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Declaration of Fructose and Fructose-Related Adverse Effects in Commercial Drug Preparations in European Countries

Hereditary fructose intolerance is a potentially life-threatening condition that is estimated to affect about 1 in 20 000 individuals. It is characterised by deficiency of the hepatic enzyme aldolase B. Clinical symptoms after fructose exposure include abdominal pain, vomiting, hypoglycaemia, convulsions, enlarged liver and spleen, moderate to severe kidney and liver damage, and even death. Until recently, the only available diagnostic tool was exposure to fructose, usually by intravenous infusion in a controlled clinical setting. Genotyping is now available; however, it is complicated by the fact that the disorder can be induced by at least 20 different mutations.[1] Despite these tools, patients often remain undiagnosed for decades after having learned in early childhood more or less unconsciously to avoid food which they associate with the symptoms.

In the past, there have been case reports of a fatal outcome in patients with undiagnosed hereditary fructose intolerance who received intravenous solutions containing fructose or sorbitol.[2-4] Despite these publications, fructose and its derivatives, e.g. sorbitol (derived by reduction of fructose) and sucrose (a disaccharide formed by fructose and dextrose, also called saccharose), are still widely used in commercial drug preparations. Fructose is said to be the sweetest known sugar. This may explain its use, mainly as a sweetener/taste optimiser, in pharmaceutical preparations. Its use might further be explained by the fact that the amount contained in drug preparations is generally not considered to put patients at an increased risk for serious adverse effects. Nevertheless, in 1997 the European Union (EU) issued a guideline requiring that fructose-containing drugs should be labelled with a warning saying that, "This medicinal product contains '×' g of fructose. When taken according to dosage recommendations, each dose supplies up to '×' g of fructose. Unsuitable in hereditary fructose intolerance. Due to the possibility of not yet detected congenital fructose intolerance, this medicinal product should only be given to babies and infants after consultation with a doctor".[5] Similar warnings are required for sucrose and sorbitol.

In order to investigate whether the texts in drug catalogues from European countries are harmonised with this request, a survey of the Internet resources of the Norwegian, Swedish, German, and British catalogues (Felleskatalogen,[6] Farmaceutiska specialiteter i Sverige [FASS],[7] Rote Liste,[8] and electronic Medicines Compendium [eMC],[9] respectively) using the integrated search function on the web sites, was carried out. A total of 14 drug preparations being marketed in all four countries and where at least in one country fructose or a fructose derivative was declared, was identified (table I). A warning against use in patients with hereditary fructose intolerance was found in nine of these 14 preparations in the eMC,[9] in five in the German Rote Liste,[8] in five in the Swedish FASS,[7] and in only four preparations in the Felleskatalogen[6] (Norway as a member of the European Economic Area has to follow EU medicines legislation). Surprisingly, a further three preparations listed in the eMC[9] contained a warning in the patient information leaflet, but not in the professional information. Some texts contain only a general warning on 'known hypersensitivity against any of the excipients'. Only three of the 14 preparations were adequately and nearly identically labelled in all four countries. A special example is topiramate (Topimax®[1] capsules). Topimax® capsules contain sucrose in the form of 'sugar spheres'. However, neither sucrose nor 'sugar spheres' were listed as an excipient in the Norwegian drug catalogue. Another issue that makes Topimax® capsules a special case is that the active substance, topiramate is in itself a

1 Use of tradenames is for product identification only and does not imply endorsement.

Table I. Declaration of fructose and fructose derivatives and presence of warnings against the use of fructose-containing drugs in patients with hereditary fructose intolerance in various European online drug catalogues

