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## CHEMOTHERAPY IN CHRONIC URINARY TRACT INFECTION

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THE management of the urinary tract infections is one of the main challenges for the urologist dealing with spinal cord injury patients. We use sulphonamides and other antibacterial substances sparingly, to control many severe infections that are seldom encountered in other Rehabilitation Centres. Like Bors, we believe that the developing of auto-immunity is one of the paths in this difficult task and forced diuresis may help in the control of even some acute pyelonephritis.

A new antibacterial combination was tested in the treatment of chronic urinary tract infections resistant to other drugs. A pyrimidine derivative, trimethoprim, that acts with sulphonamides in a synergic and bactericidal manner, and sulfamethoxazole (Gantanol<sup>1</sup>); expecting a greater intensity of action, broader spectrum of activity, transforming a bacteriostatic into bacteriocidal effect and diminishing the development of resistance in a number of bacteria.

Chemically, trimethoprim is 2, 4-diamino-5 (3', 4', 5'-trimethoxybenzyl)-pyrimidine. Its molecular formula is C<sub>14</sub>H<sub>18</sub>N<sub>4</sub>O<sub>3</sub>, and its molecular weight 290.3. Gantanol contains as active substance 5-methyl-3-sulfanilamido-isoxazole.

We used this combination in two dosages:

<sup>1</sup> F. Hoffmann-La Roche & Co. Ltd., Basle, Switzerland.

Ro 6-2580/4<sup>1</sup> (Gantanol 500 mg. + trimethoprim 50 mg) and  
 Ro 6-2580/9 and 11<sup>1</sup> (Gantanol 400 mg. + trimethoprim 80 mg.).

### METHOD AND MATERIAL

Ro 6-2580/4 combination was tested for five days in a series of 51 patients, out of which 31 had neurogenic bladders or G.U. obstructions, 14 carried stones and 20 were free of obstructions.

All of them had, prior to treatment, a bacterial count above 10,000 colonies and over 50,000 W.B.C. per ml. of mid-stream urine passed first thing in the morning.

TABLE I  
 Chronic Urinary Infections treated with RO 6-2580/4—Results

Urine Culture	5th day		8th day*		
	No	%	No	%	
Negative . . . . .	12	23·5	12	24·5	
Positive {	< 5000 colonies . . . . .	12	23·5	13	26·5
	5000-10,000 colonies . . . . .	3	6·0	4	8·0
	> 10,000 colonies . . . . .	24	47·0	20	41·0
Total . . . . .	51	100·0	49	100·0	

\* Two patients were not registered on the 8th day.

The following tests were performed prior, at the end and at least three days after treatment: complete blood count, alkaline phosphatase, transaminase, bilirubin, B.U.N., cholesterol and eritrosedimentation rate. In five hospitalised patients these tests were performed daily.

We arrived at the results shown in Tables I to IV.

Out of 24 patients who ended up with a colony count over 10<sup>4</sup>, 12 were obstructed, including nine with lithiasis, 15 of these patients were submitted then to antibiotics with very good results in three, good in three, fair in five and four failures although no one sterilised the urine culture.

In a second group, 32 patients with chronic urinary tract infections without known obstructions were placed on a regime of Ro 6-2580/9-11 (Gantanol 400 mg. + trimethoprim 80 mg.) one or two tablets twice a day for seven days with the same laboratory controls at the beginning, end and three days after the treatment. A colony count below 10,000 and diminishing white cell excretion was considered a sign of success. Thirty-one per cent. of patients were cured and 59 per cent. improved.

The urinary white cell excretion diminished below 100,000 × ml. in 57 per cent. of the patients three days after treatment. The W.B.C./H.P.F. below five was found in 38 per cent. three days after treatment, as compared with 1,000,000 W.B.C. × ml. and 10 W.B.C./H.P.F. in 90 per cent. and 87 per cent. prior to it.

<sup>1</sup> F. Hoffmann-La Roche & Co. Lth., Basle, Switzerland.

TABLE II  
Chronic Urinary Tract Infections treated with Ro 6-2580/4—Urinary  
White Cell Count

W.B.C. × ml. of Urine	Before treatment		5th day (end of treatment)		8th day*	
	No	%	No	%	No	%
0-50,000	—	—	25	49	23	47
50,001-100,000	5	10	2	4	6	12
100,001-200,000	4	8	5	10	6	12
200,001-300,000	5	10	3	6	—	—
300,001-400,000	2	4	—	—	3	6
400,001-500,000	3	6	—	—	—	—
500,001-600,000	4	8	2	4	—	—
600,001-700,000	1	2	—	—	1	2
700,001-800,000	1	2	2	4	1	2
800,001-900,000	5	10	1	2	—	—
900,001-1,000,000	1	2	—	—	—	—
1,000,001-2,000,000	2	4	3	6	3	6
more than 2,000,000	18	35	8	16	6	12

\* Two patients were not registered on the 8th day.

TABLE III  
Urinary Tract Infections—Follow-up of the Bacterial Colonies Count

Colonies × ml. of Urine	Before treatment		5th day (end of treatment)		8th day*	
	No	%	No	%	No	%
0-5000	—	—	26	50	27	54
5001-10,000	—	—	2	4	4	8
10,001-20,000	—	—	5	10	1	2
20,001-30,000	1	2	4	8	4	8
30,001-40,000	—	—	—	—	—	—
40,001-50,000	—	—	2	4	3	6
50,001-60,000	—	—	5	10	—	—
60,001-70,000	2	4	—	—	4	8
70,001-80,000	9	18	—	—	3	6
80,001-90,000	15	29	2	4	1	2
90,001-100,000	6	12	3	6	—	—
100,001-150,000	13	25	1	2	2	4
150,001-200,000	5	10	1	2	—	—

\* Two patients were not registered on the 8th day.

