Maturitas 107 (2018) 103–109

Contents lists available at ScienceDirect

Maturitas

journal homepage: www.elsevier.com/locate/maturitas

Review Article

Choosing a medication brand: Excipients, food intolerance and prescribing in older people

Amy Page*, Christopher Etherton-Beer

Western Australian Centre for Health and Ageing, University of Western Australia

ARTICLE INFO

Keywords:
Generic medications
Brands
Excipients

ABSTRACT

Multiple brands of the same active ingredient may be available for the same strength, administration route and dose form. Generic brands needs to demonstrate bioequivalence to the originator brand, but the appearance of the generic and originator brands are not required to match. This variation is possible because different brands may vary in the excipients used in the formulation. Excipients are inactive ingredients, and typically make up about 90% of the formulation of an individual medication. Individual preferences or requirements may affect tolerance of particular excipients, such as the use of animal products. The different appearance of brands can affect medication management for some people. This review discusses the potential for excipients to alter the individual response to or tolerance of a medication brand.

1. Introduction

Medications come in many different formulations, and multiple brands of the same active ingredient may be available in the same strength, administration route and dose form. Generic brands are required to demonstrate bioequivalence to the original brand prior to marketing authorisation [1]. Australian pharmacies, for example, are only permitted to substitute brands if the two brands are bioequivalent.

Bioequivalence does not mean that the brands are identical. While comparable plasma concentrations of the active ingredient(s) are achieved after healthy people take both brands, and the same clinical response can be expected, bioequivalent brands can differ substantially. The appearance – shape, colour, size – of the generic and originator brands are not required to match [2]. For example, tablet forms of the common antihypertensive ramipril are available in white, yellow, red and pink [3].

Such variation is possible because different pharmaceutical products vary in the excipients used in the formulation [1]. The inactive ingredients are excipients, which typically make up about 90% of the formulation of an individual medication [4]. The term encompasses all ingredients – except the active ingredient – found in pharmaceutical preparations. They are used to colour and flavour pharmaceutical preparations, and to enhance the product's performance. Binders hold all the ingredients together to provide structure and strength, diluents add bulk to allow small quantities to be measured accurately and disintegrants enhance dispersion of the dose-form in the gastro-intestinal tract (Table 1) [5,6]. Some common excipients and their function are listed in Table 2 [5,6].

The many different excipients included in a brand are available from the manufacturer [4]. Excipients generally are listed in the written information generally available online, namely the Product Information or Consumer Medicine Information leaflets [4]. In Australia, the manufacturer must declare the presence, but not the quantity, of specific ingredients including lactose, gluten and tartrazine [3,7]. This information must be on the label, except for prescription-only medications where it is an option to provide the information in the written information [3,7].

Excipients may affect individual responses to different brands. This concern can be linked to individual preference or requirements (such as for vegetarians or individuals with religious dietary restrictions) or physiological response (including adverse reactions and intolerances), as well as adherence which could be impacted by differences in the physical appearance of brands of active medicines. This review discusses the potential for excipients to alter the individual response or tolerance to a medication brand.

2. Methods

This paper examines the effect that excipients have on the choice of brand without respect to whether the formulation is the originator or generic brand. The emphasis is on the acceptability, safety and tolerability of the excipients themselves, and the effect that has on brand choice. Given the frequency of polypharmacy among older people [8], we have focused on the effect that excipients have on brand choice in

* Corresponding author.
E-mail address: amy.page@uwa.edu.au (A. Page).

http://dx.doi.org/10.1016/j.maturitas.2017.11.001
Received 23 October 2017; Accepted 1 November 2017

Table 1
Common reasons excipients are used during manufacturing medications.

Category	Function	Example excipients
Binders	Achieve the desired strength for the medication	Cellulose
	glues the powder together to form granules or tablets	Calcium carbonate
		Carbomers
		Gelatin
		Hydrogenated vegetable oil
		Lactose
Coatings and films	Protect medication from moisture	Hypromellose
	Assist to swallow medication	Beeswax, white
	Allow for medication release at a specific location in the gastrointestinal system	Calcium carbonate
		Carnauba wax
Colourants	Identify medication	Calcium
	Protect light-sensitive ingredients	Carmine
	Dies (water-soluble) and pigments (water-insoluble)	Iron oxide
		Quinoline yellow
		Tartrazide
		Titanium dioxide
Diluents	Provide bulk for the active ingredient;	Lactose
	improve properties such as cohesion	Simeticone
		Talc
		Cellulose, microcrystalline
		Calcium carbonate
Disintegrants	Promote dissolution in the gastrointestinal tract	Cellulose, microcrystalline
		Croscarmellose sodium
		Crospovidone
		Povidone
		Sodium starch glycolate
Glidants	Help powders to flow	Talc
		Starch
Lubricants	Prevents the product adhering to equipment during manufacturing or other surfaces	Castor oil, hydrogenated
		Vegetable oil, hydrogenated
		Macrogol
		Magnesium stearate
		Sodium benzoate
		Sodium lauryl sulfate
		Talc

older people.

