIN FREQUENCY	3
DOMESTIC	URIN IMPAIRED	1
DOMESTIC	URIN RETENT	4
DOMESTIC	URTICARIA	9
DOMESTIC	UTER DIS	3
DOMESTIC	UTER FIBROID ENLARGE	1
DOMESTIC	VAGINITIS	345
DOMESTIC	VASODILAT	4
DOMESTIC	VISION ABNORM	1
DOMESTIC	VOMIT	10
DOMESTIC	VULVOVAGINITIS	5
DOMESTIC	WEIGHT DEC	1
FOREIGN	CERVIX DIS	2
FOREIGN	PREGN UNINTEND	1
DOMESTIC		2959
FOREIGN		3
THE GRAND TOTAL IS		2962

Toxic Shock Syndrome and the Vaginal Contraceptive Sponge

Gerald Faich MD, MPH; Kay Pearson, RPh; David Fleming, MD; Solomon Sobel, MD; Charles Anello, ScD

• Thirteen confirmed cases of toxic shock syndrome temporally related to use of the vaginal contraceptive sponge have been reported. The observed risk of toxic shock syndrome in sponge users may be elevated above estimated background rates, but this risk remains very low. Traumatic manipulation of the sponge, use during menstruation or the puerperium, and prolonged retention of the sponge may additionally increase toxic shock syndrome risk. As with all contraceptives, risks must be balanced against benefits.

(*JAMA* 1986;255:216-218)

TOXIC shock syndrome (TSS) associated with staphylococcal infection was first recognized in 1978,[1] although cases undoubtedly occurred before that time.[2] *Staphylococcus aureus* has often been isolated from patients with TSS, particularly phage group 1.[3,4] The illness is thought to be caused by a staphylococcal toxin,[4] although the exact pathogenesis of the disease remains unclear. Host immune status may also play a role in susceptibility to the syndrome.[3]

For editorial comment see p 242.

In 1980, epidemiologic investigations of an increase in the number of the reported cases of TSS led to the description of an association between TSS, tampon use, and menstruation.[5,6] Since that time, most reported cases of the syndrome have continued to occur in women during menstruation.[4] Nonmenstrual cases related to wounds, the postpartum period, and vaginitis have been reported.[7,8] Cases have also been reported in conjunction with the use of the contraceptive diaphragm.[9,10] The present article reviews reported TSS cases temporally related to use of the vaginal contraceptive sponge and discusses risk implications of these cases.

The vaginal contraceptive sponge (Today) was first marketed for over-the-counter sale in July 1983. The sponge, a polyurethane device impregnated with nonoxynol 9 spermicide, has a combination of features not duplicated by other contraceptives. First, because of its over-the-counter status, it is readily available. Second, in some patients its efficacy may approach that of the diaphragm and spermicide jellies.[11] Third, it can be left in place and provide continual contraception for a 24-hour period.

Preapproval trials of the sponge, while large,[12] were not sufficient to rule out the possibility of TSS. This and the experience with tampon-associated TSS led to the inclusion of a description of the symptoms of TSS in the package insert for the sponge.[13] In addition, users were instructed not to leave the sponge in place for more than 30 hours and not to use the sponge during menstruation.

METHODS

Surveillance for sponge-related TSS cases is based on information received by the Adverse Drug Reaction Reporting System at the Food and Drug Administration (FDA),[14] the Centers for Disease Control (CDC) TSS Surveillance System,[15] and postmarketing surveillance conducted by the manufacturer (VLI Corp, Irvine, Calif). The first two of these surveillance sources were in place before the sponge was marketed. The manufacturer's surveillance is primarily based on reports it receives from health care providers and consumers through a toll-free telephone hot line, which is listed in the package insert supplied with the product. The manufacturer is required to transmit any reports of adverse reactions to the FDA.[13]

Each TSS case report is recorded by the FDA and the CDC on a CDC TSS surveillance form and is reviewed and classified by the CDC. A sponge-related case is defined as one in which the standard criteria,[16,17] as outlined in Table 1, are met and in which the onset of illness occurs within 48 hours following sponge insertion. For reports that only noted the date of sponge use, it was assumed that

From the Center for Drugs and Biologics, Food and Drug Administration, Rockville, Md (Drs Faich, Sobel, and Anello and Ms Pearson), and the Respiratory and Special Pathogens Epidemiology Branch, Centers for Disease Control, Atlanta (Dr Fleming).

