

Clinical Communications

Allergic reactions to polyethoxylated castor oil derivatives: A guide to decipher confusing names on pharmaceutical labels

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Clinical Implications

- Castor oil derivatives are a rare cause of vehicle-induced hypersensitivity reactions, and various synonyms complicate a proper allergy workup. Here we provide an overview of the chemical structures, synonyms, and a list of the drugs containing Kolliphor RH 40 or Kolliphor EL.

TO THE EDITOR:

Anaphylaxis to a vehicle is rare, but a pitfall in the diagnosis of drug allergy as it can be present in various unrelated products. Clarity concerning the products containing the culprit vehicle is therefore pivotal. However, in the case of castor oil derivatives, many different or seemingly similar names are being used in medicinal, pharmaceutical, and cosmetic industry, complicating this advice for allergic patients.

We report on a 50-year-old man experiencing anaphylaxis on sequential intramuscular administration of vitamin B12 (Sterop, containing cyanocobalamin, sodium chloride, and water for injection) and vitamin A (Nepalm, containing sodium benzoate, retinol palmitate, alpha tocopherol, and polyethoxylated hydrogenated castor oil 40 or Kolliphor RH40). Within 5 minutes after injection of vitamin A, he developed diffuse urticaria and facial angioedema accompanied with malaise. His general practitioner did not dare to administer any treatment, in particular adrenalin, because the patient had a history of Wolff-Parkinson-White syndrome. Instead, he called an ambulance. By the time of arrival (estimated 15-20 minutes later), his vital signs were stable and symptoms resolved without further treatment 6 hours later. The patient had no history of allergic disease.

Allergy workup (detailed in Table E1, available in this article's Online Repository at www.jaci-inpractice.org) demonstrated a transiently elevated tryptase (11.6 µg/L 4 hours after the event vs 6.7 µg/L at baseline), negative specific IgE for latex, chlorhexidine, and *Ricinus* seed (ImmunoCAP, ThermoFisher Scientific, Uppsala, Sweden). Skin testing (ST) using sequential skin prick testing (SPT) and intradermal testing (IDT) was positive for vitamin A Nepalm (IDT 1/10,000 dilution), whereas skin and provocation testing for vitamin B12 Sterop was negative. Next, the vitamin A Nepalm components were tested separately rendering negative results for sodium benzoate (SPT), retinol palmitate, and alpha-tocopherol (SPT, IDT for multivitamin products Cernevit, Vitalipid). SPT for Kolliphor RH40 in Neoral soft capsules and Tegretol CR capsules was negative. However, IDT for Kolliphor EL in Neoral-Sandimmun was positive (1/10,000 dilution). Given

the clinical presentation, the transient tryptase increase, and positive ST for vitamin A Nepalm and Neoral-Sandimmun IV (containing polyethoxylated hydrogenated castor oil 40 and polyethoxylated castor oil 35, respectively), an allergy to all castor oil derivatives was concluded. Tolerance for vitamin A substitution without polyethoxylated hydrogenated castor oil 40 was demonstrated via provocation testing.

A pitfall for the allergy workup and patient advice in our case was the various synonyms used for castor oil derivatives in product leaflets, industry, and literature. To disentangle the heterogeneity in terminology for these derivatives, we provide an overview of the chemical structures and synonyms (Figure 1), and drugs containing these vehicles (summarized in Table I), followed by a concise overview of hypersensitivity reactions to these vehicles.

Castor oil is a vegetable oil extracted from the castor plant (*Ricinus communis*). It is a mixture of saturated and unsaturated fatty acid esters linked to glycerol. The main fatty acid is ricinoleic acid, which accounts for approximately 90% of the mixture.

