US 20080234226A1

(19) **United States**

(12) **Patent Application Publication**

Erichsen et al.

(10) **Pub. No.: US 2008/0234226 A1**

(43) **Pub. Date: Sep. 25, 2008**

(54) **USE OF IRON(III) COMPLEX COMPOUNDS FOR THE PREPARATION OF A MEDICAMENT FOR ORAL TREATMENT OF IRON DEFICIENCY STATES IN PATIENTS WITH CHRONIC INFLAMMATORY BOWEL DISEASE**

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(21) Appl. No.: **12/064,053**

(22) PCT Filed: **Aug. 22, 2006**

(86) PCT No.: **PCT/EP2006/065532**

§ 371 (c)(1),
(2), (4) Date: **Apr. 21, 2008**

(30) **Foreign Application Priority Data**

Aug. 25, 2005 (EP) 05107790.7

Publication Classification

(51) **Int. Cl.**
A61K 31/721 (2006.01)
A61P 1/00 (2006.01)

(52) **U.S. Cl.** **514/59**

(57) **ABSTRACT**

The use of iron(III) complex compounds with carbohydrates or derivatives thereof for the preparation of a medicament for oral treatment of iron deficiency states in patients with chronic inflammatory bowel disease, in particular Crohn's disease and colitis ulcerosa, is disclosed.