Use of trade names is for identification only and does not imply endorsement by the Public Health Service.

Reprint requests to Center for Drugs and Biologics, Food and Drug Administration, Room 15B39 (HFN-700), Rockville, MD 20857 (Dr Faich).

Table 1.—Case Definition of Toxic Shock Syndrome[1,6]

Fever: Temperature, ≥ 38.9 °C
Rash: Diffuse macular erythroderma
Desquamation: Palms and soles 1 to 2 wk after onset
Hypotension: Systolic BP < 90 mm Hg or orthostatic drop in diastolic BP > 15 mm Hg or orthostatic dizziness[6]
Multisystem involvement (≥ 3 of the following):
- Gastrointestinal: Vomiting or diarrhea at onset
- Muscular: Myalgia or elevated creatine phosphokinase level
- Mucous membrane: Vaginal, or oropharyngeal or conjunctival hyperemia
- Renal: Elevated serum urea nitrogen or creatinine levels or aseptic pyuria
- Hepatic: Elevated bilirubin, SGOT, or SGPT levels
- Hematologic: Platelets, ≤ 100,000/cu mm
- Central nervous system: Disorientation or altered consciousness without focal neurologic signs

Negative results for the following, if obtained:
- Blood (except *Staphylococcus aureus*), throat, or cerebrospinal fluid cultures: rise in titer to Rocky Mountain spotted fever, leptospirosis, or rubeola

*SGOT indicates serum glutamic-oxaloacetic transaminase; SGPT, serum glutamic-pyruvic transaminase; BP, blood pressure.

Table 2.—Sponge-Related Cases of Toxic Shock Syndrome

Date of Onset, mo/yr	Insertion-to-Onset Interval, hr	Predisposing Conditions	Removal Difficulty	Fragmentation
10/83	24	Post partum	No	No
11/83	11	. . .	Yes	Yes
11/83	48	Prolonged retention	Yes	Yes
1/84	12	. . .	No	No
1/84	14	. . .	Yes	Yes
3/84	24	. . .	No	No
4/84	9	Menstruation	Yes	No
7/84	48	. . .	No	No
7/84	36	. . .	No	No
7/84	48	. . .	No	No
8/84	36	. . .	No	No
10/84	24	. . .	No	No
10/84	24	Post partum	No	No

the sponge was inserted at 10 PM so that an insertion-to-onset interval could be estimated.

For risk estimates, two assumptions were made. First, it was assumed that risk is independent for each use of the sponge and that sponges are used on nonmenstrual days. Second, it was assumed that the average menstruating woman is "nonmenstrual" five sixths of the time, or 304 days per year.[7] Thus, to convert annual incidence rates per 100,000 women to rates per nonmenstrual day, the annual rate was divided by 304 and multiplied by 10 to give a rate per million women-nonmenstrual days.

RESULTS

Case Review

As of Nov 1, 1984, seventeen cases of TSS in sponge users had been reported. In two of these, onset had occurred more than 48 hours after sponge insertion and in two the incubation period was unknown. Thus, 13 cases of sponge-related TSS were identified. An additional ten cases of probable TSS in sponge users were reported; these lacked one criterion of TSS (Table 1), most commonly desquamation. Only the confirmed sponge-related TSS cases were used in this analysis. Four of these cases were briefly reviewed elsewhere.[8]

All 13 of the patients with sponge-related TSS were hospitalized and recovered; all had vaginal cultures that were positive for *S aureus*. Patients ranged in age from 18 to 37 years (mean, 24.6 years) and resided in nine states. Four of the cases had potentially predisposing factors (Table 2): one patient used the sponge during menstruation, two were postpartum (37 and 56 days), and one left the sponge in place for more than 30 hours (four days). In four of the 13 cases, difficulty with sponge removal was noted, and in three of these the sponge was fragmented when finally removed.

