DRUGS AND RHINITIS
(Possibilities and limitations)

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Introduction

Since respiration goes on all life along, disturbances in the ventilatory function of the nose are felt as very annoying. This especially counts for the occlusion of, or obstruction in the nasal airway as a consequence of a swelling of the mucous membranes and of rhinorrhoea. Practically everybody is once of twice a year the victim of a rhinitis while for many people it is a continuous threat.

Primary factors in vasomotor rhinitis

I. Constitutional hyperreactivity of the mucous membranes in the nose to various stimuli. Possibly a disbalance in the autonomic regulations is involved (19, 20, 40).
II. Allergic processes. Mediators such as histamine, acetylcholine, serotonin, heparin and bradykinin, formed when allergen and antibody interact, act as inductors of a vasodilatation and hypersecretion (23, 37, 51).
III. Infections, too, are a contributive factor in a number of cases of vasomotor rhinitis. The hypersecretion, the exsudate formed and the local swelling caused by the inflammation will contribute to the congestion (21, 61).
IV. Irritants such as SO_2 and NO_2, components in air pollution, may play a role.
V. Hyperplasia of the nasal mucosa and polyposis which may be secundary in nature.
VI. Iatrogenic rhinitis. A variety of drugs can act as causal or additional factors in rhinitis. Especially certain types of hypotensive drugs, such as reserpine, which cause a disregulation in the autonomic nervous system, have to be mentioned in this respect. Drugs may also act as haptens in the development of allergic hypersensitivity (16, 52). Chemicals which are able to act as histamine liberators may cause a histaminergic rhinitis, without involvement of antigen-antibody interaction.

Secondary factors in vasomotor rhinitis

1. The vasodilatation and increased permeability of the vascular walls caused by histamine and the vasodilatation caused by the parasympathetic section of the autonomic nervous system which bring about a swelling of the mocous membranes.

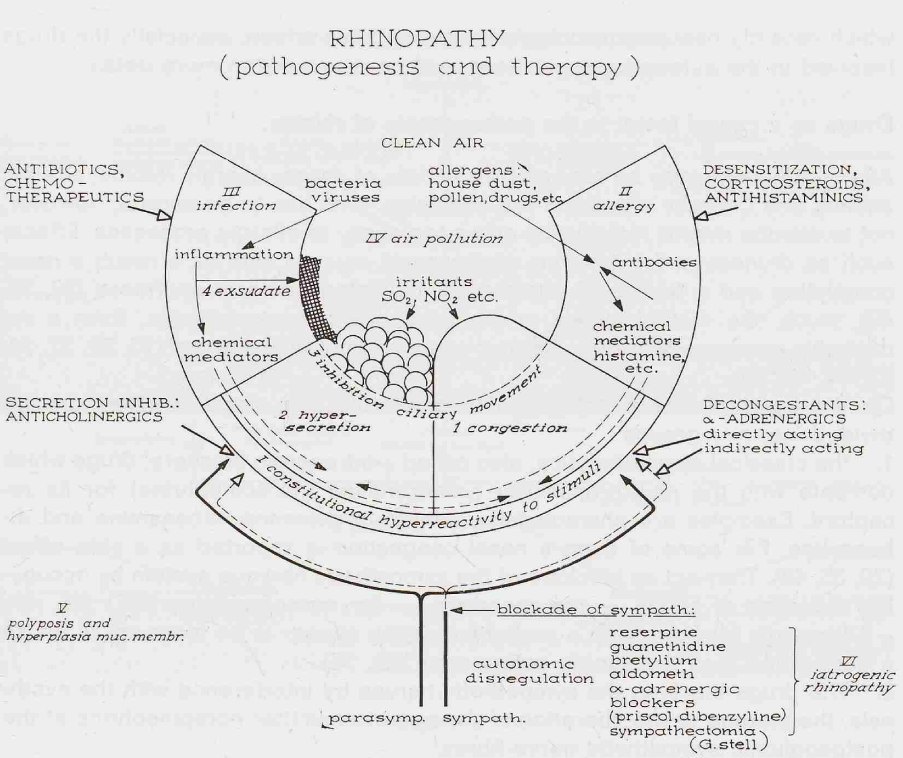


Figure 1.

