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(54) Titre : UTILISATION DE CREATINE PHOSPHATE OU D'ACIDE PHOSPHOENOLPYRUVIQUE POUR LE TRAITEMENT DE TUMEURS

(54) Title: USE OF CREATINE PHOSPHATE OR PHOSPHOENOLPYRUVIC ACID FOR THE TREATMENT OF TUMOURS

(57) Abrégé/Abstract:
The present invention relates to the use of compounds having a phosphoamide linkage or an enol phosphate linkage for the preparation of drugs intended for the treatment of tumors. Advantageously, these compounds are selected from creatine phosphate and phosphoenolpyruvic acid. The invention is applicable especially to the treatment of tumors resistant to chemotherapy.

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PATENT APPLICATION

Entitled : Use of creatine phosphate or phosphoenolpyruvic acid for the treatment of tumours

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ABSTRACT OF THE DISCLOSURE

The present invention relates to the use of compounds having a phosphoamide linkage or an enol phosphate linkage for the preparation of drugs intended for the treatment of tumors.

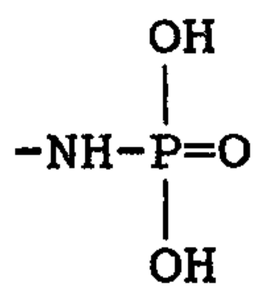
Advantageously, these compounds are selected from creatine phosphate and phosphoenolpyruvic acid.

The invention is applicable especially to the treatment of tumors resistant to chemotherapy.

Use of creatine phosphate or phosphoenolpyruvic acid for the treatment of tumours

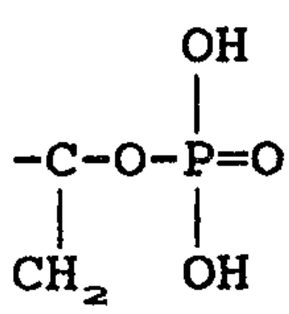
The present invention relates to the use of compounds having a phosphoamide linkage or an enol phosphate linkage for the preparation of drugs intended for the treatment of tumors.

Within the framework of the present description, compound having a phosphoamide linkage is understood as meaning any compound whose chemical structure contains a group



A preferred example of such compounds is creatine phosphate, also called phosphocreatine, which is a widespread substance in vertebrates, being present especially in the striated muscle but absent from the blood and extracellular fluids. Another example is arginine phosphate, which is found in the muscles of invertebrates.

Likewise, compound having an enol phosphate linkage is understood as meaning any compound whose chemical structure contains the group



A preferred example of such compounds is phosphoenolpyruvic acid, which is an intermediate endogenous metabolite involved in glycolysis and which,

under physiological conditions, is therefore localized in the cells and absent from the blood.

The phosphoamide or enol phosphate linkages of the abovementioned compounds belong to the family of so-called energy-rich linkages.

The documents EP-A-0 199 117 and EP-A-0 222 257 disclose in general terms the use of phosphocreatine and its sodium salt in crystalline form for the treatment of heart diseases and in particular myocardial infarction.

The document WO 83/02391 describes in general terms pharmaceutical compositions containing a salt of phosphoenolpyruvic acid mixed with adenosinetriphosphoric acid (ATP), said compositions being intended for the treatment and prevention of the damage caused to cells by ischemia.

The document US-4 769 318 relates to solutions containing various phosphoenolpyruvic acid derivatives, said solutions being intended for the preservation of blood.

Finally, the document EP-A-239-357 describes the use of the monosodium salt of phosphoenolpyruvic acid for the treatment of heart or kidney diseases associated with ischemia.

It has been discovered, and this is the basis of the present invention, that compounds having a phosphoamide linkage or an enol phosphate linkage have particularly valuable, unknown pharmacological properties and especially a particularly remarkable anti-tumoral activity.

Thus the present invention relates mainly to the use of at least one compound having an energy-rich linkage, selected from a phosphoamide linkage or an enol phosphate linkage, for the preparation of drugs intended for the treatment of tumors.

In one currently preferred embodiment, the abovementioned compound having an energy-rich linkage is creatine phosphate and its pharmaceutically acceptable salts, in particular the sodium salts.

