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Kurtz

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[54] **SUTURES HAVING LONG-LASTING BIOCIDAL PROPERTIES**

[75] Inventor: **Leonard D. Kurtz,** Woodmere, N.Y.

[73] Assignee: **Sutures, Inc.,** Coventry, Conn.

[*] Notice: The portion of the term of this patent subsequent to Feb. 15, 1989, has been disclaimed.

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Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 851,739, Aug. 20, 1969, abandoned, which is a continuation-in-part of Ser. No. 648,247, June 23, 1967, abandoned.

[52] **U.S. Cl.** **128/335.5;** 424/26

[51] **Int. Cl.** **A61l 17/00**

[58] **Field of Search** 424/26; 128/335.5

[56] **References Cited**

UNITED STATES PATENTS

861,231	7/1907	Clark	424/26 X
2,743,268	4/1956	Stieff	424/181 X
2,751,910	6/1956	Howes	424/26 X
2,830,011	4/1958	Parker et al.	424/181
3,069,320	12/1962	Vitalis	424/181
3,235,556	12/1966	Wakeman et al.	260/286
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FOREIGN PATENTS OR APPLICATIONS

788,968	1/1958	United Kingdom	424/329

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The Merck Index, Eighth Edition; Merck & Co., Inc., Rahway, N.J. U.S.A., pgs. 485, 771, 790 & 848.

Primary Examiner—Frederick E. Waddell
Attorney, Agent, or Firm—Larson, Taylor and Hinds

[57] **ABSTRACT**

Sutures are provided with long-lasting biocidal properties against both gram-negative and gram-positive bacteria by incorporating substantially water-insoluble salts of an acid antibiotic and a basic antibiotic into the body of the suture. The sutures can be prepared by sequentially impregnating the sutures with aqueous solutions of the respective antibiotics or by first forming the water-soluble salt of the antibiotic and impregnating the suture with an organic solution of the water-insoluble salt.

8 Claims, No Drawings

SUTURES HAVING LONG-LASTING BIOCIDAL PROPERTIES

This is a continuation in part of my U.S. application Ser. No. 851,739 filed Aug. 20, 1969, now abandoned, which in turn is a continuation in part of application Ser. No. 648,247, filed June 23, 1967, now abandoned.

The present invention relates to sutures having long-lasting anti-bacterial properties and to methods of providing such sutures.

There have been several attempts to provide anti-bacterial material in sutures. For example, U.S. Pat. Nos. 861,231, and 2,751,910 relate to providing germicidal sutures.

Also, antibiotics have been previously employed to coat or impregnate various textile materials in order to induce therein bactericidal properties. As noted in U.S. Pat. No. 2,830,011 to Parker et al, however, except for neomycin such materials have been limited to single-use purposes and have been discarded or thrown away following such single use. The reason for this was the fact that the antibiotics were not sufficiently stable or substantive and consequently could not remain in active acti-bacterial form therein following cleaning operations prior to reuse. Consequently, use of antibiotics as impregnants has been limited and their commercial acceptance has not been as widespread as their characteristics indicate.

It is thus desirable that the biocides should be tenaciously held by the suture to prevent repid leaching and yet the biocide cannot be so intimately held that its anti-bacterial activity is lost. The problem in the art has been to provide feasible techniques to make sutures with long-lasting anti-bacterial properties.

Sutures having long-lasting biocidal properties are provided according to the invention by providing uniformily throughout the body of the suture a substantially water-insoluble salt of an acid antibiotic and basic antibiotic. The bactericide is actually incorporated within the body of the suture and is not merely deposited on the surface thereof. The insoluble anti-bacterial salts of the invention comprise a cation of a basic antibiotic and an anion of an acid antibiotic and have been found surprisingly to provide long-lasting effectiveness against both gram-positive and gram-negative bacteria despite their high water-insolubility. In general, the solubility in water at 25°C of the antibiotic salts of the invention does not exceed about 4.0 mg. per ml. and preferably does not exceed 2.0 mg. per ml. In fact, the particularly preferred antibiotic salts of the invention have a solubility of less than 1.0 mg. per ml. yet exhibit extraordinary effectiveness against both gram-positive and gram-negative bacteria. While the biocidal materials are substantially insoluble in water, they are generally soluble in organic solvents (e.g. methyl and ethyl alcohol, ether, ethyl acetate, benzene, chloroform, acetone, dimethylsulfoxide and other common organic solvents) and can generally be dissolved in aqueous organic solvents.

Thus, in accordance with the present invention a persistent reservoir of a water-insoluble agent is established within the suture which offers broad spectrum antibiotic activity.

Suitable basic antibiotics which may be used to form the substantially water-insoluble salts of the invention include those classified as polypeptides, sugars and bases. Among the polypeptides may be mentioned bacitracin, polymyxins, tyrothricin and vancomycin. Sugars include neomycin, erythromycin, streptomycin, vancomycin and nystatin. Bases include cycloserine, tetracycline, aureomycin and terramycin. The preferred basic antibiotics are gentamicin and polymixin B.