2. The increased secretion and possibly the formation of an aberrant secrete under influence of the parasympathetic predominance and the local irritation which contribute to the obstruction of the nasal airway.
3. The inhibition of ciliary movement and the consequential impairment of the transport of the mucus carpet is an additional factor. The inhibition can be caused by locally applied drugs or local changes in the pH (37, 59, 61).
4. The formation and accumulation of exsudate due to inflammation also contribute to the obstruction.
Fig. 1 summarizes in a schematic way the factors which may be involved in the pathophysiology of allergic and non-allergic vasomotor rhinitis.
These factors may act singly or in combination.

Drugs and rhinitis

The great variety of pathological conditions with main symptoms in the nose, the easy approach to the mucous membranes there and the capacity of these membranes to absorb drugs (47), strongly promoted the local (nasal) application of a large variety of drugs (25, 46, 47, 50). Usually the aim is a local action. In some cases, however, the nose only serves as a route of application. Drugs applied locally may lead to general effects; on the other hand, drugs applied generally may elicit side effects in the nose. Those groups of drugs for

which recently new pharmacological aspects have arisen, especially the drugs involved in the autonomic regulations, will be discussed in more detail.

Drugs as a causal factor in the pathogenesis of rhinitis.

Allergic diseases may be caused by a variety of drugs. Allergic rhinitis, allergic asthma and Quincke's oedema are examples. One has to be careful, however, not to ascribe rhinitis induced by drugs too easily to allergic processes. Effects such as dryness and hyperemia of the nasal mucosa with as a result a nasal congestion and a feeling of obstruction, indicated as nasal stuffiness (29, 35, 49), much like that observed in the case of vasomotor rhinitis, form a remarkable component in the action of various hypotensive drugs (10, 22, 32, 34, 43, 44, 48, 50).

On the basis of pharmacological characteristics the drugs involved can be divided into two groups:

1. the classical sympatholytics, also called α-adrenergic blockers, drugs which compete with the neurotransmitter noradrenaline (norepinephrine) for its receptors. Examples are phentolamine, dihydro-ergotamine, dibenamine and dibenzyline. For some of them a nasal congestion is reported as a side effect (29, 35, 48). They act as blockers of the sympathetic nervous system by occupying the sites of action — the receptors — for norepinephrine (NE) (28, 48). α-Adrenergic blockers with a prolonged action appear to be more apt to cause a congestion than the shortly acting ones (29, 35).
2. The drugs blocking the sympathetic nerves by interference with the synthesis, the storage or the liberation of the neurotransmitter norepinephrine at the postganglionic sympathetic nerve-fibres.

Reserpine and its derivatives block the response to the indirectly acting adrenergic drugs, which act by liberation of NE, while the response of the organs to directly acting α-adrenergic drugs, which act as substituents for NE on its specific receptors, remains unchanged or even is increased after reserpine. Also stimulation of the sympathetic nerves is ineffective after reserpinization. After infusion of NE a response to the indirectly acting adrenergic drugs and to nerve stimulation is obtained again. The analysis of the action of reserpine shows that it causes a depletion of the sympathetic nerves as far as NE is concerned (4, 5, 11, 13, 14, 34, 43). The stores of this mediator located in intracellular storage granules are emptied. (fig. 2).

These granular reserve stores must be differentiated from the stores of NE, ready for liberation by nerve impulses, also called the mobile pool. It is probably this mobile pool from which the indirectly acting adrenergic drugs liberate NE (see fig. 2). The nasal congestion observed as a frequent side effect in treatment with reserpine and reserpine derivatives (22, 32, 34, 44) is probably due to a disbalance in the autonomic regulation caused by the suppression or elimination of the sympathetic component.

