Acta Tuberculosea Japonica Vol. 5, No. 1-2, 1-6, 1955

# Attempted Cleansing of Tuberculous Cavity by Inhalation of Vapor of Methylmetacrylate

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(Received for publication May 26, 1955)

## I. Introduction

This study was performed before the advent of modern chemotherapy of tuberculosis in Japan—in 1947–1950. The clinical results were not as good as those of modern chemotherapy. However, as it is known today that chemotherapy is limited in its clinical effect and there are patients with tuberculous cavities who are tenaciously resistant to chemotherapy, there is a possibility that in the future a treatment such as this gas-therapy may be investigated as a type of local chemotherapy of tuberculous cavities. This is the reason that I report this old investigation now.

Pathological studies suggest that a tuberculous cavity can heal not only by obstruction of the draining bronchus and by subsequent extinction of the cavity, but also by the cleansing of the cavity wall followed by epithelisation of the inner surface of the cavity. This cleansing of cavity walls develops very slowly naturally, but modern chemotherapy markedly accelerates it, especially isoniazid. In addition, gas-therapy is a method which may help the cleansing of cavity walls by bacteriostatic and bactericidal action and by adequate stimulation of tissue reaction.

In 1881 R. Koch investigated the effect of various vaporizing oils on various bacteria, and he found that several oils, especially mustard oil, had a very strong bactericidal effect. Since then the bactericidal effects of various oils on various bacteria, including tubercle bacilli, have been studied by many investigators. However, there have been only a few investigations of the bactericidal and bacteriostatic actions of vapors of organic compounds other than oils. In Japan Endo paid special attention to ether and recently Kitamoto et al. have investigated the bactericidal effects of vapors of xylol, benzol, ether, menthol and capric acid on tubercle bacilli.

## II. In vitro experiments with reference to the tuberculostatic actions of vapors.

Yonezu performed in vitro experiments by the following two methods.

(*1*) *Cover-glass method.*

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Homogeneous suspensions of human type tubercle bacilli (F strain) and avian type tubercle bacilli (Cho-Kyo strains) are prepared (1 mg. bacilli in 1 ml. of saline solution). A loopful of this suspension is smeared on the surface of a cover-glass, and is dried in a incubator. A small sterilized cotton ball is moistened with a definite volume of the organic compound to be tested, and placed in a sterilized Petri dish. The organic compound evaporates in this Petri dish causing it to be filled to saturation with the vapor. The smeared cover-glass is thrown quickly into this dish with the smeared surface up. After a definite time the cover-glass is taken out and thoroughly washed with with 1 ml. of saline solution by rubbing the smeared surface with a loop. This saline solution is poured into a test tube onto Oka-Katakura culture medium. The time of placing the cover-glass into the Petri dish is varied, and the bactericidal effects of vaporizing substances on tubercle bacilli are measured as a function of acting times.

*(2) Double test tubes method*

Suspensions of tubercle bacilli are prepared (1 mg. in 1 ml. of saline solution). A loopful of this bacillary suspension is smeared on Oka-Katakura medium. This test tube is placed unplugged in a large test tube (ca. 150 ml. volume). Various volumes of tested organic compound are dropped into these large tubes. After plugging tightly with rubber plugs and parafin oil, they are placed in an incubator to cultivate tubercle bacilli and to estimate the bacteriostatic power of the tested compound.

*(3) Results*

We tested 28 organic solvents and 20 monomers of polymerising organic compounds. Among the organic solvents we found the following four substances to be strong tuberculostatic agents—chloroform, ethylether, ethylenchlorhydrin and pyridin and among the monomers the following five substances—vinyl acetate, methyl-acrylate, metyl-vinylketon, styrol and acrylnitril.

Tests of bacteriostatic ability by the double test-tube method show that polymerising organic compounds are generally stronger than organic solvents. It is interesting that methylmetacrylate does not have a strong bactericidal effect in the cover-glass method, but it shows a stronger bacteriostatic action by the double test-tube method than chloroform which is a very strong bactericidal agent.

