Oily fish, liquid wax esters and keriorrhoea – a review

Peter Michael Barling, Yi Huan Foong

Abstract: Keriorrhoea is the involuntarily passing of orange oil per rectum. One of us (PMB) had the misfortune to experience this symptom, together with considerable gastrointestinal disturbances for a prolonged period of time after consumption of a deep sea fish, orange roughy, which is rich in liquid wax esters (LWEs). This paper presents a summary of available evidence concerned with the physiology and pathology of ingestion of LWEs, which can enter the human diet in substantial amounts from consumption of several species of deep-sea fish. LWEs are poorly digested and absorbed by the human body. They generally cause keriorrhoea when ingested deliberately or accidentally. Jojoba oil, which is a plant LWE, together with certain nutritional products (e.g. olestra) and medical (e.g. Orlistat) which are not LWEs may mimic the effects of LWEs, and cause similar gastrointestinal disturbances. This paper discusses the potential effects of LWEs as components of gastrointestinal micelles, and predicts that the orange oil which is leaked from a bout of keriorrhoea may contain considerable volumes of triacylglycerols (TAGs).

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Introduction

It began about two hours after consuming somewhat more than half of an orange roughy fish one lunchtime. The entire fish, complete with its skin, had been cooked to delicious perfection in a Cantonese-style restaurant in Sandringham, an inner up-market suburb of Auckland New Zealand. For the remainder of that day, I (PMB) felt nauseous. Next morning I still felt nauseous, and moreover I was considerably alarmed to find that I was passing involuntarily a considerable volume of orange oil per rectum (keriorrhoea). I was wondering whether I had a problem with my pancreas or bile flow. However, I phoned my fellow diner to enquire whether she had suffered similar symptoms. Indeed she had! If anything, her symptoms were worse. For the next 10 days or so, both of us suffered bouts of nausea. The keriorrhoea subsided quite rapidly, but the other gastrointestinal symptoms, including discomfort and nausea, persisted for approximately two weeks. On further enquiry, I discovered another sufferer from the same condition, a colleague who had also consumed whole orange roughy at a Chinese restaurant one evening. This prompted an investigation of the phenomenon, hence the present review.

Keriorrhoea is commonly described as 'oily diarrhoea' or 'orange oily leakage'. The term keriorrhoea was first proposed by Berman *et. al.* in 1981 (Greek keras, wax, and diarrhein, to flow through).[1] To be more specific, keriorrhoea refers to the symptoms observed in cases where certain oily fish or other foods containing indigestible LWEs are consumed in large amounts, resulting in an involuntary anal discharge of orange or brownish green liquid.[2] Associated gastrointestinal (GI) symptoms include nausea, vomiting and stomach cramps. Keriorrhoea is different from ordinary diarrhoea in that it does not cause a significant loss of intestinal water.[3] This review is focussed on the effects, and their causes and consequences, of wax ester consumption in humans.

Wax esters are esters of long chain fatty acids with long chain fatty alcohols. Some wax esters (such as those in beeswax) are solid. Others are liquid at 37°C.[4] Liquid wax esters (LWEs) are made up of fatty acids and fatty alcohols of between 10 to 30 carbon atoms.[5] LWEs are more hydrophobic and less dense than triacylglycerols (TAGs).[6]

LWEs are present in the skin and (sometimes) muscles of certain deep-sea fish species to help in buoyancy control and to provide a source of stored energy.[7] Oilfish (*Ruvettus pretiosus*) and escolar (*Lepidocybium flavobrunneum*) are members of the *Gempylidae* family of fishes. They are commonly found in deep waters of tropical and subtropical seas. They possess a high level of

International Medical University, 126, Jalan Jalil Perkasa 19, Bukit Jalil, 570000 Kuala Lumpur, MALAYSIA

Address for Correspondence:

Prof Peter Barling, International Medical University, 126, Jalan Jalil Perkasa 19, Bukit Jalil, 570000 Kuala Lumpur, MALAYSIA

Email: peter_barling@imu.edu.my

body lipids, which comprise approximately 20% of their wet weight. The major component, contributing to more than 90% of these lipids, is LWEs.[3] The collective name given to the LWEs in these two fishes is " gempylotoxin" due to their laxative and purgative effects.[8,9] Oilfish and escolar have been miss-labelled as butterfish, codfish and even white tuna in restaurants and fish markets.[10,11]

Orange roughy (*Hoplostethus atlanticus*) is also a deep-sea fish rich in wax esters which are found predominantly in the skin, skeleton and swim bladder, but at lower levels in muscle tissue. For this reason, buoyancy has been suggested to be their major function in this *spp*.[12,13] Removal of the skin and superficial flesh significantly reduces the oil composition, and is generally regarded as rendering their muscle fillets edible. However, deep-skinned orange roughy fillets still contain 5.5% total lipids with as much as 93% liquid wax esters.[14]

Jojoba oil is extracted from the seeds of the jojoba plant (*Simmondsia chinensis*). Jojoba seeds are comprised almost entirely of a mixture of wax esters comprising very-long-chain (C20, C22 and C24) monounsaturated fatty acids and alcohols.[15] These LWEs serve as a primary storage reserve for post-germination growth. Jojoba oil has been proposed as a frying medium to enhance the shelf life of fried foods.[16,17] However, animal studies have demonstrated incomplete digestion of jojoba oil wax esters, with damage to the GI tract.[18] In spite of potential toxicity to children through accidental ingestion, jojoba oil is widely used in cosmetic products and as an industrial lubricant.