Guanethidine and its derivatives have a mode of action which is to a certain degree comparable with that of reserpine (8, 17, 33, 34, 54). (See fig. 2). They are used as antihypertensives and also give as a side effect nasal congestion, although less frequently than in the case of reserpine (10, 44, 49).

Aldometh (α-methyl-DOPA) and related sympathetic blocking drugs act as "false substrates" for the enzymes involved in the biosynthesis of the neuro-

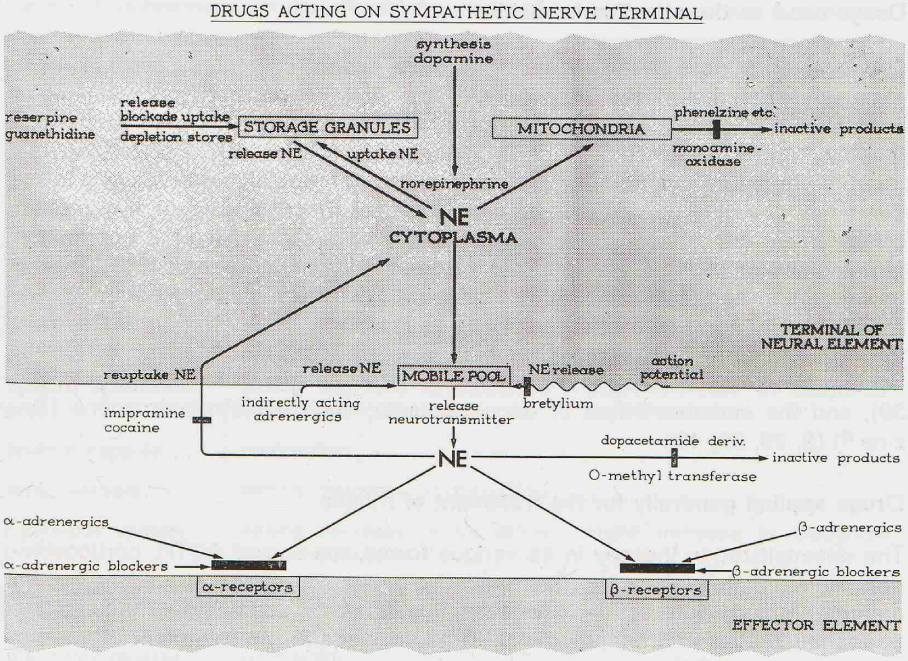


Figure 2.

transmitter norepinephrine (NE). The consequence is an inhibition of the synthesis of norepinephrine by substrate competition and a displacement of norepinephrine by a false transmitter (11, 13, 18, 33, 34, 34, 43, 54) (See fig. 2). Aldometh is used as an antihypertensive. One of the side effects is nasal congestion (10, 44).

Bretylium ("Darenthin") and related adrenergic blocking drugs can cause nasal congestion. They appear to act by blockade of transmission of the nerve pulses, the action potentials, along the sympathetic nerve fibres (See fig. 2). The consequence is a blockade of the sympathetic nerves and a decrease in response to indirectly acting sympathomimetics (4, 5, 26, 34, 43, 47).

Also sympathectomy or lesion of the ganglion stellatum results in a congestion of the conchae in the nose at the side of the ectomy or lesion (31, 45, 53).

Rhinorrhoea is known as a side effect of drugs applied for general treatment, such as the iodides used as expectorants.

A number of drugs are applied locally in the nose with as a purpose a general action. Examples are nasal applications of antidiuretic hormone (24) and of oxytocin (60, 62) as snuff. Another well-known example is the use of cocaine snuff ("snow") by addicts (58). Local side effects may be the consequence of the use of the nose as a route of application. Take for instance the damage to the mucous membranes due to the prolonged vasoconstriction induced by cocaine (28).

