Pharmacological Agents With Effects on Voice

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There are numerous pharmacological agents with effects on speech production and voice. Agents can alter either the production of speech, vocal quality, or both by acting centrally or peripherally at any level of the vocal tract from the bellows (diaphragm) to the vibrator (larynx), the articulator (tongue), or the resonator (sinuses). This report deals with the agents that act peripherally. A summary of those agents is found in Table 1.

Most of the agents with laryngeal effects act through the autonomic nervous system to create endolaryngeal changes, resulting in voice alterations. Some agents act through other mechanisms to create the changes observed. Most of the changes created by pharmacological agents are transient and reversible, but some may be permanent. Excellent reviews of the subject have been published by Lawrence,[1] Harris,[2] Martin,[3] and Sataloff.[4]

A basic foundation of pharmacology concerns the fact that individuals may react differently to a particular medication. The recommended dose of a medication may or may not be suitable for a particular patient based on individual responses, size, age, and concurrent medical problems. In dealing with voice patients, it is important to remember that very minor alterations of laryngeal function can be significant; close attention to minor variables, such as the effects of medicines, is necessary. The complete history taken when a patient with a voice disorder presents for evaluation must include a discussion of current drug therapy and known idiosyncratic reactions to medications taken in the past. Patients typically respond quite predictably to the various categories of pharmacological agents, and it is this fact that allows the following discussion. However, the careful clinician always pays close attention to an individual's history of response to a medication, even though that response is not part of the known pharmacodynamics of that particular drug. A list of agents that can exert beneficial effects on the larynx is found in Table 2. The agents in Table 3 are known to produce adverse effects.

AUTONOMIC NERVOUS SYSTEM

Understanding the basic physiology of the autonomic nervous system, and how pharmacological agents affect that system, offers a rational way to evaluate pharmacological agents and their potential effects on voice. A brief review of that system will be discussed.

The two large divisions of the peripheral autonomic nervous system are the sympathetic and parasympathetic systems. These two systems have opposing effects on smooth muscle, glandular activity, and organ function. The primary neurotransmitter of the sympathetic nervous system is norepinephrine or noradrenaline. Compounds that stimulate this system are said to have adrenergic effects. The neurotransmitter of the parasympathetic system is acetylcholine, and compounds stimulating this part of the system are said to have cholinergic effects.

When the sympathetic system is stimulated, the heart rate is accelerated, the blood pressure increases, blood flow is shifted from the skin and splanchnic regions to the skeletal muscles, bronchioles and pupils dilate, and saliva and mucous gland secretions decrease. Most people realize that during periods of rage and fright, the heart races, the palms sweat, a dry throat occurs, and the face becomes pale. On the contrary, when the parasympathetic nervous system is stimulated the heart rate slows, the skin flushes, and excess saliva appears in the mouth.

The terminology regarding the pharmacological agents with effect on the autonomic

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TABLE 1. Pharmacologic Agents With Effects on Voice

1. Antihistamines
   a. Amines
   b. Piperazines
   c. Piperidines
2. Sympathomimetics
3. Antitussives
4. Antihypertensives
   a. Diuretics
   b. Alpha adrenergic agonists
   c. Angiotension converting enzyme inhibitors
5. Psychotropic drugs
   a. Tricyclic antidepressants
   b. Major tranquilizers
6. Anticholinergics
   a. Scopolamine
   b. Antidiarrheals
7. Vitamins
8. Hormones
9. Wetting agents
   a. Guiafenesin
   b. Iodinated glycerol
10. Medications for GERD
11. Miscellaneous

nervous system can become confusing unless one remembers that basic differences between adrenergic and cholinergic stimulation. The pharmacological agents that affect the adrenergic impulses are said to be either sympathomimetic if they stimulate it, or sympatholytic if they interfere with it. The pharmacological agents that affect the cholinergic side are said to be parasympathomimetic if they stimulate it; and parasympatholytic, or more commonly, anticholinergic, if they interfere with it.[5]

THE RESPIRATORY TRACT SECRETION

The respiratory tract secretion is primarily water that contains glycoproteins linked by disulfide bonds.[2] The volume and character of the secretion is influenced by multiple factors: autonomic activity, diseases, ambient environmental conditions, state of body hydration, and medications. The effect of medications on the secretion is the primary focus of this discussion.