In another embodiment, the compound having an energy-rich linkage is phosphoenolpyruvic acid and its pharmaceutically acceptable salts, in particular the sodium salts.

Tumors capable of being treated with the drugs obtained according to the invention are more particularly fresh tumors or tumors which have become resistant to chemotherapy, examples being adenocarcinomas (colon, pancreas, stomach, bronchi, kidneys, breasts, uterus, ovaries); epidermoid carcinomas (upper respiratory-digestive tract, bronchi, urinary tract, anus, skin); malignant melanoma; soft tissue sarcomas; leukemias; lymphomas; and multiple myeloma.

These drugs will generally be prepared by conventional processes and administered intravenously, in the form of a bolus or an intermittent or continuous perfusion, intraarterially, intraperitoneally or intramuscularly, at doses which can vary from 50 mg to 5 g/kg of body weight per 24 h.

According to one particular characteristic of the invention, the drug is a composition in the form of dosage units.

Advantageously, the dosage unit contains from 0.1 to 50 g of active principle.

In a preferred embodiment, this drug is formulated as an injectable preparation containing from 0.1 to 50 g of active principle.

In one advantageous embodiment, the abovementioned active principle of the drug can be diluted in a bulking agent compatible with the mode of administration. Such bulking agents are well known to those

skilled in the art and the following are examples of particularly advantageous bulking agents:

- mannitol;
- sorbitol;
- phosphate buffer comprising anhydrous sodium dihydrogenphosphate/sodium hydrogenphosphate;
- citrate buffer comprising sodium citrate/ citric acid;
- lactic buffer comprising sodium lactate/ lactic acid;
- sodium chloride.

In our advantageous embodiment, the abovementioned active principle can be diluted in a reconstituting solvent appropriate for the mode of administration.

Reconstituting solvents are well known to those skilled in the art. The following may be mentioned as examples:

- water for injectable preparations;
- 0.9% NaCl;
- 5%-15% glucose solution;
- 10-20% mannitol;
- 20-30% sorbitol;
- trisodium citrate solution.

The present invention also aims to cover a method of treating human tumors, said method comprising the administration of a therapeutically effective amount of at least one compound having a phosphoamide linkage or an enol phosphate linkage.

The pharmacological properties of the compounds having a phosphoamide linkage or an enol phosphate linkage were demonstrated by using different studies to evaluate the effects of creatine phosphate on a variety of tumoral cells.

The effects observed are indisputably due to

the presence of a phosphoamide linkage in this molecule.

Complementary tests on phosphoenolpyruvic acid suggest that analogous pharmacological properties can be obtained from compounds having an enol phosphate linkage.

The experimental protocols and the results making it possible to demonstrate the pharmacological properties of the compounds having a phosphoamide linkage or an enol phosphate linkage are now given below.

According to an aspect of the invention, use of at least one compound having an energy-rich linkage, selected from a phosphoamide linkage or an enol phosphate linkage to inhibit or to reduce the tumoral growth in a mammal.

According to another aspect of the invention, pharmaceutical compositions having an antitumoral activity to inhibit or to reduce tumoral growth in a mammal, comprising as active ingredient, at least one compound having an energy-rich linkage selected from a phosphoamide linkage or an enol phosphate linkage, in combination with a pharmaceutically acceptable carrier.

1. METHOD

1.1 Principle

The tumor is created in nude mice by the sub cutaneous inoculation of cancerous cells. An intra-peritoneal injection of creatine phosphate, hereafter designated UP 999-247, or NaCl is given 6 or 7 days a week, one week after inoculation. During the treatment, the animals are weighed and the size of the tumor is measured every week.

1.2 Procedure

1.2.1 Development of the cancer of human origin in nude mice

4 Week—old nude mice of the Swiss strain are raised in an isolator (sterile environment) under pressure.

Human cancer cell lines, namely Caco2 (colon), SK-MEL5 (melanoma), Capan-1 (pancreas) and NCl-H69 (small cell lung), are cultivated in different media containing from 10 to 20% of fetal calf serum and 1% of non—essential amino acids.

5×10^6 (SK—MEL5), 9×10^6 (Caco2), 2×10^5 (Capan-1) and 2.3×10^6 (NCl—H69) cells in PBS his

inoculated subcutaneously into the right side of each mouse. The operation is performed in a hood under sterile conditions.

