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Tutorial

Drugs and Vocal Function

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Summary: Relatively little literature exists documenting the effects of pharmacological agents upon the voice. Our understanding of this subject is facilitated through review of the few studies that have been performed, as well as through understanding of the principles of action of drugs in various classes. Such study provides a reasonable basis for understanding and predicting the effects of drugs on the voice. **Key Words:** Pharmacologic agents—Drugs—Voice.

As unlikely as it may seem, the study of the effects of drugs on the voice is a largely overlooked field. Compared to the body of pharmacological literature related to the effects of drugs on any number of other daily activities, such as eating, sleeping, driving, etc., the literature on the effects of drugs on the voice is minuscule. Moreover, much of the existing literature is in the form of isolated case studies or anecdotal reports.

The aims of this article are to review what has been learned about the effects of drugs on the voice in the few well-controlled studies that have been done and to set out some rational expectations about the effects of drugs on the various determinants of voice production. In the latter case, we will extrapolate our knowledge of the pharmacological effects of various classes of drugs to the effects one could reasonably expect them to have on the voice.

BASIC PRINCIPLES OF DRUG ACTION

When considering the actions of drugs on any biological function, there are a number of basic principles concerning drug action that should be kept in mind. These are biological variations, dose–response relationships, multiplicity of actions, and the placebo effect.

Biological variation

The person-to-person variability in the response to drugs is quite large. This is due in some measure to the genetically determined biochemical variability in persons and to such factors as the presence of disease, the level of stress present, the use of other drugs, and the nutritional status of the person taking the drug. One person may not respond in the "normal" or average manner, either in the kind (qualitatively) or to the degree (quantitatively) of response that is expected. Therefore, the possibility of the unexpected response should always be kept in mind.

Dose–response relationships

In general, the response to a drug is proportional to the dose given. In other words, the greater the dose, the greater the response. Many drugs, however, have "ceiling effects" beyond which additional increases in the dose will not increase the desired effect but likely will increase the toxic effects. On the other hand, certain drug effects, especially those of an allergic nature, do not have a clear dose–effect relationship. In these cases, the effect may be all-or-none, meaning that if the effect occurs (such as the occurrence of an allergic drug

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reaction) it occurs in its full-blown form and may be caused by a minute amount of the drug substance.

Many drug dose–effect relationships are not simply linear but rather follow an S-shaped relationship. In this classic dose–effect relationship, the effect is very small at small doses, but as the dose is increased the effect increases very rapidly and then tails off as the ceiling effect is reached. If one contemplates the implications of this situation, one can easily appreciate the importance of precise dosage adjustments; a bit too much may place the patient at risk of developing drug toxicity, whereas a bit too little may cause the loss of effectiveness of the therapy.

Multiplicity of actions

A guiding principal one should never forget is that no drug does only one thing. While we tend to think of drugs in terms of their intended uses, they all have additional, often unwanted, actions. It is usually these unwanted actions, or "side effects," that cause problems. When we consider the effects of drugs on the voice, most of the actions will be of this kind.

Placebo effect

The placebo effect (from Latin, meaning "I shall please") is an important but poorly appreciated phenomenon. The expectation of effect may determine, in part or totally, the kind of effect or the degree of effect that is obtained after the taking of a drug. While some studies have attempted to identify persons who are "placebo responders," current evidence seems to indicate that virtually all people may, at various times, respond to drugs in this manner. A corollary principal is that the set (the situation that the person taking the drug feels herself or himself to be in) and setting (the environment in which the drug is taken or administered) have significant influences on drug response.

For the purposes of this discussion, the term "drug" refers to a diverse group of chemicals that are taken for their pharmacological actions. We will not confine ourselves to a consideration of prescription drugs, but also will consider those drugs sold without prescription, the so-called over-the-counter (OTC) drugs.

