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THIOETHER SPERMICIDAL METHOD AND COMPOSITION

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This application is a continuation-in-part of my copending application for U.S. Letters Patent, Serial No. 768,048, filed October 20, 1958, entitled "Spermicidal Composition," now abandoned.

The present invention relates to an improved spermicidal method involving the topical application of a spermicidal composition of the type disclosed in my aforesaid application Serial No. 768,048 to the mucous membranes and surfaces of the vaginal cavity, preparatory to coitus, to thereby reduce the incidence of pregnancy in a female human.

The principal objective of the present invention is to provide an effective and safe method of reducing the incidence of pregnancy in a female human through the topical intravaginal application of an improved spermicidal composition comprising an inert, nonirritative vehicle and a highly surface active spermicidal agent consisting of a thioether having the generic formula

$$R—S—(R'O)_nH$$

in which n is an integer of at least 2, but not more than 20, in which R is an aliphatic radical containing 6 to 20 carbon atoms, and in which R' is an alkylene radical selected from the group consisting of ethylene and propylene radicals.

It is another object of this invention to provide an improved spermicidal composition which is safe for human use, which does not tend to be neutralized by body fluids when in contact with mucous surfaces, which is stable and possesses a comparatively long "shelf life" without loss of efficacy, and which is simple and easy to apply and use.

In accordance with the present invention, I have discovered that the incidence of pregnancy in the female human may be effectively reduced by introducing into the vaginal cavity, prior to coitus, a spermicidal composition consisting of an inert, nonirritative vehicle or carrier in which is dispersed a relatively small percentage of an active spermicidal agent consisting of a thioether having the generic formula $R—S—(R'O)_nH$, in which n is an integer of at least 2, but not more than 20, in which R is an aliphatic radical containing from 6 to 20 carbon atoms, and in which R' is an alkylene radical selected from the group consisting of ethylene and propylene radicals. The inert vehicle or carrier for the thioether may take any one of several well-known and acceptable forms of nontoxic and nonirritative pharmaceutical vehicles, such as a jelly, cream, aerated foam, or a body-soluble tablet or suppository.

Certain of the thioethers encompassed by the aforementioned general formula are available on the commercial market and have heretofore been proposed for use as detergents and/or wetting agents. (As for example, see: U.S. Patents Nos. 2,494,610 to Davidson and 2,565,986 to Olin.) Generally, the thioethers usable in this invention may be prepared by reacting an aliphatic mercaptan having from 6 to 20 carbon atoms with ethylene oxide, propylene oxide, ethylene carbonate, or propylene carbonate.

The R radical may consist of either a branched or straight chain alkyl radical, such as hexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl, tridecyl, tetradecyl, pentadecyl, hexadecyl, heptadecyl, octadecyl, nonadecyl and eicosyl.

Certain of the thioethers usable in this invention are chemically designated as dodecylthiopoly (ethyleneoxy) ethanol, polyethylene glycol dodecylthioether, dodecyl polyoxyethylene thioether, and dodecylthiopoly oxyethylene ethanol.

As a result of various experiments and tests, I have found that superior spermicidal activity is obtained when the aliphatic radical R in the aforementioned generic formula contains from 10 to 16 carbon atoms, and where the value of n is at least 4 but not more than 16, and where R' is an ethylene radical. Such tests also indicate that where the value of n is less than 2 or more than 20, the spermicidal activity of the resulting thioether is markedly decreased.

The proportion of the active, thioether spermicidal agent present in the overall spermicidal composition may range from 1% to 10% by weight of the composition, but preferably from 2% to 4%. The balance of the composition, as previously indicated, is made up of a suitable, safe-for-human-use pharmaceutical vehicle or carrier, such as a jelly, cream, aerated foam, soluble tablet or suppository. The only limitations on the selection of the particular vehicle or carrier are that it be nonreactive with the thioether spermicidal agent and that it not be toxic, irritative or otherwise unsafe for human usage in its intended environment. For example, where a jelly-type composition is desired, the inert vehicle may consist of one or more suitable thickening agents, an humectant, a buffering agent, a preservative and water. In such a jelly, water would constitute approximately 75% to 95% by weight thereof. In a cream-type composition, the inert vehicle may consist of a suitable cream base, an emulsifier, an humectant, a buffering agent and water in an amount equal to about 60% to 85% by weight of the composition. In a tablet form, the vehicle may be composed of a water-soluble starch, lactose, or dextrose. In a suppository, the vehicle may be selected from such materials as beeswax, or solid polyethylene glycol distearate, etc. It will thus be apparent to anyone skilled in the pharmaceutical art that the inert vehicle or carrier for the thioether spermicidal agent may take any one of several well-known forms of vehicles or carriers commonly employed in other spermicidal compositions, so long as the particular vehicle selected does not react with or decrease the spermicidal activity of the thioether active ingredient and is safe and nonirritative for human use in its intended environment.

