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(54) Benevnelse **USE OF ODIPARCIL IN THE TREATMENT OF MUCOPOLYSACCHARIDOSIS**

(56) Anførte publikasjoner

EP-A1- 0 421 829

MYERS ALAN L ET AL: "Characterization of total plasma glycosaminoglycan levels in healthy volunteers following oral administration of a novel antithrombotic odiparcil with aspirin or enoxaparin", JOURNAL OF CLINICAL PHARMACOLOGY, vol. 48, no. 10, octobre 2008 (2008-10), pages 1158-1170, XP002719465, ISSN: 0091-2700

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Use of odiparcil in the treatment of a mucopolysaccharidosis

The present invention relates to the use of odiparcil, or of a pharmaceutical composition containing this compound, in the treatment of a mucopolysaccharidosis.

Technical background of the invention

Mucopolysaccharidoses (MPSs) are degenerative genetic diseases linked to an enzymatic defect. In particular, MPSs are caused by the deficiency or the inactivity of lysosomal enzymes which catalyze the gradual metabolism of complex sugar molecules called glycosaminoglycans (GAGs). These enzymatic deficiencies cause an accumulation of GAGs in the cells, the tissues and, in particular, the cell lysosomes of affected subjects, leading to permanent and progressive cell damage which affects the appearance, the physical capacities, the organ function and, in most cases, the mental development of affected subjects.

Eleven distinct enzymatic defects have been identified, corresponding to seven distinct clinical categories of MPS. Each MPS is characterized by a deficiency or inactivity of one or more enzymes which degrade mucopolysaccharides, namely heparan sulfate, dermatan sulfate, chondroitin sulfate and keratin sulfate.

Mucopolysaccharidosis type III (MPS III) or Sanfilippo disease is a lysosomal storage disease, of the mucopolysaccharidosis group, characterized by severe and rapid intellectual degradation. The first symptoms appear between 2 and 6 years old: behavioral problems (hyperkinesia, aggressiveness) and intellectual degradation, and sleeping problems with very moderate dysmorphic signs. The neurological damage becomes more marked around the age of 10 years old, with loss of psychomotor acquisitions and of communication with the entourage. Epilepsy often occurs after the age of 10 years old. The disease is due to the presence of undegraded heparan sulfate owing to the defect in one or other of the four enzymes required for its catabolism, responsible for one of the four types of MPS III: type IIIA (heparan sulfamidase), type IIIB (alpha-N-acetylglucosaminidase), type IIIC (acetylCoA: alpha-glucosaminide-N-acetyltransferase) and type IIID (N-acetylglucosamine-6-sulfate sulfatase). There

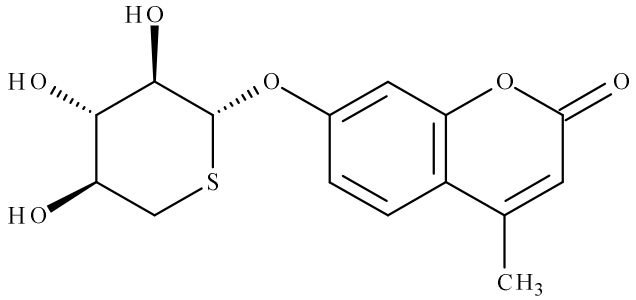
is at the current time no effective treatment for this disease.

Mucopolysaccharidosis type VI (MPS VI) or Maroteaux-Lamy disease is a lysosomal storage disease, of the mucopolysaccharidosis group, characterized by severe somatic involvement and an absence of psycho-intellectual regression. The prevalence of this rare mucopolysaccharidosis is between 1/250 000 and 1/600 000 births. In the severe forms, the first clinical manifestations occur between 6 and 24 months and are gradually accentuated: facial dysmorphia (macroglossia, mouth constantly half open, thick features), joint limitations, very severe dysostosis multiplex (platyspondyly, kyphosis, scoliosis, pectus carinatum, genu valgum, long bone deformation), small size (less than 1.10 m), hepatomegaly, heart valve damage, cardiomyopathy, deafness, corneal opacities. Intellectual development is usually normal or virtually normal, but the auditory and ophthalmological damage can cause learning difficulties. The symptoms and the severity of the disease vary considerably from one patient to the other and intermediate forms, or even very moderate forms also exist (spondyloepiphyseal-metaphyseal dysplasia associated with cardiovascular involvement). Like the other mucopolysaccharidoses, Maroteaux-Lamy disease is linked to the defect of an enzyme of mucopolysaccharide metabolism, in the case in point N-acetylgalactosamine-4-sulfatase (also called arylsulfatase B). This enzyme metabolizes the sulfate group of dermatan sulfate (Neufeld et al.: " The mucopolysaccharidoses" The Metabolic Basis of Inherited Diseases, eds. Scriver et al, New York, McGraw-Hill, 1989, p. 1565-1587). This enzymatic defect blocks the gradual degradation of dermatan sulfate, thereby leading to an accumulation of dermatan sulfate in the lysosomes of the storage tissues. At the current time, there is just one medicament authorized for the treatment of this disease: Naglazyme® (recombinant human galsulfase), the cost of which is extremely high (in the United States, it is about $ 350 000 per year). An alternative to this treatment is bone marrow allograft.

