

# A Refractory Fixed Drug Reaction to a Dye Used in an Oral Contraceptive

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*A young woman presented with a classic fixed drug eruption (FDE) after taking the inactive green pills of her oral contraceptives (OCs). The patient's history was unique in that the FDE did not occur every time she took the inactive pills but was refractory, occurring every third month within hours after she took the green pills. After discontinuing the green pills but continuing the active oral contraceptive pills, the patient has not experienced a recurrence of the rash in more than 2 years. This case report reviews the unusual phenomenon of refractory periods in FDEs and highlights the importance of understanding this phenomenon in the diagnosis of drug eruptions.*

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## Case Report

A 23-year-old white woman presented with a 2-year history of a recurrent facial rash that began one month after starting oral contraceptives (OCs). The rash recurred approximately every third month, with itching and burning developing in the same areas of the face within hours after the patient took the first inactive green pill. Over time, dusky brown maculae developed in a perioral and periocular distribution (Figure). Biopsy findings confirmed an eosinophil-containing lichenoid

infiltrate consistent with a fixed drug eruption (FDE). The inactive green pills were thought to be responsible for this classic FDE. The patient was instructed to continue taking her active pills but to discontinue the inactive green pills. She has remained free of recurrence for more than 2 years and continues to take OCs. Rechallenge was considered but not attempted.

## Comment

FDEs account for approximately 16% of cutaneous drug reactions, usually presenting as dusky brown oval patches that recur in the same location. An acute inflammatory phase develops within hours of drug exposure; in its extreme form, the inflammation can result in blistering. The inflammatory phase is followed by postinflammatory hyperpigmentation resulting in the classic brown discoloration.<sup>1</sup>

This case highlights the occurrence of an unusual refractory period that can be associated with FDEs. During the refractory period, exposure to the offending agent does not result in the drug eruption, but subsequent exposures may cause a reaction.<sup>2,3</sup> The refractory period may last weeks to months,<sup>4</sup> and the phenomenon has been reported with exposure to phenolphthalein, arsenicals, and antipyrene.<sup>5</sup> Chargin and Leifer<sup>5</sup> discuss 2 types of refractory period (also called *tissue exhaustion*): one type is a temporary loss of sensitivity to a single member of a drug class, and the other is a temporary loss of sensitivity to all members of a group. The authors also suggest that some cases of this apparent refractory period are actually due to an inadequate dose of the offending drug; that is, an FDE occurs with higher doses, whereas there is no reaction to the drug at a lower dose. Awareness of this refractory period can greatly improve diagnosis and treatment of FDEs.

The inactive green pills of Ortho Tri-Cyclen<sup>®</sup> contain the dyes FD&C Blue No. 2 and D&C Yellow No. 10.<sup>6</sup> The active hormone white pills contain no dye, and the blue active pills contain the dye FD&C Blue No. 2. All pills, both active hormone

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Periocular fixed drug reaction due to dye in an inactive pill of an oral contraceptive.

and inactive, contain the inert ingredients lactose, magnesium stearate, cellulose, and starch. The only ingredient unique to the green pills is the dye D&C Yellow No. 10<sup>6</sup>; this finding strongly implicates the dye as the etiologic agent in this FDE. D&C Yellow No. 10 is frequently used in the United States as a drug additive<sup>4</sup> and is contained in common over-the-counter medications such as yellow-coated acetaminophen and Benadryl<sup>®</sup> capsules. Allergy to several yellow dyes has previously been reported but not allergy to D&C Yellow No. 10.<sup>7,8</sup> To our knowledge, this is the first reported case of an FDE due to D&C Yellow No. 10.

OCs are responsible for many different types of cutaneous drug reactions including melasma, acne, erythema nodosum, erythema multiforme, alopecia, and lupus erythematosus.<sup>9</sup> Although many references list OCs as a common cause of FDEs, reports in the literature are rare.<sup>10</sup> To our knowledge, there have been no recent reports in the English literature of a dye in an inactive OC pill dye causing an FDE. Understanding that a cutaneous drug reaction may be due to a drug additive and not to an active drug can help in identifying cause and effect relationships in cutaneous drug eruptions.

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