Advances in Pharmacoepidemiology & Drug Safety

Abraham Cherian, Adv Pharmacoepidem Drug Safety 2012, 1:1
DOI: 10.4172/2167-1052.1000103

Research Article Open Access

Improved Drug Modification to Treat Porphyria Cutanea Tarda

Chikoo Cherry Abraham Cherian*

Karunya University, Karunya Nagar, Coimbatore-641114, Tamil Nadu, India

Abstract

Porphyria cutanea tarda (PCT) also known as the "vampire disease" is the most common type of porphyritic 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 Hydroxychloroquinone. 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 antiporphyric activity. Quercertin, a phytochemical present in guweed bestows the wonder to treat porphyria. This experiment is dedicated to make the drug hydroxychloroquinone safer and more efficient in the treatment of porphyria. It is manifested by combining it with a gumweed phytochemical quercertin which is originally a flavinoid. 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; Hydroxychloroquinone; Gumweed; Quercertin; 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. Porphyrins 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 vesiculobulIous 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 manfacture 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].

***Corresponding author:** Chikoo Cherry Abraham Cherian, B.Tech Bioinformatics, Karunya University, Karunya Nagar, Coimbatore-641114, Tamil Nadu, India, Tel: 9600817392; E-mail: chik.cherry@gmail.com

Received November 04, 2011; **Accepted** January 31, 2012; **Published** February 06, 2012

Citation: Abraham Cherian CC (2012) Improved Drug Modification to Treat Porphyria Cutanea Tarda. Adv Pharmacoepidem Drug Safety 1:103. doi:10.4172/2167-1052.1000103

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

The Protein Data Bank (PDB) is a repository for the 3-D structural data of large biological molecules, such as proteins and nucleic acids. The accession number of quercertin (1gqg) is entered in the search space and the 2D structure of the protein is analyzed.

Docking of hydroxychloroquinone with quercertin

AutoDock is a suite of automated docking tools. It is designed to predict how small molecules, such as substrates or drug candidates, bind to a receptor of known 3D structure [6]. Docking was tried to be done between hydroxchloroquinone and quercertin. But the PDB id of hydroxchloroquinone is still unavailable in the website. Therefore, its docking could not be performed.

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] Hydroxychloroguine Hydroxychloroquine sulfate Hydroxychloroquinum [inn-latin] Idrossiclorochina [dcit] Oxichlorochinum 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	$C_{18}H_{26}ClN_3O$
InChI Key	InChIKey=XXSMGPRMXLTPCZ-UHFFFAOYSA-N
InChI	InChI=1S/C18H26ClN3O/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/h6-9,13-14,23H,3-5,10-12H2, 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) NC1=CC=NC2=C1C=CC(Cl)=C2
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 usin 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 hydroxchloroquinone with quercertin 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 quercertin originally a flavinoid has the unique property to attach itself to fluoroquinolones.

So it can be proposed that hydroxychloroquinone anatomically similar to fluoroquinolones can serve as a template for the flavinoid quercertin for attachment. This modified superior drug which also has additional health benefits bestowed by gumweed phytchemical quercertin 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, diahorrea, in some cases even myopathy. Gumweed extract which contains the phytochemical quercertin has proven to show antiporphyric activity. The plant extract can be applied externally to subside rashes caused by porphyria [10]. Hydroxychloroquinone 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 quercertin to interact with fluoroquinolones can be exploited to come to the fact that it can combine with hydroxychloroquinone because of its homologous properties to fluoroquinolones. Therefore to make this drug safer and more effective the addition of quercertin (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 Hydroxychloroquinone commercially known as Plaquenil. It is widely used to treat PCT, but, it also has many side effects involving nausea, vomiting, diarrhoea and other symptoms. The aim is to make the drug hydroxychloroquinone safer and effective. It is implemented by combining it with a phytochemical quercertin derived from the gumweed extract. Quercertin a flavinoid extracted from Gumweed extract has shown to possess anti porphyric activities. Quercertin is known to combine with fluoroquinolones which is an antibiotic. Hydroxychloroquinone shows analogous properties to that of fluorochloroquinone. Using this principle, keeping this drug as target, quercertin 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

1. Anderson K (2007) The porphyrias. In: Goldman L, Ausiello D, eds. Cecil Medicine. 23rd ed. Philadelphia, Pa: Saunders Elsevier: chap 229.
2. Bleasel NR, Varigos GA (2000) Porphyria cutanea tarda. Australas J Dermatol 41: 197-206.
3. Van Meter JR, Tierney KR, Pittelkow MR (2011) Iron, genes, and viruses: the porphyria cutanea tarda triple threat. Cutis 88: 73-76.
4. Di Padova C, Marchesi L, Cainelli T, Gori G, Podenzani SA, et al. (1983) Effects of phlebotomy on urinary porphyrin pattern and liver histology in patients with porphyria cutanea tarda. Am J Med Sci 285: 2–12.
5. Wollina U, Köstler E, Koch A, Riedel H, Stölzel U (2009) Does chloroquine therapy of porphyria cutanea tarda influence liver pathology? Int J Dermatol 48: 1250-1253.
6. Wishart DS, Knox C, Guo AC, Cheng D, Shrivastava S, et al. (2008) "DrugBank: a knowledgebase for drugs, drug actions and drug targets". Nucleic Acids Res 36: 901–906.
7. Richard H, Pamela C (2006) Lippincott's Illustrated Reviews: Pharmacology (edn).
8. Peitsch WK, Lorentz K, Goebeler M, Goerdt S (2007) Subacute cutaneous lupus erythematosus with bullae associated with porphyria cutanea tarda. J Dtsch Dermatol Ges 5: 220-225.
9. Frank J, Poblete-Gutiérrez P (2010) Porphyria cutanea tarda--when skin meets liver. Best Pract Res Clin Gastroenterol 24: 735-745.
10. Wild Rose College of Natural Healing, Grindelia integrifolia – Gumweed.
11. Hilliard JJ, Krause HM, Bernstein JI, Fernandez JA, Nguyen V, et al. (1995) A comparison of active site binding of 4-quinolones and novel flavone gyrase inhibitors to DNA gyrase. Adv Exp Med Biol 390: 59–69.