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Oral manifestations of drug therapy

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During the course of providing patient care, the dental practitioner may encounter a variety of oral abnormalities. A number of these may have developed because of a complication of the patient's concurrent drug therapy for a medical condition. The probability that these drug reactions will occur is increased because of current, wide spread attitudes on the part of both patients and health care providers in the United States. These include a ubiquitous demand for and use of medications (prescription and/or over-the-counter) for the treatment of acute and chronic diseases, as well as a multitude of nonspecific and trivial ailments. In addition, the pharmaceutical manufacturers are engaged in mass marketing of their products that are being promoted for a plethora of diseases. A heightened awareness about health issues has also been stimulated by mass media coverage of health-related issues in the daily news reports. Internet web sites that are dedicated to health-oriented content are providing additional sources for information about diseases and treatment options.

This environment has heightened awareness about the practice of medicine and increased demands for treatment [1]. As a consequence, it has been estimated that at least 90% of office visits to a physician result in a prescription being given [2]. Another trend, the current and dramatic growth of our aging population with its better access to health care, will also intensify the need for medications for the management of acute and chronic diseases that are more prevalent in the elderly. A survey of a sample of Medicare subscribers found that more than 90% had visited a physician in 1997 [3]. Two recent indicators lend additional support to the prevalence of drug use in the United States. Data from pharmaceutical manufacturers revealed that more than 2.04 billion prescriptions were dispensed during the calendar year 2000 [4]. This was in addition to the $19 billion that were spent on over-the-counter medications that year [5].

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In addition, economic constraints and other obstacles that may restrict access to health care providers, as well as a better-informed public, have increased the desire to engage in self-medication. As a consequence, there has been a proliferation of over-the-counter agents and herbal medicines that are available in growing numbers of retail distributors. These trends have been further stimulated by renewed interest in alternative or complementary medicine that promotes the use of a variety of "natural" therapeutic agents whose effects, potential side-effects, and interactions have not been tested or documented [6]. Finally, biological and technological advances that are advancing our understanding of disease mechanisms are also enabling the development of new drugs for specific disease intervention or prevention.

In the modern dental practice, therefore, the practitioner should anticipate and needs to determine if an oral symptom or abnormality is a manifestation of an adverse drug reaction.

Classification of drug reactions

An oral side effect of a drug is considered to be the consequence of an undesirable effect or one that is "noxious and unintended" [7,8].

A variety of oral conditions may develop as complications from the use of drugs. The older literature appropriately labeled one such oral manifestation "stomatitis medicamentosa." Among more recent reviews of medication side effects, one report cited 46 orofacial abnormalities that were attributed to more than 150 medications [9]. In another report, 259 oral side-effects were identified and attributed to 113 of the 200 medications that were most frequently prescribed in 1992 [10].

Because of the number and variability of clinical manifestations that drug side effects can induce in the oral cavity, efforts have been made to classify and delineate these abnormalities. When the topic of adverse drug reactions was previously reviewed in *The Dental Clinics of North America* in 1984, eight categories of clinical manifestations were described [11]. Another periodical that regularly reports on dental therapies has also categorized eight types of drug reactions that may be encountered [12].

For the purposes of this article, six categories or descriptions of oral complications have been selected. The criteria used included side effects that are more likely to be encountered by the general dental practitioner, and complications that may result from drugs that are more frequently prescribed, or which are used over the long term for the management of chronic diseases. The categories of drug reactions and the medications that may cause them are summarized in Table 1.

One of the most frequent complications of drug therapy, xerostomia or dry mouth, will be discussed elsewhere in this issue.

