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ORIGINAL ARTICLE

Potential oral manifestations of cardiovascular drugs

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OBJECTIVE: The aim of this work was to determine the frequency and nature of oral manifestations secondary to use of cardiovascular drugs.

METHODS: Five hundred and thirty one patients attending an adult cardiology clinic in Saudi Arabia were questioned about the occurrence of oral dryness, dysgeusia, or burning sensation and were clinically evaluated for the presence of oral mucosal or gingival disease. Data were statistically analyzed with chi-squared tests, odds ratios and Student's *t*-test.

RESULTS: Oral symptoms and/or signs were recorded in 75 (14.1%) patients with xerostomia being the most common (7.5%), followed by lichenoid (lichen planus-like) lesions (3.6%) and dysgeusia (1.9%). Xerostomia was significantly more frequent in patients with a history of diabetes mellitus and in female patients ($P < 0.05$). There were no statistically significant differences ($P > 0.05$) between patients with or without oral manifestations when age, gender, cardiovascular risk factor, cardiac disease, type of cardiac drug used or the number of medications were assessed. There was a trend for xerostomia to be less frequent in patients receiving therapy with angiotensin converting enzyme inhibitors and a slight trend of xerostomia to be more likely with increased number of non-cardiac and total number of agents per subject. The number of non-cardiac and total medications taken by patients with potential oral manifestations tended to be greater than that of patients without oral manifestations.

CONCLUSIONS: The frequency of potential oral manifestations in patients receiving cardiovascular agents was 14.1%. The occurrence and character of the oral manifestations had no significant relation with individual cardiac drugs, although there was a trend for oral manifestations to be likely with increasing number of drugs.

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Introduction

Adverse drug reactions (ADRs) can involve any body system and can be mistaken for signs of underlying disease. The mouth and associated structures can also be affected by many drugs or chemicals (Abdollahi *et al*, 2008). A wide spectrum of drugs can give rise to a number of adverse oral manifestations, particularly oral mucosal ulceration and/or dry mouth and many cardiovascular drugs (CVDs) have the potential to induce such adverse reactions (Porter and Scully, 2000). Drugs used for the treatment of cardiovascular disease were implicated in ADRs by about 3% of patients seen in an ADR clinic (Tran *et al*, 1998) but the precise extent of such reactions is not known as most are asymptomatic and go unreported. As the spectrum of available CVDs widens and the numbers of patients requiring such therapies continue to increase, the number of relevant drug prescriptions is also expected to rise. Accordingly, it can be predicted that the occurrence of ADRs, including those affecting the oral tissues will increase. The exact frequency of adverse effects by CVDs upon the oral tissues is unknown; hence it is not possible to predict if in the future there will be a need for specialized care of such disease. Hence, the aim of the present study was to determine the frequency and character of potential adverse drug reactions in the mouth in a large cohort of patients regularly receiving CVDs.

Materials and methods

The study group comprised patients attending the adult cardiology clinic, during the months of July and August 2008, at the Prince Sultan Cardiac Center, Riyadh, Saudi Arabia for their regular cardiac follow up. All patients were receiving one or more group of cardiovascular-active drugs (e.g. alpha-adrenergic blockers, angiotensin converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), anti-arrhythmics,

beta-adrenergic blockers (BABs), calcium-channel blockers (CCBs), cardiac glycosides (digoxin), direct peripheral vasodilators, diuretics (potassium sparing, loop diuretics and thiazides), lipid lowering drugs (statins), platelets inhibitors (aspirin and clopidigrel) and I*f*-channel inhibitors (ivabradin). Ethical approval was obtained from the Research and Ethics committee of Prince Sultan Cardiac Center, Riyadh Saudi Arabia. Age, gender, CVD risk factors, type of CVDs, and drug history were obtained from all patients in their native language (Arabic).

A history of all oral symptoms (dysgeusia, xerostomia, and dysphagia) as well as for oral lesions (lichenoid lesions, aphthae, gingival overgrowth) was obtained from all patients and included onset, duration, constant or intermittent, initiating/precipitating factors, and associated manifestations such as dysarthria or dysphagia was recorded. All patients were clinically examined for the presence of oral disease [e.g. white lesions, ulceration or swelling(s)]. In addition, teeth and gum were examined for discolouration and gingival enlargement. The study did not include confirmatory investigations such as histopathological examination of lesional tissue, hence all diagnoses pertaining to visually detected oral disease must be considered to be probable rather than definitive.