EFFECTS OF DRUGS

The following discussion has been arranged according to the effects of drugs on the various determinants of voice production. Six potential influences will be considered: Drugs that influence proprioception and coordination; drugs that influence airflow; drugs that influence fluid content of the tissues of the vocal apparatus; drugs that influence secretions of the upper respiratory tract; drugs that cause changes in the structure of the vocal folds; and drugs that influence hearing.

Drugs that influence proprioception and coordination

Proprioception, the sense of body position in space, and coordination, the coordinated control of voluntary muscular movement, are both necessary for optimum voice production. The complex learned control of movements of the vocal apparatus and the coordinated control of respiration are very vulnerable to the action of a variety of drugs. One only has to reflect on the slurred and slowed speech of the person under the influence of alcohol to appreciate this fact. Indeed, the CNS, the major site of action of alcohol, is the most vulnerable component of the proprioception/coordination interplay. Any agent that is stimulating or sedating is likely to be detrimental to the conscious control of fine muscle movement. The slowing or speeding of neuronal function is likely to influence timing and the precise execution of complex maneuvers. For these reasons the use of either stimulants or depressants of the CNS can be expected only to be detrimental to vocal performance. Anecdotes to the contrary notwithstanding, it is implausible that vocal performance could be improved by the preperformance use of these drugs.

CNS stimulants

Stimulants of the CNS are of several varieties. Included are the amphetamines and a variety of related agents used in the control of appetite; cocaine; and the xanthines, a group of drugs that includes caffeine and theophylline. To one degree or another, all these drugs tend initially to impart a feeling of wellbeing and alertness. The widely used nonprescription diet aids contain the drug phenylpropanolamine. This agent, related chemically to amphetamine, is a weak CNS stimulant and in recommended doses may be expected to be detrimental to the control of the voice.

CNS depressants

CNS depressants are perhaps the most commonly used class of drugs in our society. The use of alcohol, the barbiturates, and the sedative hypnot-

ics such as methaqualone is pervasive. Diazepam and its relatives, often referred to as antianxiety agents or "minor tranquilizers," are among the most commonly used prescription drugs in the world. There is a large body of literature that unequivocally demonstrates that all these agents have a negative influence on muscular coordination and nerve function, often at doses below the level at which the person taking the drug may perceive a change.

Although much of the research concerning the effects of these drugs on muscular coordination, attention, and concentration has been aimed at studying the effects of their use on automobile safety, there is no question that they also have detrimental effects on voice control, causing, in large doses, slowing and slurring of speech. Smaller doses could be expected to have an impact on the control of pitch, timbre, volume, etc.

Local anesthetics

The local anesthetics, by entirely different mechanisms from those operating with the CNS stimulants and depressants, influence coordination and proprioception and therefore may influence the quality of voice production. These agents exert the majority of their action directly on the nerves outside the brain (the peripheral nerves) with which they come directly into contact. Their action is to reduce the ability of these nerves to carry the electrical impulses that are necessary if the brain is to receive information from the muscles and, in turn, control the movements of those muscles. Since these nerve impulses take information in both directions, that is to say, into the brain and out of the brain, they not only reduce sensations (hence their major use to anesthetize or reduce the perception of pain), they also reduce motor control to the anesthetized area. The loss of muscular control and the loss of the perception of the position of the lips and tongue after the use of a local anesthetic in the dental office is an experience shared by almost all. The use of topical local anesthetics on the vocal apparatus in the form of sprays, drops, or lozenges must be assumed to cause, albeit to a lesser degree because of the smaller dose, a diminution of the control of vocal function. Various lozenges and sprays are available without prescription that contain the local anesthetic benzocaine or a chemical relative. Some throat lozenge and spray products contain phenol, an agent that also possesses considerable local anesthetic activity.