TABLE 2. Agents With Potential Beneficial Effects

1. Wetting agents
   a. Guaifenesin
   b. Iodinated glycerol
2. Corticosteriods
3. Medications for reflux
   a. H_2-receptor antagonists
   b. Proton pump inhibitors
   c. Antacids
4. Sympathomimetics
5. Bronchodilators
6. Hormones

TABLE 3. Agents With Potential Adverse Effects

1. Antihistamines
   a. Amines
   b. Piperazines
   c. Piperidines
2. Sympathomimetics
3. Antitussives
4. Antihypertensives
   a. Diuretics
   b. Alpha adrenergic agonists
   c. Angiotension converting enzyme inhibitors
5. Psychotropic drugs
   a. Tricyclic antidepressants
   b. Major tranquilizers
6. Anticholinergics
   a. Scopolamine
   b. Antidiarrheals
7. Vitamins
8. Hormones
9. Miscellaneous

PHARMACOLOGICAL AGENTS WITH EFFECTS ON VOICE

There are several classes of pharmacological agents commonly used, which have effects on voice. Many of these agents have effects that decrease endolaryngeal lubrication, which in turn causes increased friction between the opposing vocal folds. Increased friction of the mucosal waves during phonation predisposes the vocal folds to traumatic changes. Some of the pharmacological agents that adversely affect voice are actually agents prescribed for their beneficial effect on respiratory tract diseases. These agents can cause adverse effects through improper dosing or idiosyncratic reactions. Careful monitoring of medications administered to treat upper respiratory tract maladies is, therefore, essential in treating voice patients to avoid unnecessary complications of therapy. The agents prescribed that are beneficial exert actions on the endolarynx in a variety of ways, which will be discussed.

ANTIHISTAMINES

Histamine is beta-amnioethylimidazole. It is primarily stored in mast cells and is one of the important mediators of allergic responses, but it has other physiological roles. Three types of histamine receptors have been identified in human tissues. H_1- and H_2-receptors are found throughout the body. H_3-receptors are only found in the central nervous system (CNS). Antihistamines are primarily H_1-receptor antagonists used either alone or in combination with a sympathomimetic for its vasoconstrictor effect. Most H_1-receptor antagonists inhibit responses to acetylcholine and, thus, exhibit anticholinergic effects. Therefore, secretions in the respiratory tract are generally decreased. The H_1-receptor antagonist dries the mucosa and the sympathomimetics, frequently used in combination with the H_1-receptor antagonist, thicken secretions as they vasoconstrict.[5] H_2-receptor antagonists have a minor effect on respiratory tract secretions.

There are different classes of H_1-receptor antagonists. The early preparations were ethanolamines. The research and development that led to their production was performed in the late 1930s and early 1940s. By the middle 1950s, ethylenediamine and alkylamines were developed. All of the amines exhibit some CNS-depression because of the blocking of central H_1 and H_3 receptors, as well as the peripheral H_1 blocking effect of drying secretions. Another class of H_1-receptor antagonists are the piperazines. Most notable of that class are meclizine and hydroxyzine. Meclizine is used primarily for motion sickness and vestibular disorders. Hydroxyzine is used for its antipruritic action. Both are H_1-receptor antagonists and have anticholinergic effects. The newest class of antihistamines to be developed is the piperidines, most notably terfenadine, astemizole, and loratadine. These agents are highly selective for H_1-receptors. They do not cross the blood-brain barrier and thus do not have CNS sedation effects. They have no effect on acetylcholine; therefore, they have no anticholinergic effects. They have very little effect on laryngeal function when properly used.

Many of the antihistamine drugs are available in this country without prescription. The potential for improper use is significant. Most of the over-the-counter preparations are a type of amine, and unsupervised use should be discouraged.

SYMPATHOMIMETICS

Sympathomimetic agents are prescribed for their decongestant effect. Their primary action is vasoconstriction, which shrinks the upper respiratory mucous membrane and reduces the secretion production. Secretion is inhibited in most glands by the sympathomimetics. This inhibition is partly from reduced blood flow, and partly from a direct effect on the glands. The water component of the secretion is reduced relatively more than the mucous component, and the secretion becomes more viscous. The sympathomimetics stimulate lacrimal gland secretion, and a small increase in mucous production and secretion from the salivary glands also occurs.[5] The combined effect of reduced water component and slight increase in mucous production may produce a sensation of excessive, viscous respiratory tract secretions.

