Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 5, 2021, Pages. 6024 - 6026
Received 15 April 2021; Accepted 05 May 2021.

Generalized Bullae – A Common Drug with an Alarming Side Effect!

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Abstract:
Paracetamol is one of the most popularly used antipyretics, analgesics by physicians all over the world. However, a drug free from side effects is seldom seen. Cutaneous manifestation forms the most common spectrum of adverse drug reactions. Here we report an 8-year-old boy presenting with a bullous fixed drug reaction following oral paracetamol.

Keyword: Fixed Drug Eruptions, Paracetamol, Pediatrics, Bullous lesion

Key message: Fixed drug eruption is a daunting experience to practicing physician and hence care should be taken while prescribing any drug bearing in mind the probability of cutaneous drug eruption in sensitive individuals.

Consent for publications: Child`s parents has consented to the submission of case report to the journal.

Introduction:

Fixed drug eruption(FDE) is a type IV hypersensitivity reaction and a common dermatological problem in children with a prevalence of 9-22%.[1] Brocq described FDE as sharply demarcated, circumscribed round or oval dermatitis that characteristically recurs in the same site each time a particular offending drug is administered. Its diagnostic hallmark is recurrence at the site as previously affected with the spontaneous resolution once the offending drug is eliminated and recurs in the same location when a similar drug is re-administered[1]. The literature reviewed that FDE to paracetamol is a rare entity, and approximately only 21 cases are published.[2] Bullous type FDE to paracetamol is extremely rare; only three such incidents occurred in children;[3,4,5]; hence we report it.

Case report:

8year old boy presented with fever, cough, and vomiting for five days for which he took Syrup. Paracetamol and cough syrups (dextromethorphan, phenylephrine &chlorpheneramine) prescribed by a private practitioner. After four hours of consuming medication, he developed raised erythematous violaceous lesion over the upper lip, chin, progressing to fingers and legs. As symptoms did not respond, another practitioner reviewed him and prescribed Mefenamic acid and Hydroxyzine, sixty minutes after drug intake his previously localized lesions worsened, and he developed a painful bullous erythematous lesion in upper lip and chin (Fig.1a&1b), an oval circumscribed bullous lesion in the dorsum of the left index finger and right leg (Fig.1c&1d), a circular well-circumscribed bullous lesion in the right second web space (Fig.1c), and a raised erythematous ovoid lesion with the lilac-colored border localized

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to both knee (Fig.1d). To date, he had four similar episodes dating in the past nine months following the paracetamol consumption. After analyzing the drug composition for standard components, the regularly encountered inciting agent was paracetamol in all of the previous episodes. Blood investigations revealed mild leucopenia with normal hemoglobin and platelet count. Infective etiologies causing cutaneous eruptions like scrub typhus, dengue, and UTI ruled out. We achieved fever control with tepid sponging and low dose steroids. A patch test and skin biopsy were not performed in our case as parents did not consent for the procedure. The lesion had resolved spontaneously on withdrawal of paracetamol, and a complete resolution was noted on follow up after four weeks.

Discussion:

Paracetamol (acetaminophen) has a consistent safety profile and low incidence of side effects; hence widely used analgesic- antipyretic drug in the pediatric population. Acetaminophen is the second most common drug leading to FDE in children.[6] The skin eruptions caused by acetaminophen are usually a non-bullous type of FDE. Bullous types of FDE are rare and require differentiation from other blistering skin lesions such as Stevens-Johnson syndrome, Toxic epidermal necrolysis. FDE's pathogenesis is still unclear though various mechanisms have been proposed; including localized delayed hypersensitivity, local enzyme deficiency, and reaginic hypersensitivity. The offending drug may act as hapten binds to the circulating protein component or on the dermis's receptor cells. The drug-protein complexes are presented to Langerhans cells in the dermis resulting in CD8+ T cell stimulation mediating the localized epidermal lesion characteristic of FDE.[7] There is a cross intolerance between acetaminophen and other non-steroidal inflammatory analgesics (NSAIDS) due to their similar action: delayed hypersensitivity reaction (T-cell mediated) and Cyclo-oxygenase-I (COX) inhibition. The cross intolerance explains the flare-up of the bullous lesion after Mefenamic acid intake in our child.[8] FDE can occur on any part of the skin and mucous membranes, including the transitional epithelium of mucocutaneous junction.[7]

The usual site of occurrence of FDE is the face, glans penis, neck, and sacral region. A total of 7 types of FDE, including classical FDE, generalized, bullous, extensive bilateral symmetrical, pulsating, wandering, and non- pigmented type, are reported in the literature. The FDE lesion resolves most of the time, spontaneously. A hyper-pigmented patch persists over months to years, but in the non-pigmented type of FDE, resolution occurs without hyperpigmentation.[2] Oral re-challenge test(provocative test) is the Gold standard for diagnosis of FDE.[1] Patch test, and skin biopsy was not performed in our case as parents had not consented. In our case, the child had a previous similar episode with paracetamol intake and there was spontaneous resolution of the lesion on withdrawal of the drug. There was no other attributable cause, and as per the WHO-UMC Causality index[9], paracetamol certainly resulted in bullous FDE. Initial management is the avoidance of suspected drugs and treatment with topical /oral steroids. In the case of cross intolerance to paracetamol and NSAIDS, management is difficult as it requires complete avoidance of all NSAIDs. In such patients, fever control with the NSAIDs are after desensitization of the offending drug or other alternative therapy with sub-threshold or low dose paracetamol; or Selective Cyclo-oxygenase II inhibitor (celecoxib).[8] Prevention of similar FDE in the future is by patient awareness, possess an allergy passport (alert card) at all times,

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predominantly followed in the western population can be adapted to avoid accidental exposure to the offending agents and maintain a list of alternative NSAIDs drugs.[10]

Conclusion:

FDE can be a frightening experience to both children and parents though not fatal. Hence practitioners should keep in mind FDE as one of the differential in cutaneous eruptions and care should be taken while prescribing antihistamine, cough syrup or even paracetamol in susceptible individuals.

Figure Caption:

Fig.1a&b a painful bullous erythematous skin lesion in upper lip and chin measuring about 0.8mm in diameter **Fig.1c** an oval shaped circumscribed bullous lesion measuring 2x3cm located in the dorsum of the left index finger, a circular well circumscribed bullous lesion measuring less than 0.5cm located in the right second web space **Fig.1d** a raised erythematous ovoid lesion with lilac colored border was localized to both knee and an oval well circumscribed bullous lesion located on right leg lateral aspect 15 cm away from lateral tubercle

Acknowledgement: We would like to thank the staffs of Community Medicine department for spending their valuable time and for their co-operation in completing the study.

Funding for the study: Nil

Conflict of interest: Nil

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Received 15 April 2021; Accepted 05 May 2021.

ENDA/EAACI Drug Allergy Interest Group Position Paper. Allergy Eur J Allergy Clin Immunol. 2016 Nov 1;71(11):1533–9.