

CLINICAL TRIAL OF ANTINICOTINE DRUG-CONTAINING FILMS

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Smoking is widely known to be a serious risk factor for ischemic heart disease [3, 5, 6] and respiratory tract diseases [6]. According to the World Health Organization, cigarette smoking has significantly increased over the last few decades: 40-70% men and 10-50% women are presently addicted to this habit [4]. Young smokers account for 30-40%. Smoking is particularly widespread in the developing countries, where unrestricted advertising of tobacco aggravated by insufficient prophylactic activity of public health service result in almost unexceptional smoking among young people. However, in the developed countries, particularly, in the United States, there is a distinct trend toward reducing smoking. Negative attitude to smoking is declared by ecological and healthy life concepts, which are becoming very popular worldwide. Nevertheless, it is usually very difficult to give up smoking, and drug treatment is required in the majority of cases [1].

There are a number of drugs that help to give up smoking. Different authors reported clinical efficacy of these drugs to vary from 15 to 80%. Anabesine and cytosine are the best known antinicotine drugs. They are available as the Tabex, Lobesil, and some other tablets for peroral intake. Relatively low efficacy and distinct side effects are disadvantages of the tablets, which are directly related to the peroral route of administration. Inside the stomach and intestine, the tablets undergo destruction induced by digestive fluids. As a result, their efficacy is significantly decreased, and products of their destruction exert unfavorable effects on the digestive system. Antinicotine drugs induce local adverse effects (irritation of mucosa, gingival hemorrhage, etc.) and generalized reaction (allergy, nasal bleeding, exacerbation of stomach ulcer, heart pain, extrasystole, vertigo, etc.). Therefore, the antinicotine drugs and modes of their administration should be improved.

Nontoxic polymer bioabsorbable films containing optimal amounts of antinicotine substance are a new promising highly effective medicinal form. Being applied to gingiva or oral cavity mucous membrane, the films are gradually dissolved providing immediate absorption of the drug by the blood, bypassing the alimentary canal. Antinicotine films developed at the All-Russian Scientific-Research and Testing Institute for Medical Instrument Engineering in cooperation with the Ékran Scientific-Manufacturing Association have passed clinical testing in the Department of Preventive Pharmacology, State Scientific-Research Center for Preventive Medicine, Ministry of Health of Russian Federation (Professor V. I. Metelitsa, Head).

The goal of the present work was to evaluate the efficacy of the films and to determine their local effects and side effects. The trial was conducted in patients with chronic nicotine addiction without concomitant diseases and in patients with various concomitant pathology (ischemic heart disease, arterial hypertension, diabetes mellitus).

Materials and Methods

Films containing 1.5 mg of anabesine, cytosine, or their equal mixture were prepared as $9.5 \times 4.5 \times 0.5$ mm oval plates. The films were applied to the gingiva under the upper lip.

The trial included three stages: 1) pharmacodynamic study; 2) clinical treatment with antinicotine drugs; 3) mass treatment with antinicotine remedies in out-patient setting.

Pharmacodynamics was followed after single intake of the test drug. Effects on cardiovascular system (arterial blood pressure AP, heart rate HR, 12-lead ECG) and carbohydrate metabolism were monitored. Values of AP and HR were measured before and 5, 10, 15, 30 min, 1, 2, 3, 4, or 5 h after application of the film. ECG was measured just before and then every two hours after application of the film. Frequency of stenocardic attacks was monitored.

The antinicotine and side effects of the drug-containing films and their effect on cardiovascular system were determined during the second and the third stages of the trial. Carbohydrate metabolism was evaluated from glycemic curves and daily glycemic and glucuretic profiles.

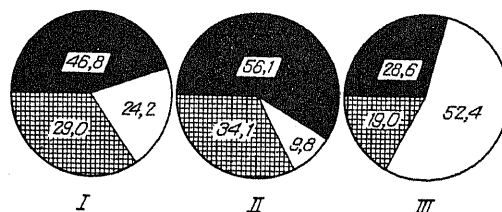


Fig. 1. Efficacy (%) of 15 day treatment with antinicotine films: I) overall effect (II + III); II) in-patient setting; III) out-patient setting. Dark sectors correspond to complete recovery, shaded sectors correspond to partial recovery, open sectors show absence of antinicotine effect.

During the first five days patients received 4-6 films per day. In cases of positive dynamics, the treatment was continued. During the fifth to eighth days patients received three films per day, two films daily during the 9th to 12th days, and one film per day during the 13th to 15th days.

The patients were advised to give up smoking from the first day of the film treatment.

The clinical outcome measure was the number of cigarettes smoked daily: complete discontinuation of smoking was considered as positive result and twofold reduction in the number of smoked cigarettes was considered as partial recovery. The clinical trial was conducted in accordance with the Methodic Recommendations for Clinical Testing of Antinicotine Drugs [2].

Results

Seventy four patients (61 male and 13 female) aged from 20 to 69 years with chronic nicotine and firm decision to give up smoking were subjected to the trial. According to anamnesis, the patients had smoked from 3 to 41 years (average of 24.6 years), the number of cigarettes smoked daily varying from 5 to 30 (average of 17.5 cigarettes).

Pharmacodynamic studies were performed in 78 patients; 15 of them received anabasine-containing films, 20 patients received cytosine-containing films, eight patients received films containing mixture of anabasine and cytosine, five patients received anabasine tablets (3 mg per tablet), and 30 patients received placebo. Sixty two patients were treated with antinicotine drug-containing films.

