11 Adverse Drug Reactions

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Adverse drug reaction is a broad term comprising many problems associated with drug use. It includes side effects, toxicity, drug–drug interactions, drug–physiology interactions, drug–laboratory test interactions, allergic reactions, and idiosyncratic reactions (Table 11–1). This chapter focuses on two aspects of adverse drug reactions, significant drug–physiology interactions (side effects) and drug–drug interactions. These two areas comprise what is commonly termed, in dentistry, drug interactions. Fortunately, severe problems from drug interactions are rare in dentistry. Avoiding the most common dental interactions is relatively simple and is outlined in this chapter.

Though an awareness of the "at-risk drugs" is important, understanding of the "at-risk patient" is even more valuable. There is a greater risk of having an adverse drug reaction in certain patients than in others. In certain high-risk patients, avoiding the use of erythromycin, ketoconazole, and metronidazole will, essentially, eliminate the risk of drug–drug interactions.

The primary drugs used in dentistry fall into five different groups: local anesthetics, analgesics, antimicrobials (antibiotics, antifungals, antivirals), sedatives, and drugs that affect the autonomic nervous system (antihistamines, sympathomimetics, and less commonly, anticholinergics). Several other drug groups are uncommonly used in general dental practice. Antidepressants, owing to their serotoninergic action are useful in chronic pain management, and corticosteroids are used to treat oral autoimmune diseases, such as lichen planus, pemphigoid, erythema multiforme, and pemphigus. Since the primary dental drugs are used for a short duration at only moderate dosage, in relatively healthy individuals, the risks of untoward reactions are minimal. At the same time, an understanding of mechanisms of adverse drug reactions assists in avoiding problems.

Mechanisms of adverse drug reactions

Drug–physiology interactions

Drugs have specific effects on body functions and are selected for these effects. For example, aspirin has an antiprostaglandin effect, which leads to the dentally useful effect of decreasing inflammation and pain. At the same time, a drug may have effects on other physiologic systems and, thus, may not be useful to the den-

Table 11–1 Definitions of Terms, All Considered To Be Adverse Drug Reactions

Term	*Definition*
Toxicity	Overdose of a drug that injures a physiologic system
Side effect	Expected or predictable undesirable effect of a drug that occurs at therapeutic doses
Drug–drug interaction	The presence of one drug effects the pharmacodynamics (absorption, distribution, metabolism, excretion) of another drug
Drug–physiology interaction	The presence of a drug alters the bodies physiology, leading to a harmful condition (may overlap with the concept of side effect)
Drug–laboratory test interaction	Drug will alter laboratory test results without impacting the physiologic system being measured—essentially a false-positive or false-negative laboratory test result
Allergic reaction	Drug triggers an immunologic response
Idiosyncratic reaction	Drug creates a physiologic or psychological response that is unpredictable and is unique to the individual

Table 11–2 Significant Drug–Physiology Interactions

Drug	*Desired Dental Response*	*Undesired Physiologic Response (In Dental Settings)*
Aspirin	Analgesic	Bleeding
Barbiturates	Sedative	Respiratory depression
Narcotics	Analgesic	Respiratory depression
Vasoconstrictors	Localize anesthetic solution	Increase cardiac excitability

tist. For example, the antiprostaglandin effect of aspirin also prevents platelets from adhering. Therefore, a side effect or drug–physiology interaction may be excessive bleeding. Such drug–physiology interactions are relatively common, but significant ones, those that are life-threatening, occur only with a few drugs used in dentistry (Table 11–2).

The second drug–physiology interaction is toxicity. This adverse drug reaction is associated with the dose of the drug and may be an extension of its therapeutic effect or may be an effect on another system. Toxic effects of drugs should not happen, since most drugs used in dentistry have a wide margin of safety between the therapeutic dose and the toxic dose. The most common reason for drug overdose is a failure to take into account the size of the patient; overdose toxicity is more common in children and the frail elderly. The second most common reason for overdose is failure to adjust dosing to take into account the patient's inability to metabolize or eliminate the drug. Therefore, if the dentist is aware of the proper dose and alert to the patient's size as well as their liver and kidney function, chances of overdosing are minimized. The practitioner must also keep in mind that the patient may be taking other medication, especially over-the-counter medication, which may have additive toxicity to the medication used in dentistry.

