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Clarithromycin in the treatment of bacterial relapses of chronic bronchitis

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Abstract. — Clarithromycin is a new semi-synthetic macrolide, Erythromycin A derivative, which is bactericidal for the most of growing aerobic and anaerobic Gram-positive and Gram-negative organisms.

The drug has also a potent activity against the pathogens surviving into intracellular medium and, just like all other macrolides, achieves its effect by inhibiting protein synthesis.

Our study investigated the efficacy and tolerability of Clarithromycin in 11 ambulatory patients (8 m, 3f) suffering from bacterial relapses of chronic bronchitis.

The macrolide was administered at the oral dosage of 250 mg twice daily for a period ranging from 7 to 11 days, only after microbiological evaluation of sputum. There was a withdrawal because one of the three bacteria isolated from sputum sample was resistant to Clarithromycin, 7 patients were clinically cured, 3 showed only clinical improvement.

In all the ten patients there was eradication of causative agents.

No adverse events or changes in biochemical and haematological tests were observed.

Key Words:

Clarithromycin, Macrolide, Relapses of COLD.

Introduction

Clarithromycin is a new 14-membered lactone ring macrolide antibiotic that structurally differs from Erythromycin A only by methylation of the 6-hydroxy position of the macrolide ring[1].

This drug, compared with Erithromycin, has improved pharmacokinetic properties for having a higher acid-stability and consequentely a better bioavailability, for achieving higher serum levels; besides Clarithromycin shows an excellent penetration in tissues and a longer elimination half-life that allows to administrate it one a day or at most twice daily[2].

Like other macrolides Clarithromycin carries on its antimicrobial activity by inhibiting the protein synthesis and particularly the 50s ribosomial fraction. This drug penetrates in polymorphonuclear leucocytes, in macrophages and in lymphocytes keeping its own antibacterial activity without interfering with the chemotaxis and the phagocytic functions of these cells[3].

It is therefore obvious the therapeutic role of Clarithromycin against the pathogens which survive in intracellular medium like the following species: Legionella, Listeria, Brucella, Toxoplasma,Clamidiae and Staphylococcus aureus[4].

The spectrum of activity of Clarithromycin is similar to all the other macrolides and includes the most of aerobic Gram-positive cocci, Gram-positive bacteria including Mycobacteria, Gram-negative bacteria, some anaerobes, Mycoplasmas and Clamidiae[5].

The excellent activity of Clarithromycin against the most common pathogens of airways and the organisms liable for the most recent "emerging infections" due to the more and more frequent drug-resistance and to the increasing number of immunocompromised patients, suggest that this drug might be the treatment of choice for the airways infections[6,7].

Therefore, on the grounds of these preliminary remarks we decided to evaluate the efficacy and tolerability of Clarithromycin* in the treatment of bacterial relapses of chronic bronchitis.

Materials and Methods

We made a screening on 40 out-patients, suffering for relapses of chronic bronchitis, at the Respiratory Diseases Clinics of I and II Faculty of Medicine of Naples. We enrolled subjects of both sexes, ranging in age from 18 to 80 yrs, without cardiovascular, hepatic or renal impairment, suffering for bacterial relapses of chronic bronchitis.

Fifty-seven sputum samples of these subjects were examined. The samples were collected and carried to the laboratory in airtight sterile containers and quickly submitted to macroscopic observation to examine colour, particular smells, presence or not of pus. Subsequently the microscopic examination, after Gram-staining, evaluated the fitness of the ratio between neutrophil leukocytes and epithelial squamous cells (NL/ESC). Only the samples with ratio NL/ESC > 5 were admitted to the study.

Therefore, only 36 samples of sputum were chemically fluidified and submitted to colture examination. We only took into account 25 sputum samples of 11 patients in which the species of growing bacteria were strains of Streptococcus pneumoniae (45%), Branhamella catarrhalis (54%), Hemophilus influentiae (18%) and Staphylococcus aureus (45%) (isolated and identified by using standard techniques). Eight patients had monobacterial respiratory infections, 4 of them had associations of the aforesaid pathogens (Table I).

