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The prolongation of drug action in the treatment of diseases of the nose and paranasal sinuses*

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SUMMARY

In order to prolong drug contact with the mucous membrane, and thus therapeutic action, cellulose polymers have been used. These polymers exert no toxic action on liver function. The release of the drug from the polymer depends on the degree of polymer viscosity. The use of drug-containing polymers in the treatment of nasal diseases and paranasal sinusitis is highly effective.

Key words: nassal drug delivery, nasal disease, paranasal sinusitis

INTRODUCTION

A local, direct action of drugs is important in the treatment of diseases of the nose and the paranasal sinuses. The instillation of aqueous solutions of drugs into the nasal cavity is commonly used for treating different forms of rhinitis; whereas aqueous solutions of antibacterial drugs are instilled into the damaged paranasal sinuses in sinusitis. Although the mucous membrane absorbs aqueous solutions very well, contact with the surfaces of the mucous membrane is short, since aqueous solutions of drugs quickly leak from the nose and paranasal sinuses. Alternatively, solutions on basis of lipids or organic solvents, which do not mix with the mucus, have been used in rhinology. However, such solutions result in a decrease of the normal function of ciliated epithelia, are not absorbed by the mucous membranes, and transfer drugs to the tissues only very slowly and in small quantities.

To prolong drug contact with the mucous membrane, and thus therapeutic action, we use cellulose polymers such as methylcellulose, carboxymethyl cellulose, carboxymethyl cellulose (sodium salt), oxypropyl methylcellulose and polyvinyl alcohol. These polymers are biologically stable and resistant to micro-organisms, and are not likely to turn sour, or to deteriorate due to molding or fermentation. They form transparent (mucous) solutions of any necessary viscosity, and are soluble in water, in which they swell. Synthetic polymers possess the stability of the given properties and are available in highly purified forms (Rabinovich, 1972; Tentsova and Alushin, 1985; Manaby, 1981).

MATERIALS AND METHODS

Toxic action of polymers on the liver function was studied experimentally in male rats. We investigated the content of the marker enzymes aspartate aminotransferase (AST) and alanine aminotransferase (AAT), which pass into the blood from the lesions in acute and chronic diseases. Serum levels of cholesterol and ß-lipoprotein were determined to study the status of lipid metabolism.

The first group of animals (N=7) was a control one; the second group (N=7) received 1 ml of a 1% solution of carboxymethyl cellulose (sodium salt) intraperitoneally, twice with an interval of 24 hours; and the third group (N=7) received 1 ml of a 1% solution of oxypropyl methylcellulose, twice with a 24-hour interval.

RESULTS

The results obtained (Table 1) show that enzyme activities in both the control and experimental groups appeared to be almost identical. Cholesterol and ß-lipoprotein concentrations did not differ significantly, demonstrating that the polymers do not influence liver function.

Table 1. Effects of polymer solutions on liver function.

Group	AST	AAT	cholesterol	lipoproteins
1	4.67	2.7	71.8	16.4
	2.04-7.2	0.87-4.4	55-90	13-17
2	5.2	3.34	78.9	18.4
	3.6-6.6	1.5-4.4	60-123	9-31
3	3.8	4.5	55.1	27.5
	2.1-5.8	3.7-4.8	28-86	15-63
	p=0.05	p=0.05	p=0.05	p=0.05

AST: aspartate aminotransferase; AAT: alanine aminotransferase

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Table 2. The effect of various polymers on transport function of the ciliated epithelium.