Table 1
Oral manifestations of drug therapies and their etiology

Gingival hypertrophy
Phenytoin (Dilantin®)
Calcium channel blockers
Nifedipine (Procardia®, Adalat®), diltiazem (Cardizem®, Dilaclor®), verapamil (Calan®, Isoptin®, Verelan® and amlodipine (Norvas®)
Cyclosporine (Neoral®, Sandimmune®)
Tooth discoloration
Tetracyclines
Minocycline (Minocin®)
Candidiasis
Broad spectrum antibiotics (tetracyclines)
Corticosteroids (prednisone)
Cancer chemotherapeutic agents (alkylating agents, antimetabolites)
Immunosuppressants
Corticosteroids
Antirejection drugs (Cyclosporine)
Xerostomic medications
Burns
Aspirin and OTC products containing phenol, eugenol, or hydrogen peroxide
Taste aberrations (metallic taste)
Oral hypoglycemics (Metformin)
Antimicrobial (Metronidazole, tetracycline)
Antipsychotic (Lithium)
Antirheumatic (Allopurinol, penicillamine, phenylbutazone, gold salts)
Cardiovascular (Enalapril)
Cancer chemotherapeutic agents (Methotrexate)
Gold compounds (Auranofin)
Immunosuppressants (Corticosteroids, antirejection drugs)
Xerostomic medications
Lichenoid drug reactions
Antibiotics
Oral hypoglycemics
Antihypertensives
Nonsteroidal anti-inflammatory agents
Gold compounds

OTC, over-the-counter.

Soft tissue abnormalities

Gingival hyperplasia

Enlargement or overgrowth of the gingiva is a recognized complication that has been associated with the administration of phenytoin (Dilantin®), some calcium channel blockers, and cyclosporine (Sandimmune®). Although the cause and effect relationship with phenytoin was identified more than 60 years ago, the mechanism by which these drugs induce the hyperplasia has not been determined.

Phenytoin

Recent estimates have found that epilepsy and other seizure disorders affect between 5–10% of the population [13]. The first drug to be used for these patients, phenytoin (Dilantin®), was still listed among the 200 most frequently prescribed drugs in the United States in 2000 [4]. Clinical studies have found that approximately one half of the patients who are on phenytoin therapy develop gingival hyperplasia [14,15]. The risk for and degree of phenytoin enlargement is increased by poor oral hygiene, accumulation of plaque, and subsequent gingival inflammation; therefore, maintenance of good home care can minimize the overgrowth. There is no evidence that the use of phenytoin in conjunction with the other drugs that cause gingival hyperplasia will have an additive effect on the overgrowth. Other pathophysiological processes, however, can result in enhancement of the hyperplasia (Fig. 1).

Calcium channel blockers

Calcium channel blockers have been used for more than 20 years for the treatment of a variety of cardiovascular diseases including angina, arrhythmias, and hypertension. These drugs may also be effective for the management of other conditions, such as atherosclerosis, Raynaud's phenomenon, migraine headaches, peripheral vascular disease, and stroke [16]. In addition, calcium channel blockers are being investigated for potential use to treat a number of other disorders [16]. Because cardiovascular disease is one of the most prevalent conditions in the United States (and remains the leading cause of death), it was estimated that in 1995 at least 6 million individuals were using a calcium channel blocker [17]. Among the 10 calcium channel blockers currently available, 3 have been found to induce gingival hyperplasia more frequently. They are nifedipine (Procardia®, Adalat®), diltiazem (Cardizem®, Dilaclor®), and verapamil (Calan®, Isoptin®, Verelan®) [18]. These three calcium channel blockers were

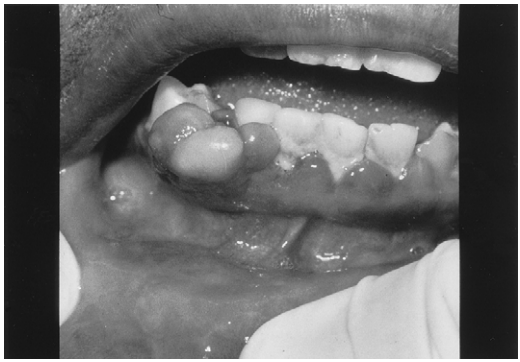

Fig. 1. Gingival hyperplasia with a concurrent pyogenic granuloma in a postpartum patient who was taking phenytoin (Dilantin®).

among the 200 most frequently prescribed medications in the United States in 2000 [4].