Every week after inoculation, the animals are weighed and the tumor is measured with a sliding caliper.

The volume of the (hemi-ellipsoidal) tumor is calculated by means of the following form (DETHLEFSEN L.A., PRWITT J.M.S., MENDELSOHN M.L., Analysis of tumor growth curves. J. Natl. Cancer Institute, 1968, 40, 389-408; RADULOVIC S., MILLER G., SCHALLY A.V., Inhibition of growth of HT-29 human colon cancer xenografts in nude mice by treatment with bombesin/gastrin releasing peptide antagonist (RC-3095). Cancer Res., 1991, 51, 6006-6009):

$$\text{Volume of tumor} = \frac{\text{width} \times \text{length} \times \text{height} \times \pi}{6}$$

1.2.2 Study relating to the effect of UP 999-247 on tumoral growth

The treatment is started 7 days after inoculation and consists of an intraperitoneal injection of UP 999-247 (treated group) or isotonic solution (control group). Each group contains from 10 to 15 mice. The animals, individually identified by a tattoo on the back, are divided up into makrolon boxes.

The duration of the treatment depends on the objective of the treatment for each study series.

When the treatment has stopped, the tumors are removed and fixed in Bouin's fixative for anatomico-pathological analysis.

1.2.3 Administration scheme

The product studied is used in 0.9% NaCl and sterilized with the aid of a 0.2 μm filter. It is

administered intraperitoneally in a volume of 1 ml/ mouse.

The controls receive 1 ml of 0.9% NaCl.

The dosing scheme is as follows:

0.04 mmol, 0.1 mmol, 0.2 mmol and 0.4 mmol per mouse and per injection.

These doses are chosen according to the maximum dose which can be used by intraperitoneal administration, and according to the plasma concentration determined beforehand in the pharmacokinetic studies.

1.2.4 Expression of the results

The following parameters are calculated from the individual values measured:

- body weight in g, mean ± standard deviation, measured every week,
- volume of the tumor in mm^3, mean ± standard deviation, measured every week.

2. RESULTS

The results are presented in the Tables below.

Study of UP 999-247 on the growth of melanoma (SK-MEL5) in nude mice

Study of the effect of a dose of 0.4 mmol/mouse

Volume of the tumor (in mm^3)

week / group	1	2	3	4	5	6	7
Control animals	59.1 ± 3.1	65 ± 6.50	97 ± 14	128 ± 14	182.8 ± 25.9	209.1 ± 28.4	264.1 ± 41
Treated animals	55 ± 4.4	37 ± 8	38 ± 7	49 ± 11	50.7 ± 13.2	64.3 ± 16.2	86.3 ± 19

n = 6 to 10

Body weight (in g)

week / group	1	2	3	4	5	6	7
Control animals	20.9 ± 0.8	20.8 ± 0.65	21.5 ± 0.7	21.5 ± 0.8	22.3 ± 0.6	22.0 ± 0.8	22.6 ± 0.8
Treated animals	20.6 ± 0.5	20.4 ± 0.5	21.9 ± 0.5	22.1 ± 0.5	22.5 ± 0.9	22.5 ± 0.7	23.7 ± 0.3

n = 6 to 10

Effect of UP 999-247 on the growth of human melanoma (SK-MEL5) in nude mice

Dose-effect study

Volume of the tumor (mm^3)

Group \ Week	1	2	3	4	5	6	7	8	9
Control animals	38.7 ± 7.3	40.6 ± 5.2	57.3 ± 8.5	84.5 ± 21.0	120.0 ± 39.0	174.0 ± 56.0	273.0 ± 85.0	366.0 ± 123.0	468.0 ± 142.0
Treated animals									
0.04 mmol	33.8 ± 3.9	27.4 ± 4.5	40.8 ± 8.5	64.9 ± 17.0	93.0 ± 25.0	150.0 ± 52.0	202.0 ± 68.0	302.0 ± 96.0	421.0 ± 125.0
0.1 mmol	36.7 ± 2.7	32.8 ± 2.6	36.5 ± 7.5	44.5 ± 10.1	83.0 ± 31.0	105.0 ± 36.0	138.0 ± 49.0	198.0 ± 82.0	220.0 ± 102.0
0.4 mmol	36.1 ± 2.6	32.4 ± 2.0	29.9 ± 4.0	32.5 ± 4.4	50.0 ± 10.0	48.0 ± 11.0	63.0 ± 13.0	85.0 ± 18.0	93.0 ± 15.0