To obtain macroglycerol hydroxystearate (Kolliphor RH40; BASF AG, Ludwigshafen, Germany, renamed from Cremophor RH40), hydrogenated castor oil is reacted with ethylene oxide (Figure 1) at a molar ratio of 1:40 (hence the synonym PEG-40 hydrogenated castor oil) yielding a mixture with variable composition with the major component identified as oxylated triglycerides of hydroxystearate. It is used as a nonionic solubilizer and emulsifier for vitamins, water insoluble active substances, and essential oils in water or mixtures of water and alcohol.^{1,8} In literature it is mostly referred to as Cremophor RH40. Similarly, macroglycerol ricinoleate (Kolliphor EL; BASF AG, formerly known as Cremophor EL) is created by combining (in this case unhydrogenated) castor oil with ethylene oxide at a molar ratio of 1:35 (hence the synonym PEG-35 castor oil), to yield a mixture with variable composition with the major component identified as oxylated triglycerides of ricinoleate (Figure 1).¹

Multiple hypersensitivity reactions have been ascribed to these castor oil derivatives (summarized in Table I), and several mechanisms have been proposed for the induction of anaphylaxis to this excipient, including (1) IgE-mediated hypersensitivity, (2) activation of the classical complement pathway, and (3) nonspecific histamine release by mast cells or basophils.³ The most reported culprit is the vehicle Kolliphor EL in intravenous (IV) paclitaxel⁸ or cyclosporine.³⁻⁶ To our knowledge, a hypersensitivity reaction to Kolliphor RH40 has only been reported once, in a patient with anaphylaxis due to cyclosporine soft capsules, tolerating parenteral Kolliphor EL in paclitaxel.⁷ Conversely, a case reported tolerance to orally administered cyclosporine (containing Kolliphor RH40) after a hypersensitivity reaction to the IV form (containing Kolliphor EL).⁴

Others reported hypersensitivity reactions to the IV administration of both Kolliphor EL and RH60 (in IV cyclosporine and tacrolimus, respectively), yet tolerating Kolliphor RH40 (in oral cyclosporine).^{5,6} This suggests different patterns of cross-reactivity between these chemically closely related molecules, and/or alludes in some patients to the importance of parenteral versus oral