Risk Analysis

As of Nov 1, 1984, according to the manufacturer, 20 million sponges had been distributed. For this analysis it is assumed that a maximum of 80% (16 million) of distributed sponges were actually used, while the remainder either went unused or had not yet been purchased. Using the sponge-related TSS cases without possible predisposing factors as a numerator, the observed rate of sponge-related TSS was nine cases per 16 million sponges. Since a case, by definition could occur within 48 hours (two days) of sponge use, this is equivalent to nine cases per 32 million nonmenstrual days of susceptibility for an observed rate of 0.28 cases per 1 million nonmenstrual days.

Precise estimates of background rates of nonmenstrual TSS do not exist. Best approximations derive from surveillance programs conducted in Utah and Minnesota. For Utah, during the two-year period from 1980 through 1981 when surveillance was most intense, one case of nonmenstrual TSS in a woman was detected that was not associated with a wound or the postpartum period. Surveillance covered the state's population of 240,000 women 19 to 39 years of age (C. R. Nichols, MPA, oral communication, Nov 15, 1984). Thus, the observed incidence was 0.21 per 10^5 women-years, or 0.007 per 10^6 nonmenstrual days.

In Minnesota, ten nonmenstrual TSS cases without predisposing factors in women 19 to 39 years of age were detected statewide from January 1980 to June 1981.[9] Using a denominator population of 600,000 women aged 19 to 39 years, an annual rate of 1.1 per 100,000 women-years can be calculated. This adjusts to 0.036 cases per 10^6 nonmenstrual days.

Dividing the observed sponge-related rate (0.28) by estimated background rates gives a crude risk ratio. Using the Utah (0.007) and Minnesota (0.036) background rates produces estimated crude risk ratios of 40 and 7.8, respectively. Put another way, TSS risk on nonmenstrual days is estimated to be 7.8 to 40 times greater for sponge users than for nonusers.

One unpublished study provides an estimate of nonmenstrual TSS derived from retrospective chart reviews of hospitalized patients with diagnoses possibly compatible with TSS. T. Halpin, MD, and L. Konchal, MPH (written communication, Nov 16, 1984) found one confirmed non-

menstrual TSS case in a woman in the child-bearing years without predisposing factors by such a review of more than 3,000 hospital records representing all such hospitalizations for a year's period of time for a population that contained 214,927 women aged 13 to 39 years. From this a nonmenstrual TSS rate of 0.015 cases per 10^6 nonmenstrual days can be calculated. Using this as a comparison rate, a crude risk ratio of 18.6 for sponge-related TSS is obtained.

COMMENT

We have identified 13 cases of TSS temporally related to sponge use. Three cases involved use during the puerperium or menstruation, both of which are contraindications for use of the sponge. One case occurred in a woman who kept the sponge in place for more than the 30 hours recommended by the manufacturer. Sponge users should be encouraged to carefully follow instructions in the package insert.

Four of the TSS cases involved difficulties with removing the sponge. Vaginal trauma and sponge fragmentation may increase TSS risk. Thus, sponge users should be particularly alert for illness following traumatic removal of the sponge.

Nine of the 13 TSS cases related to sponge use were not associated with predisposing factors. Using several estimates of the background rate of nonmenstrual TSS, we have shown that the crude risk ratio of sponge-related TSS may be elevated. This risk analysis does not control for several biases. Diagnosis and reporting of sponge-related cases probably are higher than non-sponge-related nonmenstrual cases because of the mention of TSS in the package insert, litigation, and media attention. In addition, non-sponge-related nonmenstrual cases may be less likely to be recognized because the diagnosis may not be considered in the absence of menstruation or tampon use.[11]

To some extent, the use of comparison data from Minnesota and Utah may lessen the degree of bias in our analysis. In both states, physicians were informed about clinical characteristics of TSS as part of an intensive surveillance effort. There was also considerable mass media attention given to the disease for several surveillance years. Active searches were made for diagnosed cases for all or part of the surveillance period.

Our conclusion is that the risk of nonmenstrual TSS may be increased by sponge use. This is based on the temporal association, the possible increase in the rate of occurrence of nonmenstrual TSS above estimated background rates, and the analogous, established association found between TSS and tampon use. It must be emphasized that while the risk may be elevated, it still represents a small risk. To date about one case (without predisposing factors and occurring within 48 hours of use) per 2 million sponges used has been reported.

