COMPARISON OF AMPICILLIN AND CHLORAMPHENICOL IN TREATMENT OF TYPHOID FEVER

C. SCIOLI, G. GIUSTI, G. BALESTRIERI

from *Clinica delle Malattie Infettive dell'Università di Napoli*
(Director: Prof. F. De Ritis)

ALPHA-AMINOBENZYL penicillin or ampicillin* belongs to the group of synthetic derivatives of 6-aminopenicillanic acid. They are distinguished by a prevalently bactericidal activity, not only on gram positive bacteria, sensitive to penicillin, but also on gram negative bacteria, including salmonellæ.

Ampicillin is remarkably more active than chloramphenicol or tetracycline in mice infected with *Salm. typhimurium* (Acred, 1962).

Different authors have tried ampicillin on various human salmonella infections in dosages varying from 2 to 4 g. daily. Favourable results have been reported by Stewart, Coles, Nixon and Holt (1961) in one case of peritonitis from *Salm. typhimurium*; by Ross, Lovrien, Zaremba, Bruglois and Puig (1962) in ten of 16 patients with enteritis from salmonella; by Kennedy, Wallace and Murdoch (1963) in seven of ten cases of typhoid fever; and by Muddock (1962) in three cases of *Salm. typhi* infection. A variable percentage of success has also been obtained in salmonella carriers treated with ampicillin (Trafford *et al.*, 1962; Tynes and Utz, 1962; Bullock, 1963).

Of particular interest is the work of Sleet, Sangster and Murdoch (1964) on the comparison of ampicillin and chloramphenicol in the treatment of paratyphoid fever. They gave two groups of patients with paratyphoid (a total of 145) either 2 g. of chloramphenicol or 6 g. of ampicillin daily.

The duration of the fever was used to evaluate the treatment. The temperature remained high on the average three days after

treatment with chloramphenicol and six days after ampicillin. However only one patient showed no response after ten days of treatment with ampicillin. In two patients treated with chloramphenicol and one with ampicillin clinical and bacteriological relapse with positive blood culture occurred. Moreover they saw a percentage of persistent fecal excretors in 7% of the patients treated with ampicillin and in 16% of those treated with chloramphenicol.

We knew of this work (Sleet *et al.*, 1964) while executing a similar investigation in typhoid fever.

Materials and Methods

All experimental subjects were admitted to the Clinica delle Malattie Infettive dell'Università di Napoli. Patients were included in the experiment only under the following conditions:

- (1) Age between six and 40 years
- (2) Body temperature not less than 38.5°C. in the days preceding treatment
- (3) Fever for less than 14 days before treatment
- (4) Absence of other complaints, prior or concurrent
- (5) Clinical diagnosis, confirmed by isolation of *Salm. typhi* from blood or faeces and/or from positive Widal reaction at high titer in accordance with the clinical picture and epidemiological criteria.

Forty-nine patients met these requirements. About half of these were considered severe cases because of the patients' general condition. Chloramphenicol and ampicillin were given on a random but not double blind basis. Twenty-five patients were treated with chlor-

*We are grateful to Farmitalia, Italia, for generous supplies of ampicillin "Amplital".

FIG. 1.—Percentage of patients with no fever at various days after beginning treatment.

FIG. 2.—Average of maximum temperature recorded daily in two groups of patients treated with chloramphenicol or ampicillin.

TABLE I
Duration of Fever in 45 Typhoid Patients Treated with Chloramphenicol or Ampicillin

Treatment	No. of patients	Duration of temperature after initiation of treatment average values	standard deviation	"t"	P
Chloramphenicol	25	3.6	2.48		
Ampicillin	20	6.1	2.71	3.24	<0.01

TABLE II
Percentage of Patients with No Fever at Different Times

Treatment	Days of treatment									
	1	2	3	4	5	6	7	8	9	10
Chloramphenicol	0%	8%	48%	60%	76%	80%	88%	92%	92%	92%
Ampicillin	0%	0%	0%	30%	40%	40%	65%	70%	80%	85%
χ^2	0	0.32	10.75	2.90	4.95	5.95	9.46	2.32	0.54	0.07
P		> 0.05	< 0.01	> 0.05	< 0.05	< 0.05	< 0.01	> 0.05	> 0.05	< 0.05

(*) with Yates' correction

TABLE III

Treatment	No. of patients	Interruption of the treatment for drug hypersensitivity	Failure during the treatment	Clinical bacteriological relapse	Faecal excretors of <i>S. typhi</i>
Chloramphenicol	25	0	2	1	1(*)
Ampicillin	23	3	2	2	2(**)

(*) Four months after the acute phase of the disease.

(**) Two and three months respectively after the acute phase of the disease.

amphenicol and 24 with ampicillin. The two groups were similar with respect to age and sex, date of onset of disease, and percentage of severe forms.

