Pharmaceutical compositions active on the cardiovascular system, containing 3-methylthiopropionyl L-carnitine.

Priority: 15.03.90 IT 4775990
Date of publication of application: 25.09.91 Bulletin 91/39
Publication of the grant of the patent: 17.05.95 Bulletin 95/20
Designated Contracting States: AT BE CH DE DK ES FR GB GR IT LI LU NL SE

References cited:
US-A- 4 194 006
US-A- 4 593 043

ARCHIVES OF BIOCHEMISTRY AND BIOPHYSICS, vol. 273, no. 2, September 1989, pages602-605; P.W.D. SCISLÓWSKI et al.: "Heart mitochondria metabolize 3-methylthiopropionate to C02 and methanethiol"


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Description

The present invention relates to the use of 3-methylthiopropionyl L-carnitine and the pharmacologically acceptable salts thereof for the therapeutic treatment of disorders of the cardiovascular system.

As inner salt, 3-methylthiopropionyl has formula (I)

As compound salted with a pharmacologically acceptable acid, it has formula (I')

wherein $X^-$ is the anion of the pharmacologically acceptable acid. For instance, $X^-$ can be selected from chloride, bromide, orotate, acid aspartate, acid citrate, acid phosphate, acid fumarate, lactate, acid maleate, acid oxalate, acid sulfate and glucosephosphate.

It has been recently shown by Piotr W. D. Scisłowski et al [Methionine metabolism by rat muscle and other tissues, occurrence of a new carnitine intermediate, Biochem. J. 247, 35-40 (1987)] that 3-methylthiopropionyl L-carnitine is a natural substance that is synthesized during metabolism of methionine according to the scheme:

\[
\begin{align*}
{\text{methionine}} & \quad {\downarrow} \\
{4\text{-methylthio-2-oxobutyric acid}} & \quad {\downarrow} \\
{3\text{-methylthiopropionyl-CoA}} & \quad {\downarrow} \\
{3\text{-methylthiopropionyl L-carnitine}} & 
\end{align*}
\]
Moreover, these same Authors disclose a synthesis route to the compound.

To date, 3-methylthiopropionyl L-carnitine has never been proposed as a drug. It has now been found that this compound, both as inner salt and as salt of a pharmacologically acceptable acid as previously described, is a potent drug for the therapeutic treatment of disorders of the cardiovascular system, particularly for the treatment of myocardial anoxia, cardiac ischaemia, arrhythmias and congestive heart failure.

Known compounds that are structurally related to 3-methylthiopropionyl L-carnitine, are disclosed in the Italian patent 1,170,862 (or in the corresponding US patent 4,593,043). These compounds are mercaptoacetyl-carnitines, e.g. 3-mercaptopropionylcarnitine chloride. These compounds are known to be useful for the treatment of burnings and as mucolytic agents.

Other known compounds, even more vaguely related to 3-methylthiopropionyl L-carnitine from a structural viewpoint, that exhibit, however, the same therapeutic utility as that of the compound of the present invention, are certain alkanoylcarnitines, such as propionylcarnitine and butyrylcarnitine; cf. Italian patent 1,155,813 (or the corresponding US patent 4,194,006).

Unexpectedly, however, 3-methylthiopropionyl L-carnitine has been shown to be remarkably more potent than propionyl- and butyrylcarnitine in pharmacological tests suitable to assess its effect on the myocardial contractility, antianarrhythmic effect, antifatigue effect and other still.

The compounds of the present invention are orally or parenterally administered, in any of the usual pharmaceutical forms which are prepared by conventional procedures well-known to those persons skilled in the pharmaceutical technology. These forms include solid and liquid oral unit dosage forms such as tablets, capsules, solutions, syrups and the like as well injectable forms, such as sterile solutions for ampoules and phials.

For these pharmaceutical forms the usual solvents, diluents and excipients are used. Optionally, sweetening, flavouring and preservative agents can also be present. Non limiting examples of such agents are sodium carboxymethylcellulose, polysorbate, manitol, sorbitol, starch, avicel, talcum and other agents which will be apparent to those skilled in the pharmaceutical technology.

The dose which is administered will be determined by the attending physician having regard to the age, weight and general conditions of the patient, utilizing sound professional judgement. Although effective results can be noticed at doses as low as 5 to 8 mg/kg of body weight daily, a dose of from about 10 to about 50 mg/kg of body weight is preferred. Whenever necessary, larger doses can be safely administered in view of the low toxicity of the compounds of this invention.