LWEs are minor lipid components of the external surfaces of many other animals, being present in the bodily secretions of insects and Mammalia, including humans. Human sebum consists of triacylglycerols (58%), wax esters (26%), squalene (12%) and cholesterol (4%).[19] Wax esters are unique to sebaceous cells as they are not found in any other cells.[20] In this role, they are presumed to act a water-repellant layer.[19,21] In fact the addition of jojoba oil as a component of commercial cosmetics is done for exactly this reason.[22]

Wax esters are synthesised in deep-living zooplankton[23] and certain bacteria, notably *Acinetobacter spp*.[24] In higher plants, wax esters serve as common components of the waxy cuticle of the surfaces of fruit and leaves[25], where their presumed roles are to act as protective coatings and to prevent dehydration.

In addition to natural LWEs, there are several synthetic LWEs and LWE-like products which are used for culinary and medicinal purposes. Olestra, for example, is a polyester consisting of 6 to 8 fatty acids linked to the hydroxyl groups of sucrose.[26] It has equivalent organoleptic and physicochemical properties to dietary TAGs and is used as a frying medium for some savory snacks in the United States. Olestra is neither hydrolysed nor absorbed by the GI system because of the steric hindrance of its structure to digestive lipases. It affects the absorption of lipophilic substances such as fat soluble vitamins and carotenoids when they are co-ingested.[27] Individuals consuming large quantities of olestra may experience GI symptoms including keriorrhoea, stomach cramps and nausea.[28]

Orlistat ([(2S)-1-[(2S,3S)-3-hexyl-4-oxooxetan-2-yl] tridecan-2-yl] (2S)-2-formamido-4-methylpentanoate) is also known by its trade names Xenical and Alli. It is not a LWE but behaves very similarly to one. It is a semisynthetic derivative of lipstatin, a natural lipase inhibitor isolated from the *Actinobacterium Streptomyces toxytricini*, and is likewise a potent inhibitor of pancreatic lipase (PL), which is sometimes used for treatment of obesity.[29] Orlistat interferes with the absorption of fat-soluble vitamins and beta-carotene. It causes keriorrhoea and other GI symptoms for the similar reasons that olestra and LWEs do.[30]

Ingestion of sufficient quantities of liquid wax esters from fish, plant or synthetic sources by humans leads to keriorrhoea within 1 to 36 hours. Frequent 'call to stool' also occurs, suggesting a lubricant effect of the indigestible wax esters and other associated lipids (such as potentially undigested TAGs) that have accumulated in the rectum. Sufferers may also

experience other GI-related symptoms include nausea, vomiting, headache, stomach cramps and diarrhea, as was the case for one of us (PMB). However, the symptoms seem to vary in both extent and timing, due to the variations in individual dose and susceptibility.[2,14]

Ingested LWEs are only attacked slowly by PL and other digestive lipases, passing essentially unmodified into the large intestine. As established from the personal experience outlined above, consumption of indigestible liquid wax esters from wax ester-rich foods (such as orange roughy) leads to keriorrhoea and other gastrointestinal (GI) symptoms.[2] The leaked orange oil may not only comprise LWEs, but may also contain non-digested TAGs and other products of partial lipid digestion.[31] In humans, digestion of TAGs begins in the oral cavity through the actions of lingual lipase, continues in the stomach by means of gastric lipase, and is completed by PL in the jejunum. The actions of PL require pancreatic colipase, and bile salts. The end result is the partial hydrolysis of TAGs into 2-monoacylglycerols (2-MAGs), free fatty acids (FFAs) and glycerol. The unhydrolysed TAGs, together with 2-MAGs and FFAs, form minute (ca. 1- 5 nm) micelles. These micelles exchange their contents with 2-MAGs and fatty acids in true solution. Only the latter are absorbed: they leave the lumen of the small intestine by a process of diffusion to, and then across, the plasma membranes of lining enterocytes. Micelle formation is essential to transport the products of lipid digestion to the so-called unstirred layer of fluid lining the mucosal surface. An essential prerequisite is that lipid digestion products must be emulsified by bile salts. In the absence of bile salt secretion (due to blockage of the common bile duct, for example), severe fat malabsorption occurs, resulting in steatorrhoea.