Drug–drug interactions

The classic drug–drug interactions comprise four different aspects of drug pharmacodynamics: absorption, distribution, metabolism, and excretion. Absorption is not a crucial aspect when discussing adverse drug reactions in dentistry. It is possible that food in the stomach may lower the absorption rate, but neither final blood level nor therapeutic effect is substantially altered. All drugs given for dental purposes, at the appropriate dosage, should eventually be adequately absorbed to obtain therapeutic blood levels. Certainly, if the patient regurgitates the bulk of the drug, then therapeutic blood levels cannot be obtained, and it may be necessary for the patient either to retake the drug or to receive it parenterally. In patients with malabsorption, extensive colitis, or other gastrointestinal problems, the dentist should consult with the patient's physician to establish ways of ensuring that necessary medications are given in such a way that therapeutic blood levels are achieved.

Drug distribution in the body has the potential to initiate adverse reactions. Some drugs are bound to plasma proteins; once at the site of action, the therapeutic effect is created by the free drug. A drug administered by the dentist may have a higher affinity for the plasma protein, and will therefore displace the drug already bound. This will cause higher concentrations of the original drug in the plasma and a possible toxicity reaction. This primarily occurs with highly protein-bound medical drugs that have narrow therapeutic margins of safety, such as the anticoagulant, dicumarol.

For drugs used in dentistry, problems associated with excretion are important only for those patients with significant kidney problems. When the kidney is not functioning properly, any drug excreted by the kidney is excreted more slowly. This decrease in excretion rate may allow blood levels to rise to potentially toxic levels. Some dental drugs can have a toxic effect on specific organs, including the kidney and liver. For patients with liver and kidney problems, dental drugs should be chosen so as to have minimum impact on the diseased organ (Table 11–3).

The most important area of drug–drug interactions is drug metabolism. Most drugs given in dentistry and most drugs given for medical purposes are metabolized by enzymes in the liver. The primary group of metabolizing enzymes is called the cytochrome P-450 system. These are areas in liver cells that act as latticed processing stations. These surfaces are coated with various enzymes. The cytochrome P-450 enzyme system is subdivided into isoenzyme groups. The enzymes metabolize a wide range of compounds. Some drugs induce the synthesis of these enzymes, thereby accelerating their own metabolism and the metabolism of other drugs. Some drugs inhibit these metabolizing enzymes, thereby slowing their own metabolization or slowing the metabolization of other drugs. The most serious drug–drug interactions are related to either inducing or inhibiting isoenzyme groups within the cytochrome P-450 system. In dentistry, four drugs, the antibiotics, erythromycin, clarithromycin, metronidazole, and the antifungal drug, ketoconazole, are known inhibitors of cytochrome P-450 enzymes (Table 11–4). When using any of these

Table 11–3 Dental Drugs with Toxic Effects on Specific Organs

Drug	*Use*	*Affected Organ*
Acetaminophen	Analgesia	Liver
Corticosteroids	Anti-inflammatory	Immune system
Ketoconazole	Antifungal	Liver

four drugs, the dentist should be alert to whether the patient is taking any other medication and be prepared to evaluate a possible interaction. It might be appropriate to choose a different drug to treat the oral problem.

