

The effect of a macrolide antibiotic against experimental sinusitis

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SUMMARY

The effect of a macrolide antibiotic on experimentally induced sinusitis in rabbits was evaluated. Compared with the control group, the effect on sinus mucosal pathology was significantly superior in the drug-treated groups.

Inflammation models as used in the present study will contribute to the establishment of a suitable pharmacotherapy for sinusitis.

INTRODUCTION

In a former study experimental sinusitis was successfully induced in rabbits (Maeyama, 1981) and on the rabbits with this infectious sinus model, the efficacy of proteolytic enzyme has already been evaluated (Ohya et al., 1981, 1983; Maeyama et al., 1981). We have also been studying the efficacy of various antibiotics in sinusitis and the biochemical changes of sinus pathology that take place. In this study, the effect of 3'-O-propionylleucomycin A₅, a macrolide antibiotic, on the experimental sinusitis was examined by a light microscopy (LM) and a scanning electron microscopy (SEM) (Figure 1).

MATERIALS AND METHODS

Eleven white adult rabbits were used in this study. One ml of purified egg white albumin solution in a 2.5% concentration was injected subcutaneously into the back of each rabbit four times a week for two consecutive weeks until the Arthus' phenomenon developed. Then, bilateral maxillary sinuses were sensitized with the same antigen through intramaxillary injection of one ml of the solution with a

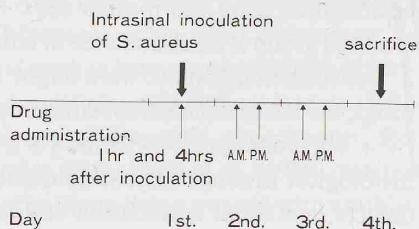


Figure 1.
Schematic illustration of the procedure of drug administration.

sterilized syringe from an anterior caudal point about 1.5 cm from the medial edge of the orbita. This procedure was performed three times a week for two consecutive weeks without any anesthesia.

The animals were then transferred to the Quarters for Experimentally Infected Animals, Institute of Laboratory Animal Sciences, Faculty of Medicine at Kagoshima University. There the following experiment was conducted in a well-controlled environment.

After *S. aureus* 209P was incubated for about 24 hrs at 37°C, one platinum loop full of the cultured bacteria was implanted in casitone semi-liquid agar (2/3 agar) and incubated for about 5 hrs at 37°C so that the bacteria could grow to the order of 10^7 per ml. One ml of this bacterial suspension was only once injected into both sinuses of each rabbit in the same way as described above.

The animals were divided into the following three groups: group 1, each rabbit was given 3"-0-propionylleucomycin A₅ in a dose of 100 mg/kg/day (N = 3); group 2, each rabbit was given the same drug in a dose of 400 mg/kg/day (N = 5); group 3 (control), each rabbit was given tartaric acid only (N = 3). The treatment was performed six times in all for three consecutive days, as is schematically shown in Figure 1.

On the day subsequent to the last administration all animals were sacrificed with an intravenous injection on Nembutal (pentobarbital) and, after macroscopic examination, dissected rapidly to prepare specimens for LM and SEM observation in the same manner as described previously (Maeyama, 1981).

RESULTS

Macroscopic findings

The mucous membranes of all the sinuses of the rabbits of groups 1 and 2 were only slightly edematous and swollen. Contrary to these findings, the mucous membranes of the six sinuses of group 3 were markedly swollen and red. Slight viscous secretion was observed only in two sinuses from group 1 and in four of group 2, whereas all the sinuses of group 3 were filled with thick, purulent, glutinous secretion in varying degrees.

LM findings

The control cases showed severe damage of the epithelial layer with infiltration of eosinophilic cells and plasma cells. Although a thickened epithelial layer was found in group 1, an abundance of ciliary area was found as was the case in group 2. Subepithelial lesions were slight in both groups. Regarding the efficacy of drugs, the lesions of each specimen were divided into four grades; namely, severe (+ + +), moderate (+ +), mild (+), slight (±). The grades were on the bases of histological findings such as epithelial thickening, epithelial metaplasia, ciliary defects, epithelial denudation and inflammatory cell infiltration. We also ob-

served changes in the subepithelial layer such as edema, inflammatory cell infiltration and glandular tissue proliferation. The efficacies of treatment in the three groups are summarized in Table 1.

