SYNERGISTIC EFFECT OF ADENYLYC NUCLEOTIDES IN DIGITALIS THERAPY


No Drawing. Filed Sept. 16, 1963, Ser. No. 309,594

17 Claims. (Cl. 167—65)

This is a continuation-in-part of application Ser. No. 858,326, filed Dec. 9, 1963, now U.S. Patent 3,104,203.

This invention relates to cardiac therapy. More particularly, this invention relates to the synergistic effects of adenylic nucleotides on the use of digitalis in cardiac therapy.

Whole-leaf digitalis and the purified cardiac glycoside derivatives of digitalis lanata and digitalis purpurea, e.g., digitoxin, digoxin, lanatoside A, and the like, have long been considered the most effective medicinal agents in cardiac therapy. The loss of cardiac reserve manifested by congestive heart failure is the result of an imbalance between cardiac muscle strength and the load imposed on the heart. Therapy is therefore usually directed toward improving the function of the failing heart muscle and reducing the work load on the myocardium. The digitalis drugs are the only commonly known agents which produce compensation through direct action on the myocardium.

The major pharmacologic effect of digitalis is its direct action on the myocardium. Digitalis increases the force of systolic contractions of the heart muscle, without altering the diastolic fiber size. The more forceful contraction results in more complete ventricular emptying with a rise in volume output. There is also an enhanced capacity to propel blood against increased peripheral resistance. At the same time the duration of systole is abbreviated, allowing greater time for both ventricular filling and heart rest. The diastolic size of the heart is reduced. Oxygen consumption is a function of the initial fiber length such a reduction in size diminishes the oxygen expenditure for any work output. The work capacity of the heart is thereby increased and a greater percentage of the liberated energy is used in mechanical processes of shortening and development of tension. The overall effect of digitalis appears to be a more efficient utilization of phosphate bond energy with a resulting increase in cardiac efficiency and output. The basic pattern of myocardial derangement that characterizes failure is thus reversed. In other words, the digitalized failing heart can do the same work with less energy, i.e., oxygen utilization, or more work with the same energy expenditure than before digitalization.

The major problem associated with digitalis therapy is the toxic manifestation of the drug which results from overdose. Although overdose is usually not a major problem in most therapeutic treatments, it is an ever present danger in digitalis therapy due to the prevalent practice of administering digitalis until the first appearance of toxic manifestations. Some of the early toxic manifestations are easily recognized and are reversible and thus unimportant. Other manifestations of digitalis overdosage are less distinctly recognized; i.e., estimation of the drug in such circumstances can lead to structural cardiac changes that are not reversible or to fatal disturbance of the cardiac mechanism.

The toxic effects of digitalis are not side effects of the drug. They are direct manifestations of excessive saturation with the drug. The most common toxic effects of all digitalis leaf preparations are gastro-intestinal, e.g.,

anorexia, nausea, vomiting and the like. Lower abdominal cramps are usually the first complaint, with or without diarrhea, and these can occur in the absence of nausea or vomiting. Parenteral administration is as effective as oral administration in producing the gastro-intestinal symptoms.

Other toxic manifestations of digitalis therapy have their source in disturbances of the central nervous system. Initially, the patient may complain of fatigue, unusual drowsiness, headache or restlessness. Further administration of digitalis can result in an increase of restlessness, periods of disorientation, occasionally an attack of delirium. Many varieties of visual disturbances can also result as cerebral toxic effects, e.g., dimness of vision, diplopia, difficulty in focusing the eyes, scotomata, yellow, green or white vision. In the late stages of poisoning, the patient may lapse into coma and die shortly thereafter.

Digitalis overdose, in itself, can aggravate failure of a diseased heart through functional disturbance of ectopic rapid heart action. Moreover, overdose can promote failure through interference with conduction or by reduction of the coronary blood flow. Due to the direct action of digitalis on the myocardium, overdose increases myocardial irritability leading to disturbance in rhythm and structural damage to the myocardium.