In the intestinal lumen, FFAs and 2-MAGs are taken up into the enterocytes and then become precursors for the biosynthesis of neutral fats. The brush-border membrane of enterocytes is separated from the bulk fluid phase by an unstirred water layer. The water layer mixes poorly with the fluid phase. Thus, the solute molecules present in the fluid phase can only enter the enterocytes by diffusion. As the solubilities of FFAs and 2-MAGs are relatively low, micellar solubilisation of lipids significantly enhances the degree of absorption as it not only facilitates exposure of TAGs therein to lipase, but also promotes the rapid exchange of monoglycerides and fatty acids into free solution within the fluid layer surrounding the micelles and adjacent to the enterocyte surface.[32,33] The multi-ligand scavenger receptor CD36/FAT4 has been claimed to be involved in the uptake of FFAs, but the evidence is strongly disputed.[34,35]

Discussion

LWEs can be easily metabolised by some organisms.[36,37] Marine species such as salmon and herring grow rapidly when feeding on the marine zooplankton *Calanus finmarchicus*, which is rich in wax esters.[36,38] Salmon have several innate mechanisms for wax esters hydrolysis. These include increased feed conversion, higher production of bile and higher activity of lipolytic enzymes in the midgut.[36] Seabirds and some passerines possess unique adaptations for wax esters assimilation (including an elevated bile salt concentration, regular retrograde movement of duodenal contents to the gizzard and the nearly equivalent hydrolysis of wax esters and TAGs[37]) that make them far more efficient than terrestrial mammals in hydrolyzing LWEs.[37,39]

While LWEs are not completely indigestible, terrestrial mammals, including humans, do not possess specific wax ester digestive lipases. Consequently any digestion of LWEs involves the same lipases which act on TAGs, but functioning at a rate which has been estimated to be between 1/10 to 1/50 the rate of hydrolysis of TAGs.[10] Moreover, the products of wax ester hydrolysis (long chain fatty acids and alcohols) are absorbed much more slowly the products of hydrolysis of TAGs.[40]

The main enzyme that hydrolyses ingested TAGs is PL. Optimum rates of TAG hydrolysis by PL demand a consistent flow of water molecules into the active site. The products of TAG hydrolysis, 2-MAGs and

protonated fatty acids, instantaneously react with water molecules to form a solution phase with numerous aqueous channels. In comparison, the hydrolysis of LWEs is greatly retarded by the strong hydrophobicity of wax esters, because it reduces their interaction with the active site of PL. The hydrolysis products of LWEs (long-chain alcohols and protonated fatty acids) do not form a solution phase. Instead, they form an oil phase in water that restricts the necessary water flow to PL.[40] Moreover, the solubilisation of wax esters by bile salts is not as efficient as the solubilisation of TAGs. All of these properties cause hindrance to wax ester hydrolysis. Consequently, when a large amount of LWEs is ingested either deliberately or accidentally, digestion and absorption do not occur to any significant extent.[31] There is a resultant pooling of large amounts of these lubricant wax esters in the rectum, which leads to keriorrhoea.[2] For the reasons described here, it would be predicted that the oily orange anal efflusion that occurs in keriorrhoea may not only contain undigested wax esters, but may also contain substantial amounts of undigested triglycerides and (possibly) 2-MAGs, together with fat-soluble vitamins, which have remained in micelles after they have been stripped of their more polar lipids during uptake of these into enterocytes. This would be predicted to occur because the highly hydrophobic character of LWEs within micelles would be expected to inhibit the diffusion of other relatively hydrophobic solutes (such as 2-MAGs and TAGs) therein. Unfortunately, no analyses of the composition of this oil appear to have been reported in the scientific literature, to confirm or refute this inference.

The intestinal damage which is seen in animals exposed to jojoba oil, and the non-specific symptoms of stomach cramping (nausea, vomiting, headache, stomach cramps and diarrhea) that can follow exposure to fish LWEs suggest that the presence of undigested micelles throughout the gastrointestinal system is not without its pathological consequences. In the case of my personal experience, and that of my co-diner, the effects lasted for two weeks, far longer than the transit time of the ingested LWEs through the GI tract. We are at a loss to explain the persistence of these symptoms for so long, unless for unknown reasons, the prolonged presence of undigested LWEs in micelles causes damage to the GI mucosa.

Conclusions

Outbreaks of keriorrhoea, as the result of consuming wax ester-rich species of fish, have become a frequent and worldwide concern. Many countries have issued special legislation and regulations restricting or preventing the trading and consumption of these fish. Despite this, keriorrhoea is still regularly, if infrequently, reported in the scientific literature and in other media.[41,42] Due to the variation in individual susceptibility to the adverse effects of LWEs and the application of different policies in different countries, a global ban on these LWE-rich species is presently almost impossible. Currently, oilfish and escolar are completely banned in Japan, Italy and South Korea, while other countries only issue guidelines and warnings about them. The consequences of deliberately or accidentally consuming substantial amounts of LWEs (or synthetic compounds with similar properties) are far from understood. The potential pathologies associated with LWE consumption are not well documented. This neglected field needs to be the subject of further research to clarify these issues. Moreover, governments need to tighten legislation to prevent the consumption of those fish species that have been identified as containing substantial quantities of WLEs, to prevent further outbreaks of keriorrhoea in the future, and to minimise any associated pathological changes to the human GI tract and to human health.

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