CASE REPORT

Permanent skin hyperpigmented lesion as a consequence of drug allergy

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Abstract

Povidone solution for topical application is an antiseptic that used in the prevention of wound infection the reported side effects of topical application of povidone mainly was irritation. We report a case of oval hyperpigmented (brown) permanent lesion following topical application of povidone as treatment for an erythematous oval lesion around the umbilicus in a 6 year old boy.

Introduction

Allergic reactions to drugs are among the most common, diverse, and important forms of immunopathologic processes in modern clinical medicine [1]. Allergic reactions to drug occur in approximately 5 % of hospitalized patients and in substantial number of outpatients with diverse acute and chronic diseases [2]. In addition , the morbidity and mortality ensuring from these reactions, the inability to use drugs of choice can prolong illnesses and induce otherwise unnecessary morbidity and mortality. Fear of recurrent allergic reactions to drugs often leads to repeated avoidance of drugs of choice. Clearly, measures that avoid, minimize, or reverse allergic reactions to drugs can have a major impact on the success, efficiency and cost of patients care [3] .

Adverse cutaneous reactions to medications are a common reason for consultations with dermatologists. Drug-induced skin disorders may manifest in a variety of ways. Drugs may cause exanthemas, urticaria, hypersensitivity syndromes, pustular eruptions, erythema multiform, toxic epidermal necrolysis, cutaneous necrosis, and abnormal pigmentation of the skin and mucosa. Although pigmentary changes caused by drugs usually result in a limited degree of morbidity, these changes may be very disturbing to the patient. Drug-induced pigmentary abnormalities may be classified into 3 groups, which are (1) hyperpigmentation/melanosis, (2) hypopigmentation/leukoderma, and (3) dyspigmentation or occurrence of unusual skin color [4].

Drug-induced pigmentation represents 10 to 20% of all cases of acquired hyperpigmentation and this hypothesis must be systematically raised in unexplained pigmented lesions especially in elderly people. The main drugs implicated in causing skin pigmentation are nonsteroidal anti-inflammatory drugs, antimalarials, amiodarone, cytotoxic drugs, tetracyclines, heavy metals and psychotropic drugs [5]. Clinical features are very variable according to the triggering molecule, with a large range of patterns and shades which are sometimes more or less reminiscent of the culprit drug. Histological findings are

very variable as well but the colored particles are often concentrated within dermal macrophages which are sometimes localized in a distinctive fashion with respect to dermal structures such as vessels or adnexes. Treatment is often limited to sun-avoidance or interruption of treatment with the offending drug but laser therapy recently gave rise to hope of a cure in some cases. These measures are often followed by a fading of the lesions but the pigmentation may last for a long time or may even become permanent in a small percentage of patients [6].

The rate of drug-induced dyspigmentation varies depending on the drug and cumulative dose. Some drugs, such as amiodarone, have been reported to have a rate of blue-gray dyspigmentation as high as 24% when the cumulative dose is greater than 200 mg. Drug-induced skin pigmentation is estimated to account for 10-20% of all cases of acquired dyspigmentation worldwide. Drug-induced pigmentation is not generally associated with increased mortality or morbidity, although it may result in considerable psychological and social impairment. Drug-induced pigmentary changes can occur in persons of any race, but hypomelanosis is seen more frequently and appears more dramatically in patients with darker-pigmented skin. Additionally, people with darker skin often exhibit more intense hyperpigmentation than individuals with fair skin. No differences are reported in the prevalence of drug-related pigmentation among males versus females. Drug-related dyspigmentation is seen in persons of all ages [7].

Povidone is an iodine compound that is used as skin disinfectant [8]. The product labeled that it may cause skin irritation [8]. However, it was reported that topical application of povidone as skin disinfectant cause allergic contact dermatitis [6-13] , generalized dermatitis with eosinophilia [14], chemical burns [15], Occupational allergic contact dermatitis [16] and sometimes the irritant contact dermatitis from exposure to povidone-iodine may resemble toxic epidermal necrolysis [17]**.** An evaluation of the irritancy potential of povidone iodine solutions as a comparison of subjective and objective assessment techniques [18] . A double-blind study has been carried out in 12 normal volunteer subjects in order to determine the relative irritancy of povidone-iodine solutions. Aqueous solutions of povidone-iodine (PI), standardized 10%, povidone-iodine (SPI) and reformulated standardized 10%, povidone-iodine (RSPI) were applied to the backs and occluded using aluminum chambers. At 1, 2, 3, 4, 5, 6, and 8 hours, chambers were removed and the degree of cutaneous irritancy assessed. As well as subjective assessment of erythema, objective measurement of skin color was performed using an erythema meter. In addition, laser Doppler blood-flow measurements have been carried out. The results show a rapid increase in cutaneous irritancy as evidenced by an increase in visual scores of erythema, increased erythema meter readings and increased cutaneous blood-How. The increase was greatest for SPI treated sites for all three methods. Statistically these differences were significant at $P<0{\cdot}05$. Thus in this controlled study it has been possible to discriminate between the similar formulations in terms of their cutaneous irritancy.

