

## Lessons from practice

## Hidden danger: maize starch excipient allergy

## Clinical record

**A** 77-year-old man with maize starch excipient allergy on peritoneal dialysis presented to the renal clinic with mild right groin pain for a week, blood pressure of 150/79 mmHg, and weight gain of 2 kg due to fluid retention. He was referred to the pharmacist to recommend a suitable diuretic in view of his known maize starch excipient allergy. The patient was diagnosed with maize starch excipient allergy two years before his current presentation, following multiple episodes of skin rashes with antihypertensive medications, which were steroid responsive. Serum IgE levels at the time of an erythematous blanching rash suspected to be due to irbesartan and hydrochlorothiazide were 12 676 kU/L (reference interval [RI], 0–148 kU/L) and 46 627 IU/mL (RI, < 100 IU/mL), respectively, with negative antinuclear antibody, extractable nuclear antigen, and antineutrophil cytoplasmic antibody tests. Following a similar reaction to valsartan and hydrochlorothiazide, the patient was suspected to be reacting to maize starch as an excipient and commenced olmesartan 20 mg tablet daily, which does not have maize starch as an excipient and was well tolerated. His other medications at home included calcitriol 0.25 µg tablet once daily, sevelamer 800 mg twice daily, and darbepoetin alfa 100 µg injections once monthly. He was diagnosed with fluid retention due to a malfunctioning peritoneal dialysis catheter as a result of constipation, and was treated with lactulose, fleet enema, and frusemide oral solution 4 mL (40 mg), given that frusemide tablets contain maize starch as an excipient.

## Discussion

Pharmaceutical excipients are substances that are included in medications during the manufacturing process not for their direct therapeutic action but to enhance stability, bioavailability, or patient acceptability of the drug. Several excipients, many of which have more than one purpose, are added to the active ingredient of the drug and on average make up about 90% of each product but can rise to 99% in some products. A 2019 study<sup>1</sup> reported that 93% of the drugs available in the market contain excipients that have a potential to cause an allergic reaction. Common excipients with the potential to cause allergy include lactose, gelatin, carboxymethyl cellulose, polyethylene glycol, and maize starch.<sup>1</sup> Although adverse reactions to excipients are relatively uncommon, cases of sensitivity to specific excipients have been reported.<sup>2,3</sup> Hence, it is important to be aware that drug allergies may not always be due to the active ingredient of that drug but can be caused by excipients.

Pharmaceutical starch, which is extracted from plant sources such as wheat, corn (maize) and potato, is

used primarily in oral solid dosage formulations where it acts as a diluent, disintegrant or binder. An extract from the Pillbox database revealed that nearly 37% of marketed medications contain maize starch as one of their critical inactive ingredients.<sup>1</sup> Although food allergy to maize is a known phenomenon with an increasing global prevalence, little emphasis is given to its presence as an excipient in medications. In Australia, food allergy is common and is estimated to currently affect about 1 in 10 babies,<sup>4</sup> 1 in 20 teens,<sup>5</sup> and 2 in 100 adults.<sup>6</sup> People who are allergic to maize food are likely to manifest allergies to maize starch excipients in medications. Therefore, excipients in medicines may not be suitable for some people with food allergies or intolerance, and individual reactions to excipients may go unnoticed, and therefore unreported, if not identified as being caused by an excipient. Reactions are often identified after a person experiences similar effects to multiple medications or reacts to one brand over another, as in our case.

In recent years, there has been increasing recognition and reporting of excipient allergies. Evaluation of excipients in allergic patients on polypharmacy is necessary, especially in those with multiple comorbid, chronic conditions, as it can determine the drugs that they are able to take as well as affect their quality of life. In patients who manifest an allergic reaction, doctors prescribing drugs often switch active ingredients rather than consider the allergy to be due to an excipient. This not only unnecessarily limits the number of active ingredients that patients can be prescribed but also leads to use of second line or third line medications for that particular indication. Additional allergy testing and expert opinion should therefore be considered for proper diagnosis and advice on treatment. Information on excipients in particular medications is freely available online in the consumer medicines information. In addition, the Monthly Index of Medical Specialties (MIMS)<sup>7</sup> also provides the list of excipients but is not available free online. Pharmacists are in an excellent position to support prescribers at the time of decision making and support people with food allergies/intolerances by providing them with written product information.

Our patient was receiving multiple medications over the years and had been switched between several antihypertensive medications owing to the occurrence of skin rashes. Using the MIMS database,<sup>7</sup> we identified antihypertensives that contain maize starch as an excipient. Even between different brands/strengths with the same active pharmaceutical ingredients, the excipients can be different. For example, with the combination of irbesartan and hydrochlorothiazide, among the two different brands (Avapro HCT and Karvezide) marketed by the same company (Sanofi-Aventis

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Australia), some strengths (eg, 300/25 mg) contain maize starch while others do not (eg, 150/12.5 mg). Further, excipients can also vary among generics; for instance, in enalapril (APO-Enalapril and Enalapril Sandoz) with only the latter containing maize starch. Because frusemide tablets contain maize starch, our patient was prescribed frusemide oral solution as a loop diuretic for fluid overload that was well tolerated.

Pharmaceutical excipients are used for various properties in medicines. These can be a source of allergy with profound effects on patient safety and may severely limit drug selection. Importantly, excipients can vary between different brands and generic medications. Our case highlights the need for heightened recognition among health care professionals of excipients as a cause of allergy.

#### Lessons from practice

- Maize starch is a common excipient used in drug products and is present in about 37% of marketed medications.
- Maize starch can be a source of allergy and have profound effects on patient safety and may severely limit drug selection for relevant patient care.
- Health care professionals should pay close attention while prescribing and dispensing medications, as different brands of the same active pharmaceutical ingredient may not contain identical excipients.

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