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Gingival Overgrowth as Adverse Drug Reaction of Calcium Channel Blockers: A Review

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Abstract :
Background: *Gingival overgrowth is an Adverse Drug Reaction (ADR) frequently encountered in thedihydropyridine (DHP) group of Calcium Channel Blockers, especially nifedipine and amlodipine. Various factors are thought to play a role as risk factors including sociodemographic, genetic, pharmacokinetics, and oral hygiene.*
Materials and Method : *This review article aimed to describe data from the results of a 2009-2020 study which reported gingival overgrowth as ADR arising from use of Calcium Channel Blockers. This review was conducted by extracting data from PubMed, Google Scholar, and ScienceDirect. From the literature, it was found that CCB is an antihypertensive group that often causes gingival overgrowth (GO), especially the dihydropyridines group.*
Results : *Based on the result of article peel obtained 4 articlesincluded in this literature review.*
Conclusion: *The wide prevalence variability is thought to occur due to differences in genetics, population characteristics, and the criteria used. Sociodemographic factors (age, gender) did not have a significant effect on GO, while oral hygiene factors and drug pharmacokinetic variables still gave mixed results, thus further research is still needed.*

Keyword: *Gingival Hyperplasia, Adverse Drug Reaction, And Calcium Channel Blockers*.

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I. Introduction

Adverse Drug Reaction (ADR) is a serious health problem where dangerous and unexpected drug reactions occur that can cause side effects in normal human doses(1). ADR is characterized by a link between a drug product and an adverse event and can be defined as an adverse event associated with drug use. This definition includes adverse drug reactions including medication errors related to drug prescription, drug preparation, drug dispensing, and drug administration (2,3).

In general, the pharmacological classification of ADR is divided into 2 major subtypes; that is, type A which are dose-dependent and predictable (non-immunological, often called intolerance), and type B (immunology-allergy) which is unpredictable and dose-independent. Most of the ADRs (> 85% of cases) were classified as type A due to the pharmacological activity of the suspected drug (4,5). Often type A is called 'augmented' and type B is called 'bizarre' (6). Then, further subdivisions were added namely type C (dose-related and time-related), type D (time-related), type E (withdrawal) and most recently the unexpected therapy failure category as type F (7). One study stated that ADR not only affects the quality of life but also affects health care costs, morbidity, and mortality rates and has the potential to influence subsequent drug use (8). ADR can occur in 10–20% of hospitalized patients and is usually the result of a misdiagnosis that occurs in hospitalized patients (9).

Calcium Channel Blocker (CCB) is a class of drugs most widely used in patients with hypertension, angina pectoris, or cardiac arrhythmia by inhibiting the calcium ion slow type (L-type). The main action of CCB is vascular dilation, negative inotrope, reducing heart rate, and slowing AV conduction. CCB is broadly divided into 3 groups, namely benzothiazepine (diltiazem), phenylalkylamine (verapamil), both of which are classified as non-dihydropyridine (non-DHP) and dihydropyridine (amlodipine, nifedipine, nicardipine, etc.) (10).

Calcium Channel Blocker is a drug-induced gingival overgrowth (DIGO). Gingival hyperplasia can also occur due to a hereditary, idiopathic, and iatrogenic history characterized by enlarged gingiva and inflammation (11,12). DIGO is more common in 1st and 2nd generation dihydropyridine CCBs (nifedipine, verapamil, diltiazem, and amlodipine). The prevalence of DIGO due to nifedipine is approximately 20–83%, whereas diltiazem, amlodipine, and verapamil are 74%, 3.3%, and 21%, respectively (13). Several factors including age (more in middle age to elderly), gender (more often in male than female) genetic predisposition,

changes in gingival connective tissue homeostasis, pharmacokinetic variables, inflammatory changes and oral hygiene are some of the factors that influence drug relationship with gingival tissue (12).

The basis of the pathogenesis of this is the influx of calcium ions. In addition, several studies have found a role for fibroblasts, fibrogenic inflammatory cytokines, and matrix metalloproteinase (MMP) (14). The pathogenesis of DIGO is divided into inflammatory and non-inflammatory pathways. Non-inflammatory pathways include collagenase disruption due to disruption of folic acid uptake, inhibition of aldosterone synthesis in the adrenal cortex thereby providing feedback on increasing adrenocorticotropic hormones, and upregulation of keratinocyte growth factors. Inflammation can result from the direct toxic effects of drugs concentrated in gingival crevicular fluid and/or bacterial plaque that increase some proinflammatory cytokines (13). In patients taking CCB and experiencing DIGO, discontinuation of CCB administration and substitution with other classes of antihypertensives is the best way. In addition, the lesions can be treated surgically or non-surgically for temporary symptom relief, as recurrences may occur if the precipitating agent continues (12).