There are two major difficulties in the use of digitalis. One is the wide variation in potency, absorption rates, and rates of elimination of the many digitalis preparations. The other is the wide range of individual susceptibility to the drug. These wide differences in individual tolerance make it necessary to depend not merely on dosage, but also upon the effect produced in each individual patient. Adherence to a routine dosage schedule can result in inadequate digitalization of some patients and the poisoning of others. In most cases, digitalis is administered initially in a "digitalizing" dose which need not exceed 2.0 grams of the whole-leaf preparation or 2.0 milligrams of a purified glycoside derivative. Thereafter, smaller daily maintenance doses are administered. While the initial digitalizing dose is nontoxic to a large percentage of patients, the daily maintenance dose often leads to excessive accumulation of the drug in the tissues. The particularly slow rate of elimination of the purified glycosides is not only a factor which produces accumulation but also leads to unusually delayed dissipation of toxic effects after the drug is discontinued. Nevertheless, digitalis and its purified glycoside derivatives are widely employed in cases of congestive heart failure, atrial flutter, atrial fibrillation, paroxysmal auricular tachycardia, hypertensive or valvular heart disease, cardiac enlargement, myocardial infarction, and the like.

Accordingly, it is an object of this invention to provide therapeutic agents which synergistically decrease the dosage requirements of digitalis.

It is another object of this invention to eliminate the toxic manifestations which are characteristic of digitalis therapy.

In accordance with the present invention, it has been found that preparations containing adenylic nucleotides, preferably adenosine-2'-3')-monophosphate, adenosine diphosphate, adenosine triphosphate, cyclic adenosine 3,5 phosphate, nicotinamide adenylate, adenosin adenylate and adenosine 5'-adenylate, as well as those compounds prepared by reacting procaine, procaine propranolol and related adenosine monophosphoric, diphosphoric and triphosphoric acids have unexpected therapeutic value in digitalis treatment of cardiac disorders. Moreover, it has been found that when the therapeutic compositions of the present invention are administered to patients undergoing digitalis therapy, a synergistic decrease in the dosage of digitalis is afforded, thereby eliminating the
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It has been found that a safe and satisfactory therapeu-
tic dosage of the adenylic nucleotides useful in this
invention can range from about 25 milligrams up to
about 300 milligrams per dosage unit. The preferred
dosage unit contains an adenylic nucleotide, preferably
adenosine-2'-3'-monophosphate, adenosine diphosphate,
adenosine triphosphate, cyclic adenosine, 3,5-phosphate,
nicotinamide adenylate, procaine adenylate, iron aden-
ylate, and the like, in an amount of from 50 to 200 milli-
grams. The especially preferred adenylic nucleotides are
nicotinamide adenylate and procaine adenylate because
they afford the quickest and most lasting relief of cardiac
failure symptoms.

The preparations of the present invention can be ad-
ministered orally, sublingually, parenterally or by sup-
pository with sublingual administration being preferred
because of the simplicity of treatment. It has been found,
however, that treatment began by injection results in
more rapid relief.

In sublingual oral or rectal administration, the above
dosage units are given four times daily. In parenteral
administration, intramuscular or intravenous injections
are usually given twice daily.

Clinical tests have been made utilizing the adenylic
nucleotides described above in the treatment of myo-
cardial diseases as hereinbefore described and it was
found that smaller, non-toxic doses of digitalis prepara-
tions could be employed to control cardiac abnormalities
if administered in combination with an adenylic nucleo-
tide in the dosages described. Moreover, it was found that
a large dose, i.e., about 100-300 mg. of an adenylic
nucleotide preferably either procaine adenylate or nicotin-
amide adenylyte could be administered in lieu of the
initial digitalizing dose subsequently followed by main-
tenance doses of digitalis, i.e. less than about 1 mg. and
preferably from about 0.25-0.35 mg. and between about
50-200 mg. of an adenylic nucleotide. Because of the
synergetic decrease in digitalis dosage when combined
with the adenylic nucleotides of the present invention,
digitalis poisoning has been substantially decreased.