Drugs used as therapeutics in rhinitis

Drugs applied locally with as an aim a local action. Examples of drugs most extensively used are: the antibiotics, such as neomycin, chemotherapeutics such as the sulfonamides and antiseptics such as protargol used to combat infections, the application of antihistamines and corticosteroids based on the allergic character of many forms of rhinitis and the decongestants, used to reduce the swelling of the mucous membranes. Besides a local therapeutic effect, these drugs may show local side effects such as rebound congestion after epinephrine and damage to the nasal mucous membranes caused by the prolonged strong vasoconstriction induced by certain decongestants (privinism). Also general side effects may be caused by the penetration of the drug into the general circulation. Examples are the central stimulant action of decongestants such as ephedrine and amphetamine (weckamines) (28, 30, 36, 39), and the sedative effect of decongestants, such as tetrahydrozoline (Tyzine ^{R}) (9, 26, 30, 46).

Drugs applied generally for the treatment of rhinitis

The desensitization therapy in its various forms, the use of ACTH, corticosteroids and antihistamines, to decrease the response of the organism to the antigen-antibody interaction, are examples. Further sedatives, tranquillizers, endoanaesthetics and antiphlogistic drugs are used in the treatment of various forms of rhinitis (59).

The decongestants

The aims for a good nasal decongestant are:
a. a small variance in sensitivity for the drug which implies a small variance in dosage,
b. quick action
c. relatively long action. Extremely long lasting and too strong vasoconstriction may cause ischemic damage of the mucous membranes,
d. no tachyphylaxis,
e. no secondary congestion, no rebound congestion,
f. no local side effects, especially no local irritation,
g. no inhibition of the ciliary movement in the respiratory tract,
h. no general symptoms such as CNS-stimulant or -depressant actions or heart actions such as tachycardia.

a. Directly acting α-adrenergic drugs

The best known α-adrenergic drugs are those most closely related to, or identical with the natural sympathetic neurotransmitter substance norepinephrine (NE). Epinephrine and phenylephrine are examples. These compounds act as substitutes for the natural endogenous neurotransmitter substance norepinephrine. They remain active after sympathetic denervation and during blockade of the sympathetic nerves caused by a depletion of the neurotransmitter substance NE. This in contrast to the "indirectly" acting compounds which as

Table I. A differentation in the effects of norepinephrine, epinephrine and isoprenaline.

organs	norepinephrine and epinephrine; α-receptors, α-adrenergic actions	epinephrine and isoprenaline β-receptors β-adrenergic actions
heart		augmentation myocardial contraction, tachycardia
muscular vessel	slight decrease in bloodflow vasoconstriction	strong increase in bloodflow, vasodilatation
brain vessels (human)	slight decrease in bloodflow vasoconstriction	slight increase in bloodflow, vasodilatation
vessels splanchnic area	strong decrease in bloodflow vasoconstriction	slight increase in bloodflow, vasodilatation
splenic capsule	contraction	
renal vessels	strong decrease in bloodflow	
cutaneous vessels	strong decrease in bloodflow vasoconstriction	slight increase in bloodflow,
vessels nasal mucosa	vasoconstriction	vasodilatation
pilomotor muscle	contraction (raising of hairs)	
bronchial tree		relaxation bronchial muscle
intestine	relaxation intestinal smooth muscle	relaxation intestinal smooth muscle
ureter	contraction	
vas deferens	contraction	
uterus	excitation, uterine contractions (depending on condition of uterus; promoted by estrogens)	inhibition uterine contractions
dilator muscle iris	contraction (mydriasis)	
striated muscle		tremorogenic action
carbohydrate metabolism	increase blood-sugar level (glycogenolysis liver)	increase blood-lactic-acid level (glycogenolysis) muscle
fat metabolism		mobilization of fat (shift from depots to liver)

mentioned act by liberating endogenous NE from the nerve endings. Besides the directly acting α-adrenergic agents, a second class of directly acting adrenergic agents, the β-adrenergic agents, are known. Isoprenaline is an example. This differentiation is based on the differentiation of the adrenergic