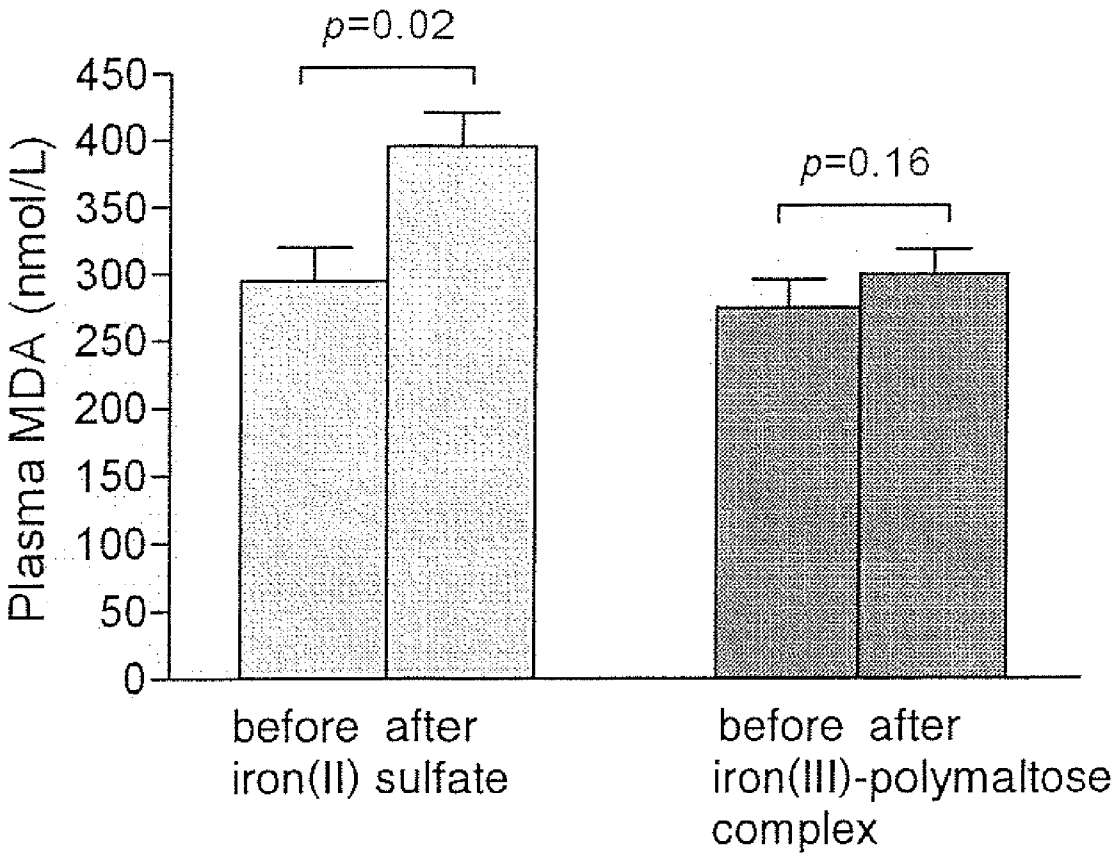

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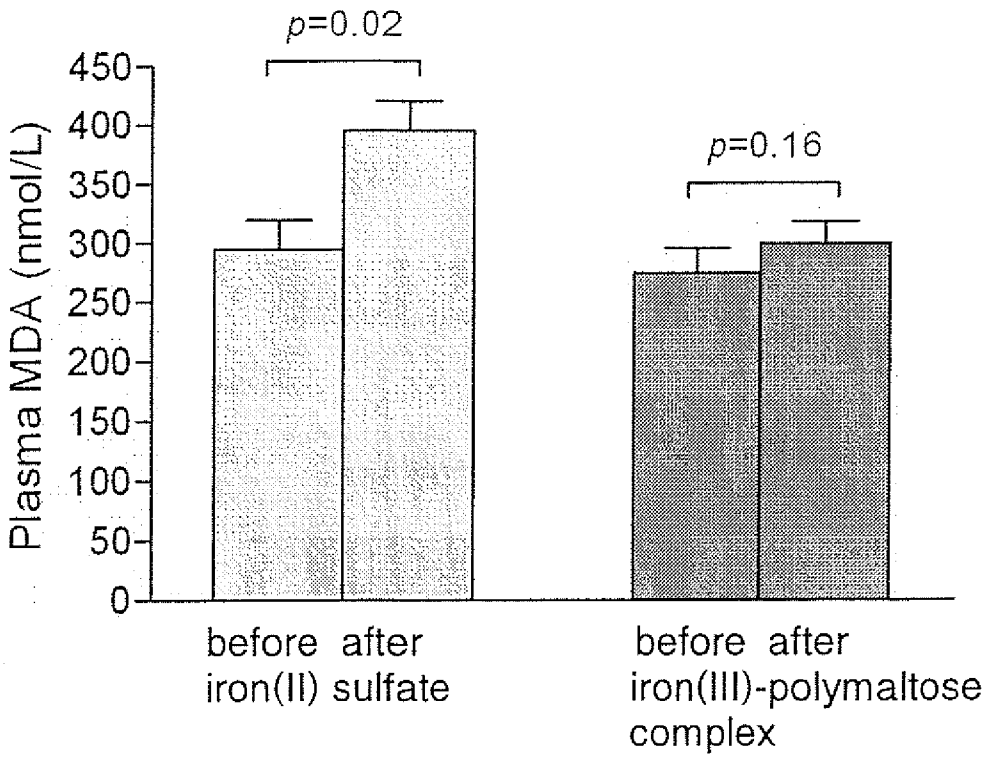
Figure 1



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USE OF IRON(III) COMPLEX COMPOUNDS FOR THE PREPARATION OF A MEDICAMENT FOR ORAL TREATMENT OF IRON DEFICIENCY STATES IN PATIENTS WITH CHRONIC INFLAMMATORY BOWEL DISEASE

[0001] The present invention relates to novel therapeutic uses of iron(III) complex compounds with carbohydrates or derivatives thereof, in particular with dextrins or oxidation products of dextrins, namely for the preparation of medicaments for treatment of iron deficiency states in patients with chronic inflammatory bowel diseases, in particular Crohn's disease and/or colitis ulcerosa.

[0002] Iron deficiency is the most frequent trace element deficiency worldwide. Approx. 2 billion people worldwide suffer from iron deficiency or iron deficiency anaemia (E. M. DeMaeyer, "Preventing and controlling iron deficiency anaemia through primary health care", World Health Organization, Geneva, 1989, ISBN 92 4 154249 7).

[0003] WO 95/35113 discloses the use of iron(III) oxide as an active compound for treatment of immunoinsuficiency diseases, in particular AIDS.

[0004] DE 1467980 discloses therapeutically usable iron injection preparations and processes for their preparation.

[0005] U.S. Pat. No. 3,076,798 discloses processes for the preparation of iron(III)-polymaltose complex compounds which are suitable for parenteral administration.