Data were presented as means ± s.d. for continuous variables and as frequencies and percentages for categorical variables. Continuous variables were compared by Student's *t*-test. Categorical variables were compared using 2-sided continuity correction chi-squared tests and odds ratios with 95% confidence intervals (CIs) were calculated. All statistical analyses were performed with SPSS software (version 16.0; SPSS, Inc., Chicago, IL, USA), with significance set at $P < 0.05$.

Results

A total of 531 patients (323 males and 208 females) were included in the study. The patient age ranged from 15 to 93 years (mean age 58.5 ± 13.8). The mean number of all medications taken per subject was 5.53 ± 2.17. Frequencies and percentages of CVD risk factors (smoking, hypertension and diabetes mellitus), type of CVDs, drug history and oral manifestations of all patients are detailed in Table 1.

Seventy nine oral abnormal features were observed or recorded in 75 patients (14.1%) and included possible Lichen planus-like (lichenoid) lesions (19 patients), aphthous-like ulceration (5), xerostomia (40), dysgeusia (10), burning mouth (3) and gingival enlargement (2). Of note, most symptoms or signs were mild and patients were either unaware of their existence and/or their potential relation to CVDs.

Fifteen out of the 19 Lichen planus-like (lichenoid) lesions occurred on the buccal mucosa. Other sites included lateral border (1) and dorsum (1) of the tongue, palatal gingival (1) and angle of the mouth (1). Sixteen of these lesions were bilateral and three were unilateral and 15 were reticular in appearance while four had plaque like appearance.

Table 1 Cardiovascular disease, risk factors types and oral symptoms and signs in 531 patients from Saudi Arabia

Variable	*Frequency*	*%*
Males	323	60.8
Females	208	39.2
Cardiovascular risk factors		
Smoking	30	5.6
Hypertension	249	46.9
Diabetes	226	42.6
Cardiovascular diseases		
Coronary artery disease	319	60.1
Valvular heart disease	113	21.3
Congenital heart disease	5	0.9
Arrhythmia	69	13.0
Heart Failure	39	7.3
Cardiovascular drugs		
Alpha-adrenergic blockers	20	3.8
Angiotensin converting enzyme inhibitors	256	48.2
Angiotensin receptor blockers	101	19.0
Antiarrythmics (Na blockers)	2	0.4
Antiarrythmics (K blockers)	25	4.7
Beta-adrenergic blockers	385	72.5
Calcium-channel blockers	132	24.9
Cardiac glycosides (Digoxin)	75	14.1
Direct acting peripheral vasodilators	156	29.4
sparing)	65	12.2
Diuretics (Loop)	180	33.9
Diuretics (Thiazides)	33	6.2
Statins	367	69.1
Platelet inhibitors (Aspirin)	380	71.6
Platelet inhibitors (Clopidigrel)	104	19.6
I*f*-Channel inhibitors (Ivabradine)	2	0.4
Warfarin	55	10.4
Oral symptoms and signs		
Lichen (lichenoid) lesions	19	3.6
Xerostomia	40	7.5
Aphthae	5	0.9
Dysgeusia	10	1.9
Burning mouth sensation	3	0.6
Gingival enlargement	2	0.4

Frequencies of CVD risk factors (smoking, hypertension and diabetes mellitus), type of CVDs and drugs used (whenever applicable) for each symptoms or signs are detailed in Table 2. The mean number of cardiac, non-cardiac and total medications taken per subject for patients with oral manifestations (total and for each manifestation) as well as for those without oral manifestations and the correspondent *P*-values are detailed in Table 3.

Xerostomia was significantly more frequent in patients with a history of diabetes mellitus and in females ($P < 0.05$) with a trend to be less frequent in patients taking ACEIs (OR = 0.491, 95% CI 0.248–0.975, $P = 0.057$) and a slight trend to be more frequent with increased number of non-cardiac and total (cardiac and non-cardiac) number of medications per subject (1.55 ± 1.32 *vs* 1.17 ± 1.18 and 6.08 ± 2.16 and 5.46 ± 2.16, $P = 0.086$ and 0.091, respectively). No significant relation was observed between xerostomia and age (mean age for patients with and without xerostomia were 58.8 ± 8.4 *vs* 58.5 ± 13.9, respectively).