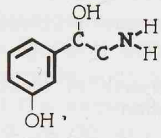
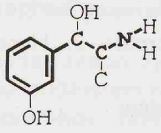
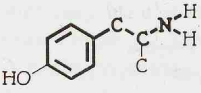
Directly acting ∝-adrenergic amines used as nasal decongestants	conc. solution in %
 epinephrine	0.1
 norphenylephrine	0.25
 metaraminol „Aramine"	0.25
 phenylephrine „Metasympatol"	0.25 – 0.5
 hydroxyamphetamine „Paredrine"	1

Table 2.

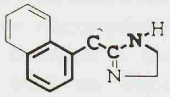
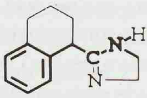
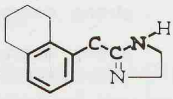
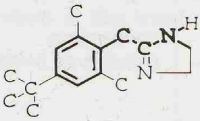
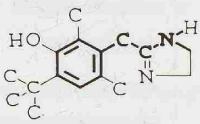
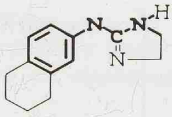
Directly (?) acting ∝-adrenergic amines used as nasal decongestants quick, long and strong action	conc. solution in %
 naphazoline „Privine"	0.05 – 0.1
 tetrahydrozoline „Tyzine"	0.05 – 0.1
 tenaphtoxaline	0.1
 xylometazoline „Otrivin"	0.1
 oxymetazoline „Nasivin"	0.025-0.05
 „Rhinospray"	0.1

Table 3.

receptors in α- and β-receptors by Ahlquist (1, 7). Epinephrine induces its effects on both receptor types. NE mainly acts on the α-receptors and isoprenaline mainly on the β-receptors, thus dividing the effects of epinephrine into two groups. Table I gives a summary in this respect. From this table also the effects of the respective blocking agents, the α-adrenergic blocking agents and the

β-adrenergic blocking agents can be derived. The α-adrenergic agents have a vasoconstrictive action, the β-adrenergic agents act as vasodilators. It will be clear that only the α-adrenergic drugs can be qualified as decongestants (2, 3, 4, 6, 7).
Epinephrine is one of the most active compounds in this respect. It is used in concentrations from 0.1 % to 0.001 %. It has a strong vasoconstricting and secretion inhibiting action and its action is quick and short. Often a secondary hyperaemia, rebound congestion and sometimes a tachycardia are observed (27, 28, 39, 46, 59). Repeated application leads to tachyphylaxis. These disadvantages have as a consequence that epinephrine is not frequently used as a nasal decongestant. NE, a compound being slightly more active as a vasoconstrictor than epinephrine, also has the disadvantage of a frequent rebound congestion. Isoprenaline, a β-adrenergic drug, acts as a vasodilator in the mucous membranes of the nose (38).
Phenylephrine and norphenylephrine are also directly acting α-adrenergic vasoconstrictors. They are reasonably quickly acting in concentrations of about 0.1 %. The action is relatively short. Rebound congestion is less frequent as in the case of epinephrine. In the doses needed these compounds are devoid of β-adrenergic actions. The same obtains for hydroxyamphetamine (Paredrine^R) which has a more prolonged action (See table 2).
The imidazoline derivatives. Naphazoline is a prototype of this group of compounds of which a great variety of derivatives is used as decongestants (Table 3). A characteristic of this group is a quick and often very prolonged action. Rebound congestion and tachyphylaxis, although described, seem not to be frequent. A disadvantage of these drugs is that chronic use may lead to damage of the nasal mucous membranes known as privinism in the case of naphazoline. Some of the compounds viz. naphazoline and tetrahydrozoline (Tyzine^R) have a remarkable depressive action on the central nervous system which is especially evident if they are used for young children (9, 30, 59).
This group of imidazoline derivatives which has in its vascular action many points of conformation with the α-adrenergic drugs probably has to be classified as a group of directly acting α-adrenergic agents (63).

