Improved Drug Modification to Treat Porphyria Cutanea Tarda

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Abstract

Porphyria cutanea tarda (PCT) also known as the “vampire disease” is the most common type of porphyric diseases. This disease occurs 1 in 50,000 people. Symptoms involve hyperpigmentation (tanning of skin) and hypertrichosis (skin manifestations mainly on top of cheeks). This disease is contributed mainly by deficiency of uroporphyrinogen decarboxylase (UROD), an enzyme that is present in the cytoplasm which aids in the synthesis of heme. The commercial drug available that is used to treat PCT is Plaquenil chemically known as Hydroxychloroquine.

This drug has shown to be effective in patients. But, in many cases it even worsens the condition of PCT in addition to its side effects. Gumweed extract shows antiporphyrin activity. Quercetin, a phytochemical present in gumweed bestows the wonder to treat porphyria. This experiment is dedicated to make the drug hydroxychloroquine safer and more efficient in the treatment of porphyria. It is manifested by combining it with a gumweed phytochemical quercetin which is originally a flavonoid. This new modified drug can be used in the treatment of porphyria cutanea tarda and also to reduce the harmful effects of plaquenil in addition to unveiling the health benefits of gumweed.

Keywords: PCT; Hydroxychloroquine; Gumweed; Quercetin; Plaquenil

Introduction

Porphyrias are a group of rare disorders passed down through families, in which an important part of hemoglobin, called heme, is not made properly. Heme is also found in myoglobin, a protein found in certain muscles. Normally, the body makes heme in a multi-step process. Porphyrias are made during several steps of this process. Patients with porphyria have a deficiency of certain enzymes needed for this process. This causes abnormal amounts of porphyrins or related chemicals to build up in the body. There are many different forms of porphyria. The most common type is PCT. PCT is recognized as the most prevalent subtype of porphyritic diseases. The disease is characterized by blistering of the skin in areas that receive higher levels of exposure to sunlight. The primary cause of this disorder is a deficiency of uroporphyrinogen decarboxylase (UROD), a cytosolic enzyme that is a step in the enzymatic pathway that leads to the synthesis of heme. While a deficiency in this enzyme is the direct cause leading to this disorder, there are a number of both genetic and environmental risk factors that are associated with PCT [1]. Excess porphyrins in the skin interact with light of approximately 400 nm-wavelength radiant energy, forming reactive oxygen species. Porphyria cutanea tarda is categorized as familial, acquired or toxic [2].

PCT is a vesiculobuluous disorder often associated with estrogens, hepatitis C virus (HCV), alcoholism, hereditary hemochromatosis (HH), and human immunodeficiency virus. Hepcidin, a peptide hormone produced by the liver, has been associated with iron metabolism in 3 common precipitating factors for PCT: HCV, HH, and alcohol consumption [3].

Typically, patients who are ultimately diagnosed with PCT first seek treatment following the development of photosensitivities in the form of blisters and erosions on commonly exposed areas of the skin. This is usually observed in the face, hands, forearms, and lower legs. It heals slowly and with scarring. Though blisters are the most common skin manifestations of PCT, other skin manifestations like hyperpigmentation (as if they are getting a tan) and hypertrichosis (mainly on top of the cheeks) also occur. PCT is a chronic condition, with external symptoms often subsiding and recurring as a result of a number of factors. In addition to the symptomatic manifestation of the disease in the skin, chronic liver problems are extremely common in patients with the PCT. These include hepatic fibrosis (scarring of the liver), cirrhosis, and inflammation. However, liver problems are less common in patients with the inherited form of the disease [4].

The diagnosis of PCT can be made based on the skin symptoms, a characteristic urinary porphyrin excretion profile, and the detection of isocoproporphyrin in the feces. In red blood cells of individuals with type II PCT, UROD activity is decreased by approximately 50% due to heterozygous mutations in the UROD gene [5].