Group \ Week	10	11	12	13	14	15	16	17
Control animals	677.0 ± 188.0	819.0 ± 218.0	1115.0 ± 247.0	1335.0 ± 288.0	1581.0 ± 348.0	1988.0 ± 443.0	2285.0 ± 535.0	3136.0 ± 708.0
Treated animals								
0.04 mmol	432.0 ± 126.0	719.0 ± 219.0	1073.0 ± 305.0	1046.0 ± 330.0	1703.0 ± 504.0	2072.0 ± 619.0	2215.0 ± 649.0	2701.0 ± 787.0
0.1 mmol	304.0 ± 147.0	411.0 ± 212.0	597.0 ± 340.0	683.0 ± 409.0	1027.0 ± 565.0	1111.0 ± 600.0	1395.0 ± 779.0	1856.0 ± 975.0
0.4 mmol	123.0 ± 39.0	130.0 ± 40.0	212.0 ± 59.0	257.0 ± 94.0	296.0 ± 106.0	295.0 ± 90.0	388.0 ± 147.0	501.0 ± 225.0

n = 5 to 9

Effect of UP 999-247 on the growth of human melanoma (SK-MEL5) in nude mice

Dose-effect study

Body weight (g)

Group \ Week	1	2	3	4	5	6	7	8	9
Control animals	17.9 ± 0.3	20.3 ± 0.3	21.2 ± 0.5	21.3 ± 0.4	21.7 ± 0.5	21.8 ± 0.6	21.7 ± 0.6	22.3 ± 0.6	22.5 ± 0.7
Treated animals									
0.04 mmol	16.3 ± 0.6	19.9 ± 0.4	20.5 ± 0.4	21.6 ± 0.4	21.5 ± 0.5	20.7 ± 0.4	21.2 ± 0.4	21.6 ± 0.4	21.8 ± 0.4
0.1 mmol	16.0 ± 0.4	19.2 ± 0.3	20.3 ± 0.3	20.9 ± 0.3	21.6 ± 0.4	21.1 ± 0.4	21.7 ± 0.4	22.1 ± 0.4	21.8 ± 0.4
0.4 mmol	17.7 ± 0.4	19.8 ± 0.3	20.7 ± 0.5	21.5 ± 0.4	22.2 ± 0.4	21.7 ± 0.5	23.4 ± 0.5	23.6 ± 0.3	24.1 ± 0.3

Group \ Week	10	11	12	13	14	15	16	17
Control animals	22.1 ± 0.6	21.9 ± 0.5	22.2 ± 0.4	23.5 ± 0.4	23.5 ± 0.5	23.5 ± 0.4	23.9 ± 0.3	24.7 ± 0.4
Treated animals								
0.04 mmol	21.1 ± 0.3	21.7 ± 0.3	22.0 ± 0.5	22.5 ± 0.4	22.8 ± 0.4	23.2 ± 0.4	23.6 ± 0.6	24.4 ± 0.8
0.1 mmol	21.9 ± 0.3	22.6 ± 0.4	22.6 ± 0.5	23.1 ± 0.4	23.7 ± 0.6	23.9 ± 0.7	24.0 ± 1.0	24.8 ± 0.2
0.4 mmol	22.9 ± 0.6	25.4 ± 0.5	25.5 ± 0.6	26.0 ± 0.6	27.5 ± 0.5	27.0 ± 0.8	26.3 ± 0.7	26.6 ± 0.6

n = 7 to 11

Study of UP 999-247 on the growth of colon cancer (CACO2) in nude mice

Dose-effect study

Volume of the tumor (in mm^3)