b. **Indirectly acting α-adrenergic drugs**

These compounds also mimic the actions of sympathetic nerve stimulation, however, they mainly act by liberating NE at the sympathetic nerve endings (14). Therefore the type of action is mainly α-adrenergic in its character, which implies a vasoconstrictive effect. This type of drugs is found especially among the non-phenolic phenylethylamines and phenylisopropylamines, such as ephedrine, amphetamine and methamphetamine.
The phenylisopropylamine derivatives differ from NE-derivatives in the absence of the phenolic OH-groups and the isopropylamine configuration instead of the ethylamine configuration in the side chain (Table 4). These characteristics make the compounds more stable, more resistant to biochemical degradation while penetration into the central nervous system is enhanced (51). Ephedrine is a prototype: it is less quickly acting than epinephrine, but it has a more prolonged action. This compound as well as many of the other drugs of this group such as amphetamine have as a side effect a central stimulant action;

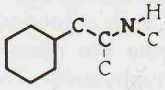
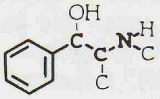
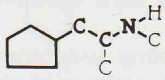
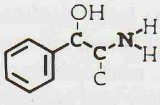
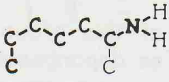
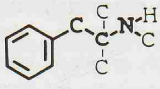
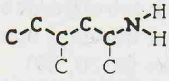
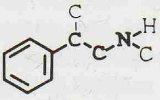
Indirectly acting aliphatic adrenergic amines used as nasal decongestants		**Indirectly acting adrenergic amines** used as nasal decongestants	
	conc. solution in %		conc. solution in %
 propylhexedrine „Benzedrex"	inhaler	 ephedrine	0.5 - 2
 cyclopentamine „Clopane"	0.5	 phenylpropanolamine „Propadrine"	1 - 3
 tuaminoheptane „Tuamine"	1 - 2 inhaler	 mephentermine „Wyamine"	0.5 inhaler
 methexamine	inhaler	 phenpromethamine „Vonedrine"	2.8

Table 4.

they are "weckamines" (15, 51, 56). Some of the compounds are used in the form of inhalers. The abuse of inhalers and other preparations containing amphetamine based on its psychopharmacological effect, is a serious contra-indication for the use of this drug as a decongestant, especially if obtainable without prescription.

Phenylpropanolamine (Propadrine R) has in its action much in common with ephedrine (28, 39, 59). The oral use of these drugs as decongestants has not much sense since in the doses tolerated no local nasal effects are obtained. The drugs may have a certain allergic action if applied orally.

The aliphatic secondary amines of which propylhexedrine (Benzedrex R) and cyclopentamine are the best known examples differ in their action from amphetamine and derivatives in the absence of a stimulant action on the central nervous system (table 4). The cyclo-alkyl and alkyl derivatives of this group are mainly used in inhalers in the form of free bases which are reasonably

volatile. The absence of a stimulant action avoids the tendency to abuse. The decongestive action is quick and relatively long lasting. The compounds of this group probably have to be classified as indirectly acting α-adrenergic drugs (15, 55).

α-Adrenergic decongestants in the treatment of iatrogenic vasomotor rhinitis

As mentioned above, the action of the indirectly acting adrenergic drugs is abolished after the depletion of the catecholamine stores by drugs such as reserpine and guanethidine. The question arises in how far these relations have consequences for the use of the indirectly acting adrenergic drugs in the case of nasal congestion induced by reserpine etc. If the pharmacologial relations described hold true under clinical conditions the consequence would be that in the case of vasomotor rhinitis, caused by adrenergic blocking drugs, such as reserpine, guanethidine, bretylium and α-methyl-DOPA, the indirectly acting adrenergic drugs must be expected to be less efficient than the directly acting ones. The clinical use of reserpine or the other norepinephrine depleting adrenergic blocking drugs will seldom go so far that a complete depletion occurs, such as is possible in pharmacological experiments. The implies that a certain responsiveness of patients with a rhinitis caused by reserpine or the other depleting drugs to indirectly acting adrenergic drugs may be maintained. Such a responsiveness would not count as a strict argument against the relations described.