This pharmacological effect is beneficial for relief when secretions are copious, but the effect can be adverse if the agents are used carelessly. These agents are readily available without prescription and the potential for improper use is significant, as it is with the antihistamines. The primary agents used are pseudoephedrine, phenylpropanolamine, and phenylephrine. All three of these agents have essentially the same effects. More than one sympathomimetic agent can be occasionally found in combination in a single product; the sympathomimetics are often combined with antihistamines for their CNS stimulation effect, which counteracts the sedation that occurs when CNS histamine receptors are blocked.

Sympathomimetics can be administered topically or systemically. Either route of therapy can be beneficial, but either can cause complications. Topically, when sprayed directly on the vocal folds, excessive dryness can occur. Taken systemically, secretions can become viscous and adhere to the endolarynx, as well as decrease overall vocal fold lubrication.

Sympathomimetics are also used to treat lower respiratory conditions. Patients with bronchospasm are unable to produce the rapid exhalation of air needed to produce normal voice when demands are great, such as in a vocal performance. Beta-adrenergic agonists (isoproterenol, albuterol) in aerosol, and methylxanthines (theophylline) taken orally, relax smooth muscle and decrease airway resistance, which can improve the voice through better breath control. Side effects of inhaled beta-adrenergic agonists are not troublesome, but the xanthines reduce lower esophageal sphincter pressure and gastroesophageal reflux may result.[6]

ANTITUSSIVES

Antitussive agents are among the most frequently used medications in medical practice. Most agents work centrally through brainstem centers, but some work peripherally through cough receptors in bronchial mucosa. The centrally acting agents are opioids or opioid derivatives, codeine, hydrocodone, and dextromethorphan (the most common). These agents can be used alone or in combination with other agents, such as expectorants or H_1-receptor antagonists (promethazine). Opioids can dry the vocal tract when administered alone[1]; however, it is the combination agents that are most likely to cause this adverse effect. Many of the combination agents are delivered in an alcohol vehicle. The potential drying effect from the diuretic action of alcohol is not significant, but it may contribute to vocal tract drying when other diuretic agents are also being used.

Bezonatate is a peripherally acting cough suppressant related to procaine. It exerts its action on cough receptors located peripherally in airway mucosa. It is not known to cause adverse effects on the vocal tract.

Expectorants, such as guaifenesin, thin secretions rather than dry them. These agents are found in many antitussive preparations. Their lack of proven efficacy will be discussed later.

ANTIHYPERTENSIVES

Antihypertensive agents are commonly used in medical practice. There are many subclasses of antihypertensives, several of which have side effects that influence vocal quality. Their mechanism of action differs considerably. If unpleasant voice effects occur with a particular agent, it is possible to change to another agent with a different mechanism of action that can alleviate the problem.

Diuretics are still commonly used agents for reduction of blood pressure. The thiazides produce a natriuretic effect with loss of sodium, potassium, and water. Loop diuretics, such as furosemide, create a marked natriuretic effect, resulting in loss of body water. Dryness of the vocal tract is commonly seen because of decreased secretions secondary to the overall decrease of body water. Diuretics are not successful in removing water from Reinke's space because the water there is protein bound.

Another subclass causing reduced vocal tract secretions are the alpha-adrenergic agonists (eg, clonidine). These agents work centrally to reduce blood pressure, but they still have the expected sympathomimetic effect on secretions.

Angiotensin-converting enzyme inhibitors are antihypertensive agents that have virtually no effect on the moisture content of the respiratory mucosa. However, coughing, apparently caused by the release of prostaglandins, is a common side effect of these agents. Chronic cough traumatizes the vocal fold. Reinke's edema can result, which affects vocal quality.