The effect of the calcium channel blockers on the gingiva is variable and unpredictable. A number of investigations have reported the incidence of hyperplasia to range from 20–83% [19,20]. The overgrowth is also influenced by the patient's compliance with oral hygiene (Fig. 2). If the patient can discontinue the therapy or be given an alternative medication, the hyperplasia will regress [18].

Cyclosporine

Cyclosporine (Sandimmune®, Neoral®) is an immunosuppressant drug that inhibits immune mechanisms that cause the rejection of transplanted organs. The drug was first used in 1978 for patients who had received kidney transplants [21]. Clinical studies have found that gingival hyperplasia develops in approximately 5–16% of patients who are taking cyclosporine [22], but in one report it occurred in 70% of the recipients [23]. The likelihood that the dental practitioner will encounter cyclosporine-induced gingival hyperplasia is increasing. In 2000, nearly 73,000 organ and bone marrow transplantations were performed in the United States [24], and patients who have received transplants are surviving for longer periods.

The clinical characteristics of cyclosporine-induced gingival hyperplasia are similar to those caused by phenytoin or the calcium channel blockers, and the overgrowth is also influenced by poor oral hygiene and the accumulation of dental plaque (Fig. 3). Discontinuance of therapy or a reduction of the cyclosporine dose may resolve the hyperplasia [25].

It has been reported that cyclosporine, when administered with a calcium channel blocker, can have an additive effect on the gingival hyperplasia [26]. This combined therapy is more likely to be used for patients who had cardiovascular disease and required a kidney, heart, or lung transplant. Corticosteroids may be used in conjunction with cyclosporine to enhance the

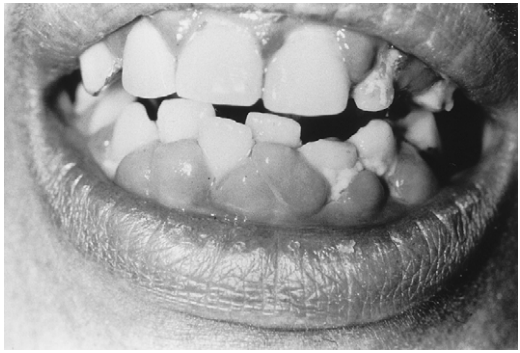

Fig. 2. Gingival hyperplasia in a patient who was taking the calcium channel blocker nifedipine.

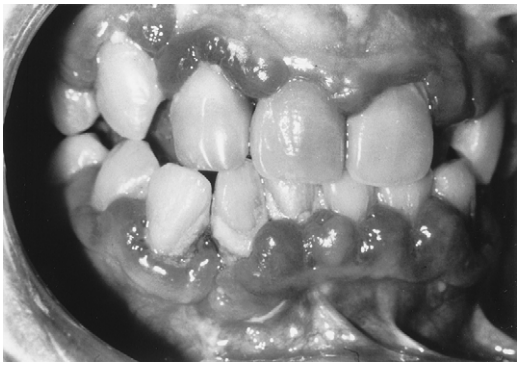

Fig. 3. A patient on cyclosporine therapy following kidney transplantation showing gingival hyperplasia, inflammation, and poor oral hygiene.

immunosupression and prevent organ rejection. This adjunctive therapy can increase the risk for oral candidiasis (see below).

Tooth discoloration

Tetracycline

In 1948, chlortetracycline, the first of the tetracyclines, was introduced. This group of antibiotics was only the fourth class of antimicrobial agents that were available at the time, which included the sulfonamides, penicillin, and streptomycin. The tetracyclines were the first "broad spectrum" antibiotics that were effective against both gram-positive and gram-negative bacteria as well as a number of other microorganisms [27]. Because of their wider range of antimicrobial activity, particularly for infections of the upper respiratory tract, and their availability for oral administration in the form of (liquid) suspensions, flavored syrups, or elixirs, they were frequently prescribed for pediatric patients.