For the purpose of evaluating preliminarily the spermicidal activity and effectiveness of the present thioethers, before actual clinical testing, a group of fifty-six thioethers having the aforementioned generic formula

$$R—S—(R'O)_nH$$

were prepared by reacting ethylene oxide with a first series of straight chain aliphatic mercaptans containing 8, 10 and 12 carbon atoms in their chains, and by reacting ethylene oxide with a second series of branched-chain aliphatic mercaptans containing 8, 12, 14, and 16 carbon atoms in their chains. In each of these series of thioethers, n had values of 2, 4, 6, 8, 10, 12, 14, and 16. Samples of these fifty-six thioethers were thereafter mixed in varying concentrations with normal saline solutions and buffered glucose saline solutions, respectively, and tested, in vitro, against different specimens of human semen to determine the amount or concentration of thioether necessary to kill or completely immobilize human sperm within given time periods of contact. As a result of these preliminary tests as well as subsequent tests, I have found that one part of a spermicidal composition containing at least 1.0% by weight of the aforementioned

thioether active ingredient and diluted with at least four volumes of normal saline or buffered glucose saline solutions is entirely effective in killing or limiting the motility of human sperm contained in five volumes of human semen within a time interval of less than five minutes following contact therewith.

In addition to the above mentioned tests, a variety of laboratory and clinical tests have been performed to verify the effectiveness and safety of the present thioether spermicidal compositions and method of using the same. Specific examples of the "in vitro" testing of the present thioether spermicidal composition and the results thereof are as follows:

EXAMPLE 1

A spermicidal jelly, identified as "Jelly 218–1%," and composed of 1% by weight of polyethylene glycol tert-dodecylthioether, 2% by weight of boric acid, 10% by weight of glycerol and 87% by weight of a jelly-forming base consisting essentially of water-soluble starch, gum tragacanth and water, was prepared and tested for its spermicidal activity using both the Brown and Gamble and Sander-Cramer techniques.The Brown and Gamble test, as described in Human Fertility, vol. 5, No. 4, August 1940, consists of mixing one volume of the spermicidal composition with four volumes of a normal saline solution to obtain a test mixture. The resulting test mixture is then mixed on a slide with an equal volume of human semen and the time for complete immobilization of the sperm is observed. The Sander-Cramer test, as described in Human Fertility, vol. 6, p. 134, 1941, is substantially the same as the Brown and Gamble test, except that a buffered glucose saline solution is used in lieu of the normal saline solution, in order to obtain more reproducible results with different specimens of human semen.

The results of the Brown and Gamble tests, using the foregoing spermicidal jelly ("Jelly 218—1%") against two different samples of human semen, showed complete immobilization of the sperm in less than five minutes with the spermicidal jelly diluted with four parts of normal saline solution and mixed with five parts of semen. Using the Sander-Cramer tests, the foregoing spermicidal jelly ("Jelly 218—1%") was shown to be capable of completely immobilizing the sperm in four different semen samples in less than five minutes when diluted with from twenty-four to twenty-nine parts of buffered glucose saline solution.

EXAMPLE 2

A second spermicidal jelly, identified as "Jelly 218—1½%," and composed of 1.5% by weight of polyethylene glycol tert-dodecylthioether, 2% by weight of boric acid, 10% by weight of glycerol and 86.5% by weight of a jelly-forming base consisting essentially of water-soluble starch, gum tragacanth and water, was prepared and tested in accordance with both the Brown and Gamble and Sander-Cramer techniques. The results of the Brown and Gamble tests, using two different samples of human semen, showed "Jelly 218—1½%" capable of completely immobilizing the sperm in less than five minutes when diluted with nine parts of normal saline solution. Under the Sander-Cramer tests, using four different samples of human semen, "Jelly 218—1½%" was shown to be capable of completely immobilizing the sperm when diluted with from thirty-nine to forty-nine parts of buffered glucose saline solution.

