

[54] **ADENOSINE-5'-ESTERS IN TREATING
ANGINA PECTORIS**

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Related U.S. Application Data

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abandoned, and a continuation-in-part of Ser. No.
28,916, April 15, 1970, abandoned.

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[58] **Field of Search**..... 424/253, 180

[56] **References Cited**

OTHER PUBLICATIONS

Giertz et al., Arch. Exper. Path. u. Pharmacol., Bd.
229, pp. 26-33, (1956).

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[57] **ABSTRACT**

A method of preventing and/or decreasing the severity
of attacks of angina pectoris by administering adeno-
sine-5'-ester to a patient suffering from or having a
history of such attacks.

4 Claims, No Drawings

ADENOSINE-5'-ESTERS IN TREATING ANGINA PECTORIS

CROSS-REFERENCE TO RELATED APPLICATION

This application is a continuation of Ser. No. 129,606, filed Mar. 30, 1971 and a continuation-in-part of Ser. No. 28,916 filed Apr. 15, 1970, both are now abandoned.

DETAILED DESCRIPTION OF THE INVENTION

Angina pectoris is a coronary syndrome characterized by a special type of paroxysmal sensation of pressing or strangling pain usually located behind the sternum or in the precordial region. The pain often radiates to the back of the left arm but may often radiate elsewhere. The attacks can vary greatly in severity and frequency.

Generally speaking, anginal pain rises from an imbalance in the heart between the supply of and the demand for oxygen. The pain is usually brought about by episodes of extreme emotional stress, exposure to cold, excitement or any other stressful situation. In summation, any sudden increase in cardiac work, any decrease in coronary blood flow or, any interference with oxygenation of the blood may cause an attack. However, anginal attacks can occur while the patient is sleeping. Therefore, anginal pain is not necessarily due to a decrease of blood flow but rather to an insufficiency of the flow in relation to the metabolic requirements or oxygen demands of the heart.

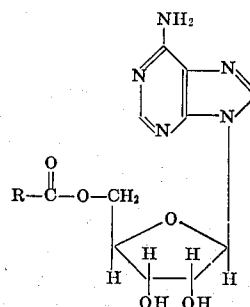
There are several available drugs useful in the management of angina pectoris attacks. Most of the therapeutic agents, such as nitroglycerin and related nitrites are coronary dilators which do not effect the underlying coronary artery pathology or myocardial cardiac damage. Accordingly, currently available therapy is symptomatic rather than curative. Nitroglycerin is probably the most widely used agent in managing acute attacks of angina, however, there has been a long standing need for a prophylactic agent which when administered to patients with a history of, or who are susceptible to attacks of angina pectoris, will prevent or reduce the severity of future attacks.

We have found certain adenosine-5'-esters to be orally active, long acting anti-anginal agents. The esters act as "sparing" agents, that is, not like adenosine itself, the compounds useful in the practice of this invention, increase the myocardial efficiency, reduce the amount of oxygen required by the heart, and reduce the actual cardiac work. Such activity is wholly unexpected, since the parent compound, adenosine is not orally active, is very rapidly metabolized and does not increase coronary sinus pO_2 and thus is not suitable as a therapeutic agent.

Geitz et al. first reported adenosine-5'-acetate as a new ester of adenosine having analgesic and antipyretic activity, *Arch. Exper. Path. u. Pharmacol.*, Bd. 229, pp. 26-33 (1956). While Gietz et al. observed that both adenosine and adenosine-5'-acetate lowered blood pressure in mice and had some effect as vasodilators, they reported adenosine-5'-acetate's blood pressure lowering effect to be only one-sixth to one-thirtieth that of adenosine itself, and further reported that adenosine-5'-acetate was 10 times weaker as a coronary dilator in isolated, perfused guinea pig heart. Since adenosine is not orally active, and is so rapidly metabolized that it is useless as a therapeutic agent, one

skilled in the art would certainly not expect the acetate to be orally active as an anti-anginal agent, and further to increase coronary sinus pO_2 .

The compounds useful in the practice of this invention are represented by the structural formula



wherein R is C_1 - C_3 alkyl. The term " C_1 - C_3 " as used herein refers to both straight and branched chain alkyl groups such as methyl, ethyl, n-propyl and iso-propyl.

The compounds of this invention can be prepared according to the method described by Brown et al., *J. Chem. Soc.* 1950, 3299 (1956).

We have found that adenosine-5'-acetate is an excellent orally-active anti-anginal agent when administered to animals in dosages of from 0.5 to 100 mg./kg. preferably 15-30 mg./kg. of body weight daily. Generally speaking, adenosine-5'-acetate is administered daily in divided doses as a prophylactic agent to prevent anginal attacks. Normally, administration of adenosine-5'-acetate will be instituted at the onset of an anginal attack and at intervals to prevent further attacks.

