Today's Treatment

Diseases of the respiratory system

Cough suppressants, expectorants, and mucolytic agents

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Many types of drugs are used to suppress cough and are often prescribed in combinations. Before dealing with the particular types of drugs used, it is worth while pausing to consider briefly the nature of cough production, its role in disease, and the desirability of suppressing it. Several good reviews of cough are available.^{1,2} The cough reflex is a protective mechanism that rids the respiratory tract of inhaled foreign bodies and also enables it to get rid of sputum. As a reflex, coughing includes three components: the sensory nerves, the cough centre, and the motor nerves.

The sensory arm originates with specialised cough receptors located in the mucosa throughout the upper airways. These may be of two types, one being more sensitive to mechanical stimulation and the other to chemical stimulation. Excitation of the cough receptors transmits afferent impulses along the vagus nerve to the cough centre. A cough centre has been shown in the medulla of cats by ablation and electrical stimulation; it is a co-ordinating neuronal network, part of which lies in scattered areas of the medulla oblongata and pons. Efferent impulses from the cough centre are transmitted through cholinergic pathways to the diaphragm and to the intercostal and abdominal muscles. Although theoretically an antitussive agent can block the cough reflex in any one of these three areas—that is, the sensory, central, or motor—most of the widely used drugs suppress cough by their central action. Herein lies one of their disadvantages, because, besides depressing the cough centre, many of them act as general cerebral depressants and may even depress respiration.

It is also worth looking at some of the common causes of cough and their remedies, which may not include the use of agents actually pharmacologically active as cough suppressants. Several obvious conditions in this category are:

- (1) In chronic bronchitis ("cigarette disease") stopping smoking may be the best cough suppressant.
- (2) In some patients the treatment of a postnasal drip, resulting either from infection or allergy, will prevent the cough.
- (3) Some patients with asthma cough more often, and this may be improved by cromoglycate or steroids, or possibly by bronchodilators.
- (4) Some patients with parenchymal lung disease, such as fibrosing alveolitis, may have a dry cough.

When do we really want to suppress cough? In established chronic bronchitis and in elderly patients with pneumonia

coughing to bring up the sputum may be a most important mechanism and should not normally be suppressed. Nevertheless, for some it is well worth considering cough suppression. These include:

- (1) Intractable cough in carcinoma of the lung.
- (2) Whooping cough, where severe paroxysms of cough may lead to vomiting.
- (3) Any condition in which cough is present and may be keeping a patient awake at night or causing disturbance at work. Cough is usually present as a symptom of colds, influenza, and mild bronchitis, but it does not necessarily follow that it should always be treated. The use of cough suppressants in such conditions has become hallowed by tradition, however, and I would like to discuss those types of drug that may be used.

Cough suppressants

Codeine is the most widely used drug and linctus codeine is familiar to everybody. Pholcodeine has a stronger action in suppressing cough, as do methadone and diamorphine, though with the latter two there is more of a problem both of addiction and of central depression. Because of increasing cost and for abuse potential, alternatives for codeine have been sought, and two that have been studied are dextromethorphan and noscapine. Space does not allow description of all the methods used to study cough, but in man this has mainly been done either by studying spontaneous cough in patients or inducing cough in volunteers by inhaling ammonia gas or citric acid. Just how far results obtained in experimentally produced cough in normal subjects relate to conditions appertaining to patients one cannot be sure, but such models are probably better than those in animals, in which mechanical and electrical stimulation have been used. Some of these methods are outlined well in an article by Salem and Aviado.³

Both dextromethorphan and noscapine have been shown convincingly to suppress cough in animals, though the results of studies in man are not so impressive. They are used mainly in North America, but their use will probably spread to Britain. The recommended dose of noscapine is 30 mg three or four times a day, which however, has proved to be ineffective in many human studies, and an appropriate dose might be nearer 100 mg. More controlled studies are needed to determine the true dose. Diazepam and clonazepam suppressed cough produced by electrical stimulation of the cough centre in cats. Nevertheless, they have not found widespread clinical use as antitussive agents in man.¹

Several studies have shown the effectiveness of antihistamines, particularly diphenhydramine, as cough suppressants. Often they need to be used in doses producing appreciable drowsiness, and they are seldom used by themselves (see below). Possibly also β -adrenergic stimulants, which are normally used as

bronchodilators, may have some antitussive action.⁴ An interesting approach to blocking the afferent side of the cough reflex was that taken by Howard. He was successful in suppressing severe intractable cough for one to six weeks after a single treatment with lignocaine by aerosol spray. Further controlled studies are needed, but this approach might be useful in particular groups of patients.⁵

Several proprietary preparations that are mixtures of some of the compounds already mentioned are available. Although these may be frowned on by purists, some evidence suggests that two components may add to the efficacy of the preparation. A recent study,⁶ for example, shows that the addition of an antihistamine to pholcodeine led to a more potent antitussive effect than that of pholcodeine alone. It would seem not too unreasonable to combine more than one of the compounds already mentioned as cough suppressants. Conversely it is illogical to combine an expectorant with a cough suppressant, though this occurs all too often in many proprietary mixtures.