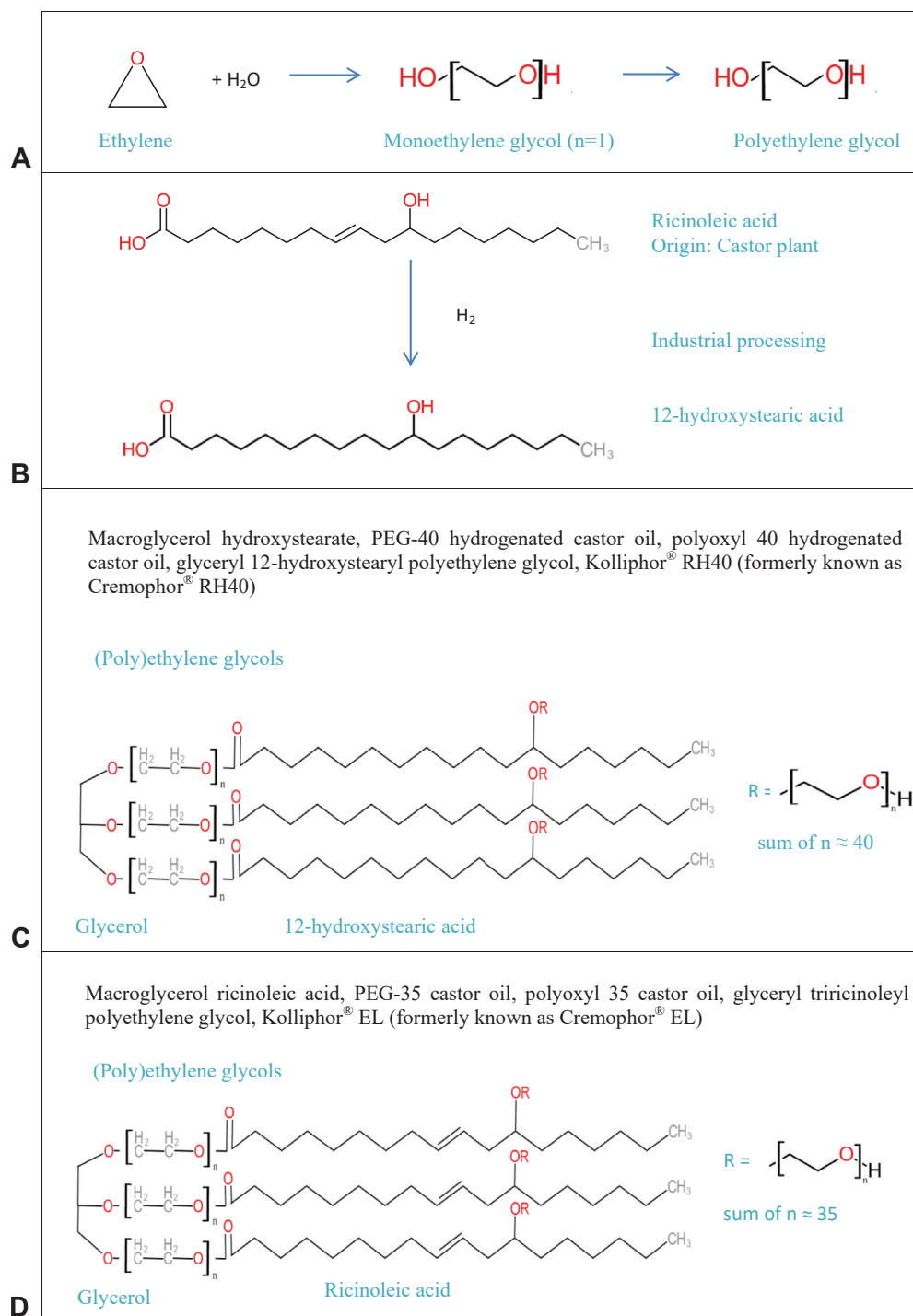


FIGURE 1. Chemical structure and generation of different polyethoxylated castor oil derivatives. **(A)** Polymerization of polyethylene glycols (PEG, details available in this article's Online Repository at www.jaci-inpractice.org), **(B)** hydrogenation of the unsaturated fatty acid transforms the liquid ricinoleic acid into a semisolid saturated 12-hydroxystearic acid, **(C)** Kolliphor RH40, and **(D)** Kolliphor EL.

administration for inducing a hypersensitivity reaction. In fact, oral tolerance might not necessarily infer parenteral tolerance as intestinal uptake is unknown and most likely also dependent on mucosal integrity. Note that of drugs containing Kolliphor RH40

(Table I), only vitamin A Nepalm is administered parentally, whereas most of the drugs containing Kolliphor EL are administered parentally, possibly also contributing to a larger number of reports of hypersensitivity reactions to Kolliphor EL.

TABLE I. List of drugs containing different types of polyethoxylated castor oil, either Kolliphor EL (syn: macroglycerol ricinoleate, polyoxyl 35 castor oil, PEG-35 castor oil) or Kolliphor RH40 (syn: macroglycerol hydroxystearate, polyoxyl 40 hydrogenated castor oil, PEG-40 hydrogenated castor oil)

Drug	Commercial name	Route	Vehicle molecule	Anaphylaxis reported
Paclitaxel	Taxol	IV	Kolliphor EL	Gelderblom et al ¹
Teniposide	Vumon	IV		
Valrubicin	Valstar	Intravesical instillation		
Ixabepilone	Ixemptra	IV		
Ritonavir	Norvir	PO (solution)		
Vitamin K	Phytonadione	IV		
Diazepam	Stesolid MR	IV		Hüttel et al ²
Alphadione	Althesin	IV		Hüttel et al ²
Cyclosporine	Sandimmun	IV		Ebo et al ³
				Moeinian et al ⁴
				Takamatsu et al ⁵
				Kang et al ⁶
	Neoral-Sandimmun	PO (capsule)	Kolliphor RH40	Kuiper et al ⁷
	Neoral-Sandimmun	PO (solution)		
Lopinavir and ritonavir	Kaletra	PO (solution)		
Carbamazepine	Tegretol	PO (prolonged release)		
Clomipramine	Anafranil	PO (sustained release)		
Vitamin A	Vitamin A Nepalm	IM		Our case

IM, Intramuscular; IV, intravenous; PO, peroral.

Of note, castor oil and its derivatives have a widespread topical use in products such as castor bean wax. Safety evaluation of these topical products did not show significant allergic potential, and a low irritative potential.⁹ Our patient did not report the use of cosmetics.