[0006] WO 04/037865 discloses the use of iron-carbohydrate complexes for treatment or prophylaxis of iron deficiency states.

[0007] WO 03/087164 discloses iron complex compounds with hydrogenated dextrins for treatment or prophylaxis of iron deficiency states.

[0008] WO 02/46241 discloses iron(III)-pullulan complex compounds and their use for treatment or prophylaxis of iron deficiency states.

[0009] WO 99/48533 discloses iron-dextran compounds for treatment of iron deficiency anaemia, which comprise hydrogenated dextran having a particular molecular weight of approx. 1,000 Dalton.

[0010] I. Maslovski, American Journal of Hematology, April 2005, vol. 78, no. 4, p. 261-264 discloses the activity of Ferrlecit®, an iron(III)-gluconate complex in sucrose having a molecular weight of 350,000, or Venofer®, an iron(III)-sucrose complex, for intravenous treatment of anaemic patients suffering from chronic inflammatory bowel disease.

[0011] G. Bodemar et al., Scandinavian Journal of Gastroenterology, May 2004, vol. 39, p. 454-458 describes iron(III)-sucrose compounds for intravenous treatment of anaemia in patients with Crohn's disease and ulcerative colitis.

[0012] DE-A-102 49 552 describes iron(III) complex compounds with maltodextrins and the (particularly preferably parenteral) use thereof for treatment of anaemia.

[0013] CH-A-694 197 describes iron(III)-polymaltose compounds for treatment of anaemia, but without giving indications of actions in the gastrointestinal tract or on IBD or Crohn's disease.

[0014] Iron sulfate is known to cause relatively frequently unpleasant dose-dependent side reactions, such as gastrointestinal disorders or a discoloration of the teeth. Iron cause side reactions or an iron poisoning. Accordingly, the LD50 value in white mice of 230 mg iron/kg is relatively low.

[0015] The use of iron-dextran is disclosed in Oski et al. "Effect of Iron Therapy on Behavior Performance in Nonanemic, Iron-Deficient Infants", PEDIATRICS 1983; volume 71; 877-880. Parenteral use of iron-dextran is disadvantageous because a dextran-induced anaphylactic shock may occur.

[0016] Inflammatory bowel diseases (IBD) include a group of diseases of the gastrointestinal tract which are characterized by intestinal inflammation and a chronic course with constant relapses. IBD has traditionally been characterized either as colitis ulcerosa or as Crohn's disease, based on clinical, radiological, endoscopic and histological criteria. Although the aetiology of IBD still requires definition, recent clinical and experimental studies suggest that the trigger and the pathogenesis of these diseases are multifactorial, and that interactions between genetic, environmental and immune factors are involved.

[0017] Inflammatory bowel diseases are not spread uniformly throughout the world. There is a clear tendency towards an increased occurrence in developed countries compared with less developed countries. The occurrence of IBD in Europe is approx. 390 cases per 100,000 people. Extrapolation of these figures to the European population of approx. 580 million gives an estimated number of 2.2 million people affected by IBD (Loftus E V, Jr., Gastroenterology 2004, 126, 11504-1517). Colitis ulcerosa and Crohn's disease are diagnosed most frequently in older adolescents and young adults, but can occur at any age.

[0018] Colitis ulcerosa is a disease of the mucous membrane which conventionally affects the rectum and then extends into the adjacent areas, so that all or part of the colon is affected. The spread is continuous, without areas of unaffected mucous membrane remaining. The main symptoms of colitis ulcerosa are violent diarrhea, rectal bleeding, mucous discharge and cramp-like abdominal pain. The severity of the symptoms correlates with the extent of the disease.

[0019] Crohn's disease can affect any region of the gastrointestinal tract from the mouth to the anus, but most frequently relates to the small intestine and/or the colon. The inflammation is transmural and segmental, normal areas existing between the areas of diseased intestine. Consequences of the inflammation include fistulation on other loops of the intestine, the urinary bladder, the vagina or the perianal skin, abdominal or perianal abscesses and narrowing of the intestine. The location and the course of the disease influence the clinical manifestations. The most frequent symptoms are diarrhea, cramp-like abdominal pain, fever, anorexia and weight loss.