Mucopolysaccharidosis type VII (MPS VII) or Sly disease is a very rare lysosomal storage disease of the mucopolysaccharidosis group. The symptomology is extremely heterogeneous: antenatal forms (nonimmune fetoplacental anasarca), severe neonatal forms (with dysmorphia, hernias,

hepatosplenomegaly, club feet, dysostosis, significant hypotonia and neurological problems evolving to retarded growth and a profound intellectual deficiency in the event of survival) and very moderate forms discovered at adolescence or even at adult age (thoracic kyphosis). The disease is due to a defect in beta-D-glucuronidase, responsible for accumulation, in the lysosomes, of various glycosaminoglycans: dermatan sulfate, heparan sulfate and chondroitin sulfate. There is at the current time no effective treatment for this disease.

Odiparcil (4-methyl-2-oxo-2H-1-benzopyran-7-yl-5-thio-β-D-xylopyranoside; CAS 137215-12-4) belongs to the thioxyloside family. This compound, described in patent application EP-A-0 421 829, corresponds to the formula:



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This compound was the subject of a clinical development (phases 1 and 2) in the treatment of thrombosis at the end of the 1990s and at the beginning of the 2000s. Its mechanism of action can be summarized in the following way: Odiparcil behaves as a substrate for an enzyme, GT1 (galactosyl transferase 1), which initiates the synthesis of GAG chains toward the dermatan sulfate/chondroitin sulfate pathway. These GAGs are cell constituents as proteoglycans (when they are bonded to proteins on a serine and a first sugar which is xylose) and are also secreted into the extracellular medium. They have varied roles, ranging from the control of coagulation (heparin/heparan and dermatan sulfate secreted into the circulation) to the regulation of growth factors (beta-glycan).

It has now been found, and this is the subject of the present invention, that odiparcil makes it possible to increase total GAG synthesis at the extracellular level and, by the same token, will contribute to reducing the intracellular GAG load by acting as a "decoy", making the residual activity of N-acetylgalactosamine-4-sulfatase more effective. It is thus possible to envision the

treatment of mucopolysaccharidoses owing to the decrease in GAG accumulation at the intracellular level.

Subject of the invention

According to a first aspect, the invention relates to odiparcil for use in the treatment of mucopolysaccharidoses characterized by an accumulation of chondroitin sulfate and/or dermatan sulfate.

Odiparcil and the process for obtaining it are described in patent application EP-A-0 421 829.

In the context of the present invention, the term "odiparcil" denotes the "β-D-xylopyranoside" form.

In one embodiment, odiparcil used in the context of the invention is at least 60%, preferably at least 70%, at least 80%, at least 90%, at least 95%, at least 98% or at least 99% in the D-configuration. In this embodiment, the odiparcil is preferably in β-anomer form.

In another embodiment, odiparcil used in the context of the invention is at least 60%, preferably at least 70%, at least 80%, at least 90%, at least 95%, at least 98% or at least 99% in the β-anomer form.

Advantageously, odiparcil is administered in a proportion of approximately 100 mg to approximately 5000 mg per day. For example, approximately 100, 250, 300, 375, 400, 500, 750, 800, 1000, 1500, 2000, 3000, 4000 or 5000 mg of odiparcil are administered daily.