Drugs that influence airflow

There are a number of drugs that are capable of changing the movement of air across the vocal folds. The usual way this is done is to constrict or dilate the tiny air passages near the terminal bronchioles, the site in the lungs where the exchange of oxygen and carbon dioxide takes place between the blood and the inspired air. The air passages contain an abundance of muscle fibers that are controlled by the autonomic nervous system, that part of the body's nervous system that is "autonomous" or beyond the usual conscious control of the individual. The moment-to-moment control of the diameter of these passageways allows the body to modulate the exchange of the gases (oxygen and carbon dioxide), increasing the size of the passageways during exercise, when the metabolic demands of the skeletal muscles and the heart require a greater oxygen intake.

Several drugs are capable of dilating the bronchioles by relaxing the smooth muscles in the walls of the bronchioles. These drugs have been developed to help deal with the common medical problem of excessive bronchoconstriction, a condition that may be brought on by a variety of allergins or by diseases such as asthma. The two major groups of bronchodilators are represented by epinephrine and its chemical relatives that exert their action directly on the receptors in the smooth muscles and by theophylline and its chemical relatives that cause the same sort of effect but by a different mechanism. Both groups of agents may be given orally or by injection and both may cause numerous side effects including nervousness and tremor.

Perhaps of more importance is the large group of drugs and foreign chemicals that cause bronchoconstriction or a reduction in airway diameter. The bronchoconstriction is usually of an allergic nature and when it occurs may be mild, causing some wheezing and little else, or it may be so severe as to be life-threatening. Many agents may act as allergins. Some of the more common are aspirin, penicillin, house dust, and pollen. Those who suffer from seasonal hay fever may experience significant bronchoconstriction that results in a reduction of lung volume, wheezing, and a reduction in respiratory (gas exchange) function.

Drugs that influence fluid content of the tissues of the vocal apparatus

A somewhat oversimplified view of the cause of edema formation (the swelling of tissue because of

the accumulation of fluids outside the blood vessels) is that any agent that causes an expansion of the size of the small blood vessels in the mucous membranes will, in turn, cause the loss of fluids through the vessel walls and congestion of the tissues. Conversely, any agent that causes constriction of the blood vessels will reduce the movement of fluids out of the blood vessel and therefore act as a decongestant. These changes are important in the context of this article because congestion of the tissues of the vocal apparatus will change the quality of the voice.

A wide variety of drugs and other substances can cause changes in fluid balance in the mucous membranes. Among those that may reduce the formation of edema are the diuretics, agents that increase the production of urine and that are commonly used in the treatment of high blood pressure, heart failue, and renal failure; corticosteroids (agents of the cortisone family) that are used to treat a variety of inflammatory and allergic conditions; and a group of agents that are referred to as "decongestants" that find wide use in cough, cold, sinus, and allergy remedies. These latter agents are found in a variety of prescription and nonprescription drugs. The decongestants are available in a variety of dosage forms including oral dosage forms (capsules, tablets, syrups, etc.), and topical sprays and solutions. One would expect that systemic dosage forms would be the only efficient way to deliver these agents to the vocal folds. Studies of the effects, if any, of preparations applied topically to the mucous membranes of the upper respiratory tract are, however, lacking.

Any of the agents that reduce edema should be beneficial to the voice if vocal fold edema is present. It should be noted however, that the long-term use, especially of the decongestants and the corticosteroids, may be detrimental in a variety of ways. For example, one study suggests that the long-term inhalation of triamcinolone, a member of the cortisone family, had a detrimental effect on laryngeal function in asthmatic patients. Likewise, the excessive use of decongestants may cause a rebound congestion and one can easily slip into a vicious spiral with a pattern of continued and more frequent use of the agents in an attempt to control the side effects that are being caused by the agent itself. Patients who have unwittingly developed a "decongestant habit" in this way come to medical attention with some regularity. The nasal mucous membranes of the these patients show characteristic lesions that are due to the long-term reduction of blood flow to the tissues; in severe cases, the mucous membranes may become necrotic and perforation of the nasal septum may occur, exactly as occurs in the chronic cocaine "snorter."