It is important to consider this risk in the proper perspective. Decisions about contraceptives must take into account comparative efficacy and safety information, ie, benefits must be balanced against risks. Risks from one contraceptive method must be compared with those associated with other methods. Risks associated with pregnancy far exceed the risks of most contraceptive means.

Physicians should be alert to the possibility of TSS even in nonmenstruating patients. When diagnosed, TSS cases should be reported to state health departments. When the contraceptive sponge is involved, reporting to the manufacturer or FDA is encouraged.

We thank Michael Osterholm, PhD, for his review and comments.

References

1. Todd J, Fishaut M, Kapral F, et al: TSS associated with phage-group I staphylococci. *Lancet* 1978;2:1116-1118.
2. Stevens FA: The occurrence of *Staphylococcus aureus* infection with a scarlettiniform rash. *JAMA* 1927;88:1957-1958.
3. Altemeir WA, Lewis S, Schlievert PM, et al: Studies of the staphylococci causation of TSS. *Surg Gynecol Obstet* 1981;153:481-485.
4. Bennett JV: Toxins and TSS. *J Infect Dis* 1981;143:531-533.
5. Bergdoll MS, Crass BA, Reiser RF, et al: A new staphylococcal enterotoxin associated with TSS. *Lancet* 1981;1:1017-1021.
6. Shands KN, Schmid GP, Dan BB, et al: TSS in menstruating women: Association with tampon use. *N Engl J Med* 1980;303:1436-1442.
7. Davis JP, Chesney JP, Wand PJ, et al: Toxic-shock syndrome epidemiologic features, recurrence, risk factors and prevention. *N Engl J Med* 1980;303:1429-1435.
8. Annual summary. *MMWR* 1983;31:186.
9. Reingold AL, Hargrett NT, Dan BB, et al: Nonmenstrual TSS. *Ann Intern Med* 1982;96:871-874.
10. Whitfield JW, Valenti WM, Magnussen CR: Toxic shock syndrome in the puerperium. *JAMA* 1981;246:1806-1811.
11. Baehler EA, Dillon WP, Cumbo TJ, et al: Prolonged use of a diaphragm and TSS. *Fertil Steril* 1982;38:248-250.
12. DeYoung PD, Martyn J, Wase H, et al: TSS associated with a contraceptive diaphragm. *Can Med Assoc J* 1982;127:611.
13. Hyde L: TSS associated with diaphragm use. *J Fam Pract* 1982;16:616-618.
14. *Today Vaginal Contraceptive Sponge User Instruction Booklet*. Irvine, Calif, VLI Corp, 1983.
15. Lee V, Turner W: FDA's adverse drug reaction monitoring program. *Am J Hosp Pharm* 1978;35:929-932.
16. *MMWR* 1982;31:201-204.
17. New drug and antibiotic regulations. *Fed Register* 50:7452-7501, Feb. 22, 1985.
18. Novak ER (ed): *Textbook of Gynecology*, ed 8. Baltimore, Williams & Wilkins Co, 1975, p 89.
19. Toxic-shock syndrome and the vaginal contraceptive sponge. *MMWR* 1984;33:43-44.
20. Osterholm MT, Forfang JC: Toxic-shock syndrome in Minnesota: Results of an active-passive surveillance system. *J Infect Dis* 1982; 146:458-464.
21. Harvey M, Horwitz RI, Feinstein AR: Diagnostic bias and TSS. *Am J Med* 1984;76:551.

Associated
Pharmacologists &
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June 25, 1984

Dr. Frank Young
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Food & Drug Administration
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CLINICAL REPORTS ON VAGINAL IRRITATION & TOXIC SHOCK SYNDROME ASSOCIATED WITH THE USE OF THE TODAY CONTRACEPTIVE SPONGE

Supplement to Citizen Petition 83P-0187/CP0002

SUMMARY

One year ago, this organization petitioned the Food & Drug Administration to withdraw its premarketing approval of the Today Contraceptive Sponge because the intravaginal animal tests recommended by the FDA Panel on Vaginal Contraceptives had not been completed and evaluated for the Sponge. At that time, there were scientific reports available to suggest that if intravaginal animal tests were performed with this contraceptive product, the Today Sponge might be shown to be a frequent cause of vaginal irritation, and to increase the incidence of toxic shock syndrome among its users. Available reports also suggested that, after long-term use of the Sponge, the incidence of tumor formation among users might increase because of the intravaginal exposure to a polyurethane and dioxane, the carcinogenic contaminant of the Sponge spermicide, Nonoxynol-9.