Case Report

About 4 year old boy presented to private clinic of general surgeon specialist with an erythematous oval lesion around the umbilicus stump and fever. All the investigations performed were normal, and FNA from umbilicus lesion indicated an inflammatory reaction only. The surgeon started treatment with systemic antibiotic and the case resolved spontaneously. After two months he developed the same complaints, and his family consulted another general surgeon and the case was treated as infection of soft tissue. He gave the child metronidazole suspension, systemic antibiotics and topical povidone. The fever resolved and there is no local tenderness in the soft tissue at the lesion site. However, there is a brown coloration of the skin lesion and do not disappeared to date (2 year duration).

The child was presented to my clinic complaining of non painful brown oval lesion around the umbilicus [Fig.1].The lesion was oval , macular , with regular margin, and of 8 X 5 cm in size. No other lesion in any part of the child skin the lesion was soft, non tender, not fixed, not indurated, and non elevated from surrounding tissue. All the investigations that include platelets count, WBC total and differential, Hb, ESR, and Abdominal ultra sound do not reveal any abnormality. Skin biopsy not performed and povidone reapplication is not performed because the patient family refused to do them.

Discussion

Drug induced rashes are the commonest side effect of many drugs. In general, the mechanisms are unknown and only 10% of such reactions results from true allergic mechanisms [19]. Immune responses to drug determinants occur in only small percentages of exposed patients, and clinical expression of drug allergy occurs in only a fraction of the responding patients [7]. Several factors have been identified that influence the expression of immune responses and clinical reactions to drugs [7]. Sustained immune responses to drugs are more likely in adults with specific HLA phenotypes and drug metabolism propensities; more likely when the drug or drug metabolites are highly reactive with proteins;; more likely with high doses and long durations of exposure; and more likely after topical rather than oral therapy [5,7].The purity and chemical state of a drug can influence the likelihood of a response [7,20]. Responses to different classes of drugs appear to be influenced by different degrees by these factors.

It seems that this case is a permanent hyperpigmented lesion due to topical application of povidone. The mechanisms by which the antiseptic produce this lesion are unknown. However, clinical expression of drug allergy appears to be influenced by genetic factors including atopy, concurrent medical therapy, concurrent medical illnesses, persistence of immune response, chemical reactivity of the drug in question, the purity and chemical state of the drug, as well as the dose, route and duration of therapy [5,7]. This case may be started as irritant contact dermatitis that results from povidone application which chemically

damages the skin. The drug applied to the affected skin 2-3 times daily and thus may act as cumulative irritant even it is with mild irritation to the skin. This reaction could be influenced by its association with other dermatoses such as atopic dermatitis, but this was not proven since the child family refused to perform skin test.

Another mechanism may be proposed to explain the development of the hyperpigmented lesion in this child case that is allergic contact dermatitis. Povidone may induce allergic contact dermatitis following topical application as reported before [15-20]. Multiple pathologic mechanisms are responsible for drug-induced pigmentation disorders. Compared with the immunological etiology underlying many drug allergies, most cases of pharmacologic pigmentation are not immunologically mediated.

The pathogenesis underlying drug-related dyspigmentation can also be categorized into 3 mechanisms, which are (1) drug or drug metabolite deposition in the dermis and epidermis, (2) enhanced melanin production with or without an increase in the number of active melanocytes, and (3) drug-induced postinflammatory changes to skin. Similarly, chemical hypopigmentation is also thought to occur through a variety of pathologic mechanisms, including a reduced number of skin melanocytes, enzymatic blockade of melanogenesis, and inhibition of melanosome transfer [21].

The pathogenesis of drug-induced pigmentation is variable according to the causative medication and can involve an accumulation of melanin, sometimes following a nonspecific cutaneous inflammation and often worsened by sun exposure, an accumulation of the triggering drug itself, a synthesis of special pigments under the direct influence of the drug or deposits of iron following damage to the dermal vessels. ICD because these agents may lead to epidermal atrophy, increasing skin fragility, and the influence of sun exposure is usually obvious in most cases, either by sun-induced melanin synthesis stimulation with formation of complexes between melanin and the causative drug or by transformation of the drug in visible particles usually taken up by dermal macrophages under the influence of sunlight [21].

In ICD the epidermal damage occurs because of a direct effect of the toxic agent on keratinocytes [22]. The irritant substances are thought to result in epidermal damage by denaturing keratin proteins, removing lipid compounds, and directly interacting with cell membranes [23]. There is no immunologically mediated component to ICD, although individuals with atopic dermatitis are more likely to develop ICD when exposed to an irritant [24]. Commonly implicated irritants include corrosive materials, alkalis, acids, organic solvents, detergents, and disinfectants. Different irritant compounds can produce different clinical manifestations, ranging from erythema to erosions, blistering, and overt necrosis. Even the histopathology of ICD can vary by the cause, with some irritants demonstrating unique characteristic findings on tissue biopsy [22]. For example, exposure to the irritant dithranol typically leads to balloon degeneration of the upper dermis while sodium lauryl sulfate characteristically causes parakeratosis and intracytoplasmic vesiculation [22].

