Analysis of Adverse Events Associated With Dental Local Anaesthetics Using Food and Drug Administration Adverse Event Reporting System Data

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ABSTRACT

Objective: Local anaesthetics (LAs), almost indispensable aspect of dental practice for pain-free procedures, occasionally leads to worrisome adverse events (AEs). We aimed to compare serious and nonserious AEs of LAs for dental reasons in the US Food and Drug Administration AE Reporting System.

Methods: We retrospectively analysed dental AE reports associated with LAs in the Food and Drug Administration AE Reporting System database from its inception to April 2024. We described AEs by patients' demographic and clinical characteristics and compared ester and amide LA-associated AEs by their severity.

Results: We identified 1956 dental cases with a significant increase of AE reports after 2017. Lidocaine and articaine were the most commonly reported LAs (40.4% and 39.2%, respectively). Serious AEs constituted 46.2%, more commonly in females than males (56.6% vs 43.4%, $P < .001$) and in those on concomitant medications (70.2% vs 42.2, $P < .001$). These were also significantly higher in epinephrine-containing LAs (70.1%) than that without (34.2%, $P < .01$). Ester LAs had increased risk of serious AEs (odds ratios [OR]: 3.86; 95% confidence intervals [CI]: 2.77-5.39), particularly as hospitalization, life-threatening event, or death. The odds of serious AEs were lower with lidocaine (OR: 0.59; 95% CI: 0.48-0.71) and articaine (OR: 0.63; 95% CI: 0.52-0.76).

Conclusion: Our study showed higher rate of serious AEs with ester LAs and those with vasoconstrictor-added practices. Besides, serious outcomes appear as more likely in females and those where additional drug use was reported.

Clinical Relevance: The integration of clinical evidence with pharmacovigilance data has the potential to influence clinicians' LA preferences in dental practice, enabling more informed and evidence-based decision-making.

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Introduction

Local anaesthetics (LAs) are essential pharmacological agents of modern dental practice[1,2] to facilitate effective and safe performance of pain-free procedures.[3] However, their potential adverse drug reactions (ADRs) could be major concerns for dentists, other healthcare professionals, and patients, often occurring immediately during the procedure or visit.[4] These reactions can be seen as a range of potential reactions, from mild to severe, from expected problems to unexpected ones, depending on the chemical structure of the LA as well as individual factors.[5]

The majority of dental procedures are performed in non-hospital clinics, which increases the importance of knowing whether the LAs used cause serious ADRs, which ADRs they are mostly cantered on, and patient demographic and clinical characteristics. The first step in a safe approach for dental patients is to identify ADRs associated with dental treatments.[6] In the absence of a comprehensive resource for identifying and capturing the causes of ADRs, biomedical

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literature[7] and spontaneous adverse event (AE) reporting systems have come to the forefront. The US Food and Drug Administration (FDA) AE Reporting System (FAERS) is an important database used for postmarketing drug safety surveillance.[8]

Although the literature covered trial- and review-based data of ADRs associated with various LAs used in dental practice,[5-7] evidence from large-scale databases remain scarce.[9] In this study, we aimed to compare the characteristics serious and nonserious AEs associated with LAs used in dental practice as reported to the FAERS database.

Methods

This cross-sectional study is based on a retrospective analysis of AE data associated with LAs used for dental purposes obtained from the FAERS database. While the FAERS data is publicly available and anonymized, we obtained ethical approval from the Medipol University Non-Interventional Clinical Research Ethics Committee (13.06.24-644). This study was conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[10]

Data collection

FAERS is a database managed by the FDA that includes AE reports related to drugs and biological products. This system includes voluntary reports of AEs, medication errors, and product quality issues for approved prescription and over-the-counter drugs submitted by healthcare providers, patients, and pharmaceutical manufacturers, aiding in the monitoring of drug safety.[11] AEs in FAERS are standardized via the Medical Dictionary for Regulatory Activities through system organ class classification, which helps harmonize heterogeneous data derived from voluntary reports for pharmacovigilance analyses. We categorized the reports as 'serious', including outcomes such as death, hospitalization, life-threatening events, disability, and congenital anomalies, or 'non-serious', involving events of more limited medical significance. Unlike clinical trials, postmarketing surveillance is crucial for identifying less common but potentially severe ADRs.[12]

