

ANTINICOTINIC THERAPEUTICAL FILMS: RESULTS OF CLINICAL TRIALS

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Smoking is one of the risk factors of ischemic heart disease [3,5,6], and produces a negative effect on the respiratory apparatus [6] for the population of the whole world. According to the World Health Organization, consumption of cigarettes has grown significantly for the past decades: 40-70% of men, from 10 to 50 per cent of women, and about 30-40 per cent of young people smoke in various countries of the world. In particular, there are a lot of smokers in developing countries where aggressive advertising of tobacco goods, on the one hand, and weak preventive explanatory work conducted by health care institutions, on the other hand, have resulted in the almost 100% ratio of smokers among young people. At the same time, in developed western countries, first of all, in the USA, there is a clear tendency for the reduction of tobacco consumption. Environmental problems and healthy life-style ideas gradually form a negative social attitude to smoking. At the same time, it is very difficult to drop smoking and in many cases application of medication treatment is required.

There are a number of drugs used for facilitation of dropping smoking, which have different efficacy. According to the data of different authors who tested those medications, it varies in the range of 15-80%. The most popular medications for the anti-smoking fight are used mainly in the form of tablets for peroral application and comprise cytisinum, anabasinum, hydrochloride or their mixtures (tabex, lobesile, etc.). The disadvantage of such tablets is their comparatively low efficacy and distinct side effects, which is related to the method of their administration. When penetrating into the digestive system, they are exposed to a destructive effect of the gastrointestinal medium, which reduces the efficacy of medications, and, at the same time, these drugs provide a highly undesirable impact on the digestive apparatus. Antinicotinic medications have local side effects (irritation of the mucous coat, gingival bleeding, etc.) as well as cause a general reaction of the whole organism (allergic symptoms, nose bleeding, exacerbation of the stomach ulcer, heaviness and pain in heart area, extrasystoles, vertigo, etc.). All this dictates the need to improve antinicotinic medications and methods of their administration.

One of the most successful solutions in the development of highly efficient antinicotinic medications are polymer films comprising a bio-soluble non-toxic carrier and incorporated optimized quantity of the antinicotinic substance. The films demonstrate good adhesion to the mucous oral cavity, and, being applied on a gum, gradually dissolve, thus ensuring penetration of the major quantity of the medication through the mucous coat directly into the bloodstream bypassing the digestive apparatus. Being developed in the All-Russian Research and Test Institute of Medical Equipment – Scientific and Production Association Ekran, antinicotinic films have undergone clinical and population studies in the Department of Preventive Pharmacology of the State Scientific Research Center of Prophylactic Medicine of the Ministry for Health Care of the Russian Federation (supervisor – Professor V.I. Metelitsa).

The tasks of the studies were to assess the efficacy of the films, to define their local and side effects. Studies were conducted both on patients suffering from chronic nicotineism without concomitant diseases and on patients with different concomitant pathologies: ischemic heart disease, arterial hypertension, and diabetes mellitus.

Materials and Methods. Films comprising anabasinum, cytisinum or their combination in equal ratios and in the form of oval plates being 9.5 x 4.5 x 0.5 mm in size were placed on the gum beneath the upper lip. The amount of the drug in a film was 1.5 mg.

The study comprised three sections: acute pharmacodynamic studies, course treatment with antinicotinic medications under clinical conditions, course treatment with antinicotinic medications in the population.

The first section included pharmacodynamic studies (PDS) with one-time intake of the medication to examine its effect on the cardiovascular system and carbohydrate metabolism, to define the local effect of medications and side effects at one-time intake as compared to placebo. At the same time, they measured arterial pressure (AP) and heart rate, recorded 12-lead electrocardiogram (ECG) showings. AP and heart rate were measured before the administration of the medications and after 5, 10, 15, 30, 60 minutes and after 2, 3, 4 and 5 hours after the application of the medication. ECG was recorded initially and 2 hours after the application of the medication. They also recorded the frequency of heart strokes.

In the second and third sections of the study (course treatment with antinicotinic medications), they assessed the antinicotinic effect, side effects as well as impact of these medications on the cardiovascular system. To assess their effect on carbohydrate metabolism, they built glycemc curves, daily glycemc and glycosuric profiles.