In one embodiment, at least approximately 0.1 mg to approximately 70 mg of odiparcil per kg of bodyweight of the patient are administered daily. For example, at least approximately 1 or 2 mg, to approximately 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65 or 70 mg of odiparcil per kg of bodyweight of the patient are administered daily.

In one embodiment, odiparcil is administered once or twice per day (for example, every 10 to 12 hours). Thus, the daily doses mentioned above can be divided up for a twice daily (bid) administration, for example a daily dose of 1000 mg will be administered in a proportion of two doses of 500 mg each. It is understood that each dose may consist of one or more pharmaceutical forms, for example a dose

of 500 mg may consist of two pharmaceutical forms of 250 mg each.

In one embodiment, odiparcil is administered in a fasted state (i.e. on an empty stomach, for example at least 1h before eating or more than 2h after eating). In another embodiment, odiparcil is administered during a food intake (i.e. at the same time as or just before eating a meal, for example approximately 20 to 30 min before a meal or within 5 min following the end of a meal).

In one embodiment, odiparcil is formulated in a pharmaceutical composition containing one or more pharmaceutically acceptable excipients, according to techniques well known to those skilled in the art, for instance those described in the book "Remington, The Science and Practice of Pharmacy, 21st Edition, Lippincott Williams & Wilkins, 2006".

Thus, according to a second aspect, the invention relates to a pharmaceutical composition containing odiparcil and one or more pharmaceutically acceptable excipients, for use in the treatment of mucopolysaccharidoses characterized by an accumulation of chondroitin sulfate and/or dermatan sulfate.

The pharmaceutical composition may be in any form suitable for the desired route of administration. This administration may be per os, lingual, sublingual, oral, rectal, topical, intravenous, intra-arterial, subcutaneous, intranasal, transdermal, intramuscular or intraperitoneal.

In one embodiment, the pharmaceutical composition contains approximately 100 to 1000 mg of odiparcil, for example 100, 125, 150, 250, 375, 400, 500 or 1000 mg of odiparcil.

In one embodiment, the pharmaceutical composition is administered by the injectable route, and comprises a vehicle which is typically a sterile aqueous solution sometimes containing, in addition to the water, one or more ingredients such as sugars, preservatives, salts, buffers, etc. The injectable suspensions may comprise a suspending agent and a given liquid vehicle.

In one embodiment, the pharmaceutical composition is administered orally. Suitable oral pharmaceutical forms include solid and liquid formulations. When the pharmaceutical composition is a solid formulation (such as, for example, gelatin capsules, tablets, dry powders), useful excipients include, in particular, diluents, lubricants, binders, disintegrating agents, fillers, etc. The solid

formulations may be coated or uncoated; when they are coated, the coating may be enteric or nonenteric. When the pharmaceutical composition is a liquid formulation (such as, for example, an elixir or a syrup), the useful excipients include, for example, water, glycols, a saline solution, alcohols, flavoring agents, etc.

Advantageously, the pharmaceutical composition is a tablet. Such a composition is prepared in one or more steps, comprising the mixing of the various constituents until a homogeneous mixture is obtained, and the compressing of the mixture so as to obtain a tablet. In one embodiment, the composition is prepared by means of a wet granulation process, which is a technique well known to those skilled in the art. For example, odiparcil, all or part of the diluent, the binder and a sufficient amount of granulating fluid (such as water) are combined, granulated, dried and ground so as to form granules. The granules are then optionally combined with the rest of the constituents and the mixture is compressed. The tablets advantageously comprise approximately 5% to approximately 90% of odiparcil, relative to the total weight of the tablet.

The invention is illustrated by the experimental section below.

Pharmacological activity

1. Results obtained on cells in culture

1.1. Bovine aortic endothelial cells

Bovine aortic endothelial cells (ECACC 92010601), cultured in 6-well plates, were incubated for 24 h in the presence of ^{35}S sodium sulfate (10 µci/ml) and of odiparcil solubilized in DMSO at various concentrations (1-10 µM; 0.1% final concentration of DMSO). The culture supernatants were recovered and the cell layers were rinsed with phosphate buffer (PBS). The culture supernatants and the rinsing solutions were combined in tubes. A solution of unlabeled dermatan sulfate (200 µg) was then added in order to serve as an entraining agent. The unincorporated ^{35}S was then removed by gel filtration on Sephadex G25 columns, the GAGs being eluted in the column exclusion fraction (V0). A solution of cetylpyridinium chloride (0.1% final concentration) was added to the eluent in order to precipitate the GAGs for 24h at room temperature. The samples were

then centrifuged and the supernatant was removed. The precipitate obtained was redissolved in 2 M magnesium chloride and the GAGs were precipitated with 5 volumes of 95% ethanol. After centrifugation, the alcoholic precipitates were redissolved in 0.9% sodium chloride and then the radioactivity was measured on an aliquot fraction after addition of scintillation fluid in counting vials.