As examples and depending on the specific pharmaceutical form of administration, the following dosages can be indicated:

<table>
<thead>
<tr>
<th></th>
<th>for the phials</th>
<th>from 5 to 500 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>for the capsules</td>
<td>from 15 to 50 mg</td>
</tr>
<tr>
<td></td>
<td>for the tablets</td>
<td>from 15 to 500 mg</td>
</tr>
<tr>
<td></td>
<td>for the oral solution</td>
<td>from 15 to 50 mg</td>
</tr>
</tbody>
</table>

**Claims**

1. Use of 3-methylthiopropionyl L-carnitine as inner salt (I)
or as a compound salted with a pharmacologically acceptable acid (I')

wherein X⁻ is the anion of the pharmacologically acceptable acid, for producing a pharmaceutical composition for treating the disorders of the cardiovascular system.

2. Use according to claim 1, wherein X⁻ is selected from chloride, bromide, orotate, acid aspartate, acid citrate, acid phosphate, acid fumarate, lactate, acid maleate, acid oxalate, acid sulfate and glucosephosphate.

3. An orally or parenterally administrable pharmaceutical composition comprising a compound of formula (I) or (I') as active principle.

4. An orally or parenterally administrable pharmaceutical composition for the therapeutic treatment of myocardial anoxia, cardiac ischaemia, arrhythmias and congestive heart failure, comprising a compound of formula (I) or (I') as active principle and a pharmacologically acceptable excipient therefor.

5. The composition according to claim 4, in unit dosage form, comprising from about 5 to about 500 mg of a compound of formula (I) or (I').

Patentansprüche

1. Verwendung von 3-Methylthiopropionyl-L-carnitin als inneres Salz (I)

oder als Verbindung, die mit einer pharmakologisch akzeptablen Säure ein Salz gebildet hat (I')
worin X \textsuperscript{-} das Anion der pharmakologisch akzeptablen Säure ist, zur Herstellung einer pharmazeutischen Zusammensetzung für die Behandlung von Erkrankungen des kardiovaskulären Systems.

2. Verwendung nach Anspruch 1, wobei X \textsuperscript{-} aus ChlORid, bromid, Orotat, saures Aspartat, saures Citrat, Hydrogenphosphat, saures Fumarat, Laktat, saures Maleat, saures Oxalat, saures Sulfat und Glukosephosphat ausgewählt ist.

3. Oral oder parenteral verabreichbare pharmazeutische Zusammensetzung, die eine Verbindung der Formel (I) oder (I') als wirksamen Grundbestandteil enthält.


5. Zusammensetzung nach Anspruch 4, in Form einer Dosierungseinheit, die etwa 5 bis etwa 500 mg einer Verbindung der Formel (I) oder (I') enthält.

Reverdications

1. Utilisation de la 3-méthylthiopropionyl L-carnitine sous forme d'un sel interne (1)

ou sous forme d'un composé transformé en sel avec un acide pharmaceutiquement acceptable (1')
dans laquelle $\text{X}^-$ est l'anion de l'acide pharmaceutiquement acceptable, pour produire une composition pharmaceutique pour le traitement des désordres du système cardiovasculaire.

2. Utilisation selon la revendication 1, dans laquelle $\text{X}^-$ est choisi parmi un chlorure, un bromure, un orotate, un aspartate d'acide, un citrate d'acide, un phosphate d'acide, un fumarate d'acide, un lactate, un maléate d'acide, un oxalate d'acide, un sulfate d'acide et le glucosephosphate.

3. Composition pharmaceutique pouvant être administrée par voie orale ou parentérale comprenant un composé de formule (1) ou (1') en temps que principe actif.

4. Composition pharmaceutique pouvant être administrée par voie orale ou parentérale pour le traitement thérapeutique d'anoxie myocardique, ischémie cardiaque, d'arythmies et de déficience congestive du cœur, comprenant un composé de formule (1) ou (1') comme principe actif et un excipient pharmaceutiquement acceptable.

5. Composition selon la revendication 4, sous forme de dose unitaire, comprenant de environ 5 à environ 500 mg d'un composé de formule (1) ou (1').