Among all the antibiotics tested, we regarded and evaluated only Clarithromycin (A 6815), Erythromycin (E 15 mg), Penicillin (P 10U) and Oxacillin (0X 10 mg).

The evaluation of the antibiotics inhibiting disc zone diameters has allowed the classification of the strains as Sensitive, Intermediate and Resistant (Table I).

Eleven patients were studied (8 males and 3 females; mean age 60.1 yrs, range 45-75 yrs).

We began therapy with Clarithromycin at the dosage of 250 mg twice daily for a mean period of oral administration of 8.4 days (range 7-10 days). All patients did not receive additional antimicrobial drugs for 20 days before treatment and during the whole period of therapy with the macrolide.

We focussed our attention to detect daily the following clinical parameters: cough, fever, dyspnea, sputum, thoracic examination (Table II).

Complete serial biochemical and haematological tests were performed, at the start and the end of treatment (Tables III, IV, V), to value adverse events (injection pain, gastric pyrosis, skin rashes, diarrhoea, changes in biochemical and haematological tests) related to the study drug.

* Kindly provided by ABBOTT

Table I. Bacterial outcome before treatment with Clarithromycin and in vitro susceptibility to antibiotics.

	Bacterial strains before treatment			In vitro susceptibility to antibiotics			
Patients	**Sputum samples**			**Clarit.**	**Eryth.**	**Penic.**	**Oxac.**
1	Strept.	pneum.		S	S	S	S
	Branh.	catarrh.	Blac+	S	S	R	R
	Haemoph.	infl.	Blac−	R	R	R	R
2	Staph.	aureus		S	S	R	S
3	Staph.	aureus	Blac−	S	S	R	I
	Strept.	pneum.		S	S	S	S
	Branh.	catarrh.	Blac+	S	S	R	R
4	Strept.	pneum.		S	S	S	S
	Branh.	catarrh.	Blac+	S	S	R	R
5	Staph.	aureus	Blac−	S	S	R	R
6	Branh.	catarrh.		S	S	S	R
7	Staph.	aureus	Blac−	S	S	S	S
8	Strept.	pneum.		S	S	S	S
9	Branh.	catarrh.		S	S	R	R
10	Haemoph.	infl.		I	I	S	R
11	Strept.	pneum.		S	S	S	S
	Branh.	catarrh.	Blac+	S	S	R	R

R = Resistant; S = Sentisive; I = Intermediate.

Results

The results are summed up in the Tables VI, VII, VIII.

We found that 7 patients (63.6%) were clinically cured, while 3 (27.3%) had only a clinical improvement. One case (9.1%) is to be considered as a withdrawal because, as Table I shows, the strains of Haemophilus influentiae were resistant to all antibacterial agents tested.

It was not necessary to evaluate the antibiotics inhibiting disc zone diameters because all the post-treatment samples of sputum showed that in all subjects there was eradication of the causative agents (isolated in sputum samples before starting of treatment).

No clinical adverse events related to the drug

Table II. Follow up of clinical parameters.

	BEFORE TREATMENT						AFTER TREATMENT					
Pz	**Cough**	**Sputum**	**Dyspnoea**	**Fever**	**Rales**	**Wheezing**	**Cough**	**Sputum**	**Dyspnoea**	**Fever**	**Rales**	**Wheezing**
1	3	3	2	1	3	2	—	—	—	—	—	—
2	3	2	2	1	2	2	0	0	0	0	0	0
3	3	3	2	0	2	1	1	0	0	0	0	1
4	2	2	1	0	1	1	0	0	0	0	0	0
5	1	2	1	0	0	1	0	0	0	0	0	0
6	3	3	2	0	2	1	1	0	0	0	1	0
7	2	2	1	0	0	2	0	0	0	0	0	0
8	1	1	1	0	1	2	0	0	0	0	0	0
9	1	1	1	0	1	1	0	0	0	0	0	0
10	2	2	2	0	2	2	1	1	0	0	0	1
11	3	2	2	1	2	2	1	0	0	0	0	1

0 = absent; 1 = slight; 2 = medium; 3 = serious.

were observed and no significant changes were found in the biochemical and haematological tests.