There are now clinical reports, which will be outlined in detail below, that suggest as many as 12% of the women who use the Contraceptive Sponge experience vaginal irritation from this product. When compared to other

vaginal contraceptives, the Today Sponge has been shown to be significantly more irritating than the diaphragm and one type of foaming suppository contraceptive. At this time there are nine cases of toxic shock syndrome (TSS) among Today Sponge users confirmed by the Centers for Disease Control (Atlanta, GA), and several additional reports that have been classified as "near-shock" because available information was not sufficient to meet all of the established criteria to confirm these cases as TSS. The carcinogenic potential of the polyurethane and dioxane in the Contraceptive Sponge are still untested in available animal models. Clinical data on side effects such as tumor formation are impossible to monitor at this point.

Toxic shock syndrome can be a lethal disease. If a woman can buy a Contraceptive Sponge, use it as recommended, and risk developing a fatal disease while using this product, the standards for safety of over-the-counter drug products, which have been established in the past by the FDA, are not being met for this product.

Although it is specified in the U.S. Code of Federal Regulations that the Commissioner of the FDA "shall furnish a response to each petitioner within 180 days of receipt of the petition" (21 CFR 10.30 (2)), no response has been made to the original petition on this matter submitted one year ago. At this time, we request that you consider the material submitted in the original petition along with the clinical data reviewed below, to provide a basis for removing the Today Contraceptive Sponge from the OTC drug market.

Detailed Statement of Grounds:

1. Vaginal Irritation

A small clinical study on the vaginal irritation caused by repeated use of the Contraceptive Sponge was reported to the FDA by Dr. Gerald Bernstein of the Univ. of So. Calif. Med. Ctr. A summary of this study was obtained through a freedom of information request as part of a letter written June 10, 1982 by Dr. William J. McCann, the Medical Officer in the Office of Metabolic and Endocrine Drugs, FDA. Dr. Bernstein reported that when 10 women wore a Contraceptive Sponge for more than 2 days, 3 of the women complained of vaginal irritation and 4 expelled the Sponge. (1) In a second study involving 15 women who attempted to wear contraceptive sponges on 7 consecutive days, 5 of the women experienced vaginal irritation. At the end of the study, four of these women presented with Class II Pap smears. (2)

A large clinical study, involving 1,400 women, which was completed here in the U.S., has shown that the Contraceptive Sponge caused significantly more vaginal irritation that the diaphragm. After one year, 12 women per 100 sponge users discontinued use of the Sponge because of vaginal irritation. This was significantly more than the discontinuation rate among diaphragm users, which was 3.7 per 100 women. This data was summarized in a recently published report by the Population Information Program at the Johns Hopkins University (3).

The results of a large international study undertaken in Bangladesh, Taiwan and Yugoslavia were also summarized by the Johns Hopkins group. (3) In that study the effectiveness and acceptability of the Sponge was compared with a foaming suppository, the Neo Sampoon, which is not sold in the U.S. The discontinuation rate because of vaginal discomfort for the Neo Sampoon was relatively

high at 9.4 per 100 women, however, even this discontinuation rate was significantly lower than the rate reported for the Contraceptive Sponge, 12.7 per 100 women (3). Thus the incidence of vaginal irritation for the Sponge in both of these clinical studies ranged between 12 and 13%.

When discomfort and problems removing the Sponge were grouped with all other reasons cited for discontinuing the use of the Sponge, the overall rate was about 50% (3).

The voluntary reports that have been submitted to the Sponge manufacturer (VLI Corp., Irvine, CA) and the FDA Drug Experience Network (4) now number in the hundreds the women who have experienced vaginal pain, fever and distress because of the Contraceptive Sponge. These reports include some categorized as "near shock" because information was inadequate to confirm the occurrence of toxic shock syndrome.