The regimen of the course treatment: the patients applied films 4-6 times a day within the first five days. In case of positive effect, the treatment continued: on the 5-8th days – one film 3 times a day, on the 9-12th days – one film two times a day, on the 13-15th days – one film 1 time a day.

From the first day of treatment the patients were recommended to quit smoking.

The effect of treatment was assessed to be positive if there was an absolute refusal of smoking, and to be partial if the number of cigarettes was reduced (by 2 times and more). Studies were conducted in accordance with the *Methodological Guidelines for Clinical Studies of Antinicotinic Medications* [2].

Results of Studies. They examined 74 patients (61 men and 13 women) at the age of 20-69 with chronic nicotineism, who had determined to quit smoking. The duration of smoking in the anamnesis was from 3 to 41 (on average – 24.6); the number of cigarettes was from 5 to 30 per day (on average – 17.5 cigarettes).

Pharmacodynamic Studies were conducted in 78 patients, and 15 of them received films with anabasinum, 20 patients received films with cytisinum, films with anabasinum and cytisinum – 8 patients, anabasinum in 0.003 g tablets – 5, placebo –30. Sixty-two patients underwent the course treatment with antinicotinic films.

The duration of film resolution with different medications did not differ significantly and made up about 1.5 hours. The time of placebo resolution also made up 1.5 hours on average.

No injurious or irritating effects on the mucous coat of the oral cavity were recorded.

In one case, a film with cytisinum evoked an unpleasant feeling in the mouth, in one case of the application of the same films they recorded short-term numbness of the lip, in three cases there were complaints about short-term heaviness in the head. Anabasinum did not evoke any side effects.

One-time application of antinicotinic films did not evoke any increase of AP or speeding-up of the heart rate either in patients suffering from cardiovascular diseases (Group 1) or in patients without these diseases (Group 2). On the contrary, patients from the first group demonstrated a decrease of diastolic AP (DAP) 10-15 minutes after the application of the films as compared to those who took placebo (82.5 ± 3.4 and 90.6 ± 3.7 ; 81.3 ± 3.8 and 88.7 ± 3.3 mmHg, respectively; $p < 0.05$). The second group demonstrated a decrease of systolic AP (SAP) after 5 and 15 minutes (107.6 ± 2.6 and 117.5 ± 4.5 ; 106.2 ± 2.5 and 116.8 ± 4.5 mmHg, respectively, $p < 0.05$), a decrease of DAP was recorded 15 and 120 minutes after the application of antinicotinic films as compared to placebo (68.8 ± 1.8 and 73.6 ± 2.0 ; $p < 0.01$; 67.4 ± 2.0 and 72.3 ± 2.3 mmHg, respectively, $p < 0.05$)

Trends in the AP changes for films with anabasinum and cytisinum are similar, yet at the application of films with anabasinum SAP and DAP decreased after 3 and 5 hours, respectively,

while at the application of the film with cytisinum this decrease starts as early as 15 minutes after the application of films.

No dynamics of heart strokes was recorded. When ECG results were analyzed, no dynamics of its showings was recorded in the course of PDS.

Course Treatment. As for 62 patients undergoing a course treatment with antinicotinic films, 23 patients received films with anabasinum, 23 patients received films with cytisinum, and 16 patients applied films with anabasinum and cytisinum.

Figure 1 shows data on the antinicotinic effect of the studied drugs in the process of their application during 15 days.

Efficacy of antinicotinic films was higher under clinical conditions in patients with cardiovascular diseases than in the population ($p < 0.05$). On the whole for the group, complete or partial effect was obtained in 75.8% of patients including full effect in one half of the patients, and only ¼ of patients who applied antinicotinic films demonstrated negative effect. Films with cytisinum, or with cytisinum in a combination with anabasinum were more effective both under clinical conditions and in the population.

The application of films with anabasinum produced full or partial effect in 65.2% of patients. None of the cases had negative effect caused by films on the mucous coat of the oral cavity.

At the application of antinicotinic films 15 (24.2%) patients out of 62 demonstrated insignificant side effects (see the Table).

Two patients with ischemic heart disease underwent 24-hour ECG monitoring. They recorded no rhythm disturbances or *ST* interval depression at the application of films in comparison with the control group.

Four patients with diabetes mellitus underwent special examination of carbohydrate metabolism, and no impact on carbohydrate metabolism ratios was revealed.