In the treatment of myocardial diseases, it is considered
preferable to administer the adenylic nucleotide in com-
bination with a digitalis preparation, at the onset of the
attack, in 1 ampule dosages intramuscularly twice daily
for about a week and thereafter 1-2 tablets four times
daily sublingually. The adenylic nucleotides in combina-
tion with a digitalis preparation can also be administered
intravenously or intramuscularly in 1/5 to 1 ampule doses
suitably diluted in physiological saline solutions or the like
as directed above. The adenylic nucleotides described above
can be used as a supplement to or in conjunction with the
conventional digitalis preparations normally administered
to relieve cardiac disorders. When so employed, the adenylic
nucleotides synergically decrease the digitalis dosage
requirements both in the initial digitalizing dose and the
subsequent maintenance doses. In some instances, a
dose of an adenylic nucleotide can be employed in
lieu of the initial digitalizing dose followed by smaller
maintenance doses of a digitalis preparation supplemented
by an adenylic nucleotide. Thus, the adenylic nucleo-
tides employed in the present invention can be admin-
istered before, after or with digitalization to synergistic-
dy decrease the initial digitalizing dose to an amount
insufficient, in itself, to cause digitalization and in some
cases even to prevent it. After digitalization, the adenylic
nucleotides are also useful in decreasing the maintenance
dosages of digitalis thereby preventing accumulation of
the digitalis preparations in the system and hastening
elimination of the purified glycosides to dissipate the
toxic effects after the drug is discontinued. It has also
been found that the adenylic nucleotides are useful in
reducing the toxic manifestations of a host already af-
flicted with digitalis poisoning. The use of the adenylic
nucleotides described above in this manner has been
found to result in a rapid and substantial improvement
of pain and other cardiac symptoms. Moreover, there are
no unpleasant side effects due to the toxicity or in-
stability of the preparations as were heretofore prevalent.

When the therapeutic preparations of this invention
are administered parenterally, they are usually given in
combination with a pharmaceutical dosage form. Suitable
pharmaceutical carriers which can be employed include
water, physiological saline solutions and the like.

In the tablet and suppository preparations of the pres-
cent invention, various binding materials such as solid
polyethylene glycols, waxes, fats, fatty acids and hydro-
genated oils can be employed. If, however, oral adminis-
tration in an entirely liquid form is desired, the bind-
ing material can be replaced by a suitable syrup base.

It is considered preferable that the orally administered
therapeutic tablet consist of from about 50 to 100 parts
by weight of an adenylic nucleotide, less than 1 part by
weight of a digitalis preparation, from about 175 to 200
parts by weight of sugar and from about 25 to 100 parts
by weight of a binding material as described above. For
example, a number of nicotinamide adenylyte sublingual
tablets were prepared. Each tablet had the following
composition:

Mg. Nicotinamide adenylate .......................... 55
Digoxin ........................................ 0.5
Polyethylene glycol 1 ................................. 75
Sugar ........................................... 190
Flavoring (oil of peppermint) ..................... Trace
Coloring (tint of Blue Color) .................... Trace

1 Polyethylene glycol having a molecular weight between
and 7000 and a viscosity of 700 to 900 centistokes at
°F.

The total formulation per tablet varied in weight from
310 to 325 milligrams. The tablet was formulated so as
to require approximately ten minutes for sublingual ab-
sorption.

Tablets and ampuls so prepared were found to be use-
ful in conjunction with or as a supplement to digitalis
preparations in the treatment of cardiac conditions.

Example I

The preferred adenylic nucleotides described herein
can be prepared as follows:

(a) Nicotinamide adenylate: prepared as described in
U.S. 2,417,841. The powdered nicotinamide adenylyte
is put in appropriate pharmaceutical dosage form.
(b) Adenosine-2'-3'-monophosphate, adenosine di-
phosphate, adenosine triphosphate, and cyclic adenosine
3,5 phosphate are commercially available. The powdered
adenosine derivative or its sodium salt is put in appro-
riate pharmaceutical dosage form.
(d) Iron adenylyte: prepared as described in U.S.
2,215,233. The iron adenylyte is put in appropriate phar-
maceutical dosage form.