Discussion

In this study the microbiological outcomes before treatment (Table I) point out that all strains isolated from sputum samples were more susceptible to Clarithromycin and Erythromycin than to Penicillin and Oxacillin. In particular the bacteria had the same susceptibility of both macrolides, but our data (Table VI) emphasize the excellent tolerability of Clarithromycin, unlike Erythromycin[8]. There was eradication of of causative agents in all subjects treated with Clarithromycin.

Many clinical studies reported in literature[5-7,9] and the above mentioned data confirm the satisfying therapeutic profile and tolerability of this drug.

Therefore, this macrolide can be used particularly in bacterial relapses of chronic bronchitis in which many conditions (reduction of mucociliary clearance, mucostasis, immunodeficiency) promote the bacterial activity and require high diffusibility and concentration of the antibiotic in the bronchial secretions.

Furthermore, in these subjects emerges a high frequency of Gram-positive bacterial strains resistant to the common antimicrobial agents and the eradication of the bacteria

Table III. Clarithromycin.

HAEMATOLOGICAL PARAMETERS *BEFORE* TREATMENT

Pz. N.	ESR (0-20 mm/h)	RBC ($4.6\text{-}6.2 \times 10^6$/ul)	Hct (42-52%)	Hb (14-18 g%)	WBC ($5\text{-}8 \times 10^3$/ul)	Neutr. (65-75%)	Lymph. (20-35%)	Mon. (2-8%)	Eos. (1-4%)	Bas. (0-1%)
1	32	5.0	48	14.6	11.2	73	22	3	2	0
2	28	5.3	43	14.3	10.8	76	20	3	1	0
3	20	4.9	42	15.8	8.2	71	24	3	1	1
4	22	5.6	50	17.0	7.3	69	25	2	3	1
5	17	3.8	42	16.3	12.5	72	22	4	1	1
6	18	4.2	43	15.6	10.2	72	21	5	1	1
7	25	4.6	44	14.7	11.6	74	20	5	1	0
8	15	3.9	42	17.2	8.0	64	32	2	2	0
9	20	4.1	44	16.9	5.8	66	29	3	2	0
10	27	4.0	43	16.2	6.2	75	22	2	1	0
11	23	3.9	42	14.0	9.5	71	25	2	1	1
$\bar{X}$	22.45	4.48	43.9	15.69	9.20	71.18	23.81	3.09	1.45	0.45

Table IV. Clarithromycin.

HAEMATOLOGICAL and URINARY PARAMETERS *BEFORE* TREATMENT

Pz. N.	Total protein (6.6-8.7 g%)	Total bilirub. (0-1 mg%)	SGOT (0-20 U/L)	SGPT (0-35 U/L)	Creatinine (0.5-1.5 mg%)	Platelets (140-340 × 10^3/ul)	URINE pH (5.5-6.5)	URINE spec. w. (1015-1028)
1	6.3	0.4	18	22	0.5	190	5.8	1015
2	6.8	0.1	14	20	1.0	240	6.1	1017
3	6.7	0.5	12	23	0.8	320	5.7	1023
4	7.1	0.2	8	20	0.9	300	5.6	1019
5	7.7	0.4	13	11	0.5	220	6.0	1016
6	7.4	0.1	15	15	0.6	142	6.1	1025
7	7.9	0.8	20	19	0.8	170	5.5	1017
8	8.2	0.3	10	8	1.2	210	5.5	1015
9	7.0	0.1	19	18	0.8	200	6.0	1020
10	6.9	0.7	11	34	1.1	305	6.3	1027
11	7.1	0.5	9	20	1.1	270	5.9	1017
$\overline{X}$	7.19	0.37	13.5	19	0.84	233	5.8	1019

Table V. Clarithromycin.