Similarly, the number of non-cardiac and total (cardiac and non-cardiac) medications taken by patients with oral manifestations had a trend to be more than

Table 2 Frequencies of oral symptoms and signs in 531 patients receiving different cardiovascular drugs

Variable	*Lichenoid* (n = *19*)	*Xerostomia* (n = *40*)	*Aphthae* (n = *5*)	*Dysgeusia* (n = *10*)	*Burning mouth sensation* (n = *3*)	*Gingival enlargement* (n = *2*)
Males	12	18[a]	1	7	0	2
Cardiovascular risk factors						
Smoking	3	1	0	0	0	0
Hypertension	11	18	2	6	0	1
Diabetes	11	25[b]	1	4	2	0
Cardiovascular diseases						
Coronary artery disease	13	24	2	6	0	1
Valvular heart disease	2	10	1	3	3	1
Congenital heart disease	1	0	0	0	0	0
Arrhythmia	3	2	1	1	0	0
Heart failure	1	3	0	1	0	0
Cardiovascular drugs						
Alpha-adrenergic blockers	1	1	0	0	0	0
Angiotensin converting enzyme inhibitors	11	13[c]	3	6	0	1
Angiotensin receptor blockers	3	11	0	2	1	1
Antiarrythmics (Na blockers)	0	0	0	0	0	0
Antiarrythmics (K blockers)	2	2	0	0	0	0
Beta-adrenergic blockers	14	33	5	8	2	2
Calcium-channel blockers	8	7	2	4	0	1
Cardiac glycosides (Digoxin)	1	6	0	2	1	0
Direct acting peripheral vasodilators	7	10	2	2	0	0
Diuretics (K-sparing)	1	8	0	2	0	0
Diuretics (Loop)	3	16	0	6	2	0
Diuretics (Thiazides)	3	3	1	0	1	1
Statins	15	31	4	6	1	1
Platelet inhibitors (Aspirin)	17	30	3	7	1	1
Platelet inhibitors (Clopidigrel)	6	10	1	3	0	0
I*f*-Channel inhibitors (Ivabradine)	0	0	0	0	1	0
Warfarin	2	1	1	2	1	1

[a]$P = 0.040$.
[b]$P = 0.013$.
[c]$P = 0.059$.

Table 3 Mean numbers of medications each person received

Mean number per subject	*Without OMs* (n = *456*)	*With OMs* (n = *75*)	*Lichenoid* (n = *19*)	*Xerostomia* (n = *40*)	*Aphthae* (n = *5*)	*Dysgeusia* (n = *10*)	*Burning mouth sensation* (n = *3*)	*Gingival enlargement* (n = *2*)
Cardiac medications	4.29 ± 1.74	4.52 ± 1.58[a]	4.89 ± 1.56[a]	4.53 ± 1.48[a]	4.20 ± 2.59[a]	5.00 ± 1.63[a]	3.00 ± 1.15[a]	4.00 ± 1.49[a]
Other medications	1.17 ± 1.18	1.43 ± 1.22[b]	1.37 ± 1.30[b]	1.55 ± 1.32[b]	1.60 ± 0.89[b]	0.80 ± 0.63[b]	2.00 ± 1.73[b]	1.00 ± 0.00[b]
Total medications	5.46 ± 2.16	5.95 ± 2.21[c]	6.26 ± 2.35[c]	6.08 ± 2.16[c]	5.80 ± 3.42[c]	5.80 ± 1.87[c]	5.00 ± 2.52[c]	5.00 ± 1.41[c]
	P-value[a]	0.251	0.118	0.348	0.942	0.206	0.287	0.821
	P-value[b]	0.094	0.523	0.086	0.349	0.103	0.494	0.002
	P-value[c]	0.080	0.160	0.091	0.836	0.585	0.938	0.725

OMs, Oral Manifestations.
[a]Compared with Cardiac medications without OMs.
[b]Compared with Other medications without OMs.
[c]Compared with Total medications without OMs.

that of patients without oral manifestations (1.43 ± 1.22 *vs* 1.17 ± 1.18 and 5.95 ± 2.21 *vs* 5.46 ± 2.16, $P = 0.094$ and $P = 0.080$, respectively).

There were no other statistically significant differences ($P > 0.05$) between patients with and without oral symptoms or signs for age, gender, type of cardiovascular risk factor, type of cardiac disease, type of cardiac drug used or the number of medications taken per subject. The apparently significant *P*-values for valvular heart disease and I*f*-channel inhibitors in the patients with burning mouth were not considered clinically relevent due to the low number of variables.