Between 1961 and 1963, clinical evidence began to appear suggesting that tetracycline could cause tooth discoloration [28]. This association was subsequently substantiated by a number of clinical and laboratory studies demonstrating that tetracycline becomes irreversibly bound to calcified tooth structures if it is administered during the calcification stages of tooth development [28]. Following these disclosures, the pharmaceutical manufacturers of these antibiotics inserted warnings that the tetracyclines were contraindicated for use in children under 8 years of age.

Minocycline

A more recent concern, however, is tetracyclince-induced discoloration of the permanent dentition after its development has been completed. This

phenomenon has been associated with another tetracycline product, minocycline (Minocin®) [29,30]. Minocycline is a semisynthetic tetracycline derivative that became available in 1972 [27]. Current indications for the use of minocycline include bronchitis, acne, genitourinary infections, and gastrointestinal ulcers suspected to be caused by *Heliobacter pylori* [31]. Minocycline has also been assessed for use in conjunction with antirheumatic drugs for the treatment of rheumatoid arthritis [32]. Following minocycline therapy, pigmentation of the skin, nails, sclera, and gingiva has occurred, but these effects are reversible after treatment is discontinued [31].

The process by which this antibiotic penetrates permanent tooth structure has not been determined, but two theories have been proposed: (1) the antibiotic is absorbed from the systemic circulation via the pulpal blood vessels into the dentin, and (2) it enters through defects in the enamel surface from the crevicular fluid [29]. Another possibility is that the drug enters the saliva from the systemic circulation and permeates exposed dentin tubules that have been exposed by attrition (Fig. 4).

The degree of minocycline discoloration can be very intense if the drug is incorporated into tooth structures during their development (Fig. 5). It has been suggested that this stain is a manifestation of drug degradation products that consist of a minocycline-hemosiderin complex [31].

Altered immunity and candidiasis

The immune system protects the body from infection. A common oral manifestation of a loss of immunity is the development of an opportunistic infection by the fungus *Candida albicans*. Oral candidiasis has several clinical manifestations that are described as pseudomembranous (white patches), atrophic (erythematous, red, or inflamed), denture stomatitis, or median rhomboid glossitis [33].

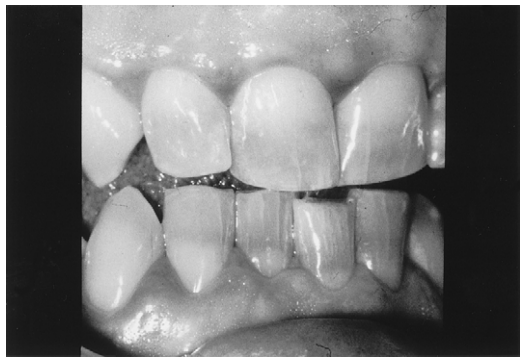

Fig. 4. Minocycline-induced discoloration of the permanent dentition in a 35-year-old patient who had been taking the medication for 3 years.

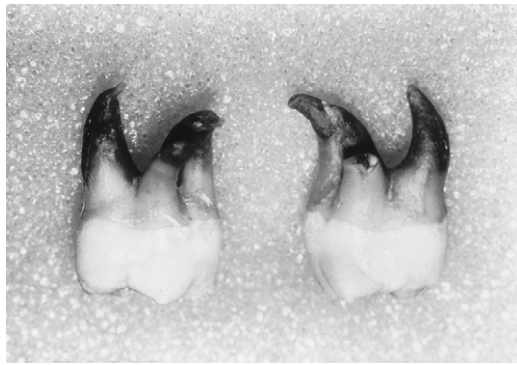

Fig. 5. Intense staining of the roots of two maxillary third molars. The patient began to take minocycline at age 17.

A number of drugs can suppress the body's immune responses and induce candidal overgrowth. These include the corticosteroids, cancer chemotherapeutic agents, and immunosuppressants (Table 1). The corticosteroids (glucocorticoids) are extensively used for their anti-inflammatory and immunosuppressant properties in the treatment of rheumatic, collagen, and similar autoimmune diseases, as well as asthma and other allergic disorders. Prednisone, a synthetic glucocorticoid was ranked 27th among the 50 most frequently prescribed drugs in 1999 [34].