In order to type the GAGs produced in the supernatants from cells in culture, the redissolved alcoholic precipitates were treated with chondroitinase ABC (*Proteus vulgaris*) in a proportion of 0.5 mU/µL, for 3 h at 37°C. After inactivation of the enzyme for 3 min at 100°C, the undigested GAGs were precipitated with 5 volumes of 95% ethanol, overnight at 4°C. After centrifugation, the alcoholic precipitates were redissolved in 0.9% sodium chloride and then the radioactivity was measured on an aliquot fraction after addition of scintillation fluid in counting vials.

GAGs of heparan sulfate type were treated with heparinase II (*Flavobacterium heparinum*) in a proportion of 4 mU/µl, for 12 h at 30°C. After inactivation of the enzyme for 3 min at 100°C, the undigested GAGs were precipitated with 5 volumes of 95% ethanol, overnight at 4°C. After centrifugation, the alcoholic precipitates were redissolved in 0.9% sodium chloride and then the radioactivity was measured on an aliquot fraction after addition of scintillation fluid in counting vials.

As can be seen in figure 1, odiparcil increases, in a dose-dependent manner, the level of ^{35}S-labeled GAGs in the culture supernatant of bovine aortic endothelial cells.

Furthermore, the enzymatic digestions suggest that the GAGs synthesized by the cells in culture are predominantly of chondroitin sulfate type.

1.2. Human fibroblasts

Normal human dermal fibroblasts (BIOAlternatives PF2) were cultured in 96-well plates for 24 h. The culture medium was then replaced with culture medium containing or not containing (control) odiparcil at various concentrations (1 µM, 3 µM, 10 µM) or the TGF-β reference at 10 ng/ml (positive control), and then the cells were incubated for 72h with addition of the ^{3}H-glucosamine radioactive label

for evaluating total GAG synthesis. At the end of the incubation, a chaotropic buffer was added to the wells of the culture plates in order to lyse the fibroblasts. The total GAGs of the cell lysates were then purified by ion exchange chromatography (Q-Sepharose column). The radioactivity incorporated into the anionic fractions was measured by liquid scintillation.

As can be seen in figure 2, odiparcil stimulates, in a dose-dependent manner, total GAG synthesis by human dermal fibroblasts (+94% at 10 μM). The data were analyzed statistically by one-way analysis of variance, followed by a Dunnett's test (* $p<0.05$ vs control; ** $p<0.01$ vs control; *** $p<0.001$ vs control).

2. Results obtained in vivo in rabbits after oral administration

Odiparcil was administered orally to New Zealand rabbits at the dose of 400 mg/kg. 4h after the administration, the animals were anesthetized and blood samples were taken on citrate tubes after catherization of the carotid artery. After centrifugation, the plasma was removed and frozen. The plasma GAGs were isolated after digestion of the proteins with Pronase E, for 48 h at 50°C. The proteins and the protein residues were precipitated by adding trichloroacetic acid and incubated overnight at 4°C. After centrifugation, the supernatants were collected, and then dialyzed against 100 volumes of phosphate buffer, for 48h at 4°C. A solution of cetylpyridinium chloride (0.1% final concentration) was added to the dialysates in order to precipitate the GAGs, for 24h at ambient temperature. The samples were then centrifuged and the supernatant was removed. The precipitate obtained was redissolved in 2M sodium chloride and the GAGs were precipitated with 5 volumes of 95% ethanol. After centrifugation, the alcoholic precipitates were redissolved in 0.9% sodium chloride and desalified on a Sephadex G25 column (PD10).

The plasma GAGs extracted were quantified by assaying the uronic acid content, modified Bitter and Muir carbazole method. The qualitative analysis of the plasma GAG extracts was carried out by HPLC of the disaccharides obtained after enzymatic digestion with chrondroitinase ABC from *Proteus vulgaris* and chrondroitinase AC from *Arthrobacter aurescens*.

