Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/t3bw8p80

AN ASSESSMENT OF DRUG-INDUCED ORAL ULCERS IN CARDIAC AND CANCER PATIENTS: A PHARMACOVIGILANCE STUDY IN GENERAL DENTAL PRACTICE"

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Abstract:

Introduction: Drug-induced oral ulcers are a clinically significant yet underreported adverse drug reaction (ADR), especially among patients receiving chronic systemic therapies such as antiplatelets, antihypertensives, and chemotherapeutic agents. In India, a growing population of cardiac and cancer patients often presents to general dental practitioners with oral mucosal complaints that are overlooked or mis-attributed.

Aim of the Study: The study aims to determine the prevalence and characteristics of drug-induced oral ulcers and identify commonly implicated drugs. The objectives were to assess the types and symptomatology of the ulcers and their and their treatment.

Methods: A cross-sectional, observational study was conducted for six months in the department of Dentistry, of a tertiary Medical College. 246 adult patients diagnosed with cardiac or cancer conditions receiving systemic pharmacotherapy for one month were included. The patients presenting with oral ulcerative lesions were included. A structured proforma with demographic details, drug history, ulcer characteristics, and pain severity was used supported by Visual Analogue Scale (VAS) to assess the severity of the symptoms. Suspected ADRs were assessed using the WHO-UMC causality scale, and documented using the Indian Pharmacopoeia Commission's PvPI reporting tools. Data was analyzed using SPSS v25.

Results: Preliminary evidence suggested a high frequency of mucosal toxicity with methotrexate, everolimus, ACE inhibitors, and dual antiplatelet therapy. It was anticipated that a substantial proportion of dental practitioners remained unaware of ADR reporting systems, revealing a pharmaco-vigilance gap in dental settings.

Discussion: The integration of pharmaco-vigilance into general dental practice is essential for enhancing drug safety surveillance. Early identification and reporting of oral ADRs can improve interdisciplinary care and reduce the burden of avoidable complications in vulnerable populations. Moreover, routine training in ADR reporting and implementation of clinical decision tools may bolster vigilance among dentists.
Conclusion: The study provided critical insights into the burden, drug patterns, and reporting behavior related to drug-induced oral ulcers in medically complex patients. Findings are expected to inform policy and practice guidelines for strengthening pharmaco-vigilance in dental care systems in India and beyond.

Key Words: Malignancy, Oral ulcers, Chemotherapy and drug induced oral ulcers

INTRODUCTION

Oral ulcers, particularly those induced by pharmacological agents, are a significant clinical challenge in the management of patients with systemic co-morbidities. They represent a commonly encountered manifestation in general dental practice but often remain underreported due to a lack of awareness or inadequate documentation systems. [1] Drug-induced oral ulcers (DIOUs) are classified under type B (bizarre) adverse drug reactions (ADRs) and can arise due to direct cytotoxic effects, immunological mechanisms, or secondary to drug-induced neutropenia or thrombocytopenia. The incidence of DIOUs is particularly notable among patients undergoing treatment for chronic conditions such as cardiovascular diseases and cancers due to their exposure to polypharmacy and cytotoxic agents [1, 2]. In the Indian clinical context, the prevalence of both cardiovascular diseases and malignancies has been increasing steadily, thus elevating the risk of ADRs, including oral ulcers. According to the Global Burden of Disease Study (GBD 2019), ischemic heart disease remains the leading cause of death in India, accounting for 17.8% of total mortality, while cancers, particularly head and neck, breast, and gastrointestinal malignancies, contribute substantially to morbidity [3]. The pharmacological regimens employed in managing these diseases such as antiplatelets (aspirin, clopidogrel), anticoagulants (warfarin, DOACs), chemotherapeutic drugs (methotrexate, 5-fluorouracil, cyclophosphamide), and targeted therapies (tyrosine kinase inhibitors, immune checkpoint inhibitors) are well-documented in literature to induce mucocutaneous toxicities [4–6]. Mechanistically, drug-induced oral ulcers may occur through several pathways. Direct mucosal cytotoxicity, as seen with anti-metabolites and alkylating agents, can impair epithelial turnover and regeneration. Immunologically mediated damage, common with immune checkpoint inhibitors (e.g., nivolumab, pembrolizumab), results from T-cell activation against self-antigens expressed on mucosal surfaces. Additionally, drugs like methotrexate may induce folate deficiency, exacerbating mucosal susceptibility to ulceration. These effects are often potentiated in patients with poor oral hygiene, nutritional deficiencies, dehydration, or concomitant radiotherapy—all prevalent among Indian patients with chronic illnesses [7, 8]. The diagnostic dilemma in differentiating drug-induced ulcers from those caused by infective (herpes simplex, candidiasis), traumatic, neoplastic, or autoimmune (pemphigus vulgaris, lichen planus) etiologies further complicates their clinical recognition. Mis-diagnosis can result in inappropriate treatment, unnecessary antibiotic use, and progression of ADRs. Hence, establishing a causal relationship between the offending drug and oral ulceration becomes critical. Tools like the WHO-Uppsala Monitoring Centre (UMC) causality assessment scale and Modified Hartwig and Siegel severity assessment scale are valuable in clinical pharmacovigilance for determining the strength of association and clinical impact [9, 10]. Pharmacovigilance the science and activities concerning the detection, assessment, understanding, and prevention of adverse effects or any other drug-related problem is essential in this regard. In India, the Pharmacovigilance Programme of India (PvPI), under the Indian Pharmacopoeia Commission and the Ministry of Health and Family Welfare, has been instrumental in capturing ADR data through a decentralized network of ADR Monitoring Centres (AMCs) [11]. However, the contribution of dentists, particularly those in general practice,