EXAMPLE 3

A third spermicidal jelly, identified as "Jelly 218—2%," and composed of 2% by weight of polyethylene glycol tert-dodecylthioether, 2% by weight of boric acid, 10% by weight of glycerol and 86% by weight of a jelly-forming base consisting essentially of water-soluble starch, gum tragacanth and water, was prepared and tested using both the Brown and Gamble and Sander-Cramer techniques. Under the Brown and Gamble tests, using sixteen different samples of human semen, "Jelly 218—2%" was shown to completely immobilize the sperm in less than five minutes when diluted with from nine to twenty-four parts of normal saline solution. The Sander-Cramer tests, using eighteen different samples of human semen, showed "Jelly 218—2%" to be capable of completely immobilizing the sperm in less than five minutes when diluted with from thirty-nine to ninety-nine parts of buffered glucose saline solution.

EXAMPLE 4

A fourth spermicidal jelly, identified as "Jelly 218—4%," and composed of 4% by weight of polyethylene glycol tert-dodecylthioether, 2% by weight of boric acid, 10% by weight of glycerol and 84% by weight of a jelly-forming base consisting essentially of water-soluble starch, gum tragacanth and water was prepared. Samples of "Jelly 218—4%" were tested in accordance with the Brown and Gamble and Sander-Cramer techniques against ten different specimens of human semen. The results of the Brown and Gamble tests showed "Jelly 218—4%" to be effective in completely immobilizing the sperm in less than five minutes at dilutions ranging from thirty-four to thirty-nine parts of normal saline solution. The results of the Sander-Cramer tests showed "Jelly 218—4%" to be effective in completely immobilizing the sperm in less than five minutes at dilutions ranging from eighty-nine to one hundred twenty-four parts of buffered glucose saline solution.

The clinical safety of the present spermicidal composition has been tested by the Margaret Sanger Research Bureau of New York, N.Y., a well-known and recognized organization concerned with clinical service, education and research in the fields of conception, infertility, contraception and marriage counselling. In these tests, a spermicidal jelly of the composition of "Jelly 218—2%," identified heretofore, was used. The purpose of certain of these tests was to determine whether the present spermicidal jelly had any adverse or harmful effects upon the genital mucosa and organs when used in recommended dosages of approximately 3 to 5 grams for 21 consecutive days. Ten married women participated in the initial 21 day test using the aforesaid "Jelly 218—2%." A preliminary pelvic examination of these subjects was made and revealed no vaginitis, cervical erosion, or other pelvic pathology. Each subject was instructed to insert, by means of a vaginal applicator, approximately 5 grams of the jelly into the vaginal cavity every night before retiring for 21 consecutive days. During this 21 day period, each woman was re-examined twice a week, with re-examinations being made from 10 to 15 hours after insertion of the jelly. Papanicolaou smears were obtained before and after the 21 day testing period. There were no complaints of itching, burning, or irritation from any of the women so tested, or from their husbands. One of the women tested reported leakage during the whole day; two reported leakage during the mornings, and seven reported just slight leakage on leaving bed. The periodic re-examinations of these women revealed very little residual material spread evenly in the vagina. The condition of the mucosa remained normal in all cases, and no changes in cytology pattern were revealed by the Papanicolaou smears.

In addition to the foregoing clinical safety test, an extensive "in vivo" test program was carried out by the aforesaid Margaret Sanger Research Bureau to further determine the effectiveness and harmlessness of "Jelly 218—2%." This test program was conducted over a period of 20 months with 319 women ranging in ages from 17 to 52 years. The "Jelly 218—2%" was distributed to each of these patients in tubes with instructions for its use with a previously fitted diaphragm. Each of the patients was advised to squeeze from the tube into the cup of the diaphragm a two inch length of the jelly (approximately 3 grams), to distribute the jelly evenly on

both surfaces and around the rim of the diaphragm before insertion thereof within the vagina, and to make this procedure part of their routine toilet habits each night before retiring. The following table is a summary of the above-mentioned test program covering a period of 20 months:

Table I

Total patients given "Jelly 218—2%"	319
Total patients reporting during 20 months' testing period	317
Total patients known to have discontinued use of "Jelly 218—2%"	50
Total patients reporting continued use of "Jelly 218—2%" nine and one-half months after start of program	213
Total patients reporting continued use of "Jelly 218—2%" twenty months after start of program	125
Total patient-months of use (based on patients reporting during twenty months' program)	3,170
Average period of use of "Jelly 218—2%"	mos. 10
Total number of accidental pregnancies reported	4
Total number of planned pregnancies reported	1
Total number of patients reporting discontinuance for aesthetic reasons (objections to odor or lubrication) (aggregating 106 patient-months of use)	31
Total number of patients reporting discontinuance of use due to irritation or itching (aggregating 12.75 patient-months of use)	5
Total number of patients reporting discontinuance of use due to desire for pregnancy	9

The results of the foregoing clinical testing program show a total of 4 reported accidental pregnancies and 1 planned pregnancy out of a total of 317 patients reporting during the twenty months' test period. Thus, multiplying the number of patients (317) by the average period of use of "Jelly 218—2%" (10 months) and dividing by 12, yields a total of approximately 264 patient-years use with 5 pregnancies. This yields a rate of 1.9 pregnancies per 100 patient-years use.

