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Adverse food–drug interactions

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ABSTRACT

Food supplements and herbal products are increasingly popular amongst consumers. This leads to increased risks of interactions between prescribed drugs and these products containing bioactive ingredients. From 1991 up to 2014, 55 cases of suspected adverse drug reactions due to concomitant intake of health-enhancing products and drugs were reported to Lareb, the Netherlands Pharmacovigilance Centre. An overview of these suspected interactions is presented and their potential mechanisms of action are described. Mainly during the metabolism of xenobiotics and due to the pharmacodynamics effects interactions seem to occur, which may result in adverse drug reactions. Where legislation is seen to distinct food and medicine, legislation concerning these different bioactive products is less clear-cut. This can only be resolved by increasing the molecular knowledge on bioactive substances and their potential interactions. Thereby potential interactions can be better understood and prevented on an individual level. By considering the dietary pattern and use of bioactive substances with prescribed medication, both health professionals and consumers will be increasingly aware of interactions and these interactive adverse effects can be prevented.

1. Introduction

With a growing population in the economically instable Western world in the 20th century, the main focus of food consumption was to alleviate hunger and to provide for necessary macro- and micronutrients (Georgiou et al., 2011; Menrad, 2003). Together with the increased possibilities to chemically produce drugs, this instigated the separate study of pharmaceutics and nutrition, where both were highly connected fields traditionally with their foundation in nature (Eussen et al., 2011). Pharmaceutical products concentrated on curing diseases or alleviating symptoms of disease (Eussen et al., 2011). The potential of food (ingredients) to affect health is recognised both in science and by consumers during the last few decades. Food intake currently not only aims to relieve hunger but is also used to enhance health, thereby shifting more towards the function of pharmaceutical products (Georgiou et al., 2011). This increased interest in the health effects of foods pushes sales of products as functional foods, health foods and food supplements (Alissa, 2014; Euromonitor International, 2015, 2013). The active ingredients of these products, the components which are shown to affect human health, are called 'bioactives' (Biesalski et al., 2009). These products are considered to be foodstuffs, but consumers also seem to get more interested in products at the interface between nutrition and pharmaceuticals as foods for special groups (traditional), herbal medicinal products and cosmoceuticals (Alissa, 2014; Euromonitor International, 2013, 2011). With more health conscious consumers using products with bioactive ingredients, the risk of serious adverse reactions due to interactions between prescribed medication and potentially bioactive compounds is increasing. Various drug–food interactions (e.g. drugs interacting with the fat content of the meal), drug–nutrient interactions (e.g. with grapefruit juice or soy) and herb–drug interactions (e.g. with ginkgo biloba or St John's wort) have been described and reviewed (Boullata and Hudson, 2012; Cheng, 2006; Fugh-Berman, 2000; Pirmohamed, 2013).

The Netherlands Pharmacovigilance Centre Lareb receives reports of health professionals, consumers and the pharmaceutical industry on experienced adverse reactions to medicines and vaccines (Netherlands Pharmacovigilance Centre Lareb, 2015). Amongst these suspected adverse reactions also interactive effects of drugs ingested with xenobiotics, as food supplements and herbal products are reported to Lareb. This paper discusses the received reports on suspected adverse effects following xenobiotics intake

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collected by Lareb and describes several other potential interactions between such substances with drugs and their mechanisms of action. This study thereby gives an overview of clinically relevant interactions and can help to focus the attention of health professionals and consumers on the possibility of interactions between prescribed medication with bioactive products as consumed supplements or herbal extracts.

2. Legal perspective

The Softenon®-affair in the 1960s, where the consumption of thalidomide by pregnant women caused birth defects in children, increased public awareness of potential adverse effects of drugs. As a result, two global measures were taken: (i) medicines must meet requirements for efficacy, quality and safety; and (ii) a system was introduced to report adverse drug reactions (Netherlands Pharmacoviglance Centre Lareb, 2015a). Hereby all legislation concerning drugs was drastically changed (Lachmann, 2012). This was the start of pharmacovigilance: all activities related to monitoring, understanding and preventing medicine-related problems including the occurrence of adverse effects (World Health Organization, 2015). In the Netherlands, these adverse effects are monitored by the Netherlands Pharmacovigilance Centre Lareb. Lareb is an independent foundation and works in close collaboration with the Medicines Evaluation Board (MEB) to maintain the spontaneous reporting system and collects and assesses reports of adverse drug reactions (Netherlands Pharmacoviglance Centre Lareb, 2015b). Reports collected are from Health care professionals, consumers and Marketing Authorization Holders (Netherlands Pharmacovigilance Centre Lareb, 2015).

