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(54) **INSERT FOR PAPILLARY DUCT.**

(57) A rodlike insert for papillary ducts made by molding chitin or its derivative, or by coating or impregnating a base material with chitin or its derivative. It is used for treating papillary duct structure or for postoperative treatment of the opening merely by inserting it into a papillary duct.

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TECHNICAL FIELD

This invention relates to an insert to be inserted into a papillary duct of dairy cattle.

5 BACKGROUND ART

Milking disorders are sometimes caused by thickening or stricture of the opening or the inner wall of a papilla due to an injury by trample under a hoof, misapplication of a milking cannula, misuse of a milker, stimulation by a teat cup liner, and the like. Further, milk leakage is caused by damage of papillary constrictor muscles.

Such milking disorders have been treated by inserting an insert into the papillary duct to dilate the duct or to stop a milk leak. Conventional inserts for this use include a bar-shaped bundle of twisted strands having a diameter of about 3 mm and a length of about 7 cm with its one end obliquely cut and the other end tied up with a ring band having a width of about 5 mm, the bundle being impregnated with an antibiotic and hardened by a binder ("Teat plug B" produced by Denka Seiyaku Co., Ltd. or "TEATOR POINT" produced by Nihon Eiken Co., Ltd.).

However, few cases are known where stricture of a papillary duct is healed by application of the above-mentioned twisted yarn bar except for the very early stage of papillary duct lesions. Once a cow suffers from papillary duct stricture, no improvement even for milking once takes place, and one cannot milk without using a cannula, which will further worsen the papillary lesion. It follows that the papillary duct seriously thickens, making milking impossible and finally needing cut section or dilation of the papillary opening. Papillitis caused by postoperative infection cannot be prevented by the conventional inserts, and papillitis develops into mastitis in most cases.

While the conventional inserts for treating papillary duct stricture have applied thereto an antibiotic, the applied antibiotic is gradually diluted with milk while being kept in the duct between milking and milking, thereby resulting in not only loss of its antimicrobial activity but contamination of milk. On the contrary, the support with reduced antimicrobial activity helps invasion of bacteria through a capillary phenomenon. Besides, long-term use of the antibiotic-impregnated insert induces development of resistant strains. From all these considerations, use of the conventional inserts has come into question as a cause inducing iatrogenic mastitis.

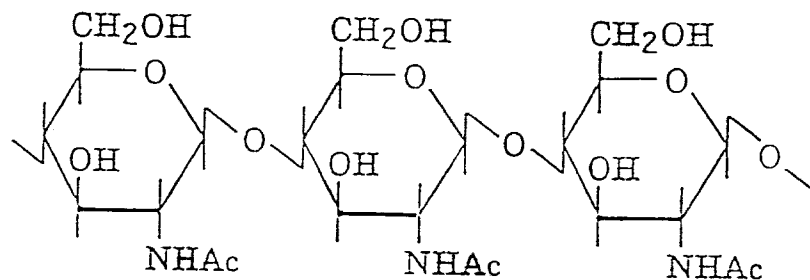
In short, conventionally employed twisted yarn bars or milking cannulae have no effect in healing papillary duct stricture or wounds or preventing and treating mastitis.

An object of the present invention is to provide a measure for papillary duct lesions or for the papillary duct after having a surgical treatment for stricture, consisting of simple insertion of a bar-shaped insert into the affected papillary duct.

DISCLOSURE OF THE INVENTION

The present invention relates to a papillary duct insert formed of chitin or a chitin derivative or a papillary duct insert comprising a support having coated thereon or impregnated therein chitin or a derivative thereof.

Chitin is a polysaccharide represented by formula:



comprising N-acetyl-D-glucosamine polycondensed through $\beta(1\rightarrow4)$ linkages which is present in crustaceans (e.g., shrimps and crabs), insects (e.g., grasshoppers and beetles), a cuttlebone, etc. Chitin which can be used in the present invention can be obtained by purifying naturally occurring crude chitin from

these sources by referring to, for example, Chitin Chitosan Kenkyukai (ed.), Chitin Chitosan Jikken Manual, Ch. 1 (Preparation of Chitin), pp. 1-7, Gihodo Shuppan K.K. (1991).

Chitin derivatives which can be used in the present invention include chemically modified chitin derivatives, such as deacetylated chitin, Chitosan (especially those having a degree of deacetylation of 80% or more), carboxymethylated chitin, hydroxyethylated chitin, and sulfonated chitin. Reference can be made to ibid, Ch. 2 (Preparation of Chitosan and Partially Deacetylated Chitin), pp. 9-17, Ch. 3 (Preparation of Chitin Derivatives), pp. 19-36, Ch. 4 (Preparation of Chitosan Derivatives), pp. 37-47.

Supports on or in which chitin or a derivative thereof is coated or impregnated include yarn, sponge, cloth, etc. made of soft and biologically harmless materials, such as silk, collagen, cellulose, nylon, polyethylene, polypropylene, polyester, Teflon, etc.