Adults were given 2 g./day of chloramphenicol or 8 g./day of ampicillin; children were given 75 mg./kg. of chloramphenicol or 250 mg./kg. of ampicillin.

Treatment was continued for 15 days. All patients were given vitamin B complex intramuscularly. When necessary, patients were given saline parenterally. No other medicament was given during the experimental period. At the end of the treatment all patients were vaccinated intramuscularly.

Treatment with ampicillin had to be discontinued in one patient after two days when severe bleeding of the intestinal tract appeared.

The patient recovered with transfusions and treatment with a combination of chloramphenicol intramuscularly and oxytetracycline intravenously. Since this complication arose within 24 hours, we do not consider that it can be traced to the treatment. The patient has been excluded from the trial.

Results

Salmonella typhi was isolated in 39 patients from the blood and/or faeces before antibiotic treatment. No strain was found resistant to either of the trial antibiotics by the disk diffusion method.

None of the patients treated with chloramphenicol showed any sensitivity. On the contrary, it was necessary to terminate administration of ampicillin to three patients. In one

patient on the third day a measles-like rash appeared. The other two, on the first and second day respectively, showed gastric sensitivity with vomiting. No signs of intolerance were seen in any of the other 20 patients.

Use of the antibiotic at high levels never provoked alterations in the blood composition, thrombocytopenia, increase in serum transaminases, urinary alterations, hyperglycemia, or increase of serum non-protein-nitrogen. None of the patients showed signs of stomatitis, with one exception, a superficial ulcer of the tongue after 13 days. Nevertheless treatment could be continued for 15 days.

The experimental groups consisted of 25 patients treated with chloramphenicol and 20 with ampicillin.

In two patients from each group the antibiotics had no effect after eight days of treatment. The fever remained high and the general toxic and sluggish condition was more pronounced. These patients were treated with a combination of antibiotics (chloramphenicol and streptomycin intramuscularly, oxytetracycline intravenously) and with prednisone. Following this treatment the temperature rapidly fell and the overall condition improved. After a few days the prednisone was gradually reduced and then eliminated. These four patients (also vaccinated) finally recovered clinically and bacteriologically.

In the other 41 patients of both groups the antibiotic treatment favourably influenced the general condition and fever. Body temperature became normal after 2-11 days. Chloramphenicol however acted more rapidly. Temperature persisted for an average of 3.6 days in the chloramphenicol treated patients, while in the ampicillin treated it lasted for an average of 6.1 days. The difference is statistically significant, as seen in Table I. Also statistically significant is the comparison of the percentage of patients with no fever at various time intervals after beginning treatment (Table II and Figure 1). It is evident by the comparison of the temperature behaviour that chloramphenicol acts more quickly (Figure 2).

Although chloramphenicol improved the general condition more rapidly, regression of hepatosplenomegaly occurred in both groups practically simultaneously.

At periodic intervals repeated faecal cultures were made in all patients. Among the patients treated with chloramphenicol there was one clinical and bacteriological relapse¹ and one

patient again excreting *Salm. typhi* four months after the acute stage (again under observation). There were two cases of clinical and bacteriological relapse¹ and two patients again excreting *Salm. typhi* in the faeces after the acute stage among the ampicillin patients.

Our observations are summarized in Table III.

Discussion

Our conclusions on the treatment of typhoid fever are analogous to those of Sleet, Sangster, and Murdoch (1961) on the treatment of paratyphoid.

Chloramphenicol acts more rapidly and must be still considered of first choice as antibiotic, especially considering the more serious nature of typhoid fever. However it is of interest that ampicillin too has a very efficient therapeutic effect.

There have been side effects in almost none of our patients, even with the high dosages used. The reactions seen were temporary and rapidly reversible after interruption of the treatment.

Therefore we consider that ampicillin is to be preferred in patients with a known sensitivity to chloramphenicol or in those particular patients from whom it would be withheld because of its myelotoxic action.

Summary

The comparative effectiveness of treatment with chloramphenicol and ampicillin has been studied in 49 patients with typhoid infection. Treatment was randomized. It appears that ampicillin is effective at the level of 8 g./day. However, chloramphenicol is notably more rapid. The temperature persisted for 3.6 days in chloramphenicol patients and for 6.1 days in ampicillin patients. There were two failures and one clinical and bacteriological relapse in the chloramphenicol group; two failures and two relapses in the ampicillin group.

