AMPICILLIN IN PAEDIATRICS

BY

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Ampicillin ('penbritin')*, 6-[D(—)- α -aminophenyl-acetamido] penicillanic acid, is a member of the semi-synthetic group of penicillins; it is active when given by mouth, and its antibiotic spectrum includes certain Gram-negative organisms.

The purpose of the present study was to assess the blood levels attainable in the paediatric age-group, the *in vitro* sensitivity pattern of selected organisms, and the response to ampicillin therapy in certain childhood diseases.

Methods and Patients

Blood Concentrations After Oral Dosage. Ampicillin was administered as a freshly prepared oral suspension in a dose of 12.5 mg./kg. to 38 children who were in hospital with a variety of acute and chronic diseases. They were not fasted and had not received antibiotics. Blood was collected before the dose and at hourly intervals afterwards. Four other children received 25 mg./kg., and seven children 50 mg./kg. The age range of all these children is shown in Table 1. The cup plate assay method for ampicillin concentrations was similar to that described by Knudsen, Rolinson and Stevens (1961).

Liquor Amnii and Cerebrospinal Fluid Concentrations. Two hours after being given 750 mg. of ampicillin, amniotic fluid was collected from four women who had obstetric indications for artificial rupture of the membranes. The fluid was assayed for ampicillin activity.

Seven children who were undergoing diagnostic or therapeutic spinal taps were given ampicillin 12.5 mg./kg. orally at various times before tapping. The cerebrospinal fluid ampicillin concentrations were assayed in a manner similar to blood. In addition, one child who was undergoing therapeutic cerebrospinal fluid drainage following craniotomy for cerebral tumour had repeated dosage and sampling over five days. One newborn baby with *Esch. coli* meningitis complicating a meningomyelocele had ventricular fluid assays performed repeatedly during a course of ampicillin of 50 mg./kg./day.

Minimal *In Vitro* Inhibitory Concentrations. Gastro-intestinal pathogens were collected from 66 children over a ten months' period. Cultures of organisms, identified by standard bacteriological techniques, were subjected to various concentrations of ampicillin under quantitative conditions previously described (Kneebone and Maxwell, 1960).

***In Vivo* Activity of Ampicillin in Childhood Gastro-enteritis.** 88 children were admitted to the trial over a period of nine months. The diagnosis of gastro-enteritis was confirmed during the first 24 hours of their admission. Ampicillin (50 mg./kg./day) or a placebo were administered as coded mixtures according to strict rotation. The colour of the vehicle and the code were changed from time to time to assure adherence to the 'double-blind' technique of study. The methods of assessing clinical and bacteriological 'cure' were as previously described (Elliott, Maxwell and Kneebone, 1963).

Clinical Trial in Childhood Pneumonia and Urinary Tract Infections. No attempt to assess the efficiency of the antibiotic by controlled trial was made. The clinical course of these two diseases was assessed, and recorded during treatment, to see whether the results accorded with previous clinical experience with other antibiotics.

Results

Blood Concentrations Attained After Single Oral Dose. Peak concentrations of mean 2.97 μ g./ml.

TABLE 1
AGE DISTRIBUTION OF CHILDREN STUDIED

Age (yrs.)	Number
<6/12	4
6/12-12/12	7
13/12-24/12	4
2-4	8
4-6	4
6-8	4
8-10	5
11-13	2
Total	38

* Supplied by the courtesy of Beecham Research Laboratories.

TABLE 2

BLOOD CONCENTRATIONS AT VARIOUS TIMES AFTER ORAL DOSE OF 12.5 mg./kg. AMPICILLIN

	Time After Dose			
	1 hr.	2 hrs.	4 hrs.	6 hrs.
Mean level with S.D. (µg./ml.)	2.06 ± 1.32	2.97 ± 2.36	1.30 ± 1.31	0.95 ± 1.62
Range (µg./ml.)	0.36 - 7.2	0.15 - 11.2	0.1 - 5.5	0 - 8.32

TABLE 3

BLOOD LEVELS (µg./ml.) AFTER 12.5 mg./kg. AMPICILLIN RELATED TO AGE-GROUPS

Age-group (yrs.)	Time After Dose			
	1 hr.	2 hrs.	4 hrs.	6 hrs.
0-1	3.26 ± 1.99	3.77 ± 1.36	1.70 ± 0.68	2.16 ± 2.60
1-3	1.69 ± 0.79	1.45 ± 0.69	0.57 ± 0.54	0.22 ± 0.53
6-12	1.93 ± 0.83	3.79 ± 2.37	1.46 ± 1.48	0.62 ± 0.65

Figures are group means with S.