## III. Toxicity of vaporizing substances especially of polymerizing substances.

The toxicity of vapors in a non-flowing quiescent state and in a flowing state were examined, using mice.

Most of the polymerising substances except ethyl- and methylmetacrylate and methylacrylate show strong toxicity.

From these tests of toxicity we found that generally substances which showed strong bacteriostatic powers were also highly toxic to animals. Methylmetacrylate and methylacrylate have low toxicity in spite of their moderately strong bacteriostatic action.

Therefore, these substances may be used in clinical experiments.

As methylmetacrylate is a monomer of ordinary plastic (poly-methylmetacrylate) and is easy to purchase, it was usually used in subsequent investigations.

Morita reinvestigated the toxicity of methylmetacrylate in detail. Results are shown in Table 1. Animals died when they inhaled vapors of higher concentration than 34 Vol. %. This is much less toxic than chloroform or ether.

Table 1.

| Concentration of vapor / State of animals | 10 Vol. % | 13 Vol. % | 20 Vol. % | 27 Vol. % | 28 Vol. % | 32 Vol. % | 34 Vol. % | 38 Vol. % | saturated |
|---|---|---|---|---|---|---|---|---|---|
| symptom | no influence | no influence | slight acceleration of respiration | paralysis of limbs marked acceleration of respiration | paralysis of limbs marked acceleration of respiration | paralysis of limbs marked acceleration of respiration | apnea or dyspnea | apnea or dyspnea | apnea or dyspnea |
| alive or dead | alive | alive | alive | alive | alive | alive | dead | dead | dead |

## IV. Experiment on the influence of methylmetacrylate gas inhalation on experimental tuberculosis in rabbits.

Sugimoto inoculated intratracheally into rabbits 10 mg. of human type tubercle bacilli (F-strain). These rabbits were placed in a box to inhale flowing vapor of metylmetacrylate for one hour every day. After one month of treatment the animals were sacrificed and examined.

No pathological change was seen in the livers, kidneys or spleens of both treated and non-treated control animals.

In the lungs of the non-treated animals there were many tubercles and caseous necrotic lesions. Alveolar septi were greatly thickened, and there were many perivascular cellular infiltrations. There was also marked cellular infiltration (mononuclears and pseudoeosine cells) into the alveoli. But there no dilatation or injection of capillary vessels were noted.

However, in the lungs of treated animals caseations of tubercles were apparently less than those of non-treated animals. Thickening of alveolar septi and perivascular cellular infiltrations were also less than in the non-treated animals. The infiltrating cells were chiefly mononuclears, and small numbers of pseudoeosine cells were seen. Dilatation and injection of capillary vessels were marked, and there were hemorrhages in many parts. Almost no cellular infiltration into alveoli was seen.

Quantitative culturing of tubercle bacilli from various organs of both treated and non-treated control animals was done.

The numbers of colonies from the lungs of treated animals were about 2/3 of those

of control animals. No colony was detected from other organs in either treated or control animals.

## V. Results of Clinical Experiments.

Patients treated with gas-therapy of methylmetacrylate are as follows.

(1) Age: 19–53

(2) Sex : 89 male, 15 female

(3) X-ray findings:

According to Turban-Gerhardt's classification 74 patients (30 patients without detailed descriptions of their diseases are omitted) are classified as follows.

First stage 1, Second stage 35, Third stage 38. All of them show mixed phthisic types in roentgenographic qualities, and no "Früh-infiltrat", caseous pneumonia or simple hilar lymphadenitis was included.

Cavities are shown in Table 2.

Table 2.

| | |
|---|---|
| large cavity (over 4 cm. in diam.) | 10 |
| medium-sized cavity (2–4 cm. in diam.) | 27 |
| small cavity (1–2 cm. in diam.) | 20 |
| unclear | 17 |

(4) Tubercle bacilli in sputum

70 patients' sputa were positive in smears. 4 patients were negative in smears but positive in culture.