We concluded that the culprit of the anaphylaxis was Kolliphor RH40 because of the positive IDT for vitamin A Nepalm, with cross-reactivity to Kolliphor EL because of positive testing for Neoral-Sandimmun IV (containing Kolliphor EL). The negative SPT for medication containing Kolliphor RH40 can be ascribed to the low sensitivity of prick testing with tablet derived drugs. The negative IDT for Paclitaxel Fresenius IV (containing Kolliphor EL) remains unexplained. We can only speculate that the presence of these heterogeneous biologically derived products might differ in these drugs. Our patient was advised to abstain from any polyethoxylated castor oil derivatives although oral tolerance cannot be excluded. Drugs containing the Kolliphor RH40 or Kolliphor EL are listed in Table I. Together, these observations argue for a comprehensive allergy workup, including ST with multiple potential cross-reactive molecules and information on all possible naming.

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ONLINE REPOSITORY

ABOUT POLYETHYLENE GLYCOLS (PEGs) AND CASTOR OIL DERIVATIVES

The numerical value (*n*) used to name PEG refers to the average number of ethylene oxide units in the cosmetic industry and to the rounded average molecular weight (MW; g/mol) in the pharmaceutical industry. As the MW of 1 unit of ethylene oxide is approximately 44 Dalton, the same compound can be named for example PEG 3350 or PEG 75 depending on the product type in which it figures. Different chemical synonyms are given to PEG depending on molecular mass. Polyoxyethylene are polymers of any molecular mass, PEGs are oligomers and polymers with molecular masses below 20,000 g/mol, and polyethylene oxide when molecular mass is above 20,000 g/mol. These hydrophilic products are widely used in cosmetic industry as surfactants, emulsifiers, cleansing agents, and skin conditioners. In medicine, PEGs are usually denoted as macrogols and used as laxatives or as vehicles in oral or parenteral drugs, the latter for drugs with a depot administration for prolonged absorption.

Different names of the Kolliphor RH40 compound: the chemical and most descriptive name is polyoxyl 40 hydrogenated castor oil. In the cosmetic industry, it is known as PEG-40 hydrogenated castor oil, according to the International Nomenclature of Cosmetic Ingredients (INCI). The medical name most widely used is macroglycerol hydroxystearate. In literature, it is most commonly referred to by one of its commercial available names, namely Kolliphor RH40 (BASF AG, Ludwigshafen, Germany, formerly known as Cremophor RH40). Similarly, different names of the Kolliphor EL compound exist: the chemical and most descriptive name is polyoxyl 35 castor oil. In the cosmetic industry, it is known as PEG-35 castor oil, according to the INCI. The medical name most widely used is macroglycerol ricinoleate. In literature, it is most commonly referred to by one of its commercial available names, namely Kolliphor EL (BASF AG). Of note, translations of the product leaflets can lead to additional synonyms.

METHODS

The clinical history indicated that anaphylaxis occurred early after intramuscular vitamin A Nepalm administration, with a preceding injection of vitamin B12 Sterop (Table E1). Skin testing for vitamin A Nepalm was positive (intradermal testing

[IDT] 1/10,000), whereas being negative in 2 healthy controls. Testing for vitamin B12 Sterop was negative (skin prick test [SPT], IDT, subcutaneous provocation testing). Vitamin A Nepalm components (retinol palmitate 100,000 IU/2 mL, alpha tocopherol, polyethoxylated hydrogenated castor oil 40, sodium benzoate) were subsequently tested separately: retinol palmitate and alpha tocopherol present in Cernevit (containing retinol palmitate 3500 IU/5 mL, alpha-tocopherol 10.2 mg/5 mL, cholecalciferol ascorbic acid, cocarboxylase, riboflavin, pyridoxine, cyanocobalamin, folic acid, dexpantenol, biotin, nicotinamide) and Vitalipid (containing retinol palmitate 3300 IU/10 mL, alpha-tocopherol 9.1 mg/10 mL, ergocalciferol, phytomenadione); sodium benzoate as an ingredient; and Kolliphor RH40 via testing with Neoral soft capsules and Tegretol CR capsules. Kolliphor EL was tested via Neoral-Sandimmun and Paclitaxel. To provide an alternative for supplementation of vitamin A, retinyl acetate (magistral preparation consisting of retinyl acetate, lactose monohydrate) was tested via oral provocation (successive doses of 10, 100, 1000, 10,000 IU/capsule were administered orally every 30 minutes with 1 hour of observation after the last dose—negative result in our case). Vitamin D3 Streuli was tested (SPT only, reintroduction at home) because the patient and his general practitioner initially refused to readminister this drug.