For this study, all FAERS reports related to amide- and ester-structured LAs classified under the Anatomical Therapeutic Chemical (ATC) Classification System code N01B were reviewed. Accordingly, the amide group LAs included articaine, lidocaine, bupivacaine, prilocaine, mepivacaine, and ropivacaine, whereas the ester group LAs consisted of tetracaine, benzocaine, procaine, cocaine, phenol, and chloroprocaine. The 'reason for use' declarations in the database for both groups of LAs were subsequently examined to determine their association with 'dental practice'. This process was carried out in detail by one dentist (F.B.) and two pharmacologists (A.A. and V.A.). Initially, each expert independently reviewed and recorded their assessments, which were then collectively discussed to reach a consensus. Data extraction from the FAERS database was completed in May 2024. The data cleaning and preprocessing phase took place from May to September 2024, followed by statistical analyses conducted between October 2024 and January 2025.

Study variables

Among the 'outcomes of interest', any reported AEs were included. The primary outcome was the classification of AEs as serious or nonserious, based on FAERS reporting criteria, where serious outcomes included death, hospitalization (admission or prolonged), life-threatening events, disability, and congenital anomalies. Secondary outcomes included the distribution of AEs based on LA chemical category (amide vs ester vs other), presence of epinephrine, and the association of serious AEs with patient demographics (sex, age group, comorbidities), concomitant medication use, country of event, and reporter type.

The obtained AE data were analysed on the basis of the serious and nonserious categories. The reasons for use were classified in accordance with the American Dental Association's Code on Dental Procedures (CDT) and Nomenclature system. Patient ages were examined in four groups: '<18 years', '18-44 years', '45-65 years', and '>65 years'.

An initial search of the FDA FAERS database via the ATC code N01B identified 92,706 cases. The reports were subsequently rescreened on the basis of the 'reason for use' column to determine their relevance to dental procedures. Cases containing terms such as 'tooth', 'teeth', 'dental', 'endodontic', 'toothache', 'pulpitis', 'periodontitis', 'periodontal disease', 'teething', 'gingival pain', 'gingivitis', or 'artificial crown procedure' were classified as dental-related (n = 1956) and included in the study. The included cases were recorded in the FAERS database between January 1998 and April 2024.

Statistical analysis

We performed the statistical analyses via Prism 10.0 and SPSS 30.0 software. Data on categorical and continuous variables were expressed as numbers and percentages or means and standard deviations, where appropriate. The chi-square test was used to compare different agents between the serious and nonserious groups. The risk levels of serious outcomes associated with amide and ester groups, as well as specific LAs, were examined using univariate logistic regression analysis, where odds ratios (ORs) and 95% confidence intervals (CI) were calculated. We used a Type-I error level of 5% to infer statistical significance.

Results

We identified 1956 cases that was reported to be associated with LAs administered for dental purposes and mainly stemmed from the United States (76.7%). The mean age was 41.9 ± 20.6 years, and 62.1% of the cases were female. Comorbidities were present in 94.4% of the cases, 14.4% reported concomitant use of other medications. Serious AEs constituted 46.2% (n = 904) among the reported cases. These AEs were also reported as more commonly in females than males (56.6% vs 43.4%, $P < .001$), in those on concomitant

Table 1 – Descriptive statistics of the dental cases, stratified by serious and nonserious cases*.

Category	Serious No. (%)	Nonserious No. (%)	Total No.	*P* value
Sex				
Female	559 (56.6)	428 (43.4)	987	*P* < .001
Male	280 (46.5)	322 (53.5)	602	
Not specified	367	65	302	
Age group, y				
<18	104 (63.0)	61 (37.0)	165	.527
18-44	305 (63.3)	177 (36.7)	482	
45-65	262 (67.7)	125 (32.3)	387	
>65	100 (63.7)	57 (36.3)	157	
Not specified	765	133	632	
Comorbidity				
Present	820 (44.4)	1027 (55.6)	1847	*P* < .001
Absent	84 (77.1)	25 (22.9)	109	
Not specified	0	0	0	
Concomitant medications				
Present	198 (70.2)	84 (29.8)	282	*P* < .001
Absent	706 (42.2)	968 (57.8)	1674	
Not specified	0	0	0	
Country				
USA	229 (18.6)	999 (81.4)	1228	*P* < .001
International	356 (95.2)	18 (4.8)	374	
Not specified	354	319	35	
Reporter				
Consumer	241 (72.8)	90 (27.2)	331	*P* < .001
Healthcare professional	596 (38.4)	957 (61.6)	1553	
Not specified	72	67	5	