TABLE IV  
Urinary Tract Infections—Bacterial Findings

Bacteria	Number of frequencies		
	Before treatment	5th day (end of treatment)	8th day
Escherichia coli . . . . .	14	4	6
Klebsiella . . . . .	9	7	2
Proteus vulgaris . . . . .	6	2	0
Pseudomonas aeruginosa . . . . .	5	5	6
Enterobacter cloacae . . . . .	5	3	3
Enterobacter aerogenes . . . . .	5	—	2
Proteus rettgerii . . . . .	3	2	1
Streptococcus faecalis . . . . .	2	1	1
Proteus mirabilis . . . . .	1	—	—
Mixed infections (Strept.+ Escher.) . . . . .	1	—	—

TABLE V  
Urinary Tract Infections—Follow-up of the Urinary White Cell Count

Leukocytes × ml. of Urine	Before treatment		At the end of treatment		3 days later*	
	No	%	No	%	No	%
0-50,000	3	9	17	53	15	53.5
50,001-100,000	2	6	2	6	1	3.5
100,001-200,000	5	16	2	6	2	7.0
200,001-300,000	2	6	2	6	2	7.0
300,001-400,000	—	—	—	—	1	3.5
400,001-500,000	2	6	—	—	1	3.5
500,001-600,000	2	6	—	—	—	—
600,001-700,000	—	—	1	3	—	—
700,001-800,000	—	—	—	—	—	—
800,001-900,000	1	3	—	—	2	7.0
900,001-1,000,000	1	3	—	—	—	—
1,000,001-2,000,000	4	12	2	6	—	—
more than 2,000,000	10	31	6	18	4	14.0
Per High Power Field						
0- 5	1	3	11	34	10	36.0
6- 10	3	9	4	12.5	3	11.0
11- 20	6	19	3	9	2	7.0
21- 30	1	3	1	3	—	—
31- 50	3	9	1	3	2	7.0
51-100	4	12	4	12.5	5	18.0
more than 100	14	44	8	25	6	22.0

\* Four patients did not follow up.

TABLE VI

## Chronic Urinary Tract Infections—Follow-up of the Bacterial Colonies Count

Colonies × ml. of Urine	Before treatment		At the end of treatment		3 days later*	
	No	%	No	%	No	%
0-10,000	—	—	22	70	20	70
10,001-20,000	1	3	4	12	3	11
20,001-30,000	1	3	—	—	—	—
30,001-40,000	1	3	—	—	2	7
40,001-50,000	3	9	1	3	—	—
50,001-60,000	2	6	—	—	1	4
60,001-70,000	1	3	—	—	—	—
70,001-80,000	1	3	—	—	—	—
80,001-90,000	4	12	1	3	—	—
90,001-100,000	3	9	—	—	—	—
100,001-150,000	5	16	—	—	1	4
150,001-200,000	4	12	1	3	1	4
more than 200,000	6	18	3	9	—	—

\* Four patients did not follow up.

TABLE VII

## Chronic Urinary Tract Infections—Bacterial Findings

Bacteria	Before treatment	At the end of treatment	3 days later
Escherichia coli . . . . .	13	2	—
Enterobacter sp. . . . .	3	1	1
Klebsiella . . . . .	3	—	—
Proteus sp. . . . .	2	—	—
Proteus rettgerii . . . . .	3	1	—
Staphylococcus aureus . . . . .	1	—	—
Aerobacter aerogenes . . . . .	1	—	—
Streptococcus faecalis . . . . .	1	1	—
Enterobacter cloacae . . . . .	1	1	—
Proteus vulgaris . . . . .	2	—	—
Piocianic b. . . . .	1	3	3
Citrobacter . . . . .	1	—	—
Proteus morgani . . . . .	—	1	—
Staphylococcus + Enterob. sp. . . . .	—	—	1
Proteus rettg. + Klebsiella . . . . .	—	—	1
Piocianic b. + Escher. coli . . . . .	—	—	1
Total . . . . .	32	10	7

Germ change: eight cases.

The bacterial count dropped below 10,000 × ml. in 71 per cent. of patients. Eight patients with fair results were placed on Gentamicin with six failures and two successes, three of these patients were later found to have unknown foreign bodies or lithiasis in the urinary tract.

The bacterial findings are shown in Table VII.

### SIDE EFFECTS

We did not find any of importance. With Ro 6-2580/4 there was a drop in platelet count in three cases and with Ro 6-2580/9-11 in four, maintaining the normal values.

In one case there was an increase of glutamic-pyruvic-transaminase above normal levels, one developed a skin rash that lasted seven days and another one had gastric intolerance.

### SUMMARY AND CONCLUSIONS

We report the clinical research of a new antibacterial combination (Gantanol + trimethoprim; F. Hoffmann-La Roche & Co. Ltd.) in the management of chronic urinary tract infections.

The combination Ro 6-2580/4 administered to 51 patients with and without G.U. obstructions ended up with 55 per cent. good results following. Kass criteria whereas the Ro 6-2580/9-11 in 32 patients without obstruction that rate increased up to the 75 per cent. of cases.

Few adverse reactions were noted.

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## THE PATHOGENESIS OF RENAL INFECTION IN SPINAL CORD INJURY<sup>1</sup>

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THE effect of the initial management of spinal cord injury patients upon subsequent changes in the upper urinary tract cannot be evaluated without an understanding of the pathogenesis of those changes. A day may be coming when infection will be avoided during treatment of the early stages of neurogenic bladder dysfunction,

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