group \ week		1	2	3	4	5	6
Control animals		51.1 ±3.7	55.9 ±5.8	71.1 ±9.9	63.0 ±7.0	74.8 ±9.5	100.2 ±13.5
Treated animals	0.04 mmol	52.3 ±7.6	55.8 ±6.9	49.5 ±5.5	42.7 ±8.0	51.4 ±6.0	84.0 ±16.0
	0.1 mmol	41.6 ±5.5	40.8 ±5.4	49.6 ±6.5	35.8 ±5.0	32.5 ±2.7	48.3 ±8.0
	0.2 mmol	45.0 ±3.0	49.1 ±4.3	48.9 ±7.3	51.0 ±11.0	45.4 ±6.6	68.4 ±13.7
	0.4 mmol	36.3 ±2.2	49.1 ±3.1	58.5 ±5.5	42.3 ±4.0	37.0 ±4.7	41.8 ±6.7

n = 8 to 10

Study of UP 999-247 on the growth of colon cancer (CACO2) in nude mice

Dose-effect study

Body weight (g)

group \ week		1	2	3	4	5	6
Control animals		19.9 ± 0.5	22.7 ± 0.4	22.9 ± 0.5	23.1 ± 0.5	23.7 ± 0.6	24.3 ± 0.5
Treated animals	0.04 mmol	19.2 ± 0.5	22.2 ± 0.6	22.2 ± 0.5	22.8 ± 0.5	23.0 ± 0.5	23.7 ± 0.6
	0.1 mmol	19.7 ± 0.5	22.3 ± 0.6	22.8 ± 0.6	22.9 ± 0.7	23.4 ± 0.5	24.3 ± 0.7
	0.2 mmol	20.1 ± 0.5	22.6 ± 0.6	22.8 ± 0.6	23.1 ± 0.7	23.6 ± 0.5	25.2 ± 0.7
	0.4 mmol	20.6 ± 0.5	23.1 ± 0.6	22.9 ± 0.5	23.6 ± 0.5	24.0 ± 0.7	25.3 ± 0.8

n = 8 to 10

Effect of UP 999-247 on the growth of small cell lung cancer (NCI-H69) in nude mice

Study of the effect of a dose of 0.4 mmol/mouse

Body weight (g)

week / group	1	2	3	4	5	6
Control animals	19.3 ± 0.5	20.1 ± 0.4	21.4 ± 0.5	21.7 ± 0.3	22.7 ± 0.3	22.5 ± 0.4
Treated animals	17.7 ± 0.2	18.7 ± 0.4	20.3 ± 0.7	20.7 ± 0.4	21.6 ± 0.4	22.2 ± 0.5

n = 13 to 15

Volume of the tumor (mm^3)

week / group	1	2	3	4	5	6
Control animals	/	29.5 ± 1.5	94 ± 48	246 ± 110	533 ± 183	941 ± 235
Treated animals	15	25	25	18.7 ± 6.2	36.5 ± 16.6	107 ± 43

n = 1 to 6

Effect of UP 999-247 on the growth of pancreas cancer (Capan-1) in nude mice

Study of the effect of a dose of 0.4 mmol/mouse

Body weight (g)

week / group	1	2	3	4	5	6
Control animals	18.8 ± 0.4	20.2 ± 0.4	21.3 ± 0.4	21.4 ± 0.15	22.6 ± 0.4	23.3 ± 0.4
Treated animals	17.9 ± 0.3	19.3 ± 0.7	20.3 ± 0.6	21.2 ± 0.5	22.4 ± 0.6	23.3 ± 0.7

n = 11 to 16

Volume of the tumor (mm^3)

week / group	1	2	3	4	5	6
Control animals	17 ± 3	33 ± 8	111 ± 17	201 ± 23	442 ± 62	671 ± 67
Treated animals	18 ± 1	23 ± 3	54.5 ± 9	116.3 ± 19	253 ± 47	499 ± 103

n = 8 to 15

The results obtained show an inhibition of tumoral growth after the administration of creatine phosphate to nude mice with various established tumors of human origin.

This inhibition is dose-dependent.

The weight change and behavior of the animals were followed over the experimental period.

A biochemical and hematological evaluation was performed on the plasma and blood collected after the animals had been sacrificed.

Under the experimental conditions described, creatine phosphate did not induce mortality.

The variations observed relate to the groups of animals treated with the highest doses studied, which cause a modest increase in the transaminases and the sodium and a decrease in the alkaline phosphatases and the formed elements of the blood.