Hydroxychloroquine is a common medication used to treat porphyria. The trade name for hydroxychloroquine in the U.S. is Plaquenil. The brand name manufacture is SANOFI AVENTIS. The medication comes in oral tablet form as 200 mg and 400mg in the US and is taken either once a week or daily depending upon the condition the medication is being used to treat [6]. Hydroxychloroquine can cause a drug-induced change in skin pigmentation and Stevens Johnson Syndrome. Stevens Johnson Syndrome is a very dangerous rash that leads to layers of dead skin that fall off. Nausea, vomiting and diarrhoea are all common side effects of hydroxychloroquine. Hydroxychloroquine can cause a drug-induced myopathy or muscle dysfunction leading to weakness [7]. PCT is regularly associated with changes in liver tissue. On the other hand, systematic investigations are lacking on whether there is a correlation between the severity of liver damage and chloroquine treatment [8]. Treatment with systemic corticosteroids and low-dose hydroxy-chloroquine led to rapid resolution of the skin changes [9].
Gumweed is a traditional medicine of California Native Americans, such as the Chumash people. Gumweed was used clinically from the 1880s until 1960 in the United States and the United Kingdom for the treatment of asthma, bronchitis, and poison ivy rash. The plant contains grindelane diterpenoids of unknown pharmacological activity. The plant extract can be applied externally to subside rashes caused by porphyria [10].

Quercetin belongs to a group of plant pigments called flavonoids that give many fruits, flowers, and vegetables their color. Flavonoids, such as quercetin, are antioxidants -- they scavenge damaging particles in the body known as free radicals, which damage cell membranes, tamper with DNA, and even cause cell death. Quercetin is contraindicated with some antibiotics as quercetin competitively binds to bacterial DNA gyrase [11].

Objective

To improve the efficiency of the drug hydroxchloroquinone in treating the disease porphyria cutanea tarda by combining it with a phytochemical quercertin derived from Gumweed.

But the PDB id of hydroxchloroquinone (DB01611) is still unavailable in the website.

The flavinoid quercertin can be classified under the class of oxidoreductases and its structural weight is 157158.89 Dalton.

Materials and Methods

This study was started in May 2011.

Identification of drug

The Drug Bank database is a bioinformatics and cheminformatics resource that combines detailed drug data with comprehensive drug target (i.e. sequence, structure, and pathway) information [6]. This database is used to study the chemical, pharmacological and pharmaceutical properties of the drug hydroxychloroquinone. The accession number DB01611 is entered in the space and the details of the drug is displayed by the database.

Structural studies of quercertin

From previous studies, we have derived that the accession number of quercertin is 1gqg. We have derived the 2D structure of quercertin from PDB using J mol viewer.

The flavinoid quercertin can be classified under the class of oxidoreductases and its structural weight is 157158.89. The molecule is called quercertin 2,3-dioxygenase. The protein has 1 polymer and has the

Results and Discussions

Identification of drug

Hydroxychloroquinone commercially known as Plaquenil is used to treat PCT. The accession number DB01611 is entered in the DrugBank database and its physical, chemical and structural studies were performed. One citation found is that its PDB id has still not been invented by the PDB database. Therefore, detailed studies of active sites in the protein molecule could not be retrieved. On the other hand, its elaborate studies on the chemical structure could be done which led us to draw impressive conclusions.

Identification

Name Hydroxychloroquine
Accession Number DB01611
Type small molecule
Groups Approved
Description A chemotherapeutic agent that acts against erythrocytic forms of malarial parasites.

Structure

Synonyms 2-((4-((7-Chloro-4-quinolyl)amino)pentyl)ethylamino)ethanol
Gen-Hydroxychloroquine 200mg Tablets HCQ
Hidroxicloroquina [inn-spanish]
Hydroxychloroquine
Hydroxychloroquine sulfate
Hydroxychloroquinum [inn-latin]
Idrossiclorochina [dcit]
Oxichlorochnum
Oxichloroquine
Oxychlorochin
Oxychloroquine

Brand names Ercoquin
Plaquenil
Quensyl

Brand name mixtures Not Available

Categories Antirheumatic Agents
Enzyme Inhibitors
Antimalarials
Dermatologic Agents