Thus, a study review is needed that describes the data from the results of research on gingival hyperplasia including prevalence, sociodemographic, pharmacokinetics, and oral hygiene in the last decade.

II. Materials And Methods

The literature used in this article was obtained from 3 databases: PubMed, ScienceDirect, and Google Scholar. The main source was obtained from PubMed with the keywords asfollows:(adverse drug reaction) AND (calcium channel blockers)) AND (gingival) independently. The search results that have been included in this review were then divided based on inclusion criteria and exclusion criteria. Inclusion criteria included research articles in English and textbooks containing information on gingival hyperplasia, adverse drug reactions, and Calcium Channel Blockers. Meanwhile, the exclusion criteria were systematic review articles, and case reports.

III. Result

Table 1. Search in PubMed

adverse drug reaction	52,612 results
calcium channel blocker	24,471 results
(adverse drug reaction) AND (calcium channel blockers)	486 results
(calcium channel blockers) AND (gingival)	138 results
(adverse drug reaction) AND (calcium channel blockers)) AND (gingival)	13 results

The main search found 25 articles (Figure 1). After screening the titles and abstracts, 9 articles did not meet the inclusion requirements so that 4 articles were included as the literature review.

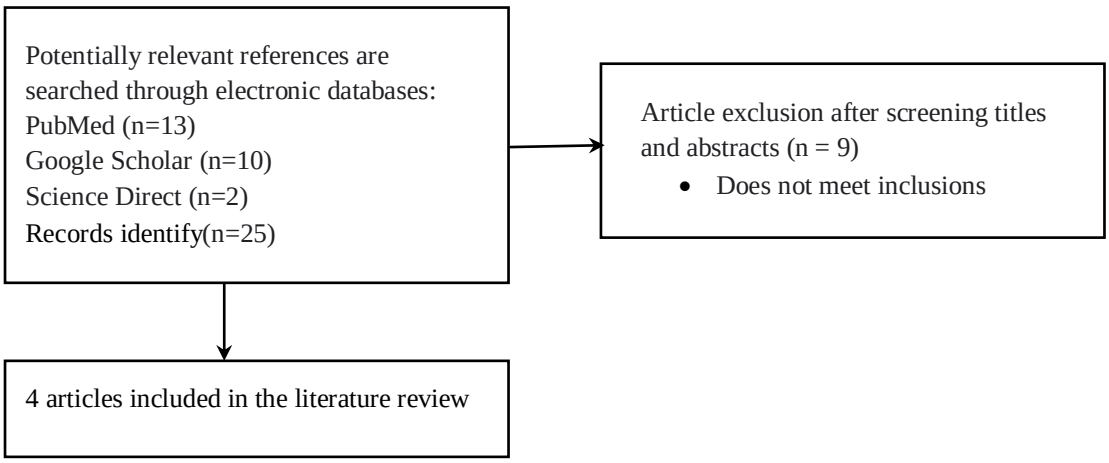

Figure 1. Chart showing article identification and selection. Although there were 25 suitable articles, only 4 were included in the inclusion criteria.

Table 1. Adverse Drug Reaction Study of gingival overgrowth due to the use of CCB

No.	Ref	Year	Objective	Result	Objective
1	18	2012	Prevalence of gingival overgrowth among elderly patients under amlodipine therapy at a large Indian teaching hospital	Cross-sectional	Patients with GO: ● 157 patients aged 60-78 years ● 50% female and 50% male ● 62.5% patients with a dose of 10 mg, ● 37.5% of patients with a dose of 5 mg ● mean plaque score: 2.95
2	15	2009	Gingival enlargement in antihypertensive medication	Comparative study	Patients who experienced GO were 81.2% of patients: ● 71.1% of patients used CCB, ● 21.5% used ACEI, ● 7.4% used beta-blocker
3	17	2015	Management of periodontal disease in patients using calcium channel blockers - gingival overgrowth, prescribed medications, treatment responses, and added treatment costs	Gingival Overgrowth Index (GOI) and Mann-Whitney test	Total 124 patients (58 females, 66 males, 4.6% of the patient population) used CCB. A total of 89 patients underwent GO, 75 of whom required treatment for GO. No difference was found between good and poor oral hygiene ($p = 0.074$). Long-term tooth loss: 0.11 teeth /patient/year.
4	16	2018	Influence of 3 calcium channel blockers on gingival overgrowth in a population of severe refractory hypertensive patients	Multivariable binary logistic regression analysis was	GO was observed in 55 patients (34.0%). Nifedipine was the most common drug (35.2%; 57 of 162). ● Patients with gingival overgrowth were 2.5 (odds ratio = 2.46; 95% confidence interval: 1.04-5.82) and 4.0 (odds ratio = 3.90; 95% confidence interval: 1.47-10.35) times more likely to use nifedipine and amlodipine, respectively, compared with patients without gingival overgrowth.