Drug (tradename in Norway/UK/Germany/Sweden)	Active substance	Substance declared (presence of warning)			
		Felleskatalogen[6] (Norway)	eMC[9] (UK)	Rote Liste[8] (Germany)	FASS[7] (Sweden)
Brufen® mikstur/Brufen syrup®/NM/Brufen® oral suspension	Ibuprofen	Sucrose, sorbitol 0.07g	Sorbitol solution 70%[a,b]	NM	Sorbitol
Brufen® brusegranulat/Brufen® granules/NM/Brufen® brusgranulat	Ibuprofen	Sucrose 3.33g per dosage unit	Pulverised sugar[a,b]	NM	Sucrose 3.33g per dosage unit
Calcium Sandoz®/NM/Calcium Sandoz® forte/Calcium-sandoz® 500mg	Calcium	Sucrose 0.868g/tablet	NM	Sorbitol	Sucrose 0.868g/tablet
Detrusitol® SR/Detrusitol® XL/Detrusitol® retard/Detrusitol® hård depotkapsel	Tolterodine	Constituents[b]	Sugar spheres (sucrose and maize starch)[b]	Sucrose[b]	Sucrose
Duphalac®/Duphalac®/Bifitera®/Duphalac®	Lactulose	ND	Fructose[b]	Fructose	ND
Kaletra®/Kaletra®/Kaletra® Lösung/Kaletra® oral lösning	Lopinavir + ritonavir	Fructose 0.8 g/mL	High fructose syrup[b]	High fructose corn syrup	High fructose corn syrup
Keflex® granulat til mikstur/Keflex® suspension/Cephalexin®-ratiopharm TS/Keflex® granulat till mixtur	Cefalexin	Sucrose 60g/bottle	Sucrose[b]	Sucrose	Sucrose 63.5 g/dL
Lanso®/Zoton® capsules/Lanzor®/Lanzo® enterokapslar	Lansoprazole	Sucrose	Sugar spheres, sucrose[a,b]	Sucrose	Sucrose
Micardis®/Micardis®/Micardis®/Micardis® tabletter	Telmisartan	Sorbitol[b]	Sorbitol[b]	Sorbitol[b]	Sorbitol 84.5mg/tablet[b]
Nexium®/Nexium®/Nexium® mups/Nexium® enterotabletter	Esomepromazole	Sucrose[b]	Sugar spheres (sucrose and maize starch)[b]	Sugar spheres (sucrose and maize starch)[b]	Sucrose[b]
Tamiflu®/Tamiflu® suspension/Tamiflu® Pulver/Tamiflu® pulver till oral suspension	Oseltamivir	Sorbitol 2.6g/90mg[b]	Sorbitol 2.6g/90 mg[b]	Sorbitol[b]	Sorbitol 26g[b]
Topimax® kapsler/Topimax® sprinkle/Topamax® Kapseln/Topimax® kapslar	Topiramate	ND	Sugar spheres	Saccharose[c]	Sugar spheres
Trileptal® mikstur/Trileptal® oral susp./Trileptal® Suspension /Trileptal® oral suspension	Oxcarbazepine	Sorbitol 175 mg/mL	Sorbitol 70%[b]	Sorbitol 70% solution[b]	Sorbitol 70% solution[b]
Videx® tyggetabletter/Videx® chewable tablets/NM/Videx® tuggtabletter	Didanosine	Sorbitol	Sorbitol[b]	NM	Sorbitol 316/333/342 mg/tablet[b]

a Patient information leaflet.

b Warning against use is given.

c A warning is given in the professional prescribing information ('Fachinformation') available from the manufacturer.

eMC = Electronic Medicines Compendium; **FASS** = Farmaceutiska specialiteter i Sverige; **ND** = no declaration of fructose or derivatives; **NM** = not marketed in this country.

fructose derivative.[10] Interestingly, a Medline search yielded three case reports of liver damage related to treatment with Topimax®.[11-13] The manufacturer's safety database contains ten cases of hepatic failure/necrosis associated with topiramate use; five of these were fatal.[14]

As shown in table I, excipients are fully declared for almost all preparations. It may, however, be too optimistic to believe that the majority of doctors were familiar with the fact that sorbitol and sucrose are fructose derivatives. Declaration of 'sorbitol' or 'sucrose' as excipients alone is therefore hardly sufficient without an explicit warning against use in patients with hereditary fructose intolerance. Apart from the aforementioned Topimax® cases, a Medline search did not reveal any other reports of liver damage induced by fructose or fructose derivatives in oral drug preparations. One explanation may be that fructose and especially its derivatives are generally thought to be nontoxic, inert excipients and therefore not even considered as possible causes of detrimental effects in respective cases.

The four drug catalogues have in common the fact that they are published by or on behalf of the pharmaceutical industry, and that they are widely used and trusted by health professionals to the extent that they are regarded as being 'official' sources of drug information. Many clinicians rely solely on the information given in these publications. The present findings show that the labelling of fructose and its derivatives is insufficient and far from being harmonised in European countries. Manufacturers and health authorities should clarify this situation. The chance that a patient with hereditary fructose intolerance will be harmed is probably small, but the risk is real.

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