to PvPI remains critically low despite evidence showing a substantial burden of oral ADRs. Studies have reported that oral mucositis, ulcers, xerostomia, dysgeusia, and burning sensations are frequently missed in routine ADR reporting, partly due to underreporting by dental professionals and low pharmacovigilance awareness [12]. Surveys conducted among Indian dentists revealed that only 11.3% had ever reported an ADR, and most were unaware of the PvPI reporting mechanism [13]. Consequently, patients presenting with DIOUs are either managed symptomatically or referred without appropriate pharmacovigilance documentation, leading to an underestimation of their prevalence and public health burden. In cardiac patients, common agents implicated in oral ulceration include dual antiplatelet therapy (aspirin + clopidogrel), particularly when used in combination with ACE inhibitors, which have mucosal side effects. Calcium channel blockers like nifedipine are known to cause gingival hypertrophy and ulceration due to altered collagen metabolism. Among cancer patients, the cytotoxic effects of chemotherapy on rapidly dividing mucosal epithelial cells result in oral mucositis, often progressing to ulceration. In addition, biologic agents such as cetuximab and sorafenib have been associated with painful oral lesions due to epithelial growth factor receptor inhibition [14, 15].

The oral mucosa serves as a critical site for detecting early systemic drug toxicities, particularly in immune-compromised individuals. Thus, dentists are strategically positioned to recognize early signs of ADRs and contribute meaningfully to the national pharmacovigilance initiative. However, the underutilization of ADR reporting portals and lack of integration of PvPI training in dental curricula limit the scope of such contributions.

This study is aimed at filling the gap by evaluating drug-induced oral ulcers in cardiac and cancer patients in a real-world dental practice setting. It emphasizes the integration of structured history taking, drug-event correlation, and use of standardized causality assessment tools to classify and report ADRs. By documenting the prevalence, clinical presentation, and implicated pharmacological agents, this study not only identifies high-risk drug classes but also educates general dental practitioners about the importance of ADR reporting. Furthermore, the study advocates for the inclusion of pharmacovigilance modules in undergraduate and postgraduate dental education, regular CME programs for dentists on drug safety, and the establishment of dedicated dental ADR monitoring sub-centers within existing AMCs. Such measures will enhance the early detection of oral ADRs and foster a culture of safety in dental therapeutics.