Drug allergies

In dentistry, drug allergies are the most common adverse drug reaction encountered. Patients frequently claim to have allergies to penicillin, aspirin, or codeine. A true allergic reaction is an immune system-mediated response to an allergen. Almost any drug or compound can be an allergen. (Actually most drugs are too small to be antigenic by themselves and must combine with a carrier protein, or hapten, to create an allergic response.) Most severe allergic reactions are immediate type, humoral (B cell) antibody-mediated reactions. The allergen (drug) exposure precipates an antibody response, and the resultant cascade of events includes histamine release that causes swelling, redness, and itching (urticaria). Most commonly, this manifests as a rash on the body, but infrequently it manifests as perioral swelling (angioneurotic edema) or swelling in the throat adequate to restrict or prevent breathing (anaphylaxis). Delayed allergic reactions are mediated through the cellular (T cell) branch of the immune system, and these usually manifest as skin rashes, blisters, and at times, oral ulcerations.

Dental management

The primary approach to allergic reactions is to avoid them by obtaining a thorough patient health history with respect to allergic reactions. The dentist should interview the patient about allergies, especially allergies to medications commonly used in dentistry, including antibiotics, pain medications, or local anesthetics. True allergic reactions to local anesthetic are extremely rare, and, even then, it is usually a reaction to the preservative; nevertheless, this information is necessary to avoid an adverse response to dental treatment.

Table 11–4 Drugs Used in Dentistry that Alter Cytochrome P-450 Enzymes

Drug	*Use*	*Effect on Cytochrome P-450 Enzymes*
Erythromycin	Antibiotic	Inhibit
Ketoconazole	Antiflangal	Inhibit
Clarithromycin	Antibiotic	Inhibit
Metronidazole	Antibiotic	Inhibit
Barbiturates	Sedative	Stimulate
Dexamethasone	Steroidal anti-inflammatory	Stimulate

When a patient claims to have had an allergic reaction, further questioning is necessary. If the patient has experienced a true immune system-mediated allergic reaction, such as redness, swelling, rash, or itching, the drug should be avoided. If the "allergic reaction" was actually an adverse physiologic response to the drug or the dental experience, such as stomach upset, dizziness, or nausea, which do not constitute an immune system-mediated reaction, it is not a true allergy. Still, the drug should be avoided, if possible, because the patient's next exposure may precipitate a true allergic response, or it may precipitate the same adverse physiologic response the patient reported. In any event, the patient will be upset at having been exposed to a drug to which he or she reported having an "allergy."

Allergic responses are treated by withdrawal of the drug and possibly antihistamines or corticosteroids. Depending on the severity of the reaction, as in the case of laryngeal swelling (anaphylaxis), it may be necessary to give an injection of epinephrine to physiologically reverse the allergic response.

The management of patients in a dental setting, to minimize the risk of other adverse drug reactions, has two aspects. The first is to avoid adverse drug reactions by identifying the patient who is at high risk. The second is to understand which specific drugs have the greatest probability of causing adverse drug reactions. The practitioner should be aware that some patients are at much higher risk of adverse drug reactions than others. Identifying these patients and treating them accordingly is the most effective way to minimize risk. Patients at greatest risk are those taking multiple medications, those who are medically compromised, and those who are taking specific medications that are closely titrated and have a narrow therapeutic index. The therapeutic dose of highly titrated drugs is just slightly less than the dose that causes adverse reactions. These drug groups are the following:

1. Anticoagulants
2. Anticonvulsants
3. Hypoglycemics
4. Cardiac glycosides
5. Lithium

It is estimated that medically complex patients, depending on the definition used, comprise from 15% to 25% of the average dental practice. The higher estimate includes in the definition of medically complex patients, cigarette smokers and patients over 55 years of age. More traditionally, the definition applies to those patients on multiple medications, those who have multiple medical problems, and patients under the age of 14 years and those older than 65 years. Certainly the decision as to whether a person is medically complex should be taken on a case-by-case basis, and varies

with the medical problem as well as the dental procedure being undertaken. Relative to adverse drug interactions, special consideration should be given to those patients who are taking highly titrated drugs. Patients taking Synthroid to normalize their thyroid levels and even those taking blood pressure medications that render them normotensive, though they would be considered medically compromised, are at low risk for adverse drug reactions in a dental setting.