Table 1. The results and efficacy of the drug therapy for each group in experimental sinusitis, based on LM findings.

treatment group no.	mucosal pathology of maxillary sinus		mucosal pathology of nasal concha	
	epithelial layer	subepithelial layer	epithelial layer	subepithelial layer
group 1 6 sides	2/6 (33.3%)	2/6 (33.3%)	4/6 (66.7%)	3/6 (50%)
group 2 10 sides	8/10 (80%)**	8/10 (80%)**	10/10 (100%)**	8/10 (80%)**
group 3 (tartaric acid)	0/6 (0%)	0/6 (0%)	1/6 (16.7%)	0/6 (0%)

results of χ^2 test ** $p < 0.01$

degree of lesion (+++)... severe

(++)... moderate

(+)... slight

(±)... almost normal

slight (+) and almost normal (±) are considered as successful treatment

SEM findings

Several sites of each sinus membrane were observed with SEM at a magnification of 1,000 and all specimens were classified according to "Classification of SEM type in the experimentally induced sinusitis" (Maeyama, 1981).

Table 2 shows the definition of SEM type classification and SEM type distribution in each group. Based on these criteria and defining types I and II as an improvement, the efficacy at the treatment in each group was evaluated (Table 3).

Group 3 (control) showed an extensive apocrine secretion with limited ciliary area. Almost all the specimens were classified as type 3 or 4. Opposed to this, groups 1 and 2, especially the latter, demonstrated abundant ciliary area and very limited apocrine secretion.

DISCUSSION

There are many reports on pharmacotherapy for sinusitis. To our knowledge, however, fundamental studies on sinusitis have been scarcely reported, except for our experimentally induced sinusitis (Maeyama et al., 1981; Ohyama et al., 1981, 1983; Ogawa et al., 1983). Our previous studies have shown that the experimental animal model, closely resembling chronic sinusitis in man, is very useful for clinicopathological evaluations of pharmacotherapeutic experiments. Regarding the usefulness of macrolide antibiotics, Yamamoto et al., (1979) isolated L-form at a high percentage from sputum of patients being treated with antibio-

tics of β -lactum. They have reported that this L-form differs markedly from its parent strain in the sensitivity to antibiotics and that antibiotics of β -lactum were ineffective for L-form, whereas macrolide antibiotic proved very effective (Yamamoto and Homma, 1978). In the present study, the prophylactic effect of 3''-0-propionylleucomycin A₅, which was derived by chemically propinylating the third position of leucomycin A₅, a kitasamycin, was evaluated using an infection model with a slight modification of the one reported on previously. The efficacy of the drug for the groups which were treated was determined mainly morphologically, especially by classification of surface ultrastructural characteristics of sinus mucosa in the experimental sinusitis (Table 2).

Table 2. SEM type distribution in individual treatment groups and the definition of SEM type classification.

treatment group no.	maxillary sinus				nasal concha			
	SEM type							
	I	II	III	IV	I	II	III	IV
group 1 6 sides	0	3	3	0	1	3	2	0
group 2 10 sides	4	4	2	0	5	4	1	0
groep 3 (tartaric acid) 6 sides	0	0	3	1	0	1	3	2

Type I: Ciliated cells are abundant, the area with a metachronal wave toward a specific direction is predominant, and no mucus is seen.

Type II: The ciliary area accounts for more than 50% but a typical metachronal wave is not always seen and the mucus is scarce.

Type III: The ciliary area accounts for less than 50%, the ciliary patterns are irregularly arranged, and the amount of mucus is moderate.

Type IV: Most of the ciliary area is replaced by both goblet cells and non-ciliated cells. There is a large amount of mucus.

In the present study the drug was administered soon after the inoculation of the micro-organisms and the animals were dissected in a relatively short period of time to examine the prophylactic effect of the drug. The drug-treated groups reacted significantly different from the control group as shown in Tables 1 and 3, but no difference in response was found between the two groups treated with different doses. The inflammation model of experimental sinusitis is expected to be useful not only for determining the efficacy of various experimental pharmacotherapies but especially for developing the most suitable pharmacotherapy for sinusitis in man.

Table 3. The efficacy of the drug therapy for each group in experimental sinusitis, based on SEM findings.

treatment group no.	maxillary sinus	nasal concha
group 1 (6 sides)	3/6 (50%)*	4/6 (66.7%)*
group 2 (10 sides)	8/10 (80%)**	9/10 (90%)*
group 3 (6 sides) (tartaric acid)	0/6 (0%)	1/6 (16.7%)

results of χ^2 test * $p < 0.05$ ** $p < 0.01$

Type I and II (Table 2) are considered as successful treatment.

ZUSAMMENFASSUNG

Die Wirkung von 3"-0-propionylleucomycin A₅ wurde für experimentall gemachte Sinusitis in Kaninchen abgeschätzt. Im Vergleich mit der Kontrollgruppe war der Effekt auf die Sinusschleimhaut-Pathologie in der durch das Antibiotikum behandelten Gruppe bedeutsam besser. Das Entzündungsmodell, die in dieser Studie verwandtete wurde, wird zur Feststellung von der Pharmakotherapie, die am wünschenswertesten in Sinusitis, beitragen.

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