Illustrative of suitable acid antibiotics are penicillins, fumagillin and cephalosporins such as cephalolexin, cephaloglycin, cephaloridine and cephalothin. The term "penicillins" as used herein means acid antibiotics which are structurally 6-substituted penicillanic acids such as Penicillins G, N, O and V, nafcillin, methicillin, oxacillin and the like.

Both the cation of the basic antibiotic and the anion of the acid antibiotic are conveniently provided in aqueous solutions of the respective antibiotics or their water-soluble addition salts. Mineral acid salts of the basic antibiotic are particularly good sources for the cations whereas the alkali metal, e.g. Na and K salts of the acid antibiotic are preferred sources for the anions. Preparation of the substantially water-insoluble salt is simply accomplished by combining these aqueous solutions of the cations and anions to form the salt which will precipitate.

The long-lasting anti-bacterial materials mentioned above can, according to the invention, be provided in situ in any suture material which is swellable but not itself particularly soluble in the solution employed for the impregnation. The substrate is simply contacted with a solution of the water-insoluble anti-bacterial salt in a solvent such as an organic solvent or which is also a swelling agent for the suture. In this manner the solvent swells the suture and the solvent plus salt will penetrate into the body of the suture material. The solvent can then be removed by evaporation, extraction, etc., and the salt will remain incorporated into the body of the suture. This impregnation procedure offers a convenient method of introducing a water-insoluble bactericide into the body of the suture that remains surprisingly effective against both gram-positive and gram-negative bacteria. In addition, this method offers the additional advantages of enabling precise determination of the concentrations of each antibiotic present in the suture. An alternative method of introducing the insoluble germicide into the suture comprises depositing the salt in situ by sequentially treating the suture with a solution of the acid antibiotic and a solution of the basic antibiotic solution or vice versa. This method has been surprisingly found to incorporate higher concentrations of the second added antibiotic in a single impregnation than can be obtained by an impregnation with the same antibiotic alone, that is, without the previously added antibiotic. In either case, the solutions will include a swelling agent which enhances impregnation into the suture. The swelling agent may be water or an organic solvent. The solutions can be heated to aid impregnation provided that the biocides are not destroyed by such heat.

The invention is further illustrated in the examples which follow.

EXAMPLE I

Twenty-five yards of size 2/0 surgical silk sutures are measured out and vacuum dried for 3 hours at 100°F. The dry weight of the suture is taken and the suture is immersed in a 10 percent aqueous solution of gentamicin sulfate maintained at approximately 100°F for

about 8 to 24 hours. After this treatment the suture is removed from the oven and blotted to remove excess water. The suture is then vacuum dried at 100°F for 16 to 24 hours and its dry weight taken to determine the mg/yd pickup.

The resulting suture is then subjected to a second treatment comprising immersing the suture in a 10 percent aqueous solution of sodium oxacillin maintained at 100°F for a period of 2–4 hours. The drying process described above is repeated and the mg/yd pickup is calculated.

The results of the above described treatments are set forth in the following Table 1.

Table 1

Antibiotic	Gentamicin Sulfate 10% aq.
Suture size	2/0
mg/yd. pickup	2.6
Antibiotic	Sodium Oxacillin 10% aq.
mg/yd. pickup	3.0
Total mg/yd. pickup	5.6

The aqueous solution employed in the above treatments are each capable of swelling the silk suture and an intra-fibrillar precipitate of gentamicin oxacillinate is thus formed well within the body of the suture. The precipitate is then held tenaciously within the body of the suture such that it is very resistant to the leaching action of body fluids and this provides a persistant reservoir for both the gentamicin and the oxacillin antibiotics. It is also resistant to repeated washings and thus provides sutures which are persistently effective against gram negative and gram positive bacteria even after repeated washings.

For comparison, a similar suture is subjected to impregnation with a 10 percent aqueous solution of sodium oxacillin alone. The pick up of oxacillin in the suture is found to be 0.4 mg/yd. Comparing the oxacillin pickup in this suture with that of the method of the present invention shows that the method of the present invention is capable of introducing larger amounts of the second added antibiotic in a single impregnation.

EXAMPLE II

The procedure of Example I is repeated substituting polymyxin B sulfate for gentamicin sulfate to provide a silk suture having incorporated therein polymyxin B oxacillinate. The results of the treatments are summarized in the following Table 2.

Table 2

Antibiotic	Polymyxin B Sulfate 10% aq.
Suture size	2/0
mg/yd. pickup	0.35
Antibiotic	Sodium Oxacillin 10% aq.
mg/yd. pickup	4.2
Total mg/yd. pickup	4.55

Comparing the pickup of oxacillin in this example with the pickup of oxacillin by impregnations with a 10 percent aqueous solution of sodium oxacillin shown in Example I demonstrates that sutures having greater amounts of the second added antibiotic can be provided.

EXAMPLE III

The procedure of Example I is repeated substituting sodium cephalothin for sodium oxacillin to provide a suture having incorporated therein polymyxin B cephalothinate. The results of the impregnations are summarized below in Table 3:

Table 3

Antibiotic	Polymyxin B Sulfate 10% ag.
Suture size	2/0
mg/yd. pickup	10.6
Antibiotic	Sodium Cephalothinate 10% aq.
mg/yd. pickup	16.3
Total mg/yd. pickup	26.9

For comparison, a similar suture is subjected to impregnation with a 10 percent aqueous solution of sodium cephalothin along. The highest level of sodium cephalothin that is incorporated in the suture is 1.0 mg/yd.