The table below shows that the treatment of the animals with odiparcil at the dose of 400 mg/kg increases by a factor of 5 the plasma GAG level (measured via the uronic acid content) compared with the control animals. From a qualitative point of view, the chondroitin-type GAGs experience an increase in their galactosamine-6-sulfate component and also in the dermatan sulfate component (chondroitin B), measured via the galactosamine-4-sulfate disaccharides (Δdi-4S DS).

	µg UA/ml plasma	Δdi-0S (%)	Δdi-4S (%)	Δdi-6S (%)	Δdi-UA2S (%)	Δdi-4S DS (%)
Control	2.1	51.1	45.8	3.1	0	0
Odiparcil	11.4	18.6	26	30.8	4.1	20.5

UA: Uronic acid
Δdi-0S: nonsulfated disaccharides
Δdi-4S: 4-sulfated disaccharides
Δdi-6S: 6-sulfated disaccharides (galactosamine-6-sulfate component)
Δdi-UA2S: 2UA-sulfated disaccharides
Δdi-4S DS: 4-sulfated disaccharides (dermatan sulfate component)

These results demonstrate that odiparcil has the capacity to increase the synthesis of total GAGs (human fibroblasts), to increase the concentration of extracellular GAGs of chondroitin type (bovine aortic endothelial cells) and to increase the synthesis of plasma GAGs, in particular for GAGs of chondroitin type. It being understood that MPS type III, VI and VII are characterized by an accumulation of intracellular GAGs, these results indicate that odiparcil has the capacity to decrease the intracellular GAG load and therefore to have beneficial effects in the treatment of said MPSs.

Example of pharmaceutical formulation

Tablet obtained by means of a wet granulation process, containing (in weight %):

Odiparcil	90%
Microcrystalline cellulose (NF or Ph Eur)	7%
Povidone or polyvinylpyrrolidone (USP or Ph Eur)	3%
Water (USP or Ph Eur)	qs for wet granulation

CLAIMS

1. Odiparcil for use in the treatment of a mucopolysaccharidosis characterized by an accumulation of chondroitin sulfate and/or dermatan sulfate.

2. Odiparcil for the use of claim 1, which is intended to be administered at a daily dose of about 100 mg to about 5000 mg.

3. Odiparcil for the use of claim 1 or claim 2, which is intended to be administered orally.

4. Odiparcil for the use of claim 3, which is intended to be administered with food.

5. A pharmaceutical composition containing odiparcil and one or several pharmaceutically acceptable excipients, for use in the treatment of a mucopolysaccharidosis characterized by an accumulation of chondroitin sulfate and/or dermatan sulfate.

6. The pharmaceutical composition for the use of claim 5, which contains from 100 mg to 1000 mg of odiparcil.

7. The pharmaceutical composition for the use of claim 5 or claim 6, which is an oral dosage form, preferably a solid form.

8. The pharmaceutical composition for the use of claim 7, which is a tablet.

Patentkrav

1. Odiparcil for anvendelse ved behandling av en mucopolysakkaridose karakterisert ved en akkumulering av kondroitin sulfat og/eller dermatan sulfat.

2. Odiparcil for anvendelse ifølge krav 1, som skal administreres i en daglig dose på ca. 100 mg til ca. 5000 mg.

3. Odiparcil for anvendelse ifølge krav 1 eller krav 2, som skal administreres oralt.

4. Odiparcil for anvendelse ifølge krav 3, som skal administreres med mat.

5. Et farmasøytisk preparat inneholdende odiparcil og én eller flere farmasøytisk akseptable tilsetningsmidler, for anvendelse ved behandling av en mucopolysakkaridose karakterisert ved en akkumulering av kondroitin sulfat og/eller dermatan sulfat.

6. Det farmasøytiske preparatet for anvendelse ifølge krav 5, som inneholder fra 100 mg til 1000 mg odiparcil.

7. Det farmasøytiske preparatet for anvendelse ifølge krav 5 eller krav 6, som er en oral doseform, fortrinnsvis en fast stoff form.