[0020] Extraintestinal manifestations of colitis ulcerosa and Crohn's disease can relate to multiple organ systems, such as eyes, skin and joints, and equally gastrointestinal organs, including the liver and gallbladder.

[0021] Treatment comprises administration of anti-inflammatory agents and under certain circumstances antibiotics, and a change in diet. An operation may occasionally be necessary. Psychotherapy is furthermore often undertaken, on the one hand for the management of stress, which is also a triggering factor, and on the other hand for treatment of depression, which often arises as a consequence of the chronic ever-recurring symptoms (see e.g. Pschyrembel, Kli-

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[0022] Iron deficiency often occurs as a complication in patients with chronic inflammatory bowel disease. Chronic intestinal bleeding can lead to more iron being lost than is taken in through food. Conventional oral iron preparations, in general iron(II) salts, often cause severe gastrointestinal side effects, which leads to a poor patient compliance. Oral iron therapy can intensify the lesions of the intestinal tissue by catalysis of the formation of reactive oxygen species. Since free iron is a potent catalyst of the formation of reactive oxygen species, oral iron(II) therapy can even be harmful for patients with chronic inflammatory bowel disease. Oral iron (II) preparations are poorly absorbed and lead to high faecal iron concentrations, and a significant content of the faecal iron is available for the catalytic activity. If iron comes into contact with the inflamed intestinal mucosa, it can increase the production of reactive oxygen species and as a result intensify tissue damage. It is therefore particularly important for patients with chronic inflammatory bowel disease to have available readily tolerated iron preparations.

[0023] Iron(III)-polymaltose complex contains iron in a nonionic form, which is less toxic. Fewer side effects occur on administration of compounds of this type, and patient compliance is improved compared with iron(II) sulfate (Jacobs, P., Wood, L., Bird, A R., Hematol. 2000, 5:77-83). However, there is not yet any experience or reports of the use of iron (III)-polymaltose complex in patients with chronic inflammatory bowel disease.

[0024] The inventors therefore had the object of discovering readily tolerated iron compounds which are suitable for treatment of iron deficiency states in patients with chronic inflammatory bowel disease.

[0025] They were able to demonstrate in a study that iron (III) complex compounds with carbohydrates, in particular with polymaltose (maltodextrin), are tolerated in particular and have a high patient compliance. In this study, it was surprising that under treatment with the iron(III) complexes no oxidative stress occurred, in contrast to treatment with iron(II) sulfate, under which a significant increase in plasma malondialdehyde (MDA), a lipid peroxidation marker, was observed.

[0026] Oxidative stress, in particular lipid peroxidation, is associated with an increased risk of suffering from cardiac infarction, cancer and atherosclerosis. Oxidative modification of low-density lipoprotein (LDL) is held responsible for atherogenesis (see references given in Tuomainen et al., Nutrition Research, vol. 19, no. 8, pp. 1121-1132, 1999).

[0027] Iron(III)-polymaltose complex compounds indeed lead to only a slow increase in the ferritin level, but are used more efficiently for haemoglobin synthesis (T.-P. Tuomainen et al., loc. cit., p. 1127). The inventors have provided the present invention on the basis of these results.

[0028] The present invention therefore provides the use of iron(III) complex compounds with carbohydrates or derivatives thereof for the preparation of a medicament for treatment of iron deficiency states in patients with chronic inflammatory bowel disease.

[0029] According to the invention, iron deficiency state is understood as meaning a state in which haemoglobin, iron and ferritin levels in the plasma are reduced and transferrin is increased, which leads to a reduced transferrin saturation.

[0030] The state to be treated according to the invention includes iron deficiency anaemia and iron deficiency without

(%). Reference values for haemoglobin, determined by flow cytometry or the photometric cyanohaemoglobin method, and reference values for iron, ferritin and transferrin are listed, for example, in the reference bank of the charity Institut für Laboratoriumsmedizin und Pathobiochemie (http://www.charite.de/ilp/routine/parameter.html) and in Thomas, L., Labor und Diagnose, TH Book Verlagsgesellschaft, Frankfurt/Main 1998. Transferrin saturation is as a rule >16% in patients without iron deficiency. The normal values are given in Table III which follows below.