What is claimed is:

1. A therapeutic composition prepared for administra-
tion into the human organism comprising a pharmaceu-
tical carrier and as the active agents therein an adenylic
nucleotide selected from the group consisting of nicotin-
amide adenylate and procaine adenylate, in combination
with a digitalis preparation selected from the group con-
sisting of whole-leaf digitalis and purified glycoside deriva-
tives thereof, said digitalis preparation being present in an
amount per dosage unit which is substantially below the
tolerance level for toxic manifestations resulting from-
said composition being effective in the treatment of
non-inflammatory cardiac abnormalities and myocardial
disorders.
2. A therapeutic composition prepared for administration into the human organism comprising a pharmaceutical carrier and as the active agents therein nicotinamide adenylate and whole leaf digitalis, said digitalis being present in an amount per dosage unit which is substantially below the tolerance level for toxic manifestations resulting therefrom; said composition being effective in the treatment of non-inflammatory cardiac abnormalities and myocardial disorders.

3. A therapeutic composition prepared for administration into the human organism comprising a pharmaceutical carrier and as the active agents therein procaine adenylate and whole leaf digitalis, said digitalis being present in an amount per dosage unit which is substantially below the tolerance level for toxic manifestations resulting therefrom; said composition being effective in the treatment of non-inflammatory cardiac abnormalities and myocardial disorders.

4. A therapeutic composition prepared for administration into the human organism comprising a pharmaceutical carrier and as the active agents therein, from about 25 to 300 milligrams per dosage unit of an about 50 molecide selected from the group consisting of nicotinamide adenylate and procaine adenylate, in combination with a digitalis preparation selected from the group consisting of whole leaf digitalis and purified glycoside derivatives thereof, said digitalis preparation being present in an amount per dosage unit which is substantially below the tolerance level for toxic manifestations resulting therefrom; said composition being effective in the treatment of non-inflammatory cardiac abnormalities and myocardial disorders.

5. A therapeutic composition prepared for injection into the human organism comprising a pharmaceutical carrier, and as the active agents therein, from about 100 to 300 milligrams per dosage unit of a member selected from the group consisting of nicotinamide adenylate and procaine adenylate, in combination with a digitalis preparation selected from the group consisting of whole leaf digitalis and purified glycoside derivatives thereof, said preparation being present in an amount per dosage unit insufficient in itself, to cause digitalization, said composition being effective in the treatment of non-inflammatory cardiac abnormalities and myocardial disorders.

6. A therapeutic composition prepared for injection into the human organism comprising a pharmaceutical carrier, and as the active agents therein; from about 50 to 200 milligrams per dosage unit of an about 1 milligram of a digitalis preparation selected from the group consisting of nicotinamide adenylate and procaine adenylate, in combination with less than about 1 milligram of a digitalis preparation selected from the group consisting of whole leaf digitalis and purified glycoside derivatives thereof, said composition being effective in the treatment of non-inflammatory cardiac abnormalities and myocardial disorders.

7. A therapeutic composition prepared for administration into the human organism comprising a pharmaceutical carrier, and as the active agents therein, from about 25 to 300 milligrams per dosage unit of an about 0.5 milligrams of a digitalis preparation selected from the group consisting of whole leaf digitalis and purified glycoside derivatives thereof, said composition being effective in the treatment of non-inflammatory cardiac abnormalities and myocardial disorders.

8. A therapeutic composition prepared for injection into the human organism comprising a pharmaceutical carrier, and as the active agents therein, from about 50 to 200 milligrams per dosage unit of an about 0.5 milligrams of a digitalis preparation selected from the group consisting of whole leaf digitalis and purified glycoside derivatives thereof, said composition being effective in the treatment of non-inflammatory cardiac abnormalities and myocardial disorders.

9. A therapeutic composition prepared for injection into the human organism comprising a pharmaceutical carrier, and as the active agents therein, from about 50 to 200 milligrams per dosage unit of an about 0.5 milligrams of a digitalis preparation selected from the group consisting of whole leaf digitalis and purified glycoside derivatives thereof, said composition being effective in the treatment of non-inflammatory cardiac abnormalities and myocardial disorders.