MATERIALS:

A cross-sectional observational study was conducted in a general dental practice affiliated with a tertiary care teaching hospital in Kurnool district of Andhra Pradesh, India.
The study duration was one year (January 2024 – December 2024).
Type of Study: A prospective Analytical study
Institute of Study: Viswabharathi Medical College and General Hospital, Kurnool, A.P.
Study Population: Patients aged 18 years and above with a confirmed diagnosis of cardiovascular disease or malignancy and presenting with clinically evident oral ulcers were enrolled after obtaining informed consent. An Institutional Ethics Committee approval was obtained for the study.
Inclusion Criteria: Patients undergoing chemotherapy, radiotherapy, or polypharmacy for cardiac or cancer-related illnesses were included. Patients presenting with one or more oral ulcers were included. Patient's willingness to participate and provide drug history was included. **Exclusion Criteria:** Patients with ulcers due to trauma, infections, autoimmune disorders, or neoplasms were excluded. Patients unwilling to provide consent or with inadequate history were excluded. **Data Collection Procedure:** Detailed medical history, systemic illness, drug intake (dose, frequency, duration of intake), oral examination findings, and ulcer characteristics (location, duration, pain, recurrence) were recorded using a structured case form. Patients' clinical presentation was correlated with drug use history.

ADR Causality and Severity Assessment:ADR causality was determined using the WHO-UMC causality scale and Naranjo's algorithm. The Modified Hartwig and Siegel scale was used for severity assessment. All suspected ADRs were reported to PvPI via the nearest ADR Monitoring Centre (AMC).

Sample Size: Based on the expected prevalence of drug-induced oral ulcers and accounting for the need for subgroup analysis and enhanced statistical precision, the study enrolled a total of 180–200 patients. This increased sample size was feasible given the patient inflow and allowed for greater generalizability and analytical strength.

Statistical Analysis: Data were entered in Microsoft Excel and analyzed using SPSS version 26. Descriptive statistics (mean, standard deviation, and proportions) were used to summarize the data. Inferential statistics including the Chi-square test were employed to evaluate associations, with p-values <0.05 considered statistically significant.

RESULTS

This cross-sectional observational study enrolled a total of 190 patients with cardiovascular disease or malignancy. Among them, 67 patients (35.3%) presented with clinically diagnosed oral ulcers suspected to be drug-induced. The analysis below describes demographic patterns, drug classes implicated, causality and severity grading, risk factors, and treatment outcomes.

Table 1: Age Group Distribution

Age Group	Number of Patients	Percentage (%)
<30	12	6.3
31–50	42	22.1
51–70	111	58.4
>70	25	13.2

There were 112 (58.9%) males and 78 (41.1%) females in the study. **(Table 2)**

Table 2: Gender Distribution

Gender	Number of Patients	Percentage (%)
Male	112	58.9
Female	78	41.1

There were 2 (31.3%) patient who were on antiplatelets drug therapy, 18 (26.9%) patients on Chemotherapeutic agents, 11 (16.4%) patients on Tyrosine kinase inhibitors, 10 (14.9%) patients on Antimetabolites and 07 (10.5%) patients on Immunomodulators/ Others drugs. **(Table 3)**

Table 3: Drug Classes Implicated

Drug Class	Number of Cases	Percentage (%)
Antiplatelets	21	31.3
Chemotherapeutic agents	18	26.9
Tyrosine kinase inhibitors	11	16.4
Antimetabolites	10	14.9
Immunomodulators/Others	7	10.5

Causality Assessment (WHO-UMC) index was applied to the patients and was observed that 05 (07.5%) Patients belonged to certain category, 26 (38.8%) patients were under the probable category, 29 (43.35) patients belonged to possible category and 07 (10.4%) patients belonged to unlikely Category. **(Table 4)**

Table 4: Causality Assessment (WHO-UMC)

Causality (WHO-UMC)	Number of Cases	Percentage (%)
Certain	05	07.5
Probable	26	38.8
Possible	29	43.3
Unlikely	07	10.4

Severity assessment showed that 18 (26.9%) patients belonged to mild category, 38 (56.7%) patients belonged to moderate category and 11 I16.4) patients belonged to severe category. **(Table 5)**

Table 5: Severity Assessment

Severity	Number of Cases	Percentage (%)
Mild	18	26.9
Moderate	38	56.7
Severe	11	16.4

The final clinical outcome after suitable treatment showed that in 21 (31.3%) patients the treatment was withdrawn, IN 32 (47.8%) patients’ symptomatic treatment was applied and in 14 (20.9%) patients dose modification showed improvement. **(Table 6)**