Agents that cause edema formation in mucous membranes are most often not drugs but rather common allergins such as dust and pollen. These agents, therefore, can have a two-pronged detrimental effect on the vocal apparatus, causing bronchoconstriction, as mentioned above, and edema of the vocal folds and air passages. It is to combat these reactions that the decongestants and bronchodilators are commonly used.

Drugs that influence secretions of the upper respiratory tract

Drying agents

In terms of frequency of exposure, agents that reduce the secretions of the upper respiratory tract may be the most important subject of this article. Many drugs cause drying of the mucous membranes by reducing the secretions that normally keep these membranes moist and lubricated. In addition, the air we breathe in air conditioned and heated spaces is often not adequately humidified and the passage of this air across the mucous membranes results in dry and irritated nasal and oropharyngeal membranes. The irritation of the mucous membranes often leads to coughing, which leads to further irritation and drying. The following are drying agents:

Antihistamines: Contained in a wide variety of prescription and nonprescription drug products. Often contained in mixtures used for the control of cough, cold and sinus remedies, sleep aids, and antimotion sickness preparations. Used judiciously, these agents may be helpful in relieving the symptoms of seasonal rhinitis. In spite of their drying action, some of the members of the group are also good cough suppressants. They are probably overused, however, and one should keep in mind that at doses that cause blockage of histamine, most cause significant side effects such as drying and drowsiness. The voice professional would likely be well advised to use these agents as infrequently as posible to avoid the drying action.

Antispasmotics: Used to reduce pain and control excessive motility arising from smooth muscle, especially of the gastrointestinal tract. Frequently used to control diarrhea.

Antitussive agents: Agents used to suppress cough.

Antipsychotic agents: Also called the "major tranquilizers." Used in the treatment of certain mental disorders, including schizophrenia.

Antidepressant agents: Used to treat depression and manic-depressive disorders. Most commonly used in "endogenous" or nonsituational depression.

Antihypertensive agents: Agents used to treat high blood pressure.

The use of many of these drugs cannot be avoided. When they are needed, their benefits far outweigh their adverse effects. For this reason, strategies for minimizing the drying effects are very important. Several common sense approaches are in order:

Avoid drying agents when possible. The choice of a cough suppressant that does not contain an antihistamine, for example, seems prudent.

If possible, raise the ambient humidity in work and living spaces by the use of a humidifier or vaporizer.

Drink copious amounts of water (8–10 full glasses per day) unless fluid restriction has been prescribed for medical reasons. Such fluid intake helps to maintain optimum salivary and mucous gland function.

Wetting agents

Unfortunately, there are no drugs available that do an adequate job of increasing mucous and salivary gland secretions. A number of agents, referred to as expectorants, are marketed for this purpose but evidence of their effectiveness is equivocal. If they are used, they should be used in full doses and one should avoid preparations that contain unneeded additional ingredients such as decongestants and antihistamines.

The most commonly used expectorant is guiafenesin. It is included in dozens of preparations and is marketed in a variety of combinations with other ingredients. These mixtures often contain cough suppressants (codeine or dextromethorphan), which may themselves be drying, as well as decongestants, and antihistamines. For dry irritated mucous membranes that do not respond to the "first aid" steps outlined above, one may wish to try one of the expectorant preparations that contain only guiafenesin. Maximum doses as recommended by the labeling of the product should be used. Most studies concerning the efficacy of these products report that several days of continued use are required for the effect to be significant.

Saliva substitutes are useful products for persons with drug-induced or environmentally caused dry mouth. These products are usually packaged as sprays and seem especially useful to people who are taking drying drugs, who have salivary gland disease, or who have undergone radiation therapy to the head and neck. They should also be useful in combating the dry mouth associated with performance anxiety. One caution that should be kept in mind with the use of these agents is that some of the products contain preservatives (usually parabens) that may be sensitizing and that may lead to sensitization-based irritation in a significant proportion of users.

