United States Patent Office 3,483,870 Patented Dec. 16, 1969

3,483,870

SURGICAL USE OF ADHESIVE COMPOSITIONS

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No Drawing. Filed Apr. 22, 1963, Ser. No. 274,848
Int. Cl. A61b 17/04; A61k 27/00; A01n 17/00
U.S. Cl. 128—334 8 Claims

ABSTRACT OF THE DISCLOSURE

This invention relates to a surgical method for joining tissue surfaces through the use of an α-cyanocrylate adhesive and more particularly to an improved method which comprises the use of a substance with the α-cyanocrylate which is particularly adapted for accelerating the bonding action under surgical conditions. The accelerating substances employed are basic organic nitrogen compounds which serve the dual function of a polymerization catalyst and a physiological active agent, such as a vasoconstrictor or local anesthetic.

The usual methods for closing incisions in flesh and for setting bone fractures, by the use of sutures, clamps, pins or the like, have many drawbacks. The use of an adhesive substance for these surgical purposes would have the advantage of permitting rapid joining of the damaged members and of permitting natural healing. However, the common adhesives are unsuitable for surgical use. Most adhesives need too much time to form a bond. Many require the use of heat or pressure or the evaporation of a solvent, all of which make them unsuitable as surgical adhesives. Other adhesives, including some that might otherwise be suitable for surgical use, are excessively irritating to the body tissues.

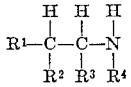
A recent surgical development is the use of methyl α-cyanoacrylate, $CH_2{:}C(CN)COOCH_3$, as a bone cement positions comprising the monomeric esters of α-cyanoacrylate polymerizes in situ without the use of heat or pressure or the evaporation of a solvent. Our co-pending application Ser. No. 225,896, filed Sept. 24, 1962, now abandoned discloses the use of surgical adhesive compositions comprising the monomeric esters of α-cyanoacrylic acid of the formula, $CH_2{:}C(CN)COOR$, wherein R is a saturated hydrocarbon radical of 2 to 10 carbon atoms, of which those of 3 to 6 carbon atoms, and most especially isobutyl, produce the most outstanding advantages. Such higher esters of α-cyanoacrylic acid have been found to be superior to methyl-2-cyanoacrylate as surgical adhesives in a number of respects. Our co-pending patent application Ser. No. 225,896, filed Sept. 24, 1962 discloses that the higher esters of α-cyanoacrylic acid have such advantages in the surgical use as superior flexibility, absence of irritating vapor, superior hydrolytic stability and more consistent formation of rapid bonds under surgical conditions.

The higher esters of α-cyanoacrylic acid are thus preferred but the methyl ester is more readily available and has advantages over conventional adhesive compositions for surgical purposes. Furthermore, although less desirable for surgical use, the α-cyanoacrylate esters wherein R is cyclohexyl or phenyl have utility as adhesives and can be employed with polymerization accelerators as described herein in accordance with the invention. Accordingly, the surgical method of the present invention can be employed with the esters of α-cyanoacrylic acid of the formula, $CH_2{:}C(CN)COOR$, wherein R is alkyl, cyclohexyl or phenyl, although the greatest advantages are obtained when R is an alkyl radical of 2 to 10 carbon atoms, preferably.

The method of the present invention is based on our discovery that certain basic organic nitrogen compounds accelerate the bonding of the α-cyanoacrylate adhesive in surgical use and also provide desirable physiological results, thus, serving a plural function as a polymerization catalyst and as a physiologically active agent.

The basic organic nitrogen compounds that produce the best results in our new method are β-substituted ethylamines of the formula:

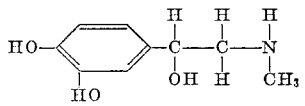
(I)



wherein R^1 can be alkyl or cycloalkyl of 4 to 6 carbon atoms but, preferably, is phenyl or phenyl substituted with hydroxy or lower alkoxy, or the like. R^2 is hydrogen, lower alkyl, preferably methyl, or hydroxyl; R^3 and R^4 are hydrogen or lower alkyl; and at least one of R^2, R^3 and R^4 is hydroxyl or lower alkyl.

The organic nitrogen compounds (I) are basic compounds which catalyze the polymerization of the α-cyanoacrylate monomers and thus accelerate the formation of a bond. This is particularly advantageous in forming surgical bonds because the bond must form quickly so that the use of clamps or sutures can be avoided or reduced to a minimum. While the ability of this class of compounds to accelerate the surgical bonding of the α-cyanoacrylate monomers without adverse physiological effects, by itself constitutes an extremely valuable characteristic, these compounds have another property which uniquely adapts them for coaction with α-cyanoacrylate adhesives in surgical uses. The organic nitrogen compounds of this class function as vasoconstrictors. Consequently, they serve to stop or inhibit the flow of blood or other fluids into the area in which the adhesive is being used. The presence of body fluids on the surfaces to be joined has been a factor that has caused the α-cyanoacrylate monomers to be less successful as surgical adhesives in some instances than would be desired. Consequently, the discovery of materials which both speed the formation of a bond and reduce the flow of fluids into the area to be adhered provides a valuable improvement in the use of α-cyanoacrylate adhesives for surgical purposes.

The compounds of type (I) which have a plural function in catalyzing polymerization and in providing a useful physiological effect during the surgical bonding are described in chapter 27 in "Pharmacology in Medicine," 2nd edition by V. A. Drill, McGraw-Hill Book Company, New York, 1958. They are referred to as adrenergic agents. Of this group of substances the ones most successful in catalyzing the reaction and in functioning as vasoconstrictors are the pressor amines of the β-phenyl ethylamine type. The prototype of the latter class of compounds and the compound that offers the greatest advantages in the method of the invention is epinephrine, also known as adrenaline, which has the formula,



and is thus a compound of type (I) wherein R^1 is 3,4-dihydroxyphenyl, R^2 is hydroxyl, R^3 is hydrogen and R^4 is methyl.

Examples of other compounds of type (I) and their structure according to the general Formula I, are given in the following table.