EXAMPLE IV

Substantially water-insoluble polymyxin B oxacillinate is first prepared by mixing together at room temperature a 10 percent aqueous solution of polymyxin B sulfate and a 10 percent aqueous solution of sodium oxacillin. The resulting precipitate of polymyxin B oxacillinate is recovered and dissolved in 75/25 ethyl alcohol/water.

20 yards of surgical silk suture size 2/0 is predried in a vacuum oven at 100°F for 3 hours. The dry weight of the suture is determined and it is placed in the saturated solution of polymyxin B oxacillinate for 2 hours. A platform is used to cover precipitate in the treating container in order to avoid surface crust on the suture. The suture is then removed from the solution, the excess solution blotted off and the suture vacuum dried for 16 hours at 100°F. The pickup of polymyxin B oxacillinate is found to be 1.2 mg/yd.

EXAMPLE V

Gentamicin oxacillinate is prepared as described in Example III by substituting gentamicin sulfate for polym xin B sulfate. A size 2/0 braided Dacron polyester (polyethylene terephthalate) surgical suture having incorporated therein gentamicin oxacillinate is prepared by following the impregnation procedure described in Example IV.

The suture material can be natural, such as silk, gut and cotton, or synthetic such as regenerated cellulose, cellulose esters, polyamides, polyacrylics, polyesters, polyvinyls and polyolefins.

Several of the anti-bacterial salts of the invention have virtually unmeasurable solubility in water. However, sutures provided with these salts exhibit long-lasting anti-bacterial activity. Therefore, it is considered appropriate to include within the meaning of substantially insoluble, those materials which have a solubility in water which ranges from substantially undetectable to about 4.0 mg per ml at 25°C.

The amount of insoluble compound provided in the suture can vary widely and large amounts can be provided by repeating the impregnation process. Antibacterial activity is achieved with very small amounts of material. In general, the amount of antibacterial ma-

terial in the suture will depend upon the intended use, and in general, up to 25 or even 50 percent by weight based on the suture material is contemplated. The minimum amount of biocide is largely a matter of choice, but trace amounts and amounts as low as 1.0 percent or 0.1 percent by weight, based on the weight of the suture, are effective. Although more anti-bacterial material can be provided in some cases, it is generally not practical to do so since lesser amounts achieve the desired persistent anti-bacterial action and the preferred amount of anti-bacterial material for sutures is therefore between 0.1 and 20 percent by weight based on the weight of the suture material.

The persistent anti-bacterial activity of sutures provided with insoluble biodical salts according to the invention is demonstrated by placing sutures prepared according to the invention as shown in the foregoing examples, in contact with organism such as Bacillus subtilis, Escherichia coli or Staphlococcus aureus. Even after repeated washings, the area around a silk suture containing the bactericides of the invention will remain clear of the organism whereas no inhibition thereof is noted when placing a similarly washed thread originally treated with an individual antibiotic in the same environment. Similarly, the persistent anti-bacterial nature of the suture is illustrated by in vivo testings in mice. Silk sutures treated according to the invention, after being implanted in mice for five days, show no growth of organisms when removed and placed in a culture medium.

The sutures to which the invention relates are, with the exception of the long-lasting biocides incorporated therein, of conventional configuration and materials. The sutures are generally sterilized and may be attached to suture needles in the usual manner and packaged in a sterile condition.

Particularly good results have been achieved with insoluble salts formed from gentamicin and penicillins, particularly the synthetic penicillins effective against gram-positive bacteria such as nafcillin, methicillin and oxacillin. The gentamicin cation is effective against pseudomonads and proteus and the synthetic penicillins are effective against penicillin resistant strains of staphglcocci. When provided in a suture according to the present invention, the antimicrobial results are excellent and there is substantially no tissue reaction.

It is claimed:

1. A surgical suture having long-lasting bactericidal properties comprising a suture strand having incorporated substantially uniformly within the body thereof throughout its length an effective amount of a substantially water-insoluble salt of a penicillin and a basic antibiotic selected from the group consisting of gentamicin and a polymyxin, said substantially water-insoluble salt being held tenaciously in said suture strand to provide a long-lasting source of both said antibiotics.

2. The surgical suture of claim **1** wherein the basic antibiotic is gentamicin.

3. The surgical suture of claim **1** wherein the basic antibiotic is a polymyxin.

4. The surgical suture of claim **1** wherein the basic antibiotic is polymyxin B.

5. The surgical suture of claim **4** wherein the penicillin is oxacillin.

6. The surgical suture of claim **1** wherein the substantially water-insoluble salt is a salt of gentamicin and oxacillin.

7. The surgical suture of claim **1** wherein the substantially water-insoluble salt is a salt of polymyxin and oxacillin.

8. The surgical suture of claim **1** wherein the suture is of a material selected from silk and gut.

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