

# Analgin Induced Fixed Drug Bullous Eruption – A Case Report

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## BACKGROUND

Cutaneous drug eruptions are one of the most common types of adverse reaction to drug therapy, with an overall incidence rate of 2–3% in hospitalized patients. The prevalence of drug eruptions has been reported to range from 2-5% for inpatients and greater than 1% for outpatients.<sup>1</sup> Fixed drug eruptions (FDE) may account for as much as 16-21% of all cutaneous drug eruptions. Most studies report fixed drug eruptions to be the second or third most common skin manifestation of adverse drug events.<sup>2</sup> The actual frequency may be higher than current estimates, owing to the availability of a variety of over-the-counter medications and nutritional supplements that are known to elicit fixed drug eruptions. Certain classes of drugs with cross-reactions within a class have been reported to elicit a fixed drug eruption with quinolones<sup>3</sup> and with non-steroidal anti-inflammatory agents.<sup>4</sup> The most common cause of FDE is trimethoprim-sulfamethoxazole followed by analgin.<sup>5</sup>

The major categories of causative agents of fixed drug eruptions include antibiotics, antiepileptics, non-steroidal anti-inflammatory agents, and phenothiazines, although numerous other agents and certain foods such as cashews and licorice have also been reported as causative agents. Ingestion of the causative agent may occur via any route, including oral, rectal, or intravenous.<sup>6</sup> Although most drug-related skin eruptions are not serious, some are severe and potentially life threatening. Serious reactions include angio-oedema, erythroderma, Stevens–Johnson syndrome and toxic epidermal necrolysis. Healthcare professionals should carefully evaluate all drug-associated rashes. It is important that skin reactions are identified and documented in the patient record so that their recurrence can be avoided.

## FIXED DRUG ERUPTION

The term fixed drug eruption describes the development of one or more annular or oval erythematous patches as a result of systemic exposure to a drug; these reactions normally resolve with hyperpigmentation and may recur at the same site with re-exposure to the drug. The most common clinical manifestation is the pigmented fixed drug eruption, which usually manifests as round or oval, sharply demarcated erythematous/edematous plaques located on the lip, hip, sacrum, or genitalia.<sup>7</sup> Local symptoms may include pruritus, burning, and pain.<sup>8</sup> Systemic symptoms are uncommon, but fever, malaise, nausea, diarrhea, abdominal cramps, anorexia, and dysuria have been reported.<sup>9,10</sup> The eruption can appear within a day to a few weeks of ingesting the causative drug and can occur on any part of the skin or mucous membranes. The site of the eruption is fixed, i.e. whenever the individual takes the causative drug the eruption occurs within hours at exactly the same site. The initial eruption is often solitary and frequently located on the lip or genitalia. Rarely, the eruption may be intraoral. With the initial fixed drug eruption attack, a delay of up to 2 weeks may occur from the initial exposure to the drug to the development of the skin lesion.<sup>11</sup>

Skin lesions develop over a period of hours but require days to become necrotic. Lesions may persist from days to weeks and then fade slowly to residual oval hyperpigmented patches. Subsequent re-exposure to the medication results in a reactivation of the site, with inflammation occurring within 30 minutes to 16 hours.<sup>9</sup> The reactivation of old lesions also may be associated with the development of new lesions at other sites.

## ANALGIN

Analgin or metamizole sodium is a pyrazolone derivative used as analgesic antipyretic, spasmolytic agent. Indicated for severe or resistant pain & fever. The drug is banned in several countries across the world, including the US, France, Armenia, Morocco, Syria, Yemen, Zimbabwe, Lithuania, Nigeria, Serbia, the Philippines, Nepal, Vietnam, Canada, Australia, New Zealand, Japan and Iran. It says that analgin

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crosses the placenta and should not be used during pregnancy. Similarly women, who are breast feeding, must not use the drug. Analgin was found in 1920s in Germany. Presently, it has been discontinued in most parts of the world. So it makes no sense for India to continue using it. Since 1920, several painkillers have come which are less dangerous and more effective. Analgin, virtually sold as over the counter (OTC) drug without prescription, isn't part of the National List of Essential Medicines (NLEM).

Analgin remained in the market worldwide until the 1970s, when it was found that it carries risk of causing severe fall of white cells (agranulocytosis), which is a potentially fatal condition. The drug is approved in India for "severe pain or pain due to tumor and also for bringing down the temperature in refractory cases when other anti-pyretics fail to do so." However, the parliamentary standing committee on health has found that the product insert of Baralgin-M and Novalgin - the two top selling brands of Analgin - recommend its use in "severe or resistant pain and fever" but the words "when other anti-pyretics fail to do so" have been omitted, thus leading to over promotion. There are number of alternative analgesics, antipyretics available in the Indian market. "With so many countries banning Analgin, not to mention unlawful over promotion by manufacturers, the CDSCO should be directed to re-examine the rationality of continued marketing of Analgin,"

Adverse reaction to analgin is anaphylactic reaction which in very rare cases may be severe and life threatening. Such reaction may develop immediately after administration of analgin or hours later, however the usual pattern is for them to occur within the first hour after administration. Typically anaphylactic reaction manifest themselves in cutaneous and mucosal symptoms such as itching burning, reddening, urticaria, swellings), dyspnoea and less frequently – gastrointestinal complaints. Milder reaction may progress to severe forms with generalized urticaria, severe angioedema, severe bronchospasm, cardiac arrhythmias, drop in blood pressure and circulatory shock. Fixed drug eruptions, rashes, stevens-Johnson syndrome, or lyell's syndrome in isolated cases.