[0031] According to M. Wick, W. Pinggera, P. Lehmann, Eisenstoffwechsel—Diagnostik und Therapien der Anämien, 4th exp. ed., Springer Verlag Vienna 1998, all forms of iron deficiency can be detected by clinical chemistry. In this context, a reduced ferritin concentration is in general accompanied by an increased transferrin in compensation and a lower transferrin saturation.

[0032] Chronic inflammatory bowel disease (IBD) is understood as meaning a chronic inflammation of the digestive tract, in particular Crohn's disease and colitis ulcerosa.

[0033] Iron(III) complex compounds with carbohydrates which can be used according to the invention preferably include those in which carbohydrates are chosen from the group consisting of dextrans and derivatives thereof, dextrins and derivatives thereof as well as pullulan, oligomers and/or derivatives thereof. The derivatives mentioned include, in particular, the hydrogenated derivatives. Iron(III) complex compounds with dextrins or oxidation products thereof are particularly preferred. Examples of the preparation of the iron(III) complex compounds according to the invention are to be found, for example, in the abovementioned patent specifications DE 14679800, WO 04037865 A1, U.S. Pat. No. 3,076,798, WO 03/087164 and WO 02/46241, the disclosure content of which, in particular in respect of the preparation processes, is to be included here in its full scope. The term "dextrins", which are preferably used according to the invention, is a collective name for various lower and higher polymers of D-glucose units which are formed on incomplete hydrolysis of starch. Dextrins can furthermore be prepared by polymerization of sugars (e.g. WO 02083739 A2, US 20030044513 A1, U.S. Pat. No. 3,766,165). Dextrins include maltodextrins and polymaltoses, which are prepared by enzymatic cleavage of, for example, maize starch or potato starch with alpha-amylase and which are characterized by the degree of hydrolysis, expressed by the DE value (dextrose equivalent). According to the invention, polymaltose can also be obtained by acid hydrolysis of starches, in particular dextrins. The preparation of the iron(III) complex compounds which can be used according to the invention is in general carried out by reaction of iron(II) or -(III) salts, in particular iron(III) chloride, with the dextrins, in particular polymaltose, or oxidation products of the dextrins in aqueous alkaline solution (pH>7) and subsequent working up. The preparation is also achieved in a weakly acid pH range. However, alkaline pH values of, for example, >10 are preferred.

[0034] The pH is preferably increased slowly or gradually, and this can be effected, for example, by first adding a weak base, for example up to a pH of about 3; further neutralization can then be carried out with a stronger base. Possible weak bases are, for example, alkali metal or alkaline earth metal

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example, alkali metal or alkaline earth metal hydroxides, such as sodium, potassium, calcium or magnesium hydroxide.

[0035] The reaction can be promoted by heating. For example, temperatures of the order of 15° C. up to the boiling temperature can be used. It is preferable to increase the temperature gradually. Thus, for example, the mixture can be first heated to about 15 to 70° C. and the temperature can be gradually increased up to the boiling point.

[0036] The reaction times are, for example, of the order of 15 minutes to several hours, e.g. 20 minutes to 4 hours, for example 25 to 70 minutes, e.g. 30 to 60 minutes.

[0037] When the reaction has taken place, the solution obtained can be cooled, for example, to room temperature and optionally diluted and optionally filtered. After the cooling, the pH can be adjusted to the neural point or slightly below this, for example to values of 5 to 7, by addition of acid or base. Bases which can be used are, for example, those mentioned above for the reaction. Acids include, for example, hydrochloric acid and sulfuric acid. The solutions obtained are purified and can be used directly for the preparation of medicaments. However, it is also possible to isolate the iron (III) complexes from the solution, for example by precipitation with an alcohol, such as an alkanol, for example ethanol. The isolation can also be carried out by spray drying. The purification can be carried out in the conventional manner, in particular for removal of salts. This can be carried out e.g. by reverse osmosis, it being possible for such a reverse osmosis to be carried out e.g. before the spray drying or before the direct use in medicaments.

[0038] The iron(III) complexes obtained have, for example, an iron content of 10 to 40% wt./wt., in particular 20 to 35% wt./wt. They are in general readily water-soluble. Neutral aqueous solutions having an iron content of, for example, 1% wt./vol. to 20% wt./vol. can be prepared therefrom. These solutions can be sterilized by means of heat.