8. Det farmasøytiske preparatet for anvendelse ifølge krav 7, som er en tablett.

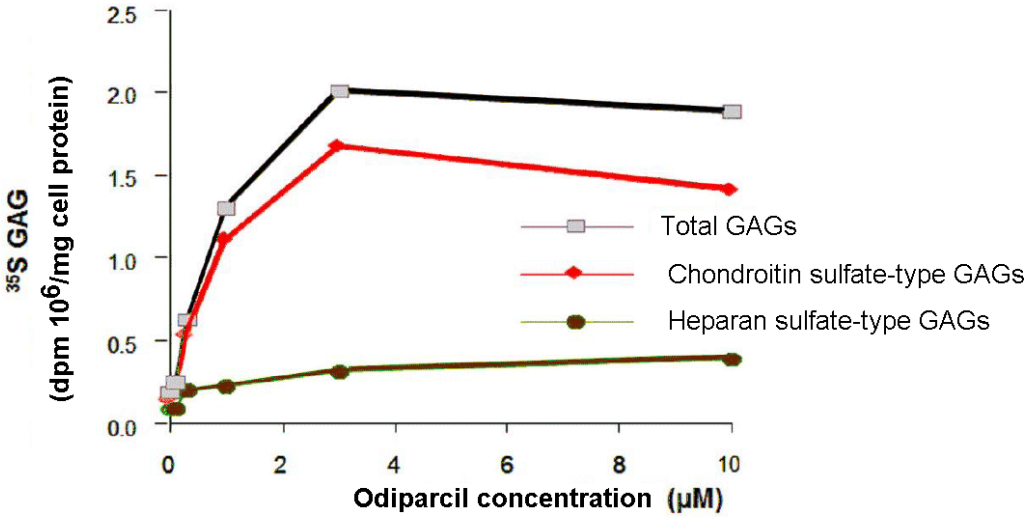
2.5
2.0
1.5
1.0
0.5
0.0
^{35}S GAG
(dpm 10^6/mg cell protein)
0
2
4
6
8
10
Odiparcil concentration (μM)
Total GAGs
Chondroitin sulfate-type GAGs
Heparan sulfate-type GAGs

FIG.1

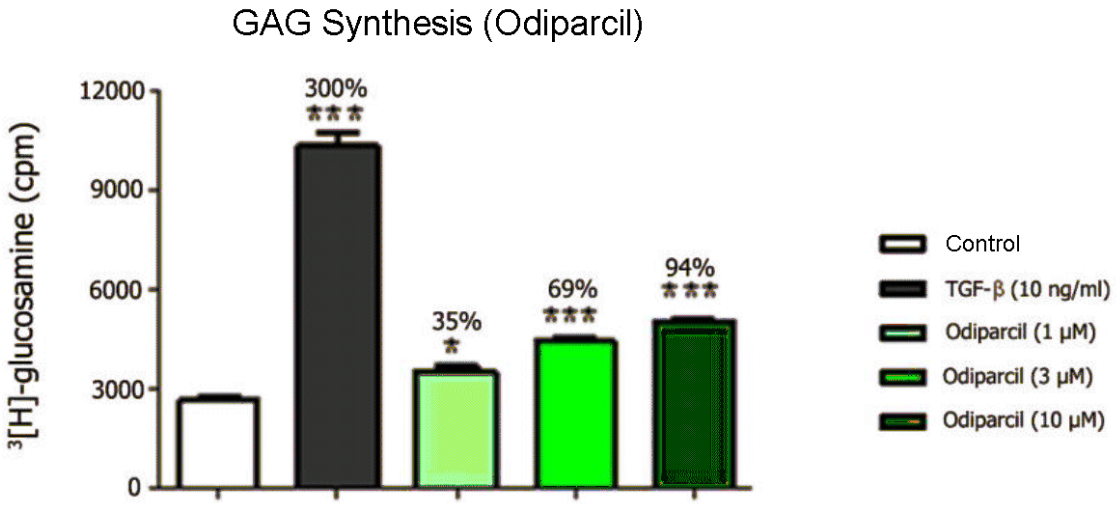
GAG Synthesis (Odiparcil)
12000
9000
6000
3000
0
^{3}[H]-glucosamine (cpm)
300%
***
35%
*
69%
***
94%
***
Control
TGF-β (10 ng/ml)
Odiparcil (1 μM)
Odiparcil (3 μM)
Odiparcil (10 μM)

FIG.2