Discussion

This study was conducted in the adult cardiology clinic at Prince Sultan Cardiac Center, Riyadh, Saudi Arabia. The majority of patients (60.1%) had coronary artery disease (CAD), which reflects the high incidence of this disease in the studied adult cardiology clinic population.

Hypertension and diabetes mellitus affected 46.9% and 42.6% of patients, respectively, which is consistent with the high prevalence of these risk factors for CAD in adults in Saudi Arabia (Al-Nozha *et al*, 2004, 2007) and represented by the high frequency of agents, such as BABs (72.5%), ACEIs (48.2%), aspirin (71.6%) and lipid lowering statins (69.1%).

Only 75 of the 531 patients (14.1%) with CVD had clinically detectable or recorded oral symptoms or signs that might represent an adverse reaction to a CVD. The most frequent oral symptom was xerostomia in 40 subjects (7.5%), which is already known to be a likely oral adverse effect of many groups of drugs (Smith and Burtner, 1994; Shinkai *et al*, 2006). However, the presently observed frequency is far below the 80.5% reported in some studies of patients receiving other drug therapies (Smith and Burtner, 1994). The second most frequent oral manifestation was lichen planus-like (lichenoid) lesions in 19 (3.6%) followed by dysgeusia in 10 (1.9%). It was not possible to establish if the lichen planus-like disease was consequent of the drugs therapy as none of the patients had been examined prior to the commencement of their drug therapy, however 14 of the 19 patients had received BABs that are known to give rise to lichenoid drug reactions (McCartan and McCreary, 1997). The frequencies of aphthous-like ulcers, burning mouth and gingival enlargement were all $< 1\%$ (0.9%, 0.6%, and 0.4%, respectively). The low frequency of gingival enlargement is perhaps surprising as many patients were receiving CCBs and it has previously been suggested that up to 38% of patients receiving this group of agents may be expected to have some degree of gingival enlargement (Marshall and Bartold, 1998).

Xerostomia was significantly more frequent in patients with diabetes mellitus and in female patients ($P < 0.05$), which is consistent with the literature (Sreebny *et al*, 1992). Xerostomia tended to be less frequent in patients taking ACEIs (OR = 0.491, 95% CI 0.248–0.975, $P = 0.057$). Despite lisinopril being known to reduce salivary flow (Sreebny and Schwartz, 1997), ACEIs are not reported to be among the drugs that may cause of xerostomia (Kuechle *et al*, 1994). A possible explanation of the ACEIs not causing xerostomia might be their protective effect against new onset diabetes mellitus (Gillespie *et al*, 2005; Aguilar and Solomon, 2006). While BABs and diuretics have been suggested to be causes of drug induced xerostomia (Persson *et al*, 1991; Streckfus, 1995), this was not observed in the present large study.

No statistically significant difference was detected between patients with and without oral manifestations and the number of cardiac drugs used. In contrast, the number of non-cardiac and total (cardiac and non-cardiac) medications was slightly increased in patients with oral symptoms or signs than those without these features (1.43 ± 1.22 *vs* 1.17 ± 1.18 and 5.95 ± 2.21 *vs* 5.46 ± 2.16, $P = 0.094$ and 0.080, respectively). This tendency might have become significant if more patients were included in the study, but it is evident that drug-related oral disease is not common in patients with drug-treated CVD. As multiple drug combinations can increase pharmacokinetic drug interactions and the potential for ADRs development (Abernethy and Flockhart, 2000; Nakagawa and Ishizaki, 2000), the increased number of medications per subject may perhaps explain the occurrence of oral symptoms and signs in patients receiving many CVDs.

Most of the oral symptoms and signs recorded or observed in the group of patients seem to have been minor, patients being unaware of their existence and/or their possible relation to CVDs. Hence, it would seem that studies that do not include detailed information of oral disease, may underestimate the exact prevalence of oral consequences of drug therapy. Nevertheless, the presently observed infrequency of significant oral symptoms and signs indicates that the oral quality of life of patients with CVD is not likely to be adversely affected by any attendant drug therapy.

In conclusion, although cardiovascular drugs have the potential to induce adverse reactions in the mouth, only 14.1% of 531 patients on these drugs had symptoms or signs that might reflect an adverse side effect. The presence of oral symptoms or signs is not significantly associated with particular groups of cardiac drugs but may be influenced by the number of drugs each person receives.

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