HAEMATOLOGICAL and URINARY PARAMETERS *AFTER* TREATMENT

Pz. N.	ESR	RBC	Hct	Hb	WBC	N.	L.	M.	E.	B.	Tot. prot.	Tot. bil.	SGOT	SGPT	Creat.	Plat.	URINE pH	URINE spec.w.
1	18	4.2	47	14.5	9.5	65	27	5	2	1	7.2	0.3	14	28	1.0	250	6.3	1020
2	20	5.1	45	14.0	9.4	62	33	3	2	0	6.9	0.2	9	19	0.6	210	6.5	1018
3	15	5.0	42	17.8	7.8	65	26	5	3	1	7.2	0.1	7	27	1.2	280	6.0	1024
4	10	5.2	44	15.3	7.0	66	30	2	2	0	6.7	0.3	8	18	1.4	270	5.8	1022
5	6	4.0	47	17.5	9.1	57	32	6	4	1	8.0	0.5	8	12	0.8	190	6.4	1020
6	7	4.1	42	14.9	8.0	66	29	2	2	1	7.0	0.4	17	26	0.7	149	6.0	1024
7	12	3.9	43	16.2	7.7	68	25	5	1	1	8.0	0.8	18	20	1.0	210	5.8	1018
8	15	4.1	44	16.5	6.9	71	24	4	1	0	7.1	0.6	8	13	0.9	230	5.9	1021
9	10	4.5	50	14.8	6.1	69	24	3	3	1	7.3	0.2	9	26	0.9	190	6.5	1020
10	15	3.8	43	16.2	5.8	70	26	2	2	0	7.4	0.6	15	32	1.2	300	6.1	1025
11	14	4.6	47	15.2	9.0	65	27	4	3	1	7.7	0.3	12	26	1.0	295	6.0	1017
$\bar{X}$	12.9	4.4	45	15.7	7.8	65	27	3.7	2	0.6	7.3	0.4	11.3	22.4	0.97	234	6.1	1020

Table VI. Clinical and bacteriological outcome after treatment with Clarithromycin.

Patients	Age (yrs)	Sex	Days of therapy	Bacteriological outcome	Clinical outcome	Adverse laboratory or clinical events
1	61	M	3	withdrawal	—	—
2	45	M	8	eradication	cured	NONE
3	66	M	9	eradication	improved	NONE
4	61	M	10	eradication	cured	NONE
5	75	M	9	eradication	cured	NONE
6	62	M	9	eradication	improved	NONE
7	59	M	9	eradication	cured	NONE
8	62	M	7	eradication	cured	NONE
9	59	F	8	eradication	cured	NONE
10	49	F	7	eradication	improved	NONE
11	62	F	8	eradication	cured	NONE

Table VII. Microbiological outcome post-treatment with Clarithromycin.

Pz.	Eradication	Withdrawal
11	10 (90.9%)	1 (9%)

Table VIII. Clinical outcome post-treatment with clarithromycin.

Pz.	Cured	Improved	Withdrawal
11	7 (63.6%)	3 (27.2%)	1 (9.09%)

it is necessary to avoid the further progression of the underlying chronic respiratory disease[9]

Riassunto. — La claritromicina è un nuovo macrolide semi-sintetico, derivato dall'eritromicina A, con azione battericida verso la maggior parte dei germi Gram – e Gram + in fase di crescita, aerobici ed anareobici.

Il farmaco, come gli altri macrolidi, esplica efficacemente la propria attività anche contro i microorganismi patogeni che sopravvivono nell'ambiente intracellulare per la sua capacità di inibire la sintesi proteica.

Il nostro studio si propone di valutare l'efficacia e la tollerabilità della Claritromicina in 11 pazienti ambulatoriali (8 m, 3 f) affetti da riacutizzazione batterica di bronchite cronica.

Il macrolide è stato somministrato per os al dosaggio di 250 mg × 2/die per un periodo compreso tra 7 ed 11 giorni, previa valutazione microbiologica dei campioni di espettorato. Uno dei pazienti è stato escluso dallo studio in quanto uno dei tre germi isolati si mostrò resistente alla Claritromicina; in 7 pazienti si ottenne la guarigione clinica; in 3 solo un miglioramento della sintomatologia. L'esame batteriologico dell'espettorato post-trattamento, documentò l'eradicazione degli agenti causali in tutti i casi. Inoltre, nei pazienti studiati, non sono stati osservati effetti collaterali o alterazioni dei parametri ematologici e biochimici monitorati.

Parole Chiave:

Claritromicina, Macrolide, Riacutizzazione di BPCO.

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