### CASE REPORT

A 71 year old male patient presented to medicine out-patient Department, Baptist hospital, Bangalore with complaints of burning sensation & painful lesion on the body since 5 days after taking novalgin (Analgin) tablet from outside pharmacy at 9.00 pm after meals for body pain. 10 minutes after taking the medication patient developed itching sensation, pain over whole body, fever & tightness surrounding the bullous & rise in temperature. Patient was taken to a local hospital and Tab. Citirizine and Inj Ciprofloxacin was given. Patient had a

similar episode 20 days before after taking analgin tablet (novalgin). Patient was a known case of bronchial asthma and diabetes and was on tab glimepride & extended release metformin once daily.

Severe bullous eruptions present over lower legs, elbow & buttocks bilaterally symmetrical. Hyper pigmented with a surrounding ring of erythema. The lesions were glaringly absent from mucocutaneous areas like oral cavity, conjunctiva & perianal region. Nikosky's sign was positive. Clinically in both situations patient has no generalized or toxic features. He was ambulant. The lesions themselves were macular pigmentations bullous lesions with clear fluid filled within the bullous and resembled erythema multiforme.

The bullous eruptions were managed with tab. Prednisolone 50 mg 1-0-0 for 3 days, Tab. Hydroxyzine 25 mg HS for 3 days & Cap Omeprazole 20 mg. the patient was stable and erosions start healing, no new blisters developed & nikolsky sign was negative.

Fig: 1a



Fig: 1b



## DISCUSSION

A study conducted by David et al.<sup>12</sup> showed that fixed drug eruption (FDE) was the most common drug eruption. Although the exact mechanism is unknown, recent research suggests a cell-mediated process that initiates both the active and quiescent lesions. The process may involve an antibody-dependent, cell-mediated cytotoxic response.<sup>13</sup> CD8+ effector/memory T-cells play an important role in reactivation of lesions with re-exposure to the offending drug.<sup>14,15</sup> The offending drug is thought to function as a hapten that preferentially binds to basal keratinocytes, leading to an inflammatory response.<sup>16</sup> Through liberation of cytokines such as tumor necrosis factor-alpha, keratinocytes may locally up-regulate expression of the intercellular adhesion molecule-1 (ICAM1). The up-regulated ICAM1 has been shown to help T cells (CD4 and CD8) migrate to the site of an insult.<sup>8,9</sup> The newly arriving and residential CD8 cells likely perpetuate tissue damage by their production of the inflammatory cytokines interferon-gamma and tumor necrosis factor-alpha. CD8 cells isolated from active lesions have also been shown to express alpha E beta 7, a ligand for E-cadherin, which may further contribute to the lymphocyte's ability to localize to the epidermis. Other cell surface molecules, such as CLA/alpha4beta1/CD4a, that bind E-selectin/vascular cellular adhesion molecule-2/ICAM1 help to further attract CD8 cells to the area. Changes in cell surface markers allow vascular endothelium to select CD4 cells for migration into active lesions. These regulatory CD4 cells likely produce interleukin 10, which has been shown to help suppress immune function, resulting in a resting lesion. As the inflammatory response dissipates, interleukin 15 expression from keratinocytes is thought to help ensure the survival of CD8 cells, helping them fulfill their effector memory phenotypes. Thus, when re-exposure to the drug occurs, a more rapid response develops in the exact location of any prior lesions.<sup>13</sup>

Medications may also follow a site-specific eruption pattern. For example, trimethoprim-sulfamethoxazole (Bactrim) has been shown to favor the genital region (especially in males) and naproxen and the oxicams involve the lips.<sup>7</sup> Resting/inactive lesions tend to appear as round or oval, gray, hyperpigmented macules. Upon reexposure, the resting hyperpigmented macules activate, developing a violaceous center encircled by concentric rings of erythema. Re-administration of the medication poses the risk of increased pigmentation, size, and number of lesions. Individuals with darker pigmentation may develop postinflammatory hypopigmented macules once the lesions have resolved.<sup>16</sup>

Considering previous history of pruritus and FDE secondary to analgin, provisional diagnosis of Bullous fixed drug

eruption was made and patient was advised to stop analgin. Our provisional diagnosis was supported by the literature review which revealed the presence of reports of bullous eruptions due to analgin. The occurrence of the lesion due to insult both the times are also characteristic of fixed drug eruption. Analyzing all the above features we came to conclusion that patient was having fixed drug eruption with bullous erythema multiform like presentation.

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