A more extensive critical study of the effectiveness of the various types of decongestants under these circumstances will be necessary. On the other hand a more refined pharmacological analysis of the mechanism of action of the various groups of decongestants especially of the group of imidazoline derivatives is required.

Data on the therapeutic approach to the vasomotor rhinitis by an attack on the parasympathetic side of autonomic innervation are scarce. Milloning et al. (45) describe a decrease in swelling of the mucous membranes after cutting the nervus petrosus superficialis major. Malcomson (42) reports on a patient with a severe vasomotor rhinitis in whom after surgical interruption of the nervus petrosus superficialis major the nasal congestion and rhinorrhoea disappeared. On the effect of a local application of anticholinergic drugs such as atropine, little information is available in the literature. In the case of a general application of these drugs, the various annoying side effects may cause the patient more trouble than the rhinitis to be treated (59). For a discussion of the role of the autonomic nervous system in the pathogenesis of vasomotor rhinitis, the reader is referred to van Lier (40, 41) and Grobler (27a).

Additives to decongestants

For the various decongestants used therapeutically as nose drops or as spray it obtains that solutions made isotonic with NaCl and buffered to a pH of about 7 are preferable. Their influence on the nasal ciliary activity is negligible then. Often means of preservation such as chlorobutanol or methylparabene and detergents to lower the surface tension are added. There is a variety of preparations composed of a decongestant with antihistamines, antibiotics or desinfectants and even with corticosteroids.

One of the disadvantages of the preparations composed of a variety of components is the increased chance of an irritation of the mucous membranes with as a consequence a vasodilatation and the inhibition of the ciliary movement in the nose with a delay in nasal clearance and therefore the induction or the prolongation of a nasal congestion. A great variety of drugs among which antihistamines, corticosteroids, desinfectants and antibiotics, are reported as inducers of rhinitis (12). The use of nonresorbable oils, such as paraffinoil, as a vehicle, is contra-indicated because of the risk of the deposition of the oil as corpus alienum in the lungs especially of children. A comparison of the various preparations on basis of a critical clinical evaluation is not possible because of a lack of data.

Summary

The pathophysiology and pharmacotherapy of vasomotor rhinitis are shortly discussed to serve as a basis for an analysis of the actions of a number of drugs. Drugs acting as a causal factor in rhinitis as well as the therapeutics got attention. Of the drugs inducing iatrogenic rhinitis the various types of adrenergic blockers, especially those which act as depletors of the stores of norepinephrine in the tissues are discussed. Among the therapeutics especially the α-adrenergic decongestants are dealt with in detail. The question is raised whether certain types of vasomotor rhinitis viz. the iatrogenic form require specific types of decongestants preferentially belonging to the group of directly acting adrenergic compounds.

RESUME

La pathophysiologie et la pharmacothérapie de la rhinite vasomotrice ont été discutées afin de servir comme base pour l'analyse des actions d'un nombre de médicaments. L'attention a été portée tant sur les médicaments qui causent une rhinite iatrogène que sur les substances thérapeutiques. Entre les substances qui provoquent une rhinite iatrogène, les types divers de sympatholytiques, spécialement ceux qui agissent comme dépléteurs des depôts de la noradrénaline dans les tissus, ont été discutés. Entre les substances thérapeutiques, spécifiquement les décongestives α-sympathomimétiques ont été traités en detail. La question a été posée si certains types de rhinite vasomotrice, notamment la forme iatrogène, exigent préférablement les types de décongestives, qui font partie du groupe des substances sympathomimétiques d'action directe.

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