Drugs that cause changes in the structure of the vocal folds

There are several drugs that cause changes in the structure of the vocal folds. The majority of these agents are pharmacologically related to testosterone, the male sex hormone. They are used in the United States in the treatment of hormonal imbalances, in the promotion of muscle mass growth (the so-called anabolic steroids), and in the treatment of fibrocystic breast disease. They cause, to varying degrees, the same irreversible deepening of the voice that one sees in males at puberty.

Many of these agents have been synthesized with the aim of retaining the ability to promote muscle mass growth while doing away with the male sex hormone activity. Athough some separation of effect has been achieved, the separation is not absolute, and voice changes in women or in prepubertal males should be expected when any of these agents are used, especially in high doses or for long periods of time.

From time to time, the idea crops up that testosterone can be effectively used in the treatment of the complaint of "tiredness" when no organic cause can be found. There seems to be no significant evidence of effectiveness of this treatment, and it is not an approved indication for these agents in this country. Various combinations of vitamins, hormones (including testosterone), and CNS stimulants are still marketed as "tonics" outside the United States, and one should be extremely cautious about the use of such medications obtained abroad.

Testosterone may also be prescribed in the treat-

ment of vasomotor menopausal symptoms ("hot flashes"), in combination with estrogens, in those women whose symptoms are not adequately controlled by estrogens alone or who are at increased risk of the development of estrogen-induced side effects. The dosage of testosterone in such preparations is small, and one would expect that such preparations would present minimal risk for inducing voice changes. Careful studies of the effects of such regimens are, however, lacking.

The drug danizol is an agent with some male sex hormone activity that is used in the treatment of fibrocystic breast disease. It is structurally related to testosterone and retains some residual male hormone activity. Long-term use is necessary for the drug to be effective and this usually results in the deepening of the voice. Before therapy is begun, one should carefully weigh the benefits of the agent (which are usually temporary, with the condition reappearing on cessation of therapy) against the adverse effects, including the chance of the irreversible deepening of the voice.

The anti-inflammatory corticosteroids, while pharmacologically unrelated to testosterone, may also induce detrimental effects on the vocal folds. Topical use of these agents appears to cause a steroid-induced myopathy that may lead to dysphonia in a significant proportion of patients who use these agents with some regularity.

Drugs that influence hearing

Some drugs may be detrimental to hearing. Inasmuch as the control of voice is intimately related to the feedback one gets from being able to hear, these drugs should be included in our discussion.

Drugs are considered to be ototoxic if they impair either vestibular (balance) or auditory (hearing) function. Although some drugs, for reasons that are not fully understood, have greater toxicity for one function than the other, the two effects do not appear to be fully separable.

Permanent changes in auditory function are due to drug-induced death of the cochlear hair cells that vibrate in the endolymph of the inner ear at sound frequencies that are perceptible. The reasons for these toxic effects are unclear but probably have to do with an upsetting of the balance of the ions (charged molecules of potassium, sodium, etc.) in the fluid that surrounds the hair cells. The ionic imbalance causes an initial loss of function and eventual death of the hair cells. Fortunately, drug toxicity may be reversible if it is detected as the initial loss of function occurs and before the hair cells die. The detection of initial hearing dysfunction is possible by means of careful audiometry, and such testing should be routinely done when potentially ototoxic drugs are used. When permanent hearing loss occurs, it usually begins with the loss of high-frequency hearing and progresses to the lower conversational frequencies.

Two major classes of drugs may cause hearing loss: certain antibiotics of a class called "aminoglycosides" or "aminocyclitols" and certain diuretics, referred to as "high-ceiling" or "loop" diuretics.