Povidone-iodine solution, commercially available as Betadine® Microbicide, is a relatively uncommon but recognized cause of ICD [24-26]. The 10-percent solution, a commonly used surgical antiseptic, contains povidone

(polyvinylpyrrolidone) and 1 percent available iodine. The solution has microbicidal activity against a broad spectrum of organisms, including bacteria, viruses, and fungi [27]. Its microbicidal effect is achieved minutes after application as the iodide ion interacts with the microbial cell membrane [27]. Reported cases of ICD caused by povidone-iodine solution have appeared within 2 days of exposure and have manifested as erythematous bullae, erosions, and eventual necrosis in a clearly marginated distribution corresponding to the areas of exposure to the solution [24-26]. Many of the lesions of ICD attributed to povidone-iodine solution have been described as chemical burns.

The reported skin findings of ICD from povidone-iodine solution resemble those of TEN both clinically and histopathologically. Like severe ICD, Toxic Epidermal necrolysis TEN typically begins as a painful burning sensation followed by an erythematous and edematous eruption. Large sections of the epidermis then slough in sheets, accompanied by full thickness epidermal necrosis [28]. Irritant contact dermatitis may resemble TEN on tissue biopsy as well. Microscopically, TEN typically shows complete necrosis of the epidermis with subepidermal blisters, a sparse mononuclear infiltrate, basalar vacuolization, and mild spongiosis [29].

Although TEN and severe ICD share many clinical and histopathological findings, distinguishing between the two entities may be possible by careful history and physical examination. A history of exposure to a known irritant, with symptoms appearing within hours to days of exposure, suggests the diagnosis of ICD [27]. A historical link between an immunocompromised state and skin sensitivity to povidone-iodine solution has also been proposed [30]. Unlike ICD, most cases of TEN are associated with reaction to a medication. Symptoms begin on average 2 weeks after exposure to the offending agent. Commonly implicated drugs include sulfonamides, anticonvulsants, non-steroidal anti-inflammatory drugs, and allopurinol [28]. On physical examination, ICD may appear as erythematous, fissured, and blistered, with a glazed or scalded skin. The diagnosis of ICD is strongly supported when lesional skin is restricted to geometric distributions suggestive of an exogenous, rather than endogenous, cause. In this case, the clue to diagnosis is the linear streaking pattern from the running solution. These types of patterns will often identify that there is an external cause. Evidence of gravitational influence on the distribution of lesional skin, such as confinement to dependent areas or restriction to skin folds, is also strongly supportive of the diagnosis of ICD [27]. Unless the mucous membranes were exposed to the irritant compound, they will not be involved in ICD

Conversely, mucous membranes are almost invariably involved in TEN [28]. The lesional skin of TEN does not typically demonstrate a clearly marginated geographic distribution. As in any case of contact dermatitis, patients with ICD should avoid exposure to the offending agent. Barrier creams, such as those containing 5-percent perfluoropolyether or dimethicone lotion, may be effective in preventing or abating ICD, should the patient come in contact with the irritant compound in the future [31]. The mainstay of treatment for ICD is irritant withdrawal and avoidance and topical application of lipid rich moisturizers. Topical corticosteroids should be used cautiously in patients with vulnerability to additional irritation [32]. We think that inflammation that occurred around the umbilicus; lead to production of certain substances, consequently these substances may react with povidone and induce this permenant Hyperpigmentation of the skin.

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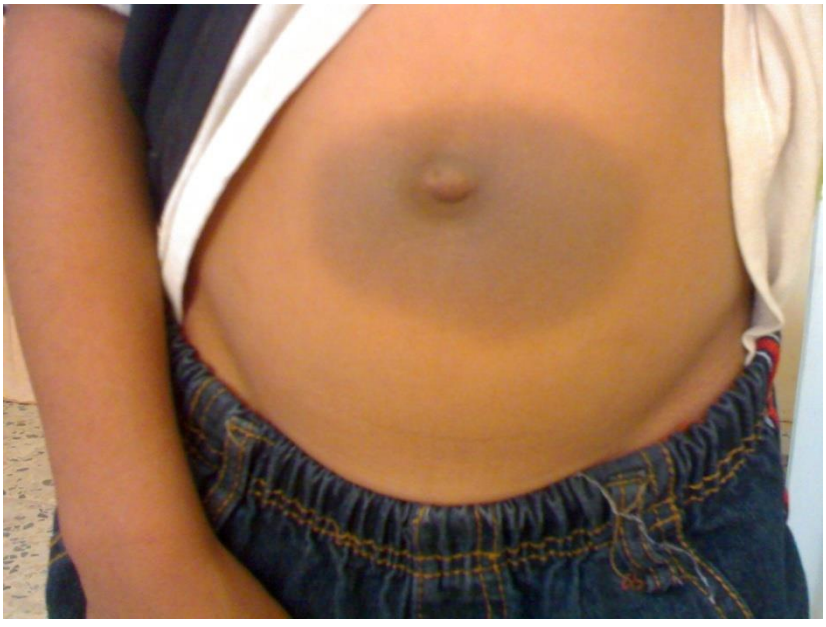

Fig.1. The permenant pigmentary lesion in a child following application of topical povidone.