* Results obtained via Chi-square for categorical variables.

medications than that those without (70.2% vs 42.2%, *P* < .001), in whom without comorbidities than in that with (77.1% vs 44.4%, *P* < .001). We found no significant effect of age groups in severity of AEs (Table 1).

Temporal trends of AE reporting exhibited increasing figures especially after the year 2016, mostly driven by those from healthcare professionals compared to the modest increase of AE reports submitted by the consumers (Figure 1A). Prior to 2017, most AEs reported to the FAERS were associated with lidocaine (25.6%), articaine (23.3%), and benzocaine (16.8%). As of 2017, most AEs were related to lidocaine (38.5%), articaine (37.1%), and mepivacaine (8.1%) (Figure 1B). Benzocaine was reported predominantly by consumers (30.5%) compared to healthcare professionals (1.5%), whereas lidocaine (39.4%) and articaine (36.6%) were reported more frequently by healthcare professionals than consumers.

Overall, amide (88.6%) and epinephrine-free (66.5%) LA preparations constituted the most frequent groups reported to the FAERS. Among the particular agents, LAs associated with AEs indicated lidocaine (40.4%), articaine (39.2%), and mepivacaine (11.1%).

Ester LAs had a significantly higher rate of serious AEs than amides (74.4% vs 42.4%, *P* < .001). Serious AEs were also significantly higher in epinephrine-containing LAs (70.1%) compared to that in epinephrine-free agents (34.2%, *P* < .01). Among the most commonly reported agents, the rate of serious AEs were significantly less in lidocaine- (42.5%) and articaine-containing (41.5%) LAs compared to the remaining counterparts (51.3%, *P* < .001 and 52.6%, *P* < .001). In contrast, these were more pronounced in AE reports containing mepivacaine (58.5%, *P* = .001), benzocaine (86.9%, *P* < .001), and prilocaine (61.1%, *P* = .01). Additionally, combined LAs were more likely to be reported as serious AEs (63.9%) than single-agent LAs (44.7%, *P* < .001) (Table 2).

The univariate logistic regression analysis in Figure 2A confirmed the significantly higher risk of serious AEs with ester LAs (OR: 3.86; 95% CI: 2.77-5.39) and lower risk with amide LAs (OR: 0.24; 95% CI: 0.17-0.33). Ester-based agents, such as benzocaine (OR: 7.85; 95% CI: 4.81-12.91), were associated with a significantly greater risk of serious AEs, whereas amide-based agents, such as lidocaine (OR: 0.59; 95% CI: 0.48-