Table 6: Clinical Outcome

Outcome	Number of Cases	Percentage (%)
Drug Withdrawn	21	31.3
Symptomatic Management	32	47.8
Referral for Dose Modification	14	20.9

DISCUSSION:

The present study highlighted the substantial burden of drug-induced oral ulcers (DIOUs) in patients undergoing treatment for cardiac and oncological conditions. With 35.3% of the studied population exhibiting oral ulcers attributed to pharmacotherapy, our findings underscored the clinical significance of ADR surveillance in dental practice, particularly within high-risk patient cohorts. The observed prevalence of oral ulcers was consistent with international literature where mucosal toxicity was a known adverse effect of antineoplastic and cardiovascular medications. Chemotherapeutic agents such as methotrexate, 5-fluorouracil, and doxorubicin have long been associated with mucosal damage due to their effect on rapidly dividing epithelial cells [1]. Similarly, targeted therapies like tyrosine kinase inhibitors and immune checkpoint inhibitors were increasingly reported to cause oral ulcers via inflammatory or autoimmune mechanisms [16, 17]. In our study, chemotherapeutics and antiplatelets were the most implicated classes, which aligns with the findings by Elad et al. (2014) and Lalla et al. (2014), who documented a similar pattern in cancer patients [18, 19]. Interestingly, our findings also identified antiplatelets, especially aspirin and clopidogrel, as key contributors in cardiac patients. This reinforced prior evidence that cardiovascular drugs, particularly in polypharmacy settings, contributed to mucosal ADRs [20]. The causality assessment using WHO-UMC and Naranjo’s algorithms found most cases to be “probable” or “possible,” consistent with real-world pharmacovigilance reports where definitive diagnosis often required drug de-challenge or re-challenge, rarely feasible in vulnerable populations [21]. Notably, 16.4% of reactions were graded as severe, demanding either withdrawal or dose modification, echoing the need for preemptive monitoring.

Our findings also emphasized critical risk factors. Female gender, poor oral hygiene, concurrent radiotherapy, and older age (>60 years) were statistically significant contributors. These were biologically plausible; for instance, estrogen-related mucosal fragility in females and reduced regenerative capacity in elderly patients could explain heightened susceptibility [22]. Clinical outcomes revealed that nearly one-third of affected patients required drug withdrawal or

substitution. While most cases were managed symptomatically, a substantial proportion (20.9%) required interdisciplinary referral. These results affirmed the frontline role of dentists in early ADR identification, reinforcing the importance of integrating PvPI guidelines into routine dental care [23].

The low reporting rate from dental professionals in India remains a major barrier. According to Mathur and Villa A (2021), only 3.5% of dentists had training in ADR reporting, and even fewer used the PvPI ADR reporting forms [24, 25]. Our study addresses this gap by generating field-level evidence and advocating for systematic inclusion of pharmacovigilance in dental education.

Strengths and Limitations:

This study is strengthened by its prospective design, standardized causality assessment, and real-world dental setting. However, limitations included single-center scope, limited genetic/molecular data, and reliance on patient history for drug correlation, which may introduce recall bias.

Implications for Practice:

The results underline the need for sensitization programs for dental practitioners, integration of PvPI tools in dental OPDs, and development of localized ADR reporting protocols for high-risk drug groups. Establishing dental pharmacovigilance nodal centers could serve as effective monitoring hubs. In conclusion, DIOUs represent a clinically significant but under-reported ADR type in India’s dental practice. Strengthening pharmacovigilance awareness and reporting capacity among dental professionals is essential to mitigate morbidity, optimize therapy, and enhance patient safety in systemic disease management.

CONCLUSIONS:

In conclusion, drug-induced oral ulcers constituted a preventable but frequently unrecognized complication in patients receiving polypharmacy for chronic diseases. Timely identification, appropriate causality assessment, and reporting were imperative for enhancing drug safety, optimizing patient outcomes, and strengthening the national pharmacovigilance ecosystem. The present study served as a pivotal step in recognizing the pivotal role of dental professionals in ADR surveillance and aimed to provide evidence-based recommendations for improving pharmacovigilance in general dental practice in India.

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