2. Toxic Shock Syndrome and the Contraceptive Sponge

Vaginal infections with various strains of Staphylococcus aureus have been associated with the onset of Toxic Shock Syndrome (TSS). Laboratory tests on the growth of S. aureus in the presence of components of the Contraceptive Sponge have produced conflicting results. A report prepared for the manufacturer of the Sponge (VLI Corp., Irvine, CA) did find that the growth of S. aureus was inhibited by the Sponge's spermicide, Nonoxynol-9, when clean sponges were innoculated with bacteria and incubated in beakers (3). However, a 1933 study by Dr. Elizabeth Baehler at the State University of New York at Buffalo (5) indicated that N-9 had no inhibitory activity on staphylococci or group B streptococci, but it was highly effective against Streptococcus pneumoniae.

At this time the Centersfor Disease Control (CDC),in Atlanta, GA, has confirmed reports on nine cases of TSS among users of the Today Contraceptive Sponge. In the CDC report on the first four TSS cases (6), it was noted that two of the TSS victims had left the Contraceptive Sponge in place for longer than the recommended 24 hours.* Of the five more recent cases of TSS, the time the sponge was left in the vagina has been determined for four of the women. In these four cases, the Sponge was left in the vagina 12, 13, 14 and less than 24 hours (7). One woman was menstruating. Despite the growing number of Sponge users who have become victims of TSS, the effect of the spermicide detergent, Nonoxynol-9, on the intravaginal absorption of TSS toxins also awaits investigation in experimental animals.

Conclusion

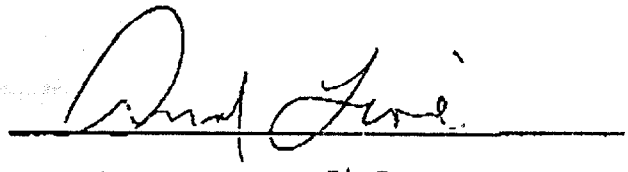
The original petition on the inadequacies in the safety testing for the Today Contraceptive Sponge summarized the available research reports that suggested that if the Sponge had been subjected to the recommended intravaginal animal tests, it would frequently be associated with vaginal irritation and it might increase the incidence of TSS and tumor formation among women who used this vaginal contraceptive. Although it is too soon to expect that clinical data will shed light on the potential carcinogenic properties of the ingredients in the Sponge, after one year of widespread use, clinical data is now available that suggests the Sponge is frequently associated with vaginal irritation and 9 confirmed cases of toxic shock syndrome have been identified among women who were using this product.

*The manufacturer claims that the Sponge is approved for 48 hour use in England and Switzerland (2). The FDA limited the product to 24 hour use in Jan. 1983.

There are a number of alternate forms of vaginal contraception with greater safety and effectiveness than the Contraceptive Sponge that are available to women. Once, again, we request that this product be withdrawn because it has not been shown to be safe enough for sale on the over-the-counter drug market.

Certification

The undersigned certifies, 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 known to the petitioner which are unfavorable to the petition.



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REFERENCES

1. "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, D.C. pp. 349-350.

2. "Today Vaginal Contraceptive Sponge: A Technical Review." B.W. Vorhauer, D.A. Edelman, B. North, R.M. Soderstrom. VLI Corp., Irvine, CA. June 1983, p. 5.

2. "New Developments in Vaginal Contraception." Population Reports, Series H, #7, Jan-Feb. 1984. Population Information Program, Johns Hopkins University, Baltimore, MD.

4. K. Pearson, Drug Experience Network, U.S. Food & Drug Administration, Personal communication, May 25, 1984.

5. "The effects of prolonged retention of diaphragms on colonization by Staphylococcus aureus of the lower genital tract." E.A. Baehler, W.P. Dillon, D.M. Dryja, E. Neter. Fertility & Sterility, Vol. 39, #2, Feb. 1983 pp. 162-166.

6. "Toxic-Shock Syndrome and the Vaginal Contraceptive Sponge," Morbidity and Mortality Weekly Report. Center for Disease Control, Atlanta, GA. Vol. 33, #4, Feb. 3, 1984. pp. 43-44, 49.

7. S. Chchi, Center for Disease Control, Atlanta, GA. Personal communication, June 19, 1984.