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(54) Title: A METHOD TO INCREASE THE EXCRETION OF NON-STEROL ENDOGENOUS HYDROPHOBIC SUBSTANCES BY INCREASING EXCRETION OF FAT VIA THE FAECES

(57) Abstract: The subject invention concerns a method to increase the excretion of non-sterol endogenous hydrophobic substances or metabolic derivatives thereof by increasing excretion via the faeces of the hydrophobic substance or metabolic derivative thereof characterisedin that the excretion of fat via the faeces is increased. The purpose of the invention is to prevent or treat conditions associated with the accumulation of non-sterol endogenous hydrophobic substances or metabolic derivatives thereof, such substances being unconjugated bilirubin and protoporphyrin. More particularly, lipstatin, orlistat, tetrahydrolipstatin, polyol fatty acids like olestra, and non-conventional doses of dietary jet are used to treat neonatal jaundice, haemolytic or erythropoietic protoporphyria.

A method to increase the excretion of non-sterol endogenous hydrophobic substances by increasing excretion of fat via the faeces

Summary of the invention

The invention concerns a method to increase the excretion of non-sterol endogenous hydrophobic substances or metabolic derivatives thereof by increasing excretion via the faeces of the hydrophobic substance or metabolic derivative thereof. Also the invention concerns a method for prevention or treatment of conditions associated with the accumulation of non-sterol endogenous hydrophobic substances or metabolic derivatives thereof.

Background of the invention

Disturbance of the homeostasis of non-sterol endogenous hydrophobic compounds in mammals, specifically in humans, can lead to accumulation of detrimental amounts of these compounds.

One example of such a compound is bilirubin. Under physiological conditions, bilirubin undergoes two conjugation reactions with glucuronic acid, derived from UDP-glucoronide, which results in the formation of bilirubin diglucuronide. Bilirubin diglucuronide is significantly more water-soluble than the parent compound, unconjugated bilirubin (UCB), and can be readily excreted via the bile into the faeces. The two conjugation reactions are catalysed by the hepatic enzyme uridine diphosphoglucuronosyl transferase (h-UDPGTbil, EC 2.4.1.17). In Crigler Najjar's disease (CN) the activity of h-UDPGTbil is completely absent (CN type I) or significantly reduced (CN type II), leading to increased serum concentrations of UCB. Increased serum levels of UCB are also found during the neonatal period, especially in preterms, during increased rates of haemoglobin degradation (for example sickle cell crisis, anaemic crisis in G6PD-deficient individual, ABO-antagonism or other forms of immune or non-immune hemolysis), or during impaired hepatic conjugation efficiency (for example viral infections, metabolic diseases, and others)(for review, see Chowdhury et al., Hereditary jaundice and disorders of bilirubin metabolism. In: Scriver CR, Beaudet AL, Sly WS, Valle D, eds. The Metabolic and Molecular Basis of Inherited Disease. New York: McGraw-Hill, Inc. 1995:2161-2208).

High serum concentrations of UCB are associated with accumulation in other organs of the body, among which the central nervous system, and with toxic effects on the central nervous system. In order to keep serum concentrations of UCB below 250 µmol/L, unconjugated hyperbilirubinemia is conventionally treated with phototherapy for many hours daily. Phototherapy (wavelength 400-460 nm) results in the formation of a variety of photoproducts which can be secreted into the bile, however, only at a relatively slow rate. After biliary secretion, the configurational isomers can spontaneously revert to the normal configuration and be absorbed from the intestinal lumen. These features of the configurational isomers obviously decrease the efficacy of phototherapy. Whereas Crigler-Najjar's disease patients (in particular type I) are usually treated lifelong by phototherapy at home, neonates with unconjugated hyperbilirubinemia are generally admitted to hospitals for phototherapeutic treatment. If phototherapy fails to lead to clinically acceptable serum concentrations of UCB, patients may need to undergo one or more exchange transfusions, which comprises a high-risk therapy with considerable morbidity and even mortality.

Alternative strategies for the treatment of unconjugated hyperbilirubinemia involve the capture of UCB or of its photoisomers in the intestinal lumen, thereby preventing their intestinal uptake and enterohepatic circulation. The first results of the intestinal UCB capture approach date back to 1983. It was demonstrated that the enteral administration of agar could serve as an adjunct to phototherapy in neonates with unconjugated hyperbilirubinemia (Odell et al., Pediatr Res 1983;17:810-814). Also, the oral administration of activated charcoal to Gunn rats was associated with a decrease in serum bilirubin concentration (Davis et al., Pediatr Res 1983;17:208-209). The capture of bilirubin in the intestinal lumen has also been attempted with cholestyramine, but only a modest benefit was obtained (Nicolopoulos et al., J Pediatr 1978;93:684-688, Tan et al., J Pediatr 1984;104:284-286). Nagyvary described and patented the use of chitosan (a polymer of N-acetyl-D-glucosamine units) to treat hyperbilirubinemia, based on the intraluminal binding of bilirubin in the intestine (US 4,363,801). Disadvantage of the use of these hydrophilic resins or resin-like materials is that these will bind a great variety of other useful components, which subsequently will be excreted. Other patents on the application of UCB adsorption to treat hyperbilirubinemic states include US 5,200,181, in which a bilirubin converting enzyme is used; US 4,593,073, in which amino acid containing polymers are used, US

5,804,218 in which zinc salts are used. None of these alternative strategies has resulted in a practically used therapy.

