GASTROINTESTINAL MOTOR-STIMULATING ACTIVITY OF MACROLIDE ANTIBIOTICS AND THE STRUCTURE-ACTIVITY RELATIONSHIP

Sir:

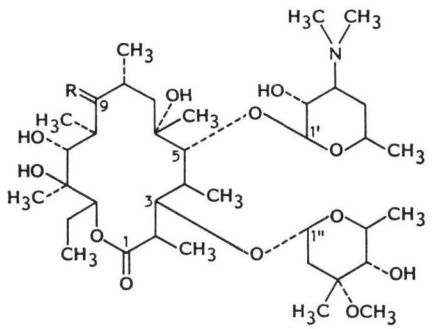
In the previous report[1], the 14-membered macrolide antibiotics, erythromycin (**1**) and oleandomycin (**2**), were clarified to stimulate gastrointestinal motor activity as a secondary effect, while the 16-membered macrolides such as leucomycin, acetylspiramycin and tylosin were inactive in motor-stimulating activity. We report here the characterization of the relationship among the chemical structure, the motor-stimulating effect and the antibacterial activity of macrolide antibiotics.

The gastrointestinal motor-stimulating activity was examined by means of chronically implanted force transducers on the serosa of the gastrointestinal tract positioned to record circular muscle contraction in the gastric body, the gastric antrum, the mid-duodenum, and the upper jejunum in conscious dogs. Contractions were recorded as the contractile waves on a polygraph through the amplifiers. Test materials were first dissolved in ethanol (1 mg/0.05 ml ethanol) and then diluted in normal saline and administered by *i.v.* bolus injection during the quiescent period in gastric motor activity in the interdigestive state. The 16-membered macrolides, leucomycin, tylosin, protylonolide and acetylspira-

Table 1. Gastrointestinal motor-stimulating activity of macrolide antibiotics.

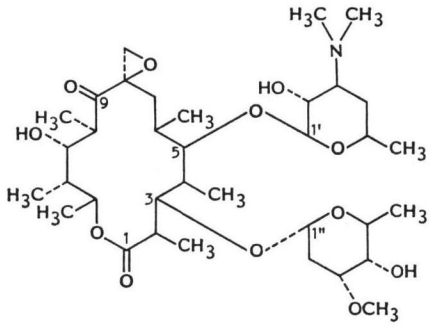
Lactone ring size	Antibiotic	Dose (mg/kg)	Relative activity*
14	Erythromycin (**1**)	1.0	1,000
	9-Dihydro-erythromycin (**3**)	1.0	650
	Oleandomycin (**2**)	1.0	100
	Pikromycin	1.0	10
	Lankamycin	2.0	0
16	Leucomycin	30.0	0
	Acetylspiramycin	25.0	0
	Tylosin	25.0	0
	Protylonolide	2.0	0
12	Methymycin	3.0	0

* The integrated value of the contractile waves induced by the administration of 1 mg erythromycin per kg was defined as 1,000.



Erythromycin A (**1**) R = O

9-Dihydroerythromycin A (**3**) R = <H/OH



Oleandomycin (**2**)

Table 2. Antibacterial activities of **1** and **3**.

Organism	MIC (μg/ml)	
	1	**3**
Staphylococcus aureus KB120 (ATCC 6538P)	0.2	6.25
S. aureus KB34 (FDA 209P)	0.4	12.5
Bacillus subtilis KB211 (ATCC 6633)	0.1	3.12
Micrococcus luteus KB212 (ATCC 934)	<0.05	0.2
Escherichia coli KB213 (NIHJ)	12.5	>100
Klebsiella pneumoniae KB214 (ATCC 10031)	6.25	>100

mycin, the 14-membered macrolides, erythromycin, oleandomycin, pikromycin and lankamycin, and the 12-membered macrolide, methymycin were examined. Quantitative comparisons of the effect among the macrolide antibiotics were analyzed by integrating the contractile waves induced in the gastric antrum from the injection time to 10 minutes. The results were summarized in Table 1. Erythromycin exhibited the strongest activity among the tested macrolides, and oleandomycin exhibited one tenth of its activity of it. The other macrolides did not induce any contractions, even at the dose levels shown in Table 1.

Furthermore, the structure-activity relationship of erythromycin was examined for the separation of the gastrointestinal motor-stimulating activity and the antibacterial activity. Carbonyl group at C-9, dimethylamino group on desosaminyl moiety and cladinose, which are essential functional groups for manifestation of antibacterial activity on erythromycin, were modified and their gastrointestinal motor-stimulating activities were examined. 3′-*N*-Oxide[2], 3′-di-de-*N*-methyl, 3′-de-*N*-methyl and its acyl derivatives[3], 3′-de(dimethylamino)-3′,4′-dehydroerythromycin[4] and 5-*O*-desosaminylerythronolide[5] were devoid of antibacterial activity and did not induce contractions in the gastrointestinal tract. However, 9-dihydroerythromycin (**3**)[6] strongly stimulated gastrointestinal motor activity, in spite of a significant decrease of antibacterial activity. These findings indicate the presence of dimethylamino group and neutral sugar at C-3 of lactone appear to be necessary for motor-stimulating activity.

In conclusion, the gastrointestinal motor-stimulating activity of macrolide antibiotics do not necessarily parallel their antibacterial activity.

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