Adenosine-5'-acetate has been found to increase coronary sinus partial pressure of oxygen (pO_2) when administered to mammals in dosages of from 0.5 to 100 mg./kg. of body weight daily either orally or by intravenous, intraportal and intraduodenal routes. However, it is preferred to administer the compound orally in a suitable dosage form such as tablets, pills, filled capsules and the like.

While adenosine-5'-acetate is the preferred compound, we have also found that the corresponding propionate, butyrate and valerate will also increase coronary sinus pO_2 when administered to mammals in dosages of from 5 to 100 mg./kg. of body weight daily. The above compounds also exhibit oral activity.

The anti-anginal activity of the compounds useful in the practice of this invention were established according to the method described by Schoepke et al., *Pharmacologist* 8:204, (1966). Generally speaking, using the Schoepke method, dogs are treated first with 5 mg./kg. of morphine administered subcutaneously and then they are anesthetized with 250 mg./kg. of barbital, administered intravenously. The femoral artery is cannulated for blood pressure measurements. Lead II of the electrocardiogram is recorded and the R-wave is used to trigger a tachygraph for heart rate determinations. The animals are placed on artificial respiration using room air and a positive pressure respirator. The right chest of each dog is opened and a cannula is placed in the coronary sinus from an incision in the right arterial appendage. A Beckman micro-electrode for measuring pO_2 is placed in the blood obtained from the coronary sinus. The drug is suspended in 50% propylene glycol and water for intravenous, intraportal and intraduodenal administration. Filled capsules are used

for oral administration. The results obtained with adenosine-5'-acetate with various dosage levels of administration are summarized in the following tables.

EXAMPLE 1

Adenosine-5'-acetate was evaluated as an anti-anginal agent following the above Schoepke et al method over a dosage range of from 0.5 to 30 mg./kg. of body weight. As can be seen from Table 1, adenosine-5'-acetate greatly increases the coronary sinus pO_2 .

TABLE 1

EFFECT OF ADENOSINE-5'-ACETATE ON CORONARY SINUS pO_2 IN ANESTHETIZED DOGS

Dose mg./kg. (50% propylene glycol)	Administration Route	pO_2 change %	Duration, min.
0.5	I. V.	162	22
1	I. V.	152	15+
2	I. V.	214	11
2	I. V.	57	20+
2	I. V.	79	8
2	I. V.	155	15
5	I. V.	172	20+
10	I. V.	300	25
5	intraportal	71	15+
10	intraportal	253	30+
15	intraduodenal	21	22
15	intraduodenal	23	45+
30	intraduodenal	39	60+
30	intraduodenal	66	50+
30	intraduodenal	55	50

No EKG changes were observed. Blood pressure and heart rate effects were small and variable, although both tended to decrease in response to the drug.

EXAMPLE 2

Adenosine-5'-acetate was administered orally to unanesthetized, closed-chest dogs having an indwelling catheter in the coronary sinus to determine the effect on coronary sinus pO_2 . The average effect on coronary sinus pO_2 is summarized in Tables 2a and 2b.

TABLE 2a

EFFECT OF ADENOSINE-5'-ACETATE ON PEAK CORONARY SINUS pO_2 BY ORAL ADMINISTRATION IN UNANESTHETIZED DOGS

Dose mg/kg	Peak pO_2 (mm Hg)	Time to Peak (hrs)	Increase in pO_2 %	Increase in pO_2 (mm Hg)
Controls (n-21)	15	—	—	—
15 (n-2)	21	3	54	6
20 (n-4)	27	2	82	12
25 (n-4)	30	2	102	15
30 (n-4)	34	2	129	19

TABLE 2b

EFFECT OF ADENOSINE 5'-ACETATE ON CORONARY SINUS pO_2 BY ORAL ADMINISTRATION IN UNANESTHETIZED DOGS

Dose mg/kg	Number of Experiments	Onset (hrs)	Duration (hrs)
Gelatin Capsule alone	3	—	—
15	3	2½	3

TABLE 2b—Continued

EFFECT OF ADENOSINE 5'-ACETATE ON CORONARY SINUS pO_2 BY ORAL ADMINISTRATION IN UNANESTHETIZED DOGS

Dose mg/kg	Number of Experiments	Onset (hrs)	Duration (hrs)
20	4	2	1.5
25	4	1.5	2
30	4	2.5	2

It can be seen from Tables 2a and 2b that in unanesthetized dogs, adenosine-5'-acetate is orally active and that the effect is dose-responderent over the test range of 15–30 mg./kg.