The other modifications are in keeping with the fluctuations normally encountered in rats.

Creatine phosphate displayed an excellent biological tolerance at doses which can range up to 2400 mg/kg, administered intravenously.

Likewise, phosphoenolpyruvic acid displayed a good biological tolerance and was administered to rats in doses of up to 500 mg/kg without inducing mortality.

Non-limiting Examples of pharmaceutical compositions based on a compound having a phosphoamine linkage or an enol phosphate linkage will be found below.

Creatine phosphate can be either in the form of a ready-to-use sterile solution or in the form of a sterile powder or lyophilizate. In this case, it may be advantageous to use a bulking agent with no pharmacological activity, which will be chosen from lactose, mannitol, a phosphate buffer comprising anhydrous

sodium dihydrogenphosphate/sodium hydrogenphosphate, a citrate buffer comprising sodium citrate/citric acid, a lactic buffer comprising sodium lactate/lactic acid, sodium chloride or a mixture of these bulking agents in any proportions, in a manner well known to those skilled in the art.

The reconstituting solvent may either be selected from the injection solvents in conventional use (0.9% NaCl, 5% or 15% glucose solution, 20-30% sorbitol, trisodium citrate solution or injectable preparation) or be any other generally available perfusion solvent.

Preferably, the pharmaceutical preparation will take the form of a sterile lyophilizate containing 25 g of creatine phosphate to be reconstituted with 100 ml of a 0.9% solution of sodium chloride.

Example 1:

- citrate buffer:	pH 7
- citric acid	0.0329%
- $Na_2HPO_4 \cdot 2H_2O$	0.253%
- glucose	5%
- water for injectable preparations →	*qsq* 100%

If a lyophilizate is used, the take-up solvent is water for injectable preparations.

Example 2:

- phosphate buffer:	pH 7.2
- $Na_2HPO_4 \cdot 2H_2O$	0.758%
- NaH_2PO_4	0.184%
- NaCl	0.44%
- water for injectable preparations →	*qsq* 100%

Example 3:

- mannitol 5%
- water for injectable preparations → *qsq* 100%

If a lyophilizate is used, the take-up solvent is water for injectable preparations.

Example 4:

- glucose 5%
- water for injectable preparations → *qsq* 100%

If a lyophilizate is used, the take-up solvent is water for injectable preparations.

Example 5:

- KH_2PO_4 0.178%
- $Na_2HPO_4 \cdot 2H_2O$ 0.953%
- glucose 2%
- water for injectable preparations → *qsq* 100%

If a lyophilizate is used, the take-up solvent is water for injectable preparations.

CLAIMS:

1. Use of at least one compound having an energy-rich linkage, selected from a phosphoamide linkage or an enol phosphate linkage to inhibit or to reduce the tumoral growth in a mammal.

2. Use according to claim 1, wherein the compound having an energy-rich linkage is creatine phosphate and its pharmaceutically acceptable salts.

3. Use according to claim 1, wherein the compound having an energy-rich linkage is phosphoenolpyruvic acid and its pharmaceutically acceptable salts.

4. Use according to claim 2 or 3, wherein the pharmaceutically acceptable salts are the sodium salts.

5. Pharmaceutical compositions having an antitumoral activity to inhibit or to reduce tumoral growth in a mammal, comprising as active ingredient, at least one compound having an energy-rich linkage selected from a phosphoamide linkage or an enol phosphate linkage, in combination with a pharmaceutically acceptable carrier.

6. Pharmaceutical compositions according to claim 5, wherein the compound having an energy-rich linkage is creatine phosphate and its pharmaceutically acceptable salts.

7. Pharmaceutical compositions according to claim 5 wherein the compound having and energy-rich linkage is phosphoenolpyruvic acid and its pharmaceutically acceptable salts.

8. Pharmaceutical compositions according to claim 6 or 7, wherein the pharmaceutically acceptable salts are the sodium salts.

9. Pharmaceutical compositions according to any of claims 5 to 7, wherein the compositions are in the form of dosage units.

10. Pharmaceutical compositions according to claim 9, wherein the dosage unit comprises from 0.1 to 50 g of an active principle.

11. Pharmaceutical compositions according to any of claims 5 to 10, wherein the compositions are in an injectable form.