THE USE AND MISUSE OF DRUGS IN SYMPTOMATIC TREATMENT OF THE ALLERGIC NOSE

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Anti-allergic drugs are used on a wide scale for topical application in rhinitis of seasonal and perennial type and for nasal polypi. Anti-allergic drugs can be applied with benefit to the allergic mucous membrane if they do not cause damage to the tissues, do not interfere with the movement of the ciliated membrane, and do not exert local delayed effects which oppose the immediate anti-allergic action (rebound effect). Absorption of the drugs via the mucous membranes should not lead to toxic side effects.

Technique

The technique of the nasal administration of drugs is simple. The drugs are used in solutions and powder form. Solutions are given as nasal drops and sprays. The former are preferred because it is easier to give directions regarding dosage. Sprays are sometimes described as nebulizers and atomizers; the latter term means only reducing bulk liquid to a spray and not reducing particles to atoms. Nasal sprays are simple. They can produce a spray of large particles since quick sedimentation on the mucous membrane is all that is needed. If the nasal passages are too obstructed the drugs may not reach the mucous membrane of the posterior parts of the turbinates. In these cases, an aerosol will give more relief, since aerosols break up the coarse droplets of a solution by the force of an oxygen bomb and the fine mist has more chance of carrying the drug through the obstructed air passages. If a drug is used which is not water soluble it can be administered in powder form by means of a nasal insufflator. The drug is placed in capsules which are pierced with a pin and inserted into the insufflator. Pressure on the bulb produces a powdery spray which is blown into each nostril in turn.

Vasoconstrictors

Anti-allergic drugs which act on the nasal mucous membrane topically are adrenaline (epinephrine in the U.S.A.), noradrenaline (norepinephrine or Arterenol in the U.S.A.), and a number of drugs, similar in chemistry and action, referred to as sympathomimetic or adrenergic drugs. To this group belong isoprenaline (isopropylnoradrenaline), with a variety of synonymous trade names such as Aleudrin, Isupren, Neodrenal, Neo-Epinine. The most widely used vasoconstrictor may be ephedrine hydrochloride. To this group belong also the amphetamines such as benzedrine, methylamphetamine (such as methedrine), dextro-amphetamine (such as dexametazine), phenylephrine hydrochloride, naphazoline hydrochloride and naphazoline nitrate. Many of these drugs are used combining several vasoconstrictors, e.g. Fenox (combining phenylephrine and naphazoline nitrate); other drugs consist of combinations of vasoconstrictors and antihistamines such as Antistin Privine (antazoline and naphazoline nitrate), vasoconstrictors and antibiotics, and last but not least vasoconstrictors and steroid hormones.

The pH of all nasal solutions should be adjusted to 5.5 to 6.5.

The topical action of members of this group is due to their constricting effect on the arterioles, capillaries and venules of the mucous membranes which takes place at the site of their deposition. Moreover, they have a relaxing effect on smooth muscle, not only of the bronchi but smooth muscle generally. The sphincters of the nasal erectile tissues often constricted in nasal allergy (Lucas, 1957) may also relax under the influence of these drugs, thus relieving stasis and oedema. These drugs inhibit also the secretory glands.

Most of the sympathomimetic drugs are less powerful than adrenaline and noradrenaline, but more prolonged in effect. The strongest action of the sympathomimetic drugs is exerted by naphazoline. Isoprenaline is a more potent dilator of smooth muscle and gives greater benefit in the obstructing rhinitis than the other preparations.
The main indication for use of these vasoconstrictors is the aim to obtain immediate relief over short periods, i.e. to help a patient to fall asleep again if the rhinitis is preventing this, to stop incapacitating brief attacks during working hours and to tide a patient over the initial phases of anti-allergic management of his disorder. Once an antihistamine drug suitable for the particular patient has been found, precautions against respiratory allergy carried out and immunization taken effect, there will probably be no need for nasal topical treatment.

**Hazards of Vasoconstrictors**

Unfortunately when applied locally the autonomic drugs give rise to unwanted side effects which are causing concern. The most common and important local side effect is the impairment of ciliary movement. It was observed in rabbits after application of adrenaline and amphetamine. Ephedrine is better tolerated by the cilia.

Another unpleasant side effect is dryness of the mouth and pharynx most marked after atropine inhalations which are used for asthma more than for rhinitis. Patients with respiratory allergy are often mouth breathers as a result of their nasal passages being blocked. The nasal airways have the function of supplying moisture to the inhaled air nearly to the point of saturation. The mouth, however, does not possess this efficient moistening mechanism and therefore the mouth breather suffers from dryness of the throat. If the drying effect of the para-sympathetic drugs is added to this, the patient may suffer great distress. In addition, these drugs may cause sensitization.

**Rebound Phenomenon**

The most important side effect is the reversal action or ‘rebound phenomenon.’

After a short period of freedom from blockage of the nasal airways, the patient experiences worse blockage than before. This is due to a secondary vasodilatation. It occurs less with ephedrine and amphetamine, more with adrenaline and its derivatives, and most with naphazoline. The reversal or rebound phenomenon has been explained in various ways. First, as the result of fatigue of the vessels owing to an overconstriction which leads to passive vasodilatation; secondly, as the result of a delayed active vasodilatation. Stimulation of sympathetic effector junctions was found to release vasoconstricting as well as vasodilating components. The vasoconstriction is of shorter duration and when it has subsided vasodilatation takes place. A third theory explains the vasodilatation by a ganglion blockade. This rebound phenomenon has led to much suffering by patients who are unaware that their drug gives relief followed by exacerbation and that a vicious circle is established, a rhinitis medicamentosa is added to their original trouble.

