Adverse Drug Reactions of the Lower Extremities

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KEYWORDS

• Drug • Pigmentation • Edema • Hand-foot-syndrome • Paronychia
• Onychomadesis • Nail

KEY POINTS

- Adverse drug reactions (ADRs) are a common dermatologic problem, and may involve any area of the skin, skin appendages, and mucosa.
- There are several ADRs that specifically affect the lower extremities.
- The nail apparatus is particularly vulnerable to toxicity from medications. Depending on the part of the nail apparatus affected, different clinical findings are observed.
- Although venous hypertension and subsequent pooling of interstitial fluid caused by venous valve incompetence is the most common cause of lower extremity edema, several medications can induce this condition, and should be considered in any patient with new-onset lower extremity edema.
- Chemotherapy agents cause several problems in the skin of the lower extremities and the nails. Recognizing and managing these ADRs is important because they can impede patients' ability to perform activities of daily living and to ambulate.

Adverse drug reactions (ADRs) are a common cause of dermatologic consultation, involving 2 to 3 per 100 medical inpatients in the United States. Female patients are 1.3 to 1.5 times more likely to develop ADRs, except in children less than 3 years of age, among whom boys are more often affected.[1] Certain drugs are more frequent causes, including aminopenicillins, trimethoprim-sulfamethoxazole, and nonsteroidal antiinflammatory drugs (NSAIDs).[2] ADRs can involve any area of the skin; the appendages, including hair and nails; as well as mucosa.

In addition, certain hypersensitivity syndromes to medications characteristically occur in conjunction with either active or latent infection with human herpes virus (HHV)–6, HHV-7, Epstein-Barr virus, cytomegalovirus, and human immunodeficiency virus. HLA type may also increase an individual's risk for ADRs to certain medications. T cells, specifically T-helper 1 (Th1) cells, are the primary inducers of ADRs. Systemic viral infections are thought to have already activated the T cells in the skin, theoretically lowering their threshold for drug binding and thereby increasing the risk of ADRs.[3]

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A skin appendage of the lower extremity that is particularly vulnerable to drug-induced changes is the nail apparatus. In general, nail abnormalities caused by medications can present with a wide range of clinical manifestations. These abnormalities tend to be dose related, and resolve with withdrawal of the offending agent. Many nail changes are asymptomatic and are more of a cosmetic nuisance, whereas others cause intense pain and impair activities of daily living and ambulation[4] (**Fig. 1**, **Table 1**).

ADVERSE DRUG REACTIONS TO TOPICAL MEDICATIONS

With regard to the ADRs of the lower extremity, the initial evaluation should include a thorough work-up of common skin eruptions of this region, such as allergic contact dermatitis and stasis dermatitis, followed by the standard evaluation for an ADR. Topical drug contact dermatitis is common in this area of the body because of the frequent nature of application of various topical medications to manage chronic conditions such as stasis dermatitis and ulcerations, among other problems that are specific to the lower extremity.

Certain medications, such as topical antihistamines, most notably topical doxepin, sensitize more often when applied topically compared with when they are administered orally. Transdermal patches have become a more common route for medication delivery, and reports of sensitization have increased with nitroglycerin, hormones, nicotine, clonidine, lidocaine, scopolamine, and fentanyl delivered in this manner. Of the medications given via transdermal patches, clonidine induces the highest rate of allergic reactions.[5]

Patients with chronic leg ulcers are at much higher risk of developing contact dermatitis to various topical antibiotics, most notably neomycin and bacitracin. The clinical presentation of neomycin sensitivity of the lower extremity can be varied because chronic cutaneous changes have often developed. Early signs are pruritic, eczematous plaques but, with prolonged use, lichenified or hyperkeratotic papules and plaques may evolve. Similar findings may be found between the toes when this medication is erroneously used to treat dermatophytosis.[6] Bacitracin sensitivity may present similarly; however, contact urticaria, and even anaphylaxis, are reported more often with bacitracin than with any other antibiotic. For this reason, overuse of these medications is discouraged.[7]

Dermatophytosis of the lower legs, feet, and nails is common, and reactions to topical antifungal agents may occur. Allergic contact dermatitis to imidazole, with a

Fig. 1. Onychomadesis.