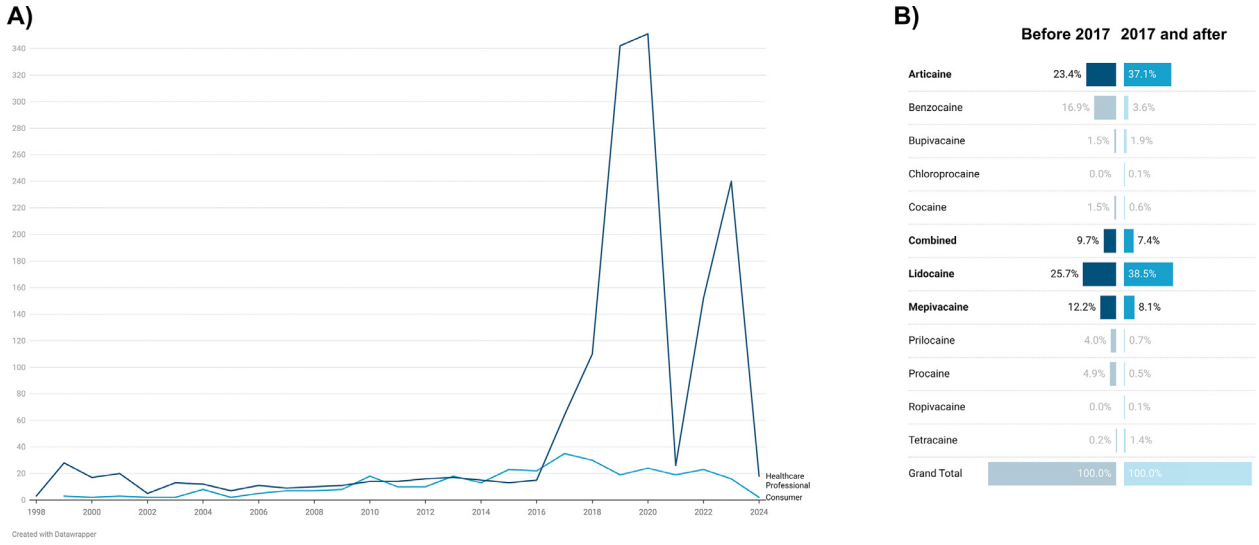

Fig. 1 – (A) Annual distribution of adverse event reports submitted to the FDA by reporter type (consumer and health care professional) from 1998 to 2024. (B) Distribution of adverse events caused by anaesthetic agents before 2017 and from 2017 onwards.

Table 2 – Distribution of serious and nonserious cases by anaesthetic group, epinephrine presence, specific local anaesthetic agents, and combined anaesthetic use, with corresponding *P* values*.

Category	Serious No. (%)	Nonserious No. (%)	Total No.	Cramer's V	*P* value
Group					
Amides	735 (42.4)	998 (57.6)	1733	0.197	*P* < .001
Esters	151 (74.4)	52 (25.6)	203		
Epinephrine					
Present	460 (70.1)	196 (29.9)	656	0.341	*P* < .001
Absent	444 (34.2)	856 (65.8)	1300		
Combined anaesthetics					
Present	99 (63.9)	56 (36.1)	155	0.104	*P* < .001
Absent	805 (44.7)	996 (55.3)	1801		
Total	904 (46.2)	1052 (53.8)	1956		
Local anaesthetics					
Lidocaine	336 (42.5)	454 (57.5)	790	0.061	*P* < .001
Articaine	318 (41.5)	448 (58.5)	766	0.076	*P* < .001
Mepivacaine	127 (58.5)	90 (41.5)	217	0.087	*P* < .001
Benzocaine	126 (86.9)	19 (13.1)	145	0.231	*P* < .001
Prilocaine	55 (61.1)	35 (38.9)	90	0.066	.004
Bupivacaine	14 (33.3)	28 (66.7)	42	0.038	.090
Procaine	17 (51.5)	16 (48.5)	33	0.014	.538
Tetracaine	9 (33.3)	18 (66.7)	27	0.031	.176
Cocaine	16 (100.0)	0 (0.0)	16	0.098	*P* < .001
Phenol	4 (80.0)	1 (20.0)	5	0.034	.12
Ropivacaine	2 (100.0)	0 (0.0)	2	0.035	.079
Chloroprocaine	1 (100.0)	0 (0.0)	1	0.024	.214
Total	1025 (48.0)	1109 (52.0)	2134		

* Chi-square test was used for statistical analysis, and Cramer's V was calculated to express the effect size.

0.71) and articaine (OR: 0.63; 95% CI: 0.52-0.76), were associated with a lower risk. Further analysis of specific serious AE outcomes demonstrated that the likelihood of hospitalization, life-threatening events, and death was significantly higher with ester-type LAs, benzocaine, and combined LA applications (Figure 2B). Notably, hospitalization risk was higher with benzocaine (OR: 2.96; 95% CI: 1.99-4.39) and overall ester-type LAs (OR: 2.19; 95% CI: 1.54-3.11), while amide-type LAs were associated with a significantly lower risk of hospitalization (OR: 0.46; 95% CI: 0.32-0.65). In terms of life-threatening events, benzocaine again showed a strong association (OR: 2.94; 95% CI: 1.98-4.36), while amide-based agents, such as lidocaine (OR: 0.80; 95% CI: 0.55-1.15) and articaine (OR: 0.55; 95% CI: 0.37-0.82), had a lower risk. Finally, the risk of death was significantly higher in patients exposed to benzocaine (OR: 2.56; 95% CI: 1.12-6.12) and overall ester LAs (OR: 2.66; 95% CI: 1.25-5.71), while articaine (OR: 0.35; 95% CI: 0.16-0.81) had a notably lower risk (Figure 2B).