EXAMPLE 3

Three anesthetized dogs, prepared according to the method of Schoepke et al. received 5 mg./kg. of adenosine-5'-acetate intravenously, and the effect of the drug on various hemodynamic parameters were recorded. As can be seen from Table 3, 5 mg./kg. of adenosine-5'-acetate decreases the left ventricular work by an average of 45%. The work decrease is considered by physicians to be therapeutically beneficial in the treatment of angina pectoris. It should be noted that adenosine, on the other hand, is reported to increase cardiac work (G. Rowe et al., *Am. Heart J.*, 64, 228, 1962).

TABLE 3

EFFECT OF ADENOSINE-5'-ACETATE (5 mg/kg I.V.) ON HEMODYNAMIC PARAMETERS (n-3) IN ANESTHETIZED DOGS

	%
Aortic pressure	–20
Heart rate	+20
Cardiac output	–25 (after transient increase)
ITT (Index of Contractility)	+60
Resistance	–35 (then a gradual increase)
Left ventricular work	–45
Stroke volume	–30

EXAMPLE 4

Adenosine-5'-acetate and adenosine were evaluated in a cross-over study to compare the effect of both substances on coronary sinus pO_2 . As can be seen from Table 4, adenosine does not significantly effect coronary sinus pO_2 .

TABLE 4

CROSSOVER STUDY WITH ADENOSINE-5'-ACETATE AND ADENOSINE

Drug (15 mg/kg, i.d.)	Dog No.	pO_2 change %	Duration min.	Overall activity rating
Adenosine-5'-acetate	1	83	80	active
Adenosine	1	12	60+	inactive
Adenosine-5'-acetate	2	61	60	active
Adenosine	2	0	0	inactive

The present invention includes within its scope pharmaceutical compositions comprising adenosine-5'-acetate in association with a pharmaceutically acceptable carrier or diluent. Adenosine-5'-acetate exhibits both oral and parenteral activity and can be for-

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mulated in dosage forms for oral, sublingual, parenteral or rectal administration.

Solid dosage forms for oral administration include capsules, tablets, pills, powders and granules. In such solid dosage forms, the active compound is admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms can also comprise, as is normal practice, additional substances other than inert diluents, e.g., lubricating agents such as magnesium stearate. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups and elixers containing inert diluents commonly used in the art, such as water. Beside inert diluents, such compositions can also include adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring and perfuming agents.

Preparations according to this invention for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions or emulsions. Examples of non-aqueous vehicles are propylene glycol, polyethylene glycol, vegetable oils, such as olive oil and injectable organic esters such as ethyl oleate. Such dosage forms may also contain adjuvants such as preserving, wetting, emulsifying and dispersing agents. They may be sterilized by, for example, filtration through a bacteria-retaining filter, by incorporating sterilizing agents into the compositions, by irradiating the compositions, or by heating the compositions. They can also be manufactured in the form of sterile solid compositions which can be dissolved in sterile water, or some other sterile, injectable medium immediately before use.

Compositions for rectal administration are suppositories which may contain, in addition to the active substance, excipients such as cocoa butter or a suppository wax.

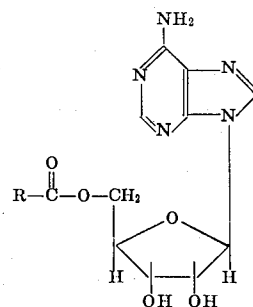
The dosage of active ingredient in the composition of this invention may be varied; however, it is necessary

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that the amount of the active ingredient be such that a suitable dosage form is obtained. The selected dosage depends upon the desired therapeutic effect, on the route of administration, and on the duration of treatment. Generally, adenosine-5'-acetate is administered in dosage levels of from 0.5 to 30 mg./kg. of body weight daily to patients in need of coronary oxygen increase or who are susceptible to attacks of angina pectoris. However, because of the low toxicity of the adenosine-5'-acetate (LD_{50} in mice of <1000 mg./kg.) dosages of up to 100 mg./kg. or more can be administered if desired.

We claim:

1. The method of increasing the supply of coronary sinus oxygen in a mammalian patient in need of said coronary oxygen increase comprising orally administering to said patient a therapeutically effective amount of a compound of the formula



wherein R is C_1 - C_3 alkyl.

2. The method of claim 1 wherein the compound is adenosine-5'-acetate.

3. The method of claim 2 wherein from about 0.5 to about 100 mg./kg. of adenosine-5'-acetate is administered to said patient.

4. The method of claim 3 wherein adenosine-5'-acetate is administered orally to said patient.

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