Addendum

1. In addition to these cases described above the following were also treated with 8 g. of

¹The organisms isolated in these three cases were sensitive to both the antibiotics by the disk diffusion method. These patients were again treated with a combination of antibiotics (chloramphenicol, streptomycin, and oxytetracycline) and were cured completely (clinically and bacteriologically) after 15 days.

ampicillin daily for three weeks:

- (a) Two permanent carriers of *Salm. typhi*, with failure probably due to chronic cholecystitis in one patient and cholelithiasis in the other.
- (b) One case of typhoid infection in an elderly woman with thyrotoxicosis, severe myocarditis, and heart failure. The patient responded favourably to ampicillin, with no fever after seven days. Treatment was continued for 20 days. She was not vaccinated. After 24 days, there was clinical relapse, cured with chloramphenicol.
- (c) One case of undulant fever cured without relapse.

2. Since submitting this paper for publication Guinchi, Sorice and Ortona (1964) have reported results of treatment of eleven cases of typhoid fever with ampicillin. Six patients who were given mixed isomers of ampicillin had persistence of fever for an average of 10 days, one patient was not cleared of infection and a further patient relapsed. Five patients treated with the D isomer were cured the temperature returning to normal, in an average of ten days.

We are grateful to Prof. De Ritis for criticism and revision of the manuscript.

REFERENCE

- ACRED, P., BROWN, D. M., TURNER, D. H., and WILSON, M. G. (1962): *Brit. J. Pharm.*, **18**, 356.
- BROWN, D. M., and ACRED, P. (1961): *Brit. med. J.*, **ii**, 197.
- BULLOCK, W. E. (1963): *Amer. J. med. Sci.*, **246**, 42.
- GUINCHI, G., SORICE, F., and ORTONA, L. (1964): *Clin. Ter.*, **29**, 97.
- KENNEDY, W. P., WALLACE, A. T., and MURDOCH, Y. McC. (1963): *Brit. med. J.*, **ii**, 962.
- KNUDSEN, E. T., ROLINSON, G. N., and STEVENS, S. (1961): *Brit. med. J.*, **2**, 198.
- MUDDOCK, C. R. (1962): *Lancet*, **i**, 918.
- ROLINSON, G. N., and STEVENS, S. (1961): *Brit. med. J.*, **ii**, 191.
- ROSS, S., LOVRIEN, E. W., ZAREMBA, E. A., BRUGEOIS, L., and PUIG, J. R. (1962): *J. Amer. med. Ass.*, **182**, 238.
- SLEET, R. A., SANGSTER, G., and MURDOCH, J. McC. (1964): *Brit. med. J.*, **i**, 148.
- STEWART, G. T., COLES, H. M., NIXON, H. H., and HOLT, R. Y. (1961): *Brit. med. J.*, **ii**, 200.
- STRATTFORD, B. C. (1962): *Med. J. Aust.*, **2**, 414.
- TRAFFORD, J. A. P., LILLCRAP, D. A., HOUSTON, J. C., MACLAREN, D. M., BARNES, R. D. S., and KNOX, R. (1962): *Lancet*, **i**, 987.
- TYNES, B. S., and UTZ, J. P. (1962): *Ann. intern. Med.*, **57**, 871.
- URI, J. (1962): *Orvosi Hetilap*, **38**, 1777.

DISCUSSION

Chairman: D. G. JAMES (London); Participants: G. K. DAIKOS (Athens); W. BRUMFITT (London); G. T. STEWART (Carshalton); S. J. SELIGMAN (Los Angeles); A. PERCIVAL (London); M. HAMBURGER (Cincinnati); J. P. DUGUID (Dundee); L. P. GARROD (Radlett); A. B. CHRISTIE (Liverpool); R. CRUICKSHANK (Edinburgh); G. AYLIFE (Birmingham); A. M. GEDDES (Edinburgh); T. PARKER (London); P. C. ELMES (Belfast).

Faecal Excretion of Ampicillin

G. K. DAIKOS: I would like to make some comment concerning the concentration of ampicillin in the intestinal lumen. Following the detailed observations of Stewart and co-workers it is generally considered that because of the great absorption of ampicillin from the higher gastro-intestinal tract and the inactivation of the minimal remainder by the penicillinase producing inhabitants of the large intestine, ampicillin cannot be recovered from the intestinal lumen.

Our experiences are different (Daikos, Kontomichalou and Bilalis, unpublished data). During quantitative studies of the bacterial

intestinal flora of 16 healthy individuals we determined the ampicillin concentration in the faeces the sixth day after an oral daily dose of 1.5 g. As it is seen in Table I the amounts of ampicillin in the faeces ranged from 250 µg./ml. to 25 µg./ml. in half of the subjects. In another four it was from 12 to 0.5 µg./ml. and in only four it was not detectable. This finding corresponds well with the observed influence of ampicillin on the intestinal flora of the same people. As can be seen in Table II and the accompanying figure this influence proved considerable and it can be compared with that exerted by the so called broad spectrum antibiotics (comparative data to be published).

Although the kinetics of intestinal ecology