IV. Discussion

Prevalence

The prevalence of GO due to CCB is still in a wide variation range from 20% to 83%. Pradhan et al., found that the prevalence of gingival hyperplasia was 81.2% of the 150 patients taking antihypertensives, 71.1% of whom were using the CCB group, 21.5% were using ACE inhibitors, and 7.4% were taking Beta-Blockers (15). One of the studies described ADR of CCB class drugs including flushing, ankle or pedal edema, gingival hyperplasia (11). Other studies have shown that ACE inhibitors can cause dry cough while beta-blockers can cause ADR such as bradycardia, headache, insomnia, and depression (16).

The study by Vidal et al., also provided a fairly wide difference in prevalence, especially in the use of amlodipine, compared with the findings of Karnik et al., (5.1%), Vidal et al., found the prevalence of GO in the amlodipine group of 27.1%. This possibility has to do with genetics and genetic variation. Until now, various studies have stated that nifedipine is the drug that most commonly causes CCB-related gingival hyperplasia compared to amlodipine. This is supported by the results of a study by Vidal et al., which compared 3 types of CCB class drugs, where amlodipine has fewer side effects such as hypotension, peripheral edema, nausea, and palpitations (17).

Amlodipine, which is a class ofdihydropyridine CCBdrugs, works by relaxing smooth muscle, reducing vascular resistance, and lowering arterial pressure. Amlodipine is used once per day and can be increased the dose if needed (18).

Sociodemography

The population using CCB increases with age starting from the age of 40-50 years, reaching a peak of up to 25% of the elderly aged 80-90% in Norway (19). There was no significant relationship between GO and age. However, nifedipine-induced GO was gender-related, with malesthree times more likely to get GO than females, but not amlodipine. Amlodipine is the preferred third generation CCB because of its advantages over the first-generation CCB. Although amlodipine has a lower risk of GO than nifedipine, the increased use of this drug especially in the elderly group has a significant impact, especially GO as ADR in this population (20).

Pharmacokinetic Variables

Gingival overgrowth (GO) is one of the adverse drug reactions (ADR) caused by CCB, especially the DHP group, which is characterized by the accumulation of the extracellular matrix in the gingival connective tissue. The onset of GO generally occurs within the first month of drug administration (19). The pharmacological profile of amlodipine and nifedipine is similar in inducing GO, presumably due to drug-cellular interactions in the gingival tissue, but to a lesser degree in amlodipine, because amlodipine has a longer half-life, volume distribution, and higher plasma steady-state than nifedipine. Thus, amlodipine tends to bind to the tissue and thus is inactive for cellular interactions which results in a lower resultant GO (20).

The study on 103 patients with a mean age of 66.53 years, was observed for 11.3 years. Most of the patients, namely 89 people (86.4%) who took CCB experienced GO. There were no statistically significant differences in drug doses or 3 drug combinations (CCB and RAASi / IRAS, CCB and non-IRAS, CCB, and statins) against GO (19).

Although there is previous literature that found a link between felodipine and gingival hyperplasia, most of this literature is case reports and indeed has much less frequency than nifedipine and amlodipine. Studies on the relationship between GO and felodipine with a higher number of patients are still few, possibly due to the frequency of using felodipine as an antihypertensive relatively rarely compared to other CCBs. This may also lead to an insignificant relationship in related studies, because of 9.2% of the sample who received felodipine, only half had GO (17). The relationship between GO and pharmacokinetic variables is still a matter of debate, where many other factors influence this local reaction which makes pharmacokinetic variables in this literature show no significant effect (20).

Oral Hygiene

Patients with good oral hygiene have less GO than patients with poor oral hygiene. However, this difference was not statistically significant (19). In contrast to previous studies, a significant influence was found between oral hygiene and gingival inflammation, as assessed by plaque and gingival scores (20). Poor oral hygiene has shown a significant association with GO, as well as contributing to developing GO in some patients (15,17). Of the 150 patients, the plaque scores were poor or moderate, none of which was good. CCB users had the worst plaque scores compared to ACE inhibitors and beta-blockers. It is unclear whether the plaque score is a cause or effect of DIGO. Therefore, small gingival enlargement can be an important factor for the early detection of DIGO in patients. Some of the risk factors for DIGO include drug variables, concomitant medications, periodontal variables, age, gender, and genetic factors (15)

V. Conclusion

CCB is one of the antihypertensive drugs which often causes adverse drug reaction (ADR) in the form of gingival hyperplasia or gingival overgrowth (GO), especially the dihydropyridines group. The broad variability of GO prevalence is thought to occur due to differences in ethnicity, race, genetics, population characteristics and the criteria used. From the 4 literatures above, demographic factors (age, gender) do not have a significant effect on GO, while oral hygiene factors and drug pharmacokinetic variables still provide mixed results, therefore, further research on a larger scale is still needed.

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