By way of comparison, the publication, Fertility and Sterility, vol. 10, No. 2 (March-April 1959), in an article appearing at pp. 177–189 entitled "Annotated Lists of Published Reports on Clinical Trials With Contraceptives" (Hartman), reports a pregnancy rate of from 4.3 to 30 pregnancies per 100 patient-years use with diaphragm plus jellies. The publication, American Journal of Obstetrics and Gynecology, (September 1959), vol. 78, No. 3, in an article appearing at p. 654 entitled "The Clinical Effectiveness of Contraceptive Methods" (Tietze), reports a pregnancy rate of from 6 to 29 pregnancies per 100 patient-years use with diaphragm plus jellies.

Thus, the results of the aforesaid clinical tests conducted by the Margaret Sanger Research Bureau indicate that the use of "Jelly 218—2%" is highly effective in reducing the incidence of pregnancy in the female human.

It will also be noted from the foregoing table that out of a total of 317 patients reporting, only 5 patients complained of irritation or itching. This represents slightly less than 1.6% of the cases reported. The corresponding percentage acceptable to the International Planned Parenthood Federation is 6% to 7%.

Having thus described my invention, what I claim is:

1. A method of decreasing the incidence of pregnancy in a female human which comprises introducing into the vaginal cavity of the female human, preparatory to an act of sexual intercourse, a spermicidal composition consisting essentially of 1% to 10% by weight of a thioether having the formula $R—S—(R'O)_nH$, in which n is an integer of at least 2, but not more than 20; in which R is alkyl containing 6 to 20 carbon atoms, and in which R' is an alkylene selected from the group consisting of ethylene and propylene, and 99% to 90% by weight of a nonreactive vehicle that is safe for human use.

2. A method of decreasing the incidence of pregnancy in a female human which comprises dispersing within the vaginal cavity of the female human, preparatory to an act of sexual intercourse, a spermicidal composition consisting essentially of 90 to 99 parts by weight of an inert, safe for human use pharmaceutical vehicle and 1 to 10 parts by weight of a thioether having the formula $R—S—(R'O)_nH$, in which n is an integer of at least 2, but not more than 20; in which R is alkyl containing from 6 to 20 carbon atoms, and in which R' is an alkylene selected from the group consisting of ethylene and propylene.

3. The method defined in claim 2, wherein said pharmaceutical vehicle comprises a jelly composed essentially of glycerol, boric acid, water-soluble starch, gum tragacanth and water.

4. A method of decreasing the incidence of pregnancy in a female human which comprises introducing within the vaginal cavity of the female human, preparatory to coitus, a spermicidal composition consisting of from 96% to 98% by weight of an inert, safe for human use pharmaceutical vehicle and from 2% to 4% by weight of a thioether having the formula $R—S—(R'O)_nH$, in which n is an integer of at least 4, but not more than 16; in which R is alkyl containing from 10 to 16 carbon atoms, and in which R' is ethylene.

5. A method of decreasing the incidence of pregnancy in a female human which comprises introducing within the vaginal cavity of the female human, preparatory to coitus, a spermicidal composition consisting of approximately 98% by weight of an inert, safe for human use pharmaceutical vehicle and approximately 2% by weight of a thioether having the formula $R—S—(R'O)_nH$, in which n is an integer of at least 2, but not more than 20, in which R is alkyl containing from 6 to 20 carbon atoms, and in which R' is an alkylene selected from the group consisting of ethylene and propylene.

6. The method defined in claim 5, wherein said thioether consists of polyethylene glycol tert-dodecylthioether.

7. A spermicidal composition consisting essentially of approximately 2% by weight of a thioether having the formula $R—S—(R'O)_nH$, in which n is an integer of at least 4, but not more than 16, in which R is alkyl containing from 10 to 16 carbon atoms and in which R' is an alkylene selected from the group consisting of ethylene and propylene; and approximately 98% by weight of a non-reactive, safe for human use jelly composed essentially of a thickening agent, an humectant, a buffering agent, a preservative and water.

References Cited in the file of this patent

UNITED STATES PATENTS

2,494,610	Davidson	Jan. 17, 1950
2,565,986	Olin	Aug. 28, 1951