Articles were included that discussed the effect of excipients on acceptability, tolerance, safety or adherence. We only included oral preparations. For relevance to current practice, we excluded reports where concerns about an individual excipient has led to a re-formulation of the product. An example of this issue were compounding incompatibilities between an excipient and an active ingredient caused effected the performance or stability of the product, which led to a re-formulation so that the issue is not a current concern.

We conducted a search in the Medline, Scopus, and Google Scholar databases using a combination of search terms including “excipient”, “brand” and specific excipient names. Articles were included if they were in English. Reference lists of identified papers were scanned for relevant studies.

3. Adverse reactions to excipients

An allergen is a substance that is harmless for most people but can produce an immune-mediated response which triggers symptoms that can range from mild to life-threatening [9] in allergic individuals. Theoretically, any dietary protein can be a potential allergen [10]. Intolerances can mimic allergic symptoms but are not immune-mediated and include responses to a broad range of triggers [11].

Adverse reactions to excipients are thought to be uncommon [12], however numerous case reports that outline patient sensitivity to a specific excipient describe allergic reactions [13–19]. The nature of these papers suggests such responses are rare but serious, though did not report fatalities. Authors generally report that their investigations determined the adverse events were confirmed allergic reactions mediated by an immune system response [18,20–26]. These reported adverse events varied from skin reactions to severe allergic reactions with documented anaphylaxis [18,20–26].

Individual reactions to excipients may go unnoticed, and thus unreported, if mild or not identified as being due to an excipient [21]. Those referenced above were typically only identified after the person experienced the same or a similar adverse effect to multiple medications, or reacted to one brand but not another [21]. Suspected reactions were generally confirmed by patch or intradermal testing [18,20–26].

3.1. Specific excipients

Colouring agents are added to medications for reasons that include ease of identification, improved acceptability and stabilising light-sensitive ingredients [4]. Many different agents may be used to produce the same or similar colours, and numerous case reports exist of allergies to colouring agents such as the yellow dye tartrazine [19]. Little research has been done to confirm the potential for pharmacological activity of these excipients. Tartrazine allergy, was not found in 26 people with atopic allergies in a pilot double-blind randomised controlled trial [17]. However, allergic responses to excipients that are intended to be inert, are likely to be rare, and thus difficult to detect in clinical trials.

Gluten triggers an immune response that causes chronic inflammation in the small intestine of people with coeliac disease which can lead to malabsorption. The exact quantity of ingested gluten that triggers an adverse effect is uncertain and may vary between people, though it may be as little as 10 mg in a day and “gluten-free” is defined by the American Food and Drug Administration (FDA) as 20 parts per million (ppm) of gluten or less [27].

Starch is used in oral formulations as a binder and disintegrant [4]. It is derived from plant sources such as wheat, corn and potato, so concerns have been expressed about the possible gluten content in wheat-derived starch. However, wheat starch is so highly processed that it is unlikely to have any remaining gluten content. In Australia and the UK, manufacturers must declare if they have used wheat starch in their printed materials [3,28,29].

Lactose is a disaccharide sugar present in milk and used as a binder and a diluent in pharmaceutical products. The lactase enzyme in the small intestine metabolises lactose into two smaller sugars, glucose and galactose, that are absorbed into the blood stream [30]. Some people have reduced or absent lactase activity so cannot completely metabolise all the lactose in the small intestine, which means some lactose reaches the large intestine [30]. The presence of lactose in the large intestine can trigger the symptoms of lactose intolerance [30] when bacteria metabolise lactose, producing gases that cause symptoms including abdominal cramps, bloating and flatulence. Lactose intolerance is distinct from a milk allergy, which is an immune reaction to milk proteins [30].

The lactose volume required to cause symptoms is variable, and can change with age [31]. It is suggested that lactose intolerant people can consume 12 g in a single dose with either no effect or only minor symptoms [32]. Oral preparations that contain lactose may range from 4 mg to 600 mg [31] so it is unlikely that a single tablet or capsule would contain sufficient lactose to cause symptoms [32]. No significant difference in symptoms after eight hours was found with 400 mg lactose compared to placebo in a blinded crossover RCT with 77 lactose-