2.1. Pharmacovigilance

Pharmacovigilance is regulated on an EU level by means of Regulation 1235/2010[1] and Directive 2010/84/EU[2]. Directive 2010/84/EU amends Directive 2001/83/EC[3] by laying down rules for pharmacovigilance. The general provisions on pharmacovigilance are described, next to the organisation of the pharmacovigilance system in Member States, the responsibilities of the marketing authorisation holder and the tasks of the Commission (European Parliament and Council of the European Union, 2010a, 2001).

Regulation 1235/2010 amends Regulation (EC) No 726/2004[4] by including pharmacovigilance as an aspect to be taken into consideration with the authorisation and supervision of medicinal products (European Parliament and Council of the European Union, 2010b). Pharmacovigilance is therefore added to the responsibilities of the EMA's Committee for Medicinal Products for Human Use. The tasks of the marketing authorisation holder and competent authorities of Member States are also further clarified (European Parliament and Council of the European Union, 2010b, 2004a).

2.2. Food and drugs

Next to regulating pharmacovigilance, EU law also defines concepts as food and drugs. Food is defined by the General Food Law[5] as any substance or product that is intended or can be expected to be ingested by humans, directly listing various exemptions in article 2 (European Parliament and Council of the European Union, 2002a). Following the amendments made by Direction 2004/27/EC[6] to Directive 2001/83/EC, drugs can be defined as either medicinal products by presentation (substance(s) presented for treating or preventing diseases in human beings) or medicinal products by definition (substance(s) administered to human beings to make a medical diagnosis or to restore, correct or modify physiological functions) (European Parliament and Council of the European Union, 2004b, 2001). Next to Directive 2001/83/EC, Regulation (EC) No 726/2004 is one of the main EU legislation on medicinal products for human use, by establishing the EMA and describing procedures to authorise and supervise drugs (European Parliament and Council of the European Union, 2004a).

The products at the interface of food and medicine are defined by and regulated under different directives and regulations. Food supplements are defined as concentrated food ingredients aiming to supplement the normal diet (European Parliament and Council of the European Union, 2002b). Herbal medicinal products are drugs with as only active ingredients herbal substances or preparations (European Parliament and Council of the European Union, 2004c, 2001). Following amendments to Directive 2001/83/EC by the Herbal Directive[7], traditional herbal medicinal products have to fulfil specific conditions laid down in Directive 2001/83/EC (European Parliament and Council of the European Union, 2004c, 2001). This directive also defines homeopathic medicinal products due to the amendment by Directive 2004/27/EC, as medicinal products prepared from homeopathic stocks in accordance with manufacturing procedures described in either the European or a Member States' Pharmacopoeia (European Parliament and Council of the European Union, 2004b, 2001). Anthroposophic medicinal products are treated equally to homeopathic medicinal products (European Parliament and Council of the European Union, 2001). Newly developed legislation on food for special medical purposes defines this category as *'food specifically processed or formulated and intended for the dietary management of patients, including infants, to be used under medical supervision'* (European Parliament and Council of the European Union, 2013). Medical devices from the last category of health-enhancing products, instruments which are used for diagnostic and/or therapeutic purposes in human beings (Council of the European Union, 1990). Although the European Commission proposed new legislation as well as recommendations on audits and assessments next to a unique identification system, currently three directives deal with medical devices: Directive 90/

[1] Regulation (EU) No 1235/2010 of the European Parliament and of the Council of 15 December 2010 amending, as regards pharmacovigilance of medicinal products for human use, Regulation (EC) No 726/2004 laying down community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, and Regulation No 1394 on advanced therapy medicinal products (Consolidated version 1 January 2011).

[2] Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010 amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use (Consolidated version 20 January 2011).

[3] Directive 2001/83 of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (Consolidated version 16 November 2012).

[4] Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (Consolidated version 5 June 2013).

[5] Regulation (EC) No 178/2002 of the European Parliament and of the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety (Consolidated version 30 June 2014).

[6] Directive 2004/27/EC of the European Parliament and of the Council of 31 March 2004 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use (Consolidated version 30 April 2004).

[7] Directive 2004/24/EC of the European Parliament and of the Council of 31 March 2004 amending, as regards traditional herbal medicinal products, Directive 2001/83 on the Community code relating to medicinal products for human use.