10. A therapeutic composition prepared for sublingual introduction into the human organism comprising a tablet containing from about 50 to 200 milligrams per unit dosage of a member selected from the group consisting of an adenylic nucleotide selected from the group consisting of nicotinamide adenylate and procaine adenylate, in combination with less than about 1 milligram of a digitalis preparation selected from the group consisting of whole leaf digitalis and purified glycoside derivatives thereof, said composition being effective in the treatment of non-inflammatory cardiac abnormalities and myocardial disorders.

11. An orally administered therapeutic composition for use in the treatment of non-inflammatory cardiac abnormalities and myocardial disorders, comprising from about 50 to 200 parts by weight of an adenyl nucleotide selected from the group consisting of nicotinamide adenylate and procaine adenylate; less than 1 part by weight of a digitalis preparation selected from the group consisting of whole leaf digitalis and purified glycoside derivatives thereof; from about 175 to 200 parts sugar; and from about 25 to 100 parts of a binding material.

12. A therapeutic composition prepared for introduction into the human organism in suppository form comprising a suitable suppository base and as the active ingredients therein from about 30 to 200 milligrams of an adenyl nucleotide selected from the group consisting of nicotinamide adenylate and procaine adenylate, in combination with less than about 1 milligram of a digitalis preparation selected from the group consisting of whole leaf digitalis and purified glycoside derivatives thereof, said composition being effective in the treatment of non-inflammatory cardiac abnormalities and myocardial disorders.

13. Method for the treatment of non-inflammatory cardiac abnormalities and myocardial disorders which comprises administering to a human organism an effective concentration of an adenyl nucleotide selected from the group consisting of nicotinamide adenylate and procaine adenylate, in combination with a digitalis preparation selected from the group consisting of whole leaf digitalis and purified glycoside derivatives thereof, said digitalis preparation being present in an amount per dosage unit which is substantially below the tolerance level for toxic manifestations resulting therefrom.

14. Method for the treatment of non-inflammatory cardiac abnormalities and myocardial disorders which comprises administering to a human organism a therapeutic composition comprising a pharmaceutical carrier and as the active ingredients thereof, from about 25 to 300 milligrams per dosage unit of a digitalis preparation selected from the group consisting of whole leaf digitalis and purified glycoside derivatives thereof; said digitalis preparation being present in an amount per dosage unit which is substantially below the tolerance level for toxic manifestations resulting therefrom.

15. Method for the treatment of non-inflammatory cardiac abnormalities and myocardial disorders which comprises administering to a human organism a therapeutic composition comprising a pharmaceutical carrier and as
the active ingredients thereof, from about 25 to 300 milligrams per dosage unit of procaine adenylate in combination with a digitalis preparation selected from the group consisting of whole-leaf digitalis and purified glycoside derivatives thereof, said digitalis preparation being present in an amount per dosage unit which is substantially below the tolerance level for toxic manifestations resulting therefrom.

16. Method for the treatment of non-inflammatory cardiac abnormalities and myocardial disorders which comprises administering to a human organism a therapeutic composition comprising a pharmaceutical carrier and as the active ingredient thereof, from about 25 to 300 milligrams per dosage unit of nicotinamide adenylate in combination with whole-leaf digitalis, said digitalis being present in an amount less than 1 milligram per dosage unit.

17. Method for the treatment of non-inflammatory cardiac abnormalities and myocardial disorders which comprises administering to a human organism a therapeutic composition comprising a pharmaceutical carrier and as the active ingredient thereof, from about 25 to 300 milligrams per dosage unit of procaine adenylate in combination with whole-leaf digitalis, said digitalis being present in an amount less than 1 milligram per dosage unit.

References Cited
UNITED STATES PATENTS
3,104,203 9/1963 Ruskin et al. ---------- 167—65
OTHER REFERENCES

ALBERT T. MEYERS, Primary Examiner.
JULIAN S. LEVITT, SAM ROSEN, Examiners.
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