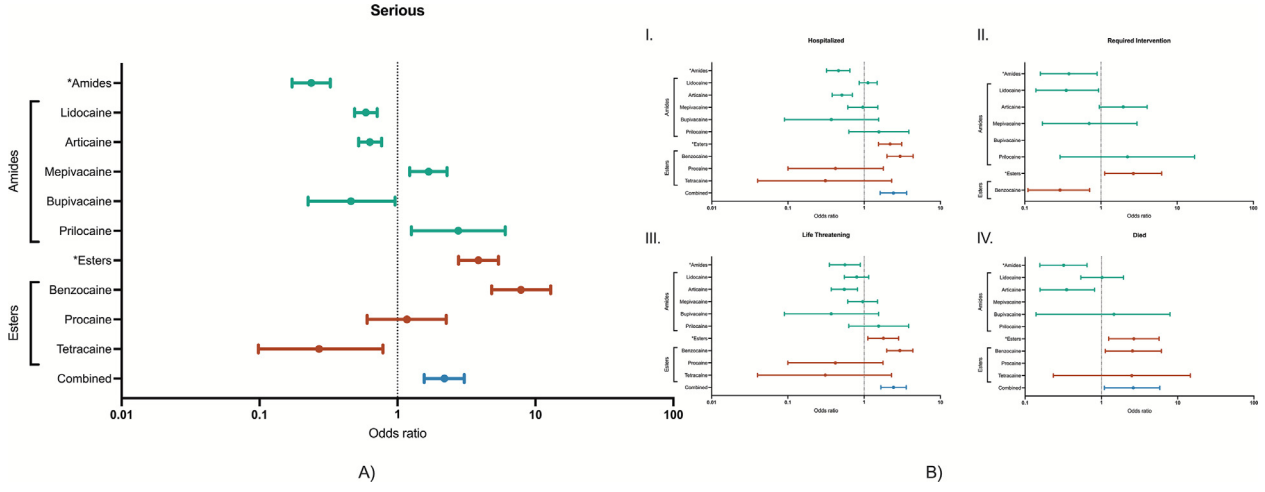

Fig. 2 – (A) Odds ratios (ORs) and 95% confidence intervals (CIs) for serious adverse events associated with different local anaesthetics based on univariate logistic regression analysis. (B) Subgroup analysis presenting ORs and 95% CIs for hospitalized cases (I), cases requiring intervention (II), life-threatening events (III), and fatalities (IV) for each local anaesthetic agent.* indicates values representing the entire chemical group.

Table 3 – Distribution of total, serious, and nonserious cases classified according to the American Dental Association's CDT (Code on Dental Procedures and Nomenclature) categories*.

CDT classification	Total No. (%)	Serious No. (%)	Nonserious No. (%)
D0: Diagnostics	10 (0.4)	1 (0.6)	9 (1.3)
D1: Preventive	31 (1.2)	29 (4.7)	2 (2.6)
D2: Restorative	95 (3.7)	49 (1.2)	46 (3.9)
D3: Endodontics	51 (2.0)	41 (1.7)	10 (2.6)
D4: Periodontics	43 (1.7)	34 (3.5)	9 (6.5)
D6/1: Implant services	7 (0.3)	4 (0.6)	3 (1.3)
D6/2: Prosthodontics – fixed	38 (1.5)	26 (1.7)	12 (3.9)
D7: Oral and maxillofacial surgery	170 (6.6)	131 (2.9)	39 (2.6)
D9: Adjunctive general services	1423 (55.2)	527 (11.0)	896 (13.0)
Other	712 (27.6)	580 (72.1)	132 (62.3)
Total	2580 (100.0)	1422 (100.0)	1158 (100.0)

* Frequency and percentage calculations were performed for the data presented.