Another example of a non-sterol endogenous hydrophobic compound in mammals, whose accumulation can lead to detrimental consequences, is protoporphyrin. Protoporphyrin (PP) is a hydrophobic intermediate in the biosynthesis of heme. Heme is an iron-containing, prosthetic group in many proteins, which function in for example oxygen en electron transport, H_2O_2 generation and degeneration, and nitric oxide synthesis. Catalysed by the enzyme ferrochelatase (EC 4.99.1.1), PP is converted into heme through the addition of a Fe^{2+}-atom. Although all mammalian cells synthesise heme, the major site is the bone marrow, where approximately 85% of the body's heme is produced for the formation of hemoglobin. The second major site of heme synthesis in mammalians is the liver (see for review Kappas et al., The Porphyrias. In: Scriver CR, Beaudet AL, Sly WS, Valle D, eds. The Metabolic and Molecular Basis of Inherited Disease. New York: McGraw-Hill, Inc. 1995:2103-2159). Under several pathophysiological conditions, for example in the disease erythropoietic protoporphyria (EPP), PP accumulates in body. EPP is an autosomal dominant, inherited disease, which is characterised by a strongly reduced activity of the ferrochelatase enzyme. Under the pathophysiological condition of PP accumulation, particularly in erythrocytes, liver and faeces increased PP concentrations are found (Romslo et al., Arch Dermatol 1982;118:668-671, Beukeveld et al., Clin Chem 1987;33:2164-2170). The clinical consequences of increased concentrations of PP in the body can be exemplified by the symptoms of EPP. At young age, EPP patients have a cutaneous photosensitivity in light-exposed areas. The mechanism of the photosensitivity involves the generation of free oxygen radicals from accumulated PP in the skin, under influence of light (wavelength 400-410 nm). The reactive oxygen radicals damage primarily the mitochondria and cellular membranes, leading to severely discomforting skin lesions (burn-like lesions, itching, oedema, scarring).

The disposal from the body of PP involves biliary secretion and subsequent loss via the stools. It is not known whether the highly hydrophobic parent molecule PP can be reabsorbed by the intestinal mucosa and undergoes enterohepatic cycling. Strong, indirect support for this possibility can be derived from the observed beneficial effects of cholestyramine on PP accumulation in EPP. It appeared that the administration of cholestyramine, in analogy to its use in hyperbilirubinemia, improved photosensitivity

and reduced hepatic PP content (Tishler et al., Methods Find Exp Clin Pharmacol 1985;7:485-491, McCullough et al., Gastroenterology 1988;94:177-181).

Description of the invention

The present invention is directed at a novel mechanism of intestinal capture of non-sterol endogenous hydrophobic compounds, specifically the induction of increased fat excretion via the faeces (steatorrhoea).

The capture of non-sterol endogenous hydrophobic compounds by luminal fat differs from the previous approaches. Calcium phosphate and activated charcoal are suggested to bind UCB for instance or its photoisomers by an adsorption process. Cholestyramine, applied in conditions in which UCB, PP and plant sterols were increased, is applied as a resin, which binds the respective molecules. The same is true for the fibrous material chitosan.

By increasing the lipophilic phase, or amount of fat, in the intestinal lumen, as disclosed according to the invention, hydrophobic compounds will dissolve or diffuse into the generated apolar phase. The apolar, lipophilic phase persists throughout the digestive tract and will drag hydrophobic compounds along the intestinal tract, which eventually will be excreted. The hydrophobic phase is virtually impermeable for polar detergents, such as bile salts. It can be expected that the absorption of fat-soluble compounds such as fat soluble vitamins, such as vitamin A, vitamin D, vitamin E, and vitamin K, will also be inhibited. To compensate for this, an increased dietary intake, either in natural or in water-soluble form, may be warranted. The induction of increased faecal fat excretion by any means increases the disposal of endogenous hydrophobic substances such as UCB and PP from the body, at least under conditions of their previous accumulation. Thus the present invention provides a method to prevent or treat conditions such as neonatal jaundice, haemolytic jaundice and erythropoietic protoporphyria.

In the examples it is described that in Gunn rats the induction of fat malabsorption, and thus, of increased faecal fat excretion, was dose-dependently related to decreased plasma UCB concentrations. A strong, inverse correlation was observed between the amount of faeces produced and the plasma UCB concentration in the rats studied. Based on the nature of the effect, namely hydrophobic diffusion, it can be anticipated that the same strategy would allow increasing the disposal from the body of

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