Sympatholytic agents are commonly used for their antihypertensive effects; as would be expected, they do not affect the vocal tract. Most commonly used are the beta-adrenergic antagonists (beta-blocking agents, such as propanolol). However, when these agents are used to relieve preperformance anxiety, they are felt to take some of the excitement out of a performance.[7]

The ganglionic blocking agents and the alpha-adrenergic antagonists are occasionally used. As would be expected, no effect on the vocal tract is seen.

PSYCHOTROPIC AGENTS

Psychotropic agents are used frequently, and there are several classes that have sig-

nificant effects on voice. The tricyclic antidepressants (amitriptyline) are strongly anticholinergic, and drying of the upper respiratory tract mucosa routinely occurs. Antidepressants of the selective serotonin reuptake inhibitor class (fluoxetine and paroxetine) are weakly anticholinergic, but they do cause mild mucosal drying. The phenothiazines (chloropromazine and thioridazine) are very strong H_1-receptor antagonists, and dryness of the vocal tract mucosa always accompanies their use. An occasional tremor is seen in patients using phenothiazines, and that tremor can affect the vocal fold muscles. Haloperidol is a butyrophenone, a class with weak H_1-receptor antagonist effect, and mucosal drying is unusual. Benzodiazepines (diazepam, lorazepam, triazolam) are not associated with anticholinergic effects. Therefore, they are not agents with direct effects on voice. However, they can have effects on speech production by action on the CNS.

ANTICHOLINERGIC AGENTS

Anticholinergic agents are commonly used for various maladies encountered in medical practice; however, their most common use is in the treatment of diarrhea. The belladonna alkaloids have very strong anticholinergic effects. Commonly encountered belladonna alkaloids are scopolamine for treatment of motion sickness, and the combination antidiarrheal agents marketed under the names Lomotil (Searle, Chicago, IL) and Donnagel (Robins, Richmond, VA). Synthetic alkaloids, (glycopyrrolate, and the combination preparation chlordiazepoxide-clidinium) have equally strong anticholinergic effects, and dryness of the vocal tract routinely occurs with their use. The anti-Parkinson's drugs, benztropine and trihexyphenidyl, dry the vocal tract because of their strongly anticholinergic properties.

VITAMINS

Large doses of vitamin C have been reported to dry the mucosa of the vocal tract by acting as a mild diuretic.[1] Isotretinoin, a retinoic acid derivative used for control of acne, dries upper respiratory tract mucosa and the skin. Dryness of the oral cavity and pharynx are commonly reported in patients on isotretinoin.

HORMONES

Hormones can influence the vocal tract. The androgenic drugs in women can masculinize the voice. Notable is danazol, used for treatment of endometriosis and fibrocystic breast disease. This is reported to irreversibly lower vocal pitch.[8] Estrogens in men can feminize the voice. This might be encountered in patients being treated palliatively for prostatic carcinoma with diethylstilbestrol. However, estrogens have not been successful in raising voice pitch when used therapeutically in males undergoing sex-change procedures. Oral contraceptives have not been reported to cause significant alterations of voice.

Thyroid hormone replacement reverses the voice changes of myxedema. Hypothyroidism causes accumulation of mucopolysaccharides throughout the body tissues. The vocal folds thicken as the condition progresses and changes occur in vocal quality. Thyroid hormone replacement reverses the vocal fold fullness, and vocal quality improves as the mucopolysaccharides dissipate.

WETTING AGENTS

Most of the agents beneficial to the larynx act by moistening the mucosa. Guaifenesin (glyceryl guaiacolate) is the most commonly used agent. Multiple preparations are available in liquid, tablet, and sustained release form. All preparations must be used in conjunction with a high volume of fluid intake. The mechanism of action is claimed to be the reduction of adhesiveness and surface tension of mucous.[9] There is a lack of convincing studies that document their efficacy, but clinical observations support their use. The benefits may come from the increased fluid intake.

Iodinated glycerol is used as an expectorant. It is said to increase the output of thin respiratory tract secretions and to liquefy mucous. It is also to be administered with large amounts of liquid to see the therapeutic benefit. The exact mechanism of action is unclear.[10] Ingestion of large amounts of iodine

can suppress release of thyroid hormone,[11] but this is rarely seen with use of expectorants.