SPT were read after 15 minutes, IDT after 20 minutes in the presence of a positive (histamine 10 mg/mL, SPT only) and negative control (saline; SPT, IDT). SPT were considered positive if a wheal of 3 mm or more occurred with accompanying flare/erythema; IDT were considered positive if wheal expansion occurred rendering an increase in diameter of 3 mm or more with accompanying flare/erythema. Drugs were diluted in saline. Capsules were crushed and resuspended in saline for SPT. Basophil activation testing was performed for vitamin A Nepalm and Paclitaxel Frenius Kabi. Flow cytometric analysis (using LSR Fortessa; BD Biosciences, San Jose, Calif) of activated basophils was performed using cells stained with phycoerythrin-conjugated anti-CD123, fluorescein isothiocyanate-conjugated anti-CD63, and Alexa Fluor 647-conjugated HLA-DR antibodies (all purchased from BioLegend, San Diego, Calif). The test included a negative control (using basophil activation buffer) and positive control using antihuman IgE (BD, PhargMingen, San Diego, Calif) and FMLP (Orpagen, Heidelberg, Germany) and was performed on basophils from the patient and a healthy control. Both drugs tested negative. Immunoblotting, dot blotting, was not performed.

TABLE E1. Overview of the allergy workup

Product name	SPT (max conc)	IDT (dilution, max conc)	BAT	Provocation test (cumulative dose)
Vitamin A Nepalm: Retinol palmitate 100,000 IU/2 mL (Excipient: Kolliphor RH40, concentration not specified)	– (undiluted)	+, 3 mm (1/10,000)	–	NP
Retinyl acetate: 10.000 IU/capsule (magistral preparation)	– (undiluted)	NP	NP	– (11,110 IU PO)
Cernevit: Multivitamin product containing retinol palmitate 3500 IU/5 mL	– (undiluted)	– (1/10)	NP	NP
Vitalipid: Multivitamin product containing retinol palmitate 3300 IU/10 mL	– (undiluted)	– (1/10)	NP	NP
Sodium benzoate (Fagron)	– (undiluted)	NP	NP	NP
Neoral soft capsules: 25 mg (Excipient: Kolliphor RH40 40.5 mg/capsule)	–, 2 mm (undiluted)	NP	NP	NP
Tegretol CR capsules: 400 mg (Excipient: Kolliphor RH 40, concentration not specified)	– (undiluted)	NP	NP	NP
Neoral-Sandimmun IV: 250 mg/5 mL (Excipient: Kolliphor EL, 650 mg/mL)	– (undiluted)	+, 4 mm (1/10,000; 0.065 mg/mL Kolliphor EL)	NP	NP
Paclitaxel Frenius Kabi: 30 mg/5 mL (Excipient: Kolliphor EL, 530 mg/mL)	– (undiluted)	– (1/600; 0.6 mg/mL Kolliphor EL)	–	NP
Ricinus oil (Fagron)	– (undiluted)	NP	NP	NP
PEG 400 (Fagron)	– (undiluted)	NP	NP	NP
Vitamin B12 Sterop: 1 mg/1 mL	– (undiluted)	– (undiluted)	NP	– (1 mL SC)
Vitamin D3 Streuli	– (undiluted)	NP	NP	NP
Chlorhexidine digluconate 2%	– (undiluted)	– (1/10,000; 0.002 mg/mL)	NP	NP
Latex (960 SQ, Alk)	– (undiluted)	NP	NP	NP

BAT, Basophil activation test; IDT, intradermal test; NP, not performed; PO, peroral; SC, subcutaneous; SPT, skin prick test.

–, negative; +, positive (the wheal diameter [in case of SPT] or wheal expansion (expressed as an increase in diameter of the initial induration [in case of IDT]) is indicated; all positive tests were accompanied with a flare reaction).