If desired, the papillary duct insert according to the present invention formed of chitin or a derivative thereof or comprising a support coated or impregnated with chitin or a derivative thereof may further be coated with starch, polyvinyl alcohol, sodium carboxymethyl cellulose, alginic acid or a salt thereof, and so on as a binder so as to have increased hardness.

The insert formed of chitin or a chitin derivative according to the present invention can be produced, for example, as follows. Yarn, sponge, cloth, etc. made of chitin or a chitin derivative is shaped into a string or bar having a diameter of from 1 to 5 mm, preferably from 2 to 3 mm. A 1 to 50 w/v%, preferably 1 to 10 w/v%, solution of a binder is coated thereon and dried to obtain a stock bar of about 3 mm in diameter, which is then cut to a length of from 1 to 10 cm, preferably from 3 to 7 cm. The tip of one end of the resulting bar is cut off at right angle or obliquely.

The insert comprising a support coated or impregnated with chitin or a chitin derivative according to the present invention can be produced, for example, as follows. A support, such as a bar, a filament; sponge, cloth, etc. is shaped into a string or bar having a diameter of from 1 to 5 mm, preferably from 2 to 3 mm, and a solution or dispersion containing 1 to 50 w/v%, preferably 1 to 10 w/v%, of chitin or a chitin derivative is coated thereon or impregnated therein. A 1 to 50 w/v%, preferably 10 to 30 w/v%, binder solution is further coated thereon and dried to prepare a stock bar having a diameter of 1 to 5 mm, preferably 2 to 3 mm. Alternatively, a support is first coated with chitin or a chitin derivative and then shaped into a string or bar, and a binder solution is coated thereon followed by drying. The resulting stock bar is cut at right angle or obliquely to a length of from 1 to 10 cm, preferably from 3 to 7 cm.

Chitin and derivatives thereof may be used either individually or in combination of two or more thereof.

The support may be prepared by mixing yarn, sponge, cloth, etc. made from the above-described soft and harmless material (e.g., silk, collagen, cellulose, nylon, polyethylene, polypropylene, polyester or Teflon) with yarn, sponge, cloth, etc. made from chitin or a chitin derivative and shaping the mixture to the above-mentioned dimensions.

The reason why application of the insert according to the present invention to papillary ducts heals papillary duct stricture or papillary duct lesions after a surgical treatment of stricture and also prevents mastitis has not yet been made clear. With the insert inserted into a papillary duct, it seems that various cells participating in healing mechanism of a wound are made to wander without inducing antixenic reaction to markedly accelerate vascularization and formation of granulations. Also possessing antimicrobial properties, the insert of the invention is believed to exert direct accelerating effects on postoperative treatment after a surgical measure for papillary duct stricture and to accelerate regeneration of the epithelium while preventing invasion of bacteria.

BEST MODE FOR THE PRESENT INVENTION

The present invention will now be illustrated in greater detail by way of Examples, but it should be understood that the present invention is not construed as being limited thereto.

EXAMPLE 1

In 1800 ml of a 4.2 v/v% acetic acid aqueous solution was dissolved 200 g of chitosan ("FLONAC C" produced by Kyowa Technos Co., Ltd.; degree of deacetylation: 83%), followed by filtration under pressure of 1 to 2 kg/cm². The solution was allowed to stand for 20 hours to prepare a dope. The dope was spun from a nozzle having 500 orifices of 0.1 mm in diameter into a 1.5 m long first coagulating-bath containing 10 l of ethylene glycol, 1.5 kg of water, and 1.8 kg of potassium hydroxide and passed through a 0.9 m long second coagulating bath containing a 50 v/v% aqueous solution of methanol at a speed of 12 m/sec to complete coagulation. The spun filament was drawn at a draw ratio of 1.17, wound around a bobbin, washed with running water as wound for 12 hours, immersed in hot water at 70 to 80 °C for 4 hours and then in

ethanol for 24 hours, re-wounded around a reel, and spontaneously dried to obtain a hank. The hank was wetted with water, and 18 filaments out of the hank were intertwined to obtain twisted yarn having a diameter of 5 mm. The twisted yarn was dipped in a 7 w/v% aqueous solution of polyvinyl alcohol (a product of Wako Pure Chemical Co., Ltd.; degree of polymerization: about 1500) to coat 1 ml of the polyvinyl alcohol per 10 cm, followed by drying under reduced pressure to obtain a stock bar having a diameter of 3 mm. The stock bar was cut to lengths of 6.5 cm, and the tip at one end of each cut bar was cut off at about 45° or at right angle with the longitudinal direction. The other end of the twisted yarn bar was fitted into a silicone tube of 5 mm in diameter and 5 mm in width to prepare a papillary duct insert. The resulting insert was designated A.

EXAMPLE 2

Papillary duct insert B having a diameter of 3 mm and a length of 6.5 m was prepared in the same manner as in Example 1, except that the twisted yarn was dipped in a 2 w/v% aqueous solution of sodium carboxymethyl cellulose (a first grade reagent produced by Nakarai Tesuku Co., Ltd.) in place of polyvinyl alcohol to pick up 0.5 ml of sodium carboxymethyl cellulose per 10 cm.