[0039] Reference may be made to U.S. Pat. No. 3,076,798 in respect of the preparation of iron(III)-polymaltose complex compounds.

[0040] In a preferred embodiment of the invention, an iron (III) hydroxide-polymaltose complex compound is used. This iron(III)-polymaltose complex compound preferably has a molecular weight in the range from 20,000 to 500,000, and in a preferred embodiment 30,000 to 80,000 Dalton (determined by means of gel permeation chromatography, for example as described by Geisser et al. in Arzneim. Forsch/Drug Res. 42(11), 12.1439-1452 (1992), paragraph 2.2.5.). A particularly preferred iron(III) hydroxide-polymaltose complex compound is the commercially obtainable Maltofer® from Vifor AG, Switzerland. In a further preferred embodiment, an iron(III) complex compound with an oxidation product of one or more maltodextrins is used. This is obtainable, for example, from an aqueous iron(III) salt solution and an aqueous solution of the product of the oxidation of one or more maltodextrins with an aqueous hypochlorite solution at a pH in the alkaline range, wherein if one maltodextrin is employed the dextrose equivalent thereof is 5 to 37 and if a mixture of several maltodextrins is employed the dextrose equivalent of the mixture is 5 to 37 and the dextrose equivalent of the individual maltodextrins involved in the mixture is 2 to 40. The weight-average molecular weight Mw of the complexes obtained in this way is, for example, 30 kDa to 500 kDa,

phy, for example as described by Geisser et al. in Arzneim. Forsch/Drug Res. 42(11), 12.1439-1452 (1992), paragraph 2.2.5.). Reference may be made, for example, to WO 2004037865 A1 in this respect, the disclosure content of which is to be included in its full scope in the present Application.

[0041] Reference may be made to WO 03/087164 in respect of the preparation of iron complex compounds with hydrogenated dextrins.

[0042] Reference may be made to WO 02/46241 in respect of the preparation of iron(III)-pullulan complex compounds.

[0043] The iron(III) hydroxide complex compounds used according to the invention are preferably administered orally. In principle, however, they can also be administered parenterally, such as intravenously, and also intramuscularly. The oral daily dose is, for example, between 10 and 500 mg iron/day of use. The dose can be taken by the patient without question over a period of several months until the iron status has improved, which is reflected by the haemoglobin value, the transferrin saturation and the ferritin value. The oral administration is preferably in the form of a tablet, a capsule, an aqueous solution or emulsion, as granules, a capsule, a gel or as a sachet. The use of solutions or emulsions is particularly preferred for children, in the form of syrups or juices, drops, etc. For this, the iron(III) hydroxide-dextrin complex compounds can be brought into the suitable administration form with conventional pharmaceutical carrier or auxiliary substances. Conventional binders or lubricants, diluents, disintegrating agents, etc. can be used for this.

[0044] The use according to the invention can be effected on children, adolescents and adults suffering from chronic inflammatory bowel diseases, preferably on adults.

[0045] The use according to the invention proceeds in particular by means of improvement in the iron, haemoglobin, ferritin and transferrin values, whereby the clinical disease activity indices of the bowel condition, abdominal pain and nausea are not impaired by the treatment according to the invention.

BRIEF DESCRIPTION OF THE FIGURE

[0046] FIG. **1** is a diagram which shows the plasma MDA levels measured in the example before and after treatment with iron(II) sulfate or iron(III)-polymaltose complex. The effect of iron(II) sulfate and iron(III)-polymaltose complex on the plasma level of malondialdehyde (MDA) in patients with chronic inflammatory bowel disease is shown. The results are expressed as the mean ±SEM. p values are given for paired comparisons.

[0047] The invention is explained and demonstrated in its mode of action by the following example.

Example

Patients

[0048] 41 patients with chronic inflammatory bowel disease (colitis ulcerosa or Crohn's disease in the active or quiescent state) and iron deficiency (defined by the mean corpuscular volume (MCV)<80 fl or s-ferritin<15 μg/l or s-soluble transferrin receptor >1.54 mg/l) were divided into two groups in accordance with the randomization principle. Patients who had received an iron therapy or blood transfusions during the 6 weeks before the study was conducted, an

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