They did not find any exacerbations in patients with cardiovascular disorders and only in one case there was an exacerbation of chronic cholecystitis; they did not reveal any influence of the study drugs on the state of carbohydrate metabolism in patients with diabetes mellitus, there were no other undesirable general effects.

Figure 2 shows data about the preservation of the effect of treatment with antinicotinic films 6-14 months after the treatment termination. It is obvious that in the group of the patients who demonstrated positive results immediately after the treatment, only 20% out of the patients who dropped smoking absolutely and 40% of them who had partial effect (i.e. those who did not drop smoking but reduced the number of cigarettes by two or more times) resumed smoking in the same quantity. The rest of the patients preserved the effect of treatment.

Side effects at the application of antinicotinic films

| Side effects | Films with anabasinum | Films with cytisinum | Films with anabasinum and cytisinum |
|---------------------------------------|-----------------------|----------------------|-------------------------------------|
| Dry mouth | 2 | - | 2 |
| Unpleasant taste in the mouth | 1 | 1 | 1 |
| Bitter taste in the mouth | 1 | - | 2 |
| Nausea | 1 | 2 | - |
| One-time vomiting | - | 1 | - |
| Salivation | 1 | - | - |
| Exacerbation of chronic cholecystitis | 1 | - | - |
| Vertigo | 1 | 1 | - |
| Headache | 1 | - | - |

Conclusions

1. Antinicotinic films based on a bio-soluble polymer as the carrier are easy to use and rather effective in the anti-smoking fight.
2. Antinicotinic films comprising anabasinum (0.0015 g), cytisinum (0.0015 g) or both of these medications with the level of 0.00075 g produced an effect in 75.8% of patients, including complete effect, i.e. full refusal of smoking in 46.8%. Films in combination with cytisinum and anabasinum, or those with cytisinum alone were most effective.
3. There were no obvious side effects requiring the withdrawal of drugs when the antinicotinic films were applied. The medication is well tolerated by patients with ischemic heart disease, arterial hypertension, and diabetes mellitus.

LITERATURE

1. *V.I. Metelitsa.* // Bulletin of the All-Union Cardiological Scientific Center. – 1987. – No. 1. – p. 112-112.
2. Methodological Guidelines for Clinical Studies of Antinicotinic Medications. – Moscow, 1986.
3. *B. Hermanson, G. Omenn, R. Kroonmal et. al.* // New Engl. J. Med. – 1988. – Vol. 319, N 21. – p. 1365-1368.
4. *O. Ledermalr.* // Wien. med. Wschr. – 1988. – Bd. 138, N 6/7. – p. 138-139.
5. *W. Schütsenberger, W. Herbinger.* // Ibid. – p. 130-132.
6. WHO. Report of the WHO Expert Committee. Community Prevention and Control of Cardiovascular Diseases. – Geneva, 1984. – p. 14.

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ANTINICOTINIC THERAPEUTICAL FILMS: RESULTS OF CLINICAL TRIALS.

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Summary. The paper gives the results of clinical trials of antinicotinic therapeutical films containing anabasinum, cytisinum or their combination in equal ratios. They were used in 74 patients with chronic nicotineism. The level of the drug in a film was 1.5 gm. The mode of its application was to apply it to the gingiva beneath the upper lip. The bio-soluble polymer carrier-based antinicotinic films are easy-to-use and rather effective in anti-smoking fight. The films produced effects in 75.8% of patients, including complete effect, i.e. full refusal of smoking in 46.8%. The films in combination with cytisinum and anabasinum, or those with cytisinum alone were most effective. There was no adverse reaction when the antinicotinic films were applied. The medication is well tolerated by patients with ischemic heart disease, arterial hypertension, and diabetes mellitus.

Figure 1. Efficacy of the course treatment with antinicotinic films during 15 days (%).

I - by group on the whole; II – under clinical conditions; III – in the population.
The dark sector – full effect; the sector with square hatching – partial effect; the light sector – no effect.

Figure 2. Remote results of treatment with antinicotinic medications.

Top-down: the 1st row of circles – before treatment; the 2nd row – direct results of treatment, the 3rd row – remote results of treatment.

Dark circles – full effect (dropped smoking); circles with square hatching – partial effect (the number of cigarettes reduced by two and more times); light circles – no effect.