EXAMPLE 3

In 300 ml of a 5 v/v% acetic acid aqueous solution was dissolved 15 g of chitosan ("FLONAC C") followed by filtration under reduced pressure to prepare a homogeneous chitosan solution. Rayon nonwoven cloth "Bemliese JF601" produced by Asahi Chemical Industry Co., Ltd.; unit weight: 60 g/m²) 9cm wide and 30 cm long was dipped in the chitosan solution for 30 minutes. The impregnated nonwoven cloth was squeezed lightly so as not to drip the liquid and then immersed in a 8 w/v% aqueous solution of sodium hydroxide for 1 hour. The cloth was washed with running water for 1 hour, soaked in hot water at 70 to 80°C for 30 minutes, and spontaneously dried to obtain chitosan-impregnated nonwoven cloth containing 0.2 g of chitosan per gram. After wetted with water, the cloth was folded in four in the width direction and twisted in the longitudinal direction. A 2 w/v% aqueous solution of sodium carboxymethyl cellulose (a first grade reagent produced by Nakarai Tesuku Co., Ltd.) was coated on the resulting bar-shaped twisted cloth at a spread of 2.0 ml/10 cm and dried under reduced pressure to obtain a stock bar of 3 mm in diameter. The stock bar was cut to lengths of 6.5 cm, and the tip was cut at an angle of about 45° or at right angles with the longitudinal direction. The other end of the bar was fitted into a silicone tube of 5 mm in diameter and 5 mm in width to prepare a papillary duct insert designated C.

Each of the inserts prepared in Examples 1 to 3 was inserted to the papillary duct of a female Holstein suffering from papillary duct stricture or a female Holstein having undergone stricturotomy for dilating the opening of the papillary duct. The cows were milked twice a day, and a fresh insert was inserted after every milking. Any change of the papilla was observed everyday. The prognostic symptoms and the state of mastitis are shown in Table 1 below.

TABLE 1

Case No.	Insert Kind	Used Tip	Particulars of Animal Age	Situation	under Mastitis	Treatment CMT	Number of Days of Treatment	Prognosis	State of Mastitis	CMT*
1	A	oblique cut	5	papillary duct stricture	none	-	10	improvement	none	-
2	A	"	5	"	observed	+++	7	sign of improvement	healed	-
3	A	cross-wise cut	6	"	none	-	14	improvement	none	-
4	B	oblique cut	6	"	"	-	14	"	"	-
5	B	cross-wise cut	5	"	"	-	14	"	"	-
6	A	oblique cut	5	after operation for dilation	"	-	14	"	"	-
7	commercially available product		5	papillary duct stricture	"	-	14	no change	infection	+++
8	commercially available product		5	after operation for dilation	"	-	7	"	"	+++

Note: * California mastitis test

-: No mastitis was recognized.

±: Suspected

+: Mastitis was recognized.

++: Mastitis was considerably recognized.

INDUSTRIAL APPLICABILITY

When the papillary duct insert of the present invention was applied to the papilla suffering from stricture or having undergone an operation for dilation of the papillary opening, improvements were observed in 5

out of 6 cases.

Case 2 showed a sign of improvement on the stricture. While no further effects could be observed because of shortage of the period of treatment, 7-day application of the insert of the present invention resulted in healing of mastitis. No influence on other mammae (any changes of milk of other normal
5 mammae of the same animal) was noted at all. Development into mastitis due to the use of the insert was not observed.

Application of insert A caused light swelling of the papilla and light pain but gave no adverse influences on the therapy and milking.

No side effect such as swelling of the papilla or pain was recognized in application of insert B.

10 Although the inserts with a crosswise cut encountered slight difficulty in inserting into the papillary duct as compared with those with an oblique cut, irritation to the papillary duct was less, and no particular disadvantage resulted when applied to lightly strictured papillae.

For comparison, a commercially available insert for a papillary duct ("TEATOR POINT") was applied to a strictured papillary duct unaffected by mastitis (Case 7) and a papillary duct after an operation for dilating
15 the opening of a strictured papillary duct (Case 8). Because mastitis occurred in 7-day application with no improvement on the stricture, the experiments were suspended.

Claims

- 20 1. An insert for a papillary duct of dairy cattle which is formed of chitin or a chitin derivative.
2. An insert for a papillary duct comprising a support having coated thereon or impregnated therein chitin or a derivative thereof.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP93/00077

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl⁵ A61D1/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Int. Cl⁵ A61D1/02

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Jitsuyo Shinan Koho 1926 - 1993

Kokai Jitsuyo Shinan Koho 1971 - 1993

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JP, Y1, 35-31046 (Gendai Seiyaku K.K.), November 18, 1960 (18. 11. 60), (Family: none)	1, 2
A	JP, Y1, 40-867 (Toshiba Seiyaku K.K.), January 12, 1965 (12. 01. 65), (Family: none)	1, 2
A	JP, Y1, 40-35735 (Shigeru Terakado), December 16, 1965 (16. 12. 65), (Family: none)	1, 2
A	JP, Y1, 44-9492 (Shigeru Terakado), April 17, 1969 (17. 04. 69), (Family: none)	1, 2



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

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Date of the actual completion of the international search

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