Corticosteroids may be used in conjunction with anti-rejection drugs following organ and bone marrow transplantation (see cyclosporine, above). This combined immunosuppressive therapy may have an additive effect on the risk for developing oral candidiasis.

Systemic treatment with corticosteroids often entails long-term use that places patients at increased risk for developing oral candidiasis. This risk is increased by smoking, denture use, dry mouth, diabetes [35], and concurrent administration of other medications that can enhance the overgrowth of candidal organisms (see Table 1).

Corticosteroids are also administered by inhalation for the treatment of asthma and other respiratory diseases. This route of administration appears to have a variable effect on candidal overgrowth that had been found to range from $<$1–7% [36,37].

Treatment with cancer chemotherapeutic agents places patients at high risk for oral infections, the majority of which are caused by *C albicans* [38]. Cancer chemotherapy also causes dry mouth, which increases the possibility of a candidal infection.

Finally, oral candidiasis can develop following a change in or suppression of the normal oral flora. This is likely to occur following the administration of antibiotics, particularly those with broad spectrum activity such as tetracycline [33]. The overgrowth is also enhanced by other environmental factors in the oral cavity, including xerostomia, smoking, and the use of dentures [35].

Chemical injuries

Chemical burns of the oral tissues are common occurrences that may be accidental (ingestion by children), or from misuse of products that are being used for self-medication. The ''aspirin burn'' probably represents the typical example of such a reaction that the dentist may encounter.

An increasing number of over-the-counter ''do it yourself'' topical agents are available for the relief of oral pain. These products may contain phenol, eugenol, or concentrated hydrogen peroxide, all of which can also burn the oral mucosa. If these remedies are used to treat dental pain that originates from the pulp or the periodontium, it is unlikely that they will provide adequate relief. The patient may then resort to prolonged or repeated applications of the material that can result in mucosal injury.

Taste aberrations

Changes in the perception of taste or ''dysgeusia'' are estimated to affect several million individuals [39]. Abnormal taste sensations have been attributed to a number of diverse systemic diseases [39], or the cause may be obscure or nondeterminable. The use of medications has also been implicated. When the side effect of a drug results in a taste aberration, it may be a direct effect of the medication, or an indirect effect that is mediated by, for example, a drug-induced overgrowth of *Candida* (see above) or xerostomia. A variety of abnormal taste perceptions can occur, but patients usually seek professional attention from the dentist for a metallic taste. Several categories of drugs have been associated with metallic taste and are listed in Table 1 [40]. This sensation may also become apparent after the placement or insertion of an amalgam restoration or metal prosthesis, which is then implicated as the cause.

Lichenoid drug eruptions

Lichen planus is considered to be a dermatologic condition but it frequently occurs on the oral mucosa. Dentists are likely to encounter patients with this disorder, particular if it causes any discomfort or concern. Lesions on the oral mucosa that resemble lichen planus have been linked to a number of medications that encompass a variety of pharmacologic categories. These include antibiotics, oral hypoglycemics, antihypertensives, nonsteroidal anti-inflammatory agents, and agents that contain heavy metals (eg, lithium, gold compounds) [39,41]. Lichenoid lesions have also been reported to result from direct contact with cinnamon [42] or as a manifestation of allergy to amalgam [43]. Patients with lichen planus should, therefore, have a comprehensive review of their drug history as part of their initial evaluation prior to initiating other diagnostic or treatment efforts.

Summary

The oral cavity may be the target organ for a number of diverse abnormalities that develop from side effects of medications. Because of the widespread and increasing use of prescription, over-the-counter, and herbal remedies, it is becoming increasingly likely that the dentist will encounter soft tissue or dental pathologies that represent a complication of a therapeutic agent. The more common abnormalities that may occur include gingival hyperplasia, tooth discoloration, candidiasis, chemical injuries, and altered taste perception. The dental practitioner is often the primary health care provider who can recognize, diagnose, treat, and/or prevent these conditions.

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