It usually takes 1.5 h to dissolve antinicotine drug-containing film of any composition, including placebo films.

The films were found to have no damaging or irritant effects on the oral cavity mucosa.

Insignificant side effects were observed in patients treated with cytosine-containing films. In one patient the film was found to induce an unpleasant sensation in mouth, short-term numbness of lip was noticed in another patient, three patients reported short-term headache. No side effects was observed in patients treated with anabasine.

Single application of antinicotine films increases neither AP nor HR in the patients of the two studied groups (with and without cardiovascular diseases). In contrast, statistically significant decrease in the diastolic AP was observed in the patients of the first group (with cardiovascular diseases) relative to the placebo-treated patients, the effect being observed 10 and 15 min after the film application (82.5 ± 3.4 and 90.6 ± 3.7 ; 81.3 ± 3.8 and 88.7 ± 3.3 mm Hg, respectively; $p < 0.05$). In the second group (patients without cardiovascular diseases), application of antinicotine films decreased systolic AP measured 5 and 15 min after the application (107.6 ± 2.6 and 117.5 ± 4.5 ; 106.2 ± 2.5 and 116.8 ± 4.5 mm Hg, respectively; $p < 0.05$) and diastolic AP measured 15 and 120 min after the application (68.8 ± 1.8 and 73.6 ± 2.0 ; $p < 0.01$; 67.4 ± 2.0 and 72.3 ± 2.3 mm Hg, respectively; $p < 0.05$) relative to placebo-treated patients.

The trends in the AP change induced by anabasine and cytosine are similar. However, the anabasine-induced decrease in systolic and diastolic AP is manifested 3 and 5 h after the film application, while similar cytosine-induced effects are observed 15 min after the application.

Neither dynamics of stenocardic attacks nor ECG parameters were found to be affected by the antinicotine treatment.

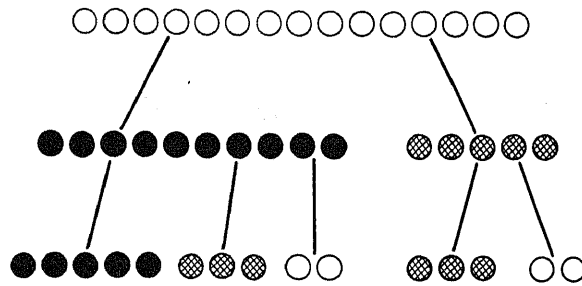


Fig. 2. Long-term results of treatment with antinicotine remedies. Top row, before treatment; middle row, immediately after treatment; bottom row, long-term results of treatment. Closed circles show complete recovery (smoking is given up irreversibly); shaded circles show partial effect (number of smoked cigarettes halved); open circles show no effect.

TABLE 1. Adverse Reactions to Antinicotine Films

Adverse reactions	Anabesine-containing film	Cytisine-containing film	Film containing mixture of anabesine and cytisine
Xeromycteria	2	—	2
Unpleasant sensation in mouth	1	1	1
Bitter taste in mouth	1	—	2
Nausea	1	2	—
Vomiting	—	1	—
Salivation	1	—	—
Exacerbation of chronic cholecystitis	1	—	—
Vertigo	1	1	—
Headache	1	—	—

Antinicotine Treatment in In-patient and Out-patient Settings. Sixty two patients received treatment with antinicotine films. Twenty three of them were treated with anabesine-containing films, 23 patients were treated with cytisine-containing films, and 16 patients were treated with films containing mixture of anabesine and cytisine.

The efficacy of the antinicotine treatment as measured over 15 days in in-patient and out-patient settings is shown in Fig. 1.

The efficacy of the antinicotine films in patients with cardiovascular diseases was higher in in-patient than in out-patient setting ($p < 0.05$). Complete or partial recovery was observed in 75.8% of the whole group, the treatment being completely effective in nearly 50% of the patients. In both in-patient and out-patient settings, the films containing cytisine or cytisine and anabesine were more efficacious than the films containing anabesine alone.

Application of anabesine-containing films resulted in complete or partial recovery of 65.2% of patients. No adverse effects of anabesine-containing films on oral mucous membrane was observed.

Fifteen of 62 patients (24.2%) treated with antinicotine films had minor adverse reactions (see Table 1).

Round-the-clock ECG monitoring of two patients with ischemic heart disease revealed no treatment-induced changes in the cardiac rhythm or suppression of the ST wave interval relative to control.

Examination of carbohydrate metabolism in four patients with diabetes mellitus revealed no antinicotine treatment-induced changes.

No exacerbations were observed in patients with cardiovascular diseases. There was only one case of chronic cholecystitis exacerbation.

The long-term (6-14 months) therapeutic effect of antinicotine films is shown in Fig. 2. Only 20% of completely recovered and 40% of partially recovered patients resumed smoking at the previous rate. The other patients demonstrate stable positive result of treatment.

Conclusions

1. Antinicotine films based on bioabsorbable polymers are an efficacious and convenient therapy against tobacco smoking.
2. Antinicotine films containing anabasine (1.5 mg), cytisine (1.5 mg), or their mixture (0.75 mg + 0.75 mg) have positive effect in 75.8% of patients with nicotinism, 46.8% of the patients giving up smoking completely. Films containing cytisine or mixture of cytisine and anabasine are most efficacious.
3. No side effects of antinicotine films requiring termination of treatment were found. No contraindications were found for patients with ischemic heart disease, arterial hypertension, or diabetes mellitus.

LITERATURE CITED

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