Aminoglycosides

This class of antibiotics encompasses several older agents (streptomycin, dihydrostreptomycin, neomycin, kanamycin) that are now seldom used systemically because of the development of bacterial resistance and the discovery of safer, more effective alternate drugs. Streptomycin, introduced shortly after penicillin, was the first of this class of antibiotics to be discovered and the first antibiotic recognized to be ototoxic. It was also with these early agents that we first appreciated that some degree of selective ototoxicity occurred; streptomycin was more detrimental to balance (vestibular function), while dihydrostreptomycin was more toxic to hearing (auditory function). In the United States, kanamycin and dihydrosteptomycin are almost never used, while streptomycin is generally reserved for the treatment of resistant cases of tuberculosis. Neomycin is never used systemically; it is a safe and effective topical agent and is sometimes given orally. Like all the agents of the class, it is poorly absorbed from the intestine, confining its action to the gastrointestinal tract and minimizing the danger of ototoxicity. In some countries of the world, streptomycin and kanamycin are still routinely used for the treatment of various infections.

A "second generation" of aminoglycoside antibiotics followed those mentioned above and are still commonly used in the United States in the treatment of serious infections of the bloodstream, the urinary tract, soft tissue, etc. The oldest of these is gentamicin, and it is generally preferred because of its high effectiveness and low cost. Gentamicin tends to be more toxic to vestibular function than to auditory function.

Amikacin, tobramycin, and netilmicin are the other members of this class. They generally have little advantage over gentamicin and are uniformly

more expensive. Amikacin appears to be primarily toxic to auditory function while tobramycin appears to be equally toxic to auditory and vestibular function. Little data are available concerning the ototoxicity of netilmicin, although such toxicity surely exists.

None of these agents should be used for trivial infections. Until the past few years, there were no good alternatives to their use when they were indicated. While the picture is changing, these agents still enjoy considerable use and are often cost-effective therapy. Several strategies may be employed to reduce the likelihood of hearing loss:

The use of alternate antibiotics, if the pathogen is sensitive to them

Routine audiometric evaluation, especially during prolonged therapy, to discover the development of ototoxicty in the early stages when it may be reversible with the discontinuation of the drug

The avoidance of dehydration, which appears to hasten the development of ototoxicity

The avoidance of the concomitant use of two ototoxic agents. The use of ethacrinic acid and one of the aminoglycoside antibiotics, for example, has been shown to increase the danger of the development of ototoxicity to a greater than additive degree.

Special caution is urged if one is undergoing antibiotic therapy outside the United States. As mentioned above, some of the older, more toxic agents may be inappropriately used, resulting in needless danger to auditory function.

It should be emphasized that these agents are dangerous to hearing only when they are given by injection. They are not effective for systemic infections nor do they reach toxic levels when they are given orally or applied topically. Additionally, the duration of therapy is important; short-term therapy (<2 weeks) carries risks of ototoxicity in the 1–3% range, whereas long-term therapy (>2 weeks) or the use of especially high doses may lead to the development of ototoxicity in 20–30% of all patients.

Loop diuretics

There are three agents in the category of loop diuretics: furosemide, bumetanide, and ethacrinic acid. Fortunately, the first two of these agents, which are much more commonly used than the third, rarely cause hearing problems. Furosemide and bumetanide are used extensively in the treatment of hypertension and in the control of fluid overload accompanying cardiac and renal failure.

Since the ototoxicity resulting from these agents is rare, it is difficult to characterize it or to accurately assess the risk. It appears that the hearing loss that sometimes occurs with furosemide is transient and disappears with therapy. Deafness caused by ethacrinic acid may, however, be permanent. The ototoxic danger inherent in the use of the newer agent bumetanide is at present unknown but may well be like that caused by its chemical relative furosemide.

The agents are so therapeutically important that avoidance of use is impossible. Competent audiological assessment before and during long-term or high-dose therapy is probably wise.

CONCLUSION

It is essential for researchers and especially clinicians to understand the principles of drug action. A review of available studies investigating the effects of drugs on the voice, combined with a thorough understanding of the actions of drugs in various classes, forms a reasonable basis for assessing and predicting pharmacological effects on the voice. Considerably more study is needed in this important and neglected area of voice research.