(5) Technique of inhalation

In most cases simple methods as follows were carried out.

A cotton ball (2–3 cm.) was moistened with 2–4 ml. of methylmetacrylate and fixed with thread on the inner surface of a glass filter. This glass filter was placed on the nose of patient in order to place the cotton ball very near to the nostrils. Thus the patient inhaled the vapor of the drug by ordinary respiration.

(6) Duration of treatment

The time of inhalation was 10–20 minutes three times a day, but was sometimes changed according to the condition of the patient. Ordinarily the duration of treatment was three months, but there were many cases of eight months or more.

(7) Clinical effects

Noticeable clinical effects were decrease of sputum and cough, improved character of sputum (purulent to serous) and decrease of tubercle bacilli in sputum. Tubercle bacilli in sputum are shown in Table 3. Examinations of sputum bacilli were performed every seven days. Disappearance (negative culture) was seen in 17.2% of treated

patients, and a decrease in 50.9%. Therefore 68.1% of patients showed more or less effect on the discharge of bacilli.

Roentgenographic changes were not apparent, because most of the patients were old fibro-caseous phthisic types.

Table 3.

| tubercle bacilli in sputum | number of patients |
|---|---|
| disappeared | 18 (17.2%) |
| decreased | 63 (50.9%) |
| unchanged | 33 (31.9%) |
| increased | 0 |

(9) Side effects

No side effects appeared in the liver, the kidney, or the blood under adequate control of the treatment. The only side effect was haemoptysis. Pulmonary bleeding was recognized in 10 patients, but most of these were very slight and usually merely bloody sputum. The heaviest haemoptysis was almost 30 ml. of blood and most of these bleedings stopped spontaneously in a few days after the suspension of the inhalation. There was no patient who showed exacerbation after the haemoptysis.

## VII. Discussion

We started to investigate this gas-inhalation therapy in order to accelerate the healing of tuberculous cavities by killing or restricting the growth of bacilli by the bacteriostatic or bactericidial action of inhaled vapor. The clinical effects may be attributed in part to this direct action of the vapor. However, we must consider another factor which may help cavity healing. This is the stimulating action of the vapor on the cavity wall or the bronchi.

This vapor of methylmetacrylate is very slightly toxic and the local stimulating action is also weak. Therefore, irritation of the bronchi was very slight and cough and sputum did not increase. In the vast majority of cases cough and sputum decreased. However, there may be a more or less stimulating action. We recognized in the experiment of rabbits' tuberculosis that the capillary vessels of the lungs were dilated and injected and often bleeding was seen in the treated animals in contrast to the non-treated. Also we recognized in clinical experiments pulmonary bleeding in several cases.

This tendency towards bleeding may be attributed to the hyperaemia caused by the stimulating action of the vapor.

This local hyperaemia may be a factor, if adequate, in accelerating the healing mechanism of tuberculous lesions and especially may accelerate the elimination of caseous substance from the cavity wall—the cleansing of the cavity.

Thus, the bacteriostatic action of vapor combined with the stimulating action of vapor on the air way especially on the cavity wall may be responsible for the clinical effect.

## VII. Summary

Vaporizing organic compounds (28 organic solvents and 20 monomers of polymerizing substances) were examined to determine the tuberculostatic and tuberculocidal power of their vapors *in vitro*. The toxicity of several substances in gaseous states which were found to be strongly tuberculostatic were examined, and we recognized that generally strongly bacteriostatic agents were also highly toxic to animals.

Methyl- and ethylmetacrylate are moderately strong tuberculostatic agents and have very low toxicity for animals. Therefore, methylmetacrylate was investigated in detail. Clinical results in 74 patients are described. 17.2% of patients showed sputum conversion and 50.9% marked decrease of dischanged bacilli after 3 to several months of treatment.

Haemoptysis of slight degree was seen in 10% of our patients. We assume that the cleansing of cavities may be accelerated by this treatment, and the bacteriostatic action and the stimulating action of the vapor on cavity walls may be responsible for the clinical effect.