Expectorants and mucolytic agents

A line in Roget's *Thesaurus*—"Hawk, spit, slobber, spew up, cough, expectorate" has some relevance. Many of the traditional expectorants owe their action not to any specific action in stimulating cough but to their being emetics and irritants. This was certainly true of ammonium chloride and ipecacuanha, while the amount of iodide contained in traditional expectorants was so low that its action was probably irritant rather than specific. Guaiphenesin has been claimed to have some specific expectorant action, but even this is in doubt. Two of the most important factors in adequate expectoration of tenacious bronchial secretions are adequate hydration and physiotherapy. Though mucolytic agents such as acetylcystine and bromhexine are used, many clinicians are not convinced of their value. Bromhexine undoubtedly alters the characteristics of sputum in vitro, but it has proved very difficult to show any objective improvement in patients in clinical trials.⁷ The combination of bromhexine with tetracycline has been claimed to lead to more effective concentrations in the sputum and therefore to better treatment of patients with chronic bronchitis. The evidence for this is conflicting, but a good review of bromhexine with or without antibiotics is available.⁸ Acetylcystine has also been inhaled, as have other preparations, including some containing

trypsin. Nevertheless, reactions to such inhalations have been frequent. In some patients—for example, with cystic fibrosis—inhalation of plain saline from a nebuliser seems to help. The value of an old-fashioned inhalation of steam in conditions such as acute laryngotracheitis should not be forgotten.

Mixtures

Drugs with a cough suppressant action are often given with other compounds for the symptomatic relief of upper respiratory tract infections, and here the combination may be justified, as, for example, in combining a nasal decongestant with a cough suppressant. Preparations such as Actifed compound linctus and Phensedyl, which contain a decongestant and codeine, would seem logical. Many of the preparations used for the symptomatic relief of cough are, of course, over-the-counter preparations that will have been affected in Britain by Part III of the Medicines Act. Among other things, this regulates the maximum amount of certain constituents that they may contain.

Cough is often produced by self-limiting diseases, such as respiratory infections, and may often therefore clear spontaneously. Nevertheless, symptoms associated with it, particularly nasal congestion, may be relieved by some of the compounds mentioned. Objective testing of cough suppression is a difficult procedure, as is assessing the effect of mucolytic agents in patients as opposed to their rheological properties in vitro. Though the Department of Health deplores the expenditure of large sums of money on cough and cold remedies, these will certainly be sought by patients. If such remedies shorten the time of absence from work of patients with upper respiratory tract symptoms they are worthwhile.

References

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- 2 Irwin, R S, et al, *Archives of Internal Medicine*, 1977, **137**, 1186.
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- 4 Empey, D W, et al, *American Review of Respiratory Disease*, 1976, **113**, 131.
- 5 Howard, P, et al, *British Journal of Diseases of the Chest*, 1977, **71**, 19.
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- 8 *Scandinavian Journal of Respiratory Disease*, 1974, Suppl No 90.

Is hormonal treatment useful in treating recurring severe depression at menstruation?

Premenstrual psychological changes have a complex aetiology not yet clarified, but hormonal treatment has an important place and should always be considered. The two commonly used approaches are with a progestogen or progesterone. With progestogens such as Primolut-N or Duphaston the usual dose is 5 mg thrice daily or 10 mg twice daily from the 18th to 25th days of the menstrual cycle. The course can be started earlier in the cycle if necessary, and in a recent study the 12th to 26th days were covered.¹ Progesterone is given from the 14th to 27th days of the cycle for three cycles by intramuscular injection (50 mg daily) or as a suppository or pessary (400 mg daily), but not by mouth.² Diuretics and pyridoxine can be used concurrently if necessary.

¹ Taylor, R, *Current Medical Research and Opinion*, 1977, **4**, 35.

² Dalton, K, *The Premenstrual Syndrome and Progesterone Therapy*. London, Heinemann, 1977.

Why stetho"scope"?

The Greek *skopein*—look at, behold, contemplate, survey—denotes primarily visual observation, but it was also used metaphorically to mean examine, inquire, and learn. In the early naming of scientific instruments (*telescopio* by Galileo in 1611 and microscope by Thomas Hobbes in 1656) -scope denoted visual observation. Later less atten-

tion seems to have been paid to this—for example, in "gyroscope" Foucault (in 1852) may have had in mind *examining* the dynamics of rotating bodies. In his *Traité de l'Auscultation Médiate* (1819) Laënnec wrote, "I have heard it designated by various epithets, all improper, and some barbarous; among the rest by those of sonometer, pectoriloquer, medical horn, etc. I have, therefore, given it the name of stethoscope, which appears to me the best to express its principal use." An attempt was made to call it stethophone¹ but "stethoscope" has stuck.

¹ Alison, S S, *Proceedings of the Royal Society*, 1858, **9**, 197.

Is a lactic-acid producing diet of any value in treating eczema?

Many rashes are lifelong with unpredictable and unexplained relapses and remissions. It is not surprising that worsening and improvement of atopic eczema—to which this question probably refers—become associated in the patient's (and doctor's) mind with various unrelated factors. The simplest way to deal with these is to tell the patient to take and withdraw the suspected article of diet in a controlled way, the doctor seeing the patient at each stage of the trial. It is essential to persist until a clear result is obtained, and although we all live in hope it will, alas, be negative. The advantage of this approach is that the patient is content that a personal interest has been taken, and he can avoid unnecessary and often expensive dietary fads.