Based on the ADA's CDT classification, the results showed that adjunctive general services constituted the largest proportion of total cases (55.2%), accounting for 11.0% of serious cases and 13.0% of nonserious cases. The 'other services' category represented 27.6% of total cases but was associated with 72.1% of serious cases. Additionally, the oral and maxillofacial surgery category accounted for 2.9% of serious cases and 2.6% of nonserious cases. In other categories, preventive, restorative, and endodontic procedures were found to have low proportions of serious cases (Table 3).

According to the Medical Dictionary for Regulatory Activities system organ class classification, the distribution of AEs for the 10 most reported LAs revealed that 'product issues' (23.7%), 'nervous system disorders' (13.5%), and 'general disorders and administration site conditions' (10.4%) were the most frequently reported categories. Lidocaine was particularly associated with 'product issues' (27.4%) and 'nervous system disorders' (11.7%), whereas articaine showed a similar pattern, being more frequently linked to 'product issues' (25.5%) and 'nervous system disorders' (16.7%). Benzocaine, on the other hand, was more strongly associated with AEs in the categories of 'product issues' (7.1%) and 'skin and subcutaneous tissue disorders' (11.6%) (Table 4).

Discussion

The findings of our cross-sectional study based on a well-recognized international AE report system, highlight certain demographic, clinical, and drug-related factors potentially influencing the severity of AEs. Accordingly, serious AEs associated with LAs were more likely to occur in females and those using concomitant medications. In addition, epinephrine-containing and ester-based preparations appear to have increased risk of serious AEs, confirming the lower odds with lidocaine and articaine, the predominant LAs reported overall.

Systematic reviews of clinical studies indicate that the most common AEs associated with dental LAs involve the cardiovascular, nervous, respiratory, and gastrointestinal systems.[5] In our study, the prominent AEs associated with lidocaine and articaine were drug inefficacy and nervous system reactions, such as hypoesthesia, dizziness, tremors, and syncope. For benzocaine, which is primarily used as a topical anaesthetic, skin and subcutaneous tissue reactions were more frequently observed. Regarding serious reactions, particularly mortality, the literature presents mixed findings. One review reported 218 deaths associated with dental procedures between 1955 and 2012, most of which were linked to general anaesthesia or sedation, with none attributed solely to LAs.[13] Another review evaluating 1645 AEs from 101 articles identified seven deaths related to LAs, one of which was associated with lidocaine alone, while the others involved combination drugs.[5] In contrast, the 39 deaths reported in the FAERS database exceed those documented in clinical studies. This discrepancy likely reflects the broader population captured through pharmacovigilance data compared to the more controlled settings of clinical studies.

Articaine and lidocaine are among the most widely used LAs in dental practice,[14,15] whereas benzocaine is one of the most commonly used topical anaesthetics, available both over-the-counter and by prescription.[16] This over-the-counter availability of benzocaine may explain the significantly higher reporting rate by consumers compared to healthcare professionals. Such findings highlight the importance of incorporating direct consumer-targeted safety warnings and precautionary measures into risk minimization strategies for benzocaine use. Despite recent clinical evidence, many clinicians still avoid using articaine, particularly for inferior alveolar nerve blocks.[17] Supporting clinical evidence with data from pharmacovigilance studies could influence clinicians' anaesthetic preferences in clinical practice. The evidence compiled from clinical studies indicates that the highest number of AEs is reported in cases involving the use of lidocaine or bupivacaine alone.[5] The findings of our study, however, suggest that articaine and lidocaine are safer than benzocaine and prilocaine in terms of reported serious AEs.

The chemical type, doses, and administration routes of LAs and their combinations are key factors influencing AE occurrence.[5] Allergic reactions are known to occur more frequently following exposure to ester compounds than following exposure to amide compounds.[4] The pharmacovigilance data obtained in this study further support the notion that ester-based LAs are less safer, as indicated by the lower number of serious reports associated with amides. The higher overall number of reported AEs for amides can be attributed to their much wider use compared to esters.[15,18] Another important factor in AE occurrence is the use of vasoconstrictors, which significantly improve the safety, suitability, and efficacy of anaesthesia, particularly in procedures lasting longer than 15 minutes.[19,20] Epinephrine, the most commonly used vasoconstrictor in current LA formulations, is available at concentrations of 1:50,000, 1:100,000, and 1:200,000. As a potent cardiovascular agent, epinephrine can increase heart rate, blood pressure, and the risk of cardiovascular emergencies at high doses.[1] Approximately 20% of all intraoral

Table 4 – Distribution of adverse events classified according to the MedDRA system organ class (SOC)*.