Acetylcysteine (Mucomyst, Apothecon [owned by Bristol-Myers Squibb], Princeton, NJ) breaks disulfide bonds holding mucous glycoproteins together, thus thinning the respiratory tract secretion.[5] This agent can be useful when viscous secretions are a problem. It is administered by aerosol.

Saliva substitutes can be soothing for the vocal tract. These are glycerin-based agents, and they are used for their topical effect. They must be used judiciously in aerosol form because of reports of lipid pneumonia secondary to aspiration of large volumes.[12]

CORTICOSTEROIDS

The corticosteroids have been very useful in the treatment of laryngeal disorders. These agents have well-known beneficial effects on the vocal tract taken orally or intramuscularly. The indication for use of these agents is tissue edema, which is protein bound. There are several agents that are commonly used. The dosage depends on several variables, including size of the individual and severity of the laryngeal edema. Prednisone, an oral preparation, is approximately five times as potent as hydrocortisone. Methylprednisolone can be administered either orally or intramuscularly. Its potency is similar to prednisone. Dexamethasone is the most potent of the agents, having approximately 25 times the strength of hydrocortisone. It is the most effective in rapidly reducing protein-bound tissue edema. Caution must be exercised when recommending these agents because there are contraindications for their use. Vocal-fold hemorrhages, acute laryngitis, and ulceration of the vocal fold mucosa are all relative contraindications for corticosteroid use, and their presence must be ruled out by a careful laryngeal examination before steroid treatment. These drugs can also cause gastric irritation and increase gastroesophageal reflux, which can have adverse effects on the voice.[6] Corticosteroids should also be used with caution just before a major performance in patients in which the medication has never been used. Although the desired effect of reducing tissue edema is usually successful, some patients are very sensitive to the effects of corticosteroids. The marked rapid shrinkage of the vocal folds that occurs may produce a very unsatisfactory voice. Corticosteroids used topically can also reduce vocal fold edema, but one must be aware of the possible development of candida superinfection with prolonged use.[13] Inhaled steroids have been reported to cause a dysphonia by inducing a dyskinesia of the intrinsic laryngeal musculature that produces vocal fold bowing.[14]

MEDICATIONS FOR GASTROESOPHAGEAL REFLUX

Patients with voice changes caused by gastroesophageal reflux disease can benefit from H_2-receptor antagonists (Cimetidine, Smith Kline Beecham, Philadelphia, PA and Ranitidine, Glaxo Inc., Research). The proton pump inhibitors (Omeprazole, Merck & Co., West Point, PA) are more effective in reducing gastric acid production, but currently the manufacturer recommends using them no longer than 2 consecutive months. Antacids are also beneficial agents in the treatment of peptic disease with gastroesophageal reflux. Aluminum-magnesium preparations are the most beneficial. Calcium preparations are effective, but they can cause rebound acid production. A comprehensive discussion of gastroesophageal reflux disease and its treatment has been published by Kaufman.[6]

MISCELLANEOUS

A few other agents need to be mentioned for their adverse effects on laryngeal function.

Topical anesthetics are to be avoided or their use very carefully monitored. Because symptoms cannot be self-monitored when topical anesthetics are used, injuries can occur that could potentially cause permanent damage to the vocal folds. Aspirin and nonsteroidal anti-inflammatory drugs should be avoided before a strenuous performance because of the possibility of a vocal fold hemorrhage, secondary to their action on platelet function. Antibiotics, if abused, can lead to superinfection of candida. Amphetamines are strong adrenergic agonists; and although they are not used often in clinical practice, dryness

of the vocal tract is routinely experienced by patients on these agents.

SUMMARY

Pharmacological agents with the most notable effects on voice exert their influences on the vocal tract through the autonomic nervous system. These agents do not have a profound effect on laryngeal function. Their effects are subtle, but they are important in certain groups of patients, such as professional voice users.

It is essential to take a thorough history of medications being used, both by prescription and nonprescription, when evaluating patients with voice disorders. It is also important to keep in mind that idiosyncratic variations may occur in response to medications, and careful monitoring is essential when patients with voice disorders are under treatment. The importance of adequate water intake should be emphasized for general hydration and for vocal tract lubrication.

Understanding the autonomic nervous system and how it is influenced by pharmacological agents makes evaluating the effect of medicines on the vocal tract simpler.

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