

## HIDDEN DANGERS: EXCIPIENTS IN DRUGS THAT CAN CAUSE HYPERSENSITIVITY REACTIONS

An excipient is an inert substance added to a drug to change dissolution or the kinetics of absorption, improve stability, influence palatability, or create a distinctive appearance. Also called additives, they are preservatives, emulsifiers, stabilizers, or thickeners.<sup>1</sup>

Drug hypersensitivity reactions are unpredictable adverse drug reactions. They manifest either within 1–6 hour following drug intake (immediate reactions) with mild to life-threatening symptoms of anaphylaxis, or several hours to days later (delayed reactions), primarily as exanthematous eruptions.<sup>2</sup>

### EXCIPIENTS

#### DYES<sup>2</sup>

- The relevance of hypersensitivity to dyes among all drug hypersensitivities remains unclear.
- According to Bhatia, 13 among 2210 patients exposed to **tartrazine** containing drugs, 83 (3.8%) had **adverse reactions, and the symptoms subsided within 24 to 48 hours of stopping.**

#### SODIUM BENZOATE<sup>2</sup>

- **Sodium benzoate (E211)** has been implicated in the onset of some types of **food-induced asthma, urticaria, or anaphylaxis.**
- It is found in anticough syrups, vitamin preparations, heparin, or antibiotic syrups.
- Recently, a high frequency of sodium benzoate hypersensitivity has been reported in children with **cutaneous reactions occurring during the amoxicillin plus clavulanic acid suspension intake.**

#### BENZYL ALCOHOL<sup>2</sup>

When used as a preservative, **benzyl alcohol can cause sensitization** by contact with topical ointments but also by a systemic way.

#### POVIDONE<sup>2</sup>

Michavila-Gomez and colleagues reported one case with an **anaphylactic reaction** occurring in a 4-year old boy after using a **prednisolone oral solution with povidone.**

#### CARBOXYMETHYLCELLULOSE<sup>2</sup>

- Carboxymethylcellulose also called **carmellose** or **croscarmellose**, sodium carboxymethylcellulose, and E466
- The **immediate hypersensitivity** of croscarmellose is primarily reported after **intra-articular infiltration of corticosteroids** but also with a **generic furosemide.**
- In immediate reactions to injectable drugs containing carboxymethylcellulose, it is reported that oral administration of carboxymethylcellulose is well tolerated owing to its weak absorption through the digestive tract.
- However, **carboxymethylcellulose anaphylaxis has been reported after contact with gut mucosa during barium enema.**

# HIDDEN DANGERS: EXCIPIENTS IN DRUGS THAT CAN CAUSE HYPERSENSITIVITY REACTIONS

## SULFITES<sup>2</sup>

- Sulfites are sulfur dioxide salts that are widely used as antioxidants in food and drugs.
- By systemic exposure, most adverse reactions have been reported with sulfites contained in food. They occur primarily in asthmatic patients and **induce exacerbation of asthma, pruritus, urticaria, angioedema, flush, or even hypotension**

## NONIONIC POLYETHOXYLATED SURFACTANTS<sup>2</sup>

- Nonionic polyethoxylated surfactants, polysorbate 80 (PS80, E433, Tween 80, polyoxyethylene sorbitan monooleate), and Cremophor-EL (CrEL 5 polyoxyethylated castor oil in 50% ethanol) activate the complement system in vitro in normal human serum and plasma.
- Therapeutic side effects, such as **acute hypersensitivity and systemic immunostimulation**, caused by intravenous medicines containing polyethoxylated detergents, can be attributed to complement activation-derived inflammatory mediators.

### Prepared by:

1. Nur Aida Murni Mamamad
2. Syahira Afiqah Mohamad Pauzi

### Edited by:

Khairul Bariah Johan @Rahmat

## PEG<sup>3</sup>

- Polyethylene glycols (PEGs) and their deethylene oxide have numerous synonyms, such as macrogol, oxyethylene polymer, and laurth-derivatives are nonionic polymers.
- Since its development, PEG polymers held a reputation for safety, nevertheless from mild to life-threatening immediate-type hypersensitivity reactions have been reported, with clinical manifestations ranging from **generalized urticaria to anaphylactic shock**.

## References

1. Barbaud A. Place of Excipients in Systemic Drug Allergy. *Immunol Allergy Clin N Am* 34 (2014) 671–679 <http://dx.doi.org/10.1016/j.iac.2014.04.006>
2. Brockow K, Przybilla B, Aberer W, Bircher AJ, Brehler R, Dickel H, Fuchs T, Jakob T, Lange L, Pfützner W, Mockenhaupt M, Ott H, Pfaar O, Ring J, Sachs B, Sitter H, Trautmann A, Treudler R, Wedi B, Worm M, Wurpts G, Zuberbier T, Merk HF. Guideline for the diagnosis of drug hypersensitivity reactions: S2K-Guideline of the German Society for Allergology and Clinical Immunology (DGAKI) and the German Dermatological Society (DDG) in collaboration with the Association of German Allergologists (AeDA), the German Society for Pediatric Allergology and Environmental Medicine (GPA), the German Contact Dermatitis Research Group (DKG), the Swiss Society for Allergy and Immunology (SGAI), the Austrian Society for Allergology and Immunology (ÖGAI), the German Academy of Allergology and Environmental Medicine (DAAU), the German Center for Documentation of Severe Skin Reactions and the German Federal Institute for Drugs and Medical Products (BfArM). *Allergo J Int.* 2015;24(3):94-105. doi: 10.1007/s40629-015-0052-6. PMID: 26120552; PMCID: PMC4479479.
3. Jover Cerdá V, Rodríguez Pacheco R, Doménech Witek J, Marco de la Calle FM, de la Sen Fernández ML. Immediate hypersensitivity to polyethylene glycols in unrelated products: when standardization in the nomenclature of the components of drugs, cosmetics, and food becomes necessary. *Allergy Asthma Clin Immunol.* 2019 Feb 19;15:9. doi: 10.1186/s13223-019-0327-4. PMID: 30820197; PMCID: PMC6381633.