SOC classification	Lidocaine No. (%)	Articaine No. (%)	Mepivacaine No. (%)	Benzocaine No. (%)	Prilocaine No. (%)	Procaine No. (%)	Tetracaine No. (%)	Bupivacaine No. (%)	Cocaine No. (%)	Total No. (%)
Product issues	418 (27.4)	376 (25.5)	90 (20.2)	28 (7.1)	32 (15.4)	4 (3.9)	10 (13.5)	24 (37.5)	1 (2.1)	926 (23.7)
Nervous system disorders	178 (11.7)	246 (16.7)	68 (15.2)	47 (11.8)	26 (12.5)	14 (13.6)	7 (9.5)	5 (7.8)	0 (0.0)	526 (13.5)
General disorders and administration site conditions	152 (10.0)	157 (10.6)	41 (9.2)	43 (10.8)	10 (4.8)	13 (12.6)	7 (9.5)	8 (12.5)	3 (6.4)	407 (10.4)
Gastrointestinal disorders	80 (5.2)	127 (8.6)	33 (7.4)	44 (11.1)	15 (7.2)	11 (10.7)	5 (6.8)	2 (3.1)	1 (2.1)	285 (7.3)
Skin and subcutaneous tissue disorders	95 (6.2)	110 (7.5)	35 (7.8)	46 (11.6)	23 (11.1)	6 (5.8)	5 (6.8)	3 (4.7)	1 (2.1)	285 (7.3)
Cardiac disorders	105 (6.9)	64 (4.3)	28 (6.3)	8 (2.0)	11 (5.3)	6 (5.8)	1 (1.4)	9 (14.1)	0 (0.0)	202 (5.2)
Eye disorders	47 (3.1)	36 (2.4)	10 (2.2)	10 (2.5)	6 (2.9)	4 (3.9)	1 (1.4)	1 (1.6)	2 (4.3)	106 (2.7)
Immune system disorders	68 (4.5)	49 (3.3)	22 (4.9)	6 (1.5)	18 (8.7)	5 (4.9)	4 (5.4)	2 (3.1)	0 (0.0)	147 (3.8)
Investigations	20 (1.3)	15 (1.0)	8 (1.8)	5 (1.3)	3 (1.4)	2 (1.9)	3 (4.1)	1 (1.6)	2 (4.3)	48 (1.2)
Blood and lymphatic system disorders	9 (0.6)	2 (0.1)	0 (0.0)	24 (6.0)	3 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.3)	37 (0.9)
Other	355 (23.2)	293 (19.9)	111 (24.9)	136 (34.3)	61 (29.3)	38 (36.9)	31 (41.9)	9 (14.1)	35 (74.5)	941 (24.1)
Total	1527 (100)	1475 (100)	446 (100)	397 (100)	208 (100)	103 (100)	74 (100)	64 (100)	47 (100)	3910 (100)

* Frequency and percentage calculations were performed for the data presented.

injections are thought to cause transient increases in adrenaline levels,[21] a finding of clinical importance given that even low concentrations can affect cardiovascular function.[22] A systematic review reported that the number of ADRs associated with epinephrine-containing LAs was 2.16 times greater than that associated with LAs without epinephrine.[5] Consistent with this, our pharmacovigilance data show a greater number of serious AEs linked to epinephrine-containing formulations, emphasizing the potential systemic effects of epinephrine.

Gender is recognized as a significant factor in the incidence of AEs, with AEs being more frequently reported in women, although the mechanisms may vary.[23] According to Hillerup and Jensen,[24] women receiving LAs have approximately twice the risk of nerve damage as men do. Our findings align with this, showing that among patients with reported gender, women were more prominently represented, and serious AEs were significantly more common in women. The literature suggests that this higher incidence may be linked to women's greater tendency to seek medical care.[25] Considering that women are more likely to visit dentists,[26-28] our findings on AE reporting support the notion that increased treatment-seeking behaviour may contribute to higher reporting rates. When evaluating age groups, while the middle-aged group had the highest number of reports, no significant differences were observed between age groups for serious AEs. This lack of distinction does not highlight any specific age group requiring prioritization in clinical practice. Although comorbidities appeared to be relevant, the absence of concomitant medications may be associated with higher reporting rates.