CAS number 18-42-3
Weight Average: 335.872
Monoisotopic: 335.176440176

Chemical Formula C_{18}H_{26}ClN_{3}O

InChI Key InChI=1S/C_{18}H_{26}ClN_{3}O/c1-3-22(11-12-23)10-4-5-14(2)
21-17-8-9-20-18-13-15(19)6-7-16(17)18/
1-2H3,(H,20,21)

IUPAC Name 2-[(4-[(7-chloroquinolin-4-yl)amino]pentyl)(ethyl)amino]ethan-1-ol
SMILES CCN(CCO)CCCC(C)
P

Mass Spec Not Available

Structural studies of quercertin

From previous studies, we have derived that the accession number of quercertin is 1gqg. We have derived the 2D structure of quercertin from PDB using J mol viewer.

The flavinoid quercertin can be classified under the class of oxidoreductases and its structural weight is 157158.89. The molecule is called quercertin 2,3-dioxygenase. The protein has 1 polymer and has the
active chains A,B,C,D. Its natural inhibitors are diethyldithiocarbamate and kojic acid.

Docking studies

The docking of hydroxchloroquine with quercetin could not be performed because the PDB accession number and the 3D structure still has not been discovered. But from previous studies we can infer that quercetin originally a flavinoid has the unique property to attach itself to fluoroquinolones.

So it can be proposed that hydroxchloroquine anatomically similar to fluoroquinolones can serve as a template for the flavinoid quercetin for attachment. This modified superior drug which also has additional health benefits bestowed by gumweed phytochemical quercetin can be used to treat porphyria cutanea tarda more effectively.

Discussion

PCT is a disease which is characterized by redness, blisters, rashes and abrupt skin erosions when exposed to sunlight. It also includes hepatic fibrosis (scarring of the liver), cirrhosis, and inflammation [3]. Hydroxychloroquine is a medication used to treat porphyria [7]. But, this drug has proven to show several side effects which include nausea, vomiting, diarrhea, in some cases even myopathy. Gumweed extract which contains the phytochemical quercetin has proven to show antiporphyrinic activity. The plant extract can be applied externally to subside rashes caused by porphyria [10]. Hydroxychloroquine has been known to worsen the condition of patients suffering with PCT [7]. Quercetin is contraindicated with some antibiotics; it may interact with fluoroquinolones [11]. The unique property of quercetin to interact with fluoroquinolones can be exploited to come to the fact that it can combine with hydroxchloroquine because of its homologous properties to fluoroquinolones. Therefore to make this drug safer and more effective the addition of quercetin (gumweed phytochemical) to this drug can render it a safer drug.

Conclusion

PCT is one of the most common types of porphyria that is caused due to the deficiency of UROD, a cytosolic enzyme that is a step in the enzymatic pathway that leads to the synthesis of heme. Typically, patients who are ultimately diagnosed with PCT first seek treatment following the development of cutaneous photosensitivity in the form of blisters and erosions on commonly exposed areas of the skin. This is usually observed in the face, hands, forearms, and lower legs. It heals slowly and with scarring. One of the treatments of this disease is the consumption of the drug Hydroxychloroquine commercially known as Plaquenil. It is widely used to treat PCT, but, it also has many side effects involving nausea, vomiting, diarrhea and other symptoms. The aim is to make the drug hydroxychloroquine safer and effective. It is implemented by combining it with a phytochemical quercetin derived from the gumweed extract. Quercetin a flavinoid extracted from Gumweed extract has shown to possess anti porphyrinic activities. Quercetin is known to combine with fluoroquinolones which is an antibiotic. Hydroxychloroquine shows analogous properties to that of fluorochloroquine. Using this principle, keeping this drug as target, quercetin is made to combine with this drug. This modified drug can be used to treat PCT more safely and effectively unveiling the medicinal value of gumweed extract.

References

10. Wild Rose College of Natural Healing, Grindelia integrifolia – Gumweed.