The other way of avoiding adverse drug reactions is to understand the drugs used in dentistry, their metabolism, effects, side effects, and toxicities. Few drugs are used in dentistry; the prescriber should know their uses and the safe maximum dose. It is not the dentist's responsibility to understand the effects, side effects, toxicity, and metabolism of all the medical drugs the patient may be using, but to understand how dental procedures and dental drugs impact the patient and the medication he or she is taking. This may be done in consultation with the patient's physician, though the dentist should not expect the physician to understand dental procedures nor the drugs used in dentistry. It is the dentist's responsibility to be aware of any medical drugs known to interact with drugs used in dentistry.

Many drug interactions are theoretically possible, but few are probable, and of the drug interactions that are probable, even fewer are serious. The adverse drug reactions noted here are considered probable; that is, they occur in more than 3% of patients. With awareness of these adverse drug reactions, familiarity with patients' health status, and use of proper drug dosage, the dentist can essentially eliminate the risk of adverse drug reactions, especially drug–drug and drug–physiology interactions.

Resources

This chapter is designed as a partial overview of adverse drug reactions. It provides precautions and information that should be adequate for the average practitioner to avoid 95% of the potential adverse drug reactions that could occur in dentistry. The resources listed in Table 11–5 provide additional specific information on certain topics, including tables on adverse drug reactions that are considered probable (ie, interactions have been reported in the scientific literature). Adverse drug reactions considered possible (ie, theoretically could occur but are not documented) also can be found in the *Journal of the American Dental Association* series on adverse drug reactions (see Table 11–5). As information available on the Internet evolves, there is no doubt that the most current information and the most accurate data available on adverse drug reactions will be accessible through a variety of Web sites. (Table 11–6 lists some Web sites that are available for on-line inquiries about adverse drug reactions.) The dentist should select one or two sites, list them in "favorites," and learn to work effectively within them to gather necessary information. Two of the sites listed have search features that can be used to find information about specific drugs. This is especially important for new drugs that are just being released. These resources often provide a superabundance of information; it is the professional responsibility of each practitioner to identify the information that is relevant to the circumstances of each patient.

Table 11–5 Resources Regarding Adverse Drug Reaction

Specific series on dental drug interactions

Moore PA, Gage TW, Hersh EV, et al. Adverse drug interactions in dental practice: professional and educational implications. J Am Dent Assoc 1999;130:47–54.

Hersh EV. Adverse drug interactions in dental practice: interactions involving antibiotics. J Am Dent Assoc 1999;130:236–51.

Haas DA. Adverse drug interactions in dental practice: interactions associated with analgesics. J Am Dent Assoc 1999;130:397–407.

Moore PA. Adverse drug interactions in dental practice: interactions associated with local anesthetics, sedatives, and anxiolytics. J Am Dent Assoc 1999;130:541–54.

Yagiela JA. Adverse drug interactions in dental practice: interactions associated with vasoconstrictors. J Am Dent Assoc 1999;130:701–9.

Useful books

Wynn RL, Meiller TF, Cossley HL. Drug information handbook for dentistry. 5th Ed. Hudson, Ohio: Lexi-Comp, 1999–2000.

Table 11–6 Internet Web Site Resources for Drugs and Drug Interaction Information

www.medscape.com. This is a searchable site or an extensive medical-based home page that can be customized for personal interest. It will send topics, such as pharmacology, updates to your computer, to allow you to keep current on areas of interest.

www.fda.gov/opacom/hpchoice.html. This site within FDA provides information on adverse reactions.

www.nlm.nih.gov. This site has a powerful search feature that looks at a large range of databases and searches out complete articles on specific topics.

www.ada.org. The American Dental Association Web site contains resources and connects to a variety of medically related sites. Members can look through a long, well-researched list of useful Web sites related to drugs and health.

www.healthgate.com. This site provides access to medicine searches as well as health news.

www.dentalgate.com. This site has two different search features, one for the World Wide Web and another for medicine, especially designed for dentistry.