Changes in pharmacovigilance reporting trends can often be attributed to factors such as guideline updates, dose adjustments, media attention, and strengthened pharmacovigilance programs.[29-31] Our findings indicated a marked increase in AE reporting in recent years, with a notable acceleration as of 2017, albeit with a decline in pandemic. One of the most significant contributors to the surge in AE reports after 2017 was the pronounced increase in cases associated with articaine. The higher frequency of events reported for articaine may be linked to existing concerns among dentists regarding the safety of this anaesthetic, leading to an increased likelihood of reporting when AEs occur. To encourage patients to report AEs, the FDA introduced the first voluntary reporting form, the FDA 3500, in 1993, followed by a more user-friendly version for consumers, the FDA 3500B, in 2013.[32] However, these initiatives are unlikely to have significantly influenced our findings, as the observed increase in reports was partly linked to articaine. Another factor that may have affected reporting patterns is the COVID-19 pandemic. While overall reporting rates for serious events did not show a notable decline,[33] a significant reduction in AE reports related to dental LAs was observed. This decline is likely due to disruptions in dental treatment practices and the resulting reduction in the use of dental LAs.

Despite the critical role that dentists play in patient safety, pharmacovigilance remains poorly understood and underutilized in the field of dentistry.[34] Studies show that dentists, second only to paramedics, have limited knowledge of pharmacovigilance and AEs[35] and report fewer cases compared to

other healthcare professionals.[30] This may be due to limited awareness of their role in pharmacovigilance and a perceived lack of pharmacological knowledge to identify AEs.[36] These seem to be reflected in our study findings, where serious AEs related to dental LAs were reported less frequently in the FAERS compared to other reports.[37] This may be explained by underreporting by dentists or the tendency of medical doctors to focus on reporting only serious cases.

One of the strengths of this study is that the drugs analysed have long been on the market, reflecting well-established usage profiles rather than those of newer drugs still in various stages of the marketing cycle. The FAERS database is a valuable resource for identifying demographic trends, associated drugs, conditions, and outcomes. However, while it informs pharmacovigilance efforts, it does not fully capture actual risks observed in clinical practice, which can only be thoroughly evaluated through clinical or cohort studies.

The limitations of this study include the lack of medical verification and incomplete information in the FAERS data. Evaluating data based on the 'reason for use' may have led to the inclusion of cases with multiple indications, such as cocaine, which is not routinely used in dentistry. However, due to the small number of such cases, individual exclusions were not feasible. Additionally, voluntary reporting introduces underreporting and reporting bias, and the dataset's potential duplicates and lack of drug utilization trends prevent the calculation of accurate reporting rates. Future studies with larger case series and prospective cohort designs are needed to validate these findings and better assess actual risks in clinical practice. Given the limitations of FAERS data, observational studies using real-world data, such as medical records and claims databases, could offer further evidence to validate and strengthen the current findings. These sources also have the potential to capture medical histories of underrepresented patient groups, often inadequately reflected in FAERS, allowing for more comprehensive analyses.

Conclusion

This study demonstrated that serious AEs related to dental LAs are more frequently reported in women, individuals using concomitant medications, and those receiving ester-based anaesthetics, while amide anaesthetics like lidocaine and articaine are associated with a lower risk. These findings underscore the importance of combining pharmacovigilance data with clinical practice insights to enhance patient safety and optimize anaesthetic selection. Given the limitations of spontaneous reporting systems, future research should focus on validating these findings through prospective cohort studies and exploring risk factors for AEs in dental practice. Increasing pharmacovigilance awareness among dentists is critical for improving the quality and accuracy of AE reporting and supporting evidence-based decision-making.

Author contributions

Ferit Bayram: Conceptualization, investigation, methodology, analysis, writing – original draft preparation, and reviewing/editing. Ahmet Akici and Volkan Aydin: Supervision, conceptualization, investigation, methodology, analysis, reviewing, and editing. Asli Apari: Investigation, analysis, and writing – original draft preparation.

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

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