For three years we have been observing with some anxiety severe cases of perennial rhinitis due to this rebound effect. The sufferer from allergic rhinitis, whether seasonal or perennial, is very eager to obtain relief. Antihistamine drugs are not always tolerated and hypo-sensitization cannot be carried out in all cases. The patient readily applies any drugs recommended for local use on the nasal mucous membrane. He may put up with sneezing attacks and watery discharge, but in the event of intense blockage, which often leads to a feeling of suffocation, will pour down his nose anything he can get at his chemist.

Fifty-two cases of rhinitis medicamentosa had been diagnosed. They suffered with intense blockage of their nasal airways, interfering with speech, swallowing and sense of smell and taste. Twenty-six had used nasal drops containing 0.025 per cent. naphazoline nitrate with 0.25 per cent. phenylephrine hydrochloride and 0.5 per cent. chlorbutol (Fenox). Thirteen had used a spray containing 0.025 per cent. naphazoline nitrate and 0.5 per cent. antazoline sulphate (Antistin Privine), and 13 cases had used various nasal drops and/or nasal sprays, tetrahydrozolol hydrochloride (Tyzanol), tuaminoheptaine sulphate (Tuamine), several preparations combining vasoconstrictors and antibiotics and/or vasoconstrictors and corticosteroids, and perhaps Fenox and Antistin Privine at times. The patients started their ‘nasal treatment’ because they suffered from an inhalant allergy or because they were troubled by blockage during an infected cold. They started using the drugs three times daily, but when the rebound effect set in they increased and increased the dose. This was observed most frequently in patients using naphazoline, especially in combination with phenylephrine (Fenox). Those patients often applied the drug every 30 minutes by day and night. Concurrently with this abuse an addiction-like status set in and it was most difficult to break the habit. Many patients were highly nervous, full of apprehension and since naphazoline differs from other sympathomimetic drugs in producing central nervous depression, the mental attitude might have been a toxic effect on brain centres.

Antihistamines did not overcome the rebound effect, whereas hydrocortisone and prednisolone did. In some cases local application of these drugs was sufficient; in others a short systemic course was needed. All patients eventually stopped using naphazoline and the amelioration of their
nasal trouble left no doubt about the diagnosis of rhinitis medicamentosa due to adrenergic drugs and in main to naphazoline.

Unfortunately, it is still possible for the patients to obtain these drugs over the counter. Education of the patient is therefore needed, and their co-operation obtained to restrict the use to the worst episodes.

**Steroid Hormones**

The second large group of anti-allergic drugs which can exert their action at the site of their deposition on the mucous membrane are steroid hormones. Of the known active adrenocortical compounds, hydrocortisone and prednisolone (deltahydrocortisone) can act locally, whereas cortisone and prednisone cannot. Hydrocortisone is soluble in water, only 1: 4,000, and hydrocortisone acetate is insoluble in water. Both drugs can be given as nasal snuff.

Herxheimer and McAllen (1956) saw good results in hay fever, using 15 mg. hydrocortisone locally daily. Good results in nasal allergy with prednisolone locally were reported by Anderson and Ogden (1956). The writer took part in two small controlled trials where patients with hay fever were treated by inhalation of either prednisolone snuff (1 mg. twice daily) or by an inert snuff containing lactose (Godfrey, Maunsell, and Pearson, 1957). The results in 1956 suggested that the daily inhalation of 2 mg. prednisolone snuff is of considerable value in the control of symptoms due to hay fever. The 1956 season was, however, unusually mild, and a further study during the pollen season of 1957, when pollen counts were much higher, showed that prednisolone snuff alone in dosages of 2-4 mg. did not sufficiently control severe cases.

It is, however, considered as a most valuable help in treatment of hay fever and can be given in conjunction with antihistamines and hyposensitization. No side effects were observed; in particular the absence of the rebound phenomenon was noted. Prednisolone as prednisolone sulphate (Predsol) can be used in watery solution. The drops are instilled three to four times daily and this treatment is of valuable help in controlling seasonal and perennial rhinitis. Polypi sometimes shrink considerably with hydrocortisone snuff as well as with prednisolone. An increase of infected episodes has not been noted.

An important use of prednisolone and hydrocortisone was mentioned previously, i.e. the counteraction of the rebound effect.

Since we have to learn more about the applications and results of the local steroid therapy it seems unfortunate that the pharmaceutical industry set out to combine vasoconstrictors and steroid hormones. For example, Cortibiotic nasal drops contain prednisolone, soframycin and the vasoconstricting phenylephrine; Hydrospray contains hydrocortisone, neomycin and the vasoconstricting propadrin; Effortelan nasal spray contains hydrocortisone, thiomersal and naphazoline nitrate, and in Delta-Fenox prednisolone is combined with two vasoconstrictors, phenylephrine and naphazoline. Other similar preparations are also on the market.

Since a certain amount of the locally applied hormones will be swallowed after travelling up the nasal passages via the naso-phyryn, one has to watch carefully for toxic general effects. In our cases neither gastro-intestinal trouble nor signs of Cushing's syndrome have been noted. Yet one should be careful and refrain from giving local steroids to patients with gastric ulcers, congestive heart failure, diabetes and tuberculosis. One should not be too enthusiastic about the improvement of the rhinitis and polypi but realize and let the patients realize that these drugs do not cure the disease but only suppress the clinical manifestations.

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