Polymer solution	prolongation of effect (in min)	movement activity (in seconds)				
		before polymer	during polymer	after polymer		
				1 min	2 min	3 min
1% OPMC	1	21±0.62	38±0.86	32±1.21	30±0.26	22±0.54
	5	22±0.35	47±1.32	40±0.26	31±0.84	22±0.92
3% OPMC	1	21±0.75	pollen did	57±0.35	38±0.52	22±0.42
	5	20±1.22	not remove	58±0.68	45±1.26	22±0.75
1% OPMC	1	21±0.67	pollen did	55±0.32	37±0.67	22±0.17
	5	22±0.53	not remove	60±0.54	42±1.32	22±0.68

OPMC: oxypropyl methylcellulose

The possiblly toxic action of polymer solutions on ciliary function was studied experimentally on the ciliated epithelium in the frog's oesophagus. The time it takes an inert particle to move along a defined segment of the middle oesophagus surface was registered, both in the presence of polymer and after its removal. The results show that decrease of transport function depends on the degree of polymer viscosity. Ciliary activity is quickly restored after removal of the polymer (Table 2).

Biological availability of diphenhydramine.HCl by its single instilliation (in the form of both aqueous and polymer solutions) was studied in the rabbit's maxillary sinus. Diphenhydramine.HCl solution was given routinely as intramuscular injections. A two-fold increase in the serum concentrations of diphenhydramine. HCl was found if a polymer solution containing this drug was introduced into the cavity, as compared with an aqueous solution. In addition, therapeutic concentrations of diphenhydramine.HCl were increased two-fold after instillation of polymer solutions, containing diphenhydramine.HCl, into the cavity in comparison to aqueous solutions. Furthermore, there is a two-fold increase in the degree of biological availability of drug-containing polymer solutions, when compared with that of aqueous solutions. Thus, our experiments show that a such polymerbased solutions result in the occurrence of drug depots in the paranasal sinuses.

DISCUSSION

The drugs prepared on a polymer base possess physiological inertness and lack irritating properties on the mucous membrane. The use of different quantities of polymers allows the preparation of solutions with different degrees of viscosity, up to ointment consistency, as well as soluble medicinal polymer films.

We will herein elaborate upon the preparation of polymer gels and soluble polymer films containing vasoconstrictive, antihistamine, and corticosteroid drugs for the treatment of acute and vasomotor rhinitis.

Here is an example of a vasoconstrictive film, containing:

- ephedrine.HCl 2 g,
- methylcellulose or oxypropyl methylcellulose 6 g,
- distilled water to make up to 100 ml.

The liquid obtained after filtration is poured out on film-processing trays of 1,000 cm^2. After drying, the films are taken from the film-protecting tray and kept in hermetically sealed polyethelene packing, 6 × 6 cm in size. Thus, 2 mg of ephedrine.HCl is contained in 1 cm^2 of the obtained film. We consider a piece of the film, 3 × 1 cm in size, as a single dose, to be put on the inferior nasal turbinates.

Using the method of quantitative analysis in the course of two years, we have established that ephedrine.HCl in films is very stable without loss of the initial concentration.

The prescription of another polymer solution containing ephedrine.HCl solution is as follows:

- ephedrine.HCl 3 g,
- oxypropyl methylcellulose and methylcellulose 1 g,
- distilled water to make up to 100 ml.

We use polymer ointments with medicinal drugs for the treatment of atrophic rhinitis, and these promote regeneration processes, improve tissue trophisity and possess stimulating properties:

- riboflavin 0.1 g,
- glucose 3.0 g,
- carboxymethyl cellulose (sodium salt) 3.0 g,
- distilled water to make up to 100 ml.

Furthermore, we use polymer gels containing antibiotics, enzymes, corticosteroids and plant extracts in different combinations, depending on clinical peculiarities of the disease, in the treatment of exudative forms of sinusitis. They are instilled into the paranasal sinuses after puncture and drainage:

- lincomycin 0.6 g,
- chymotrypsin 0.1 g,
- hydrocortisone 5.0 g,
- methylcellulose 0.6 g,
- distilled water to make up to 25 ml.

Our findings demonstrate that, while using polymer based solutions, the concentration of antibiotics contained in it may show a 5- to 6-fold increase compared with the doses recommended for aqueous solutions, without causing any decrease in transport function of the ciliated epithelium.

CONCLUSION

We have been using drugs in polymer solutions in the

treatment of diseases of the nose and paranasal sinuses in the course of more than 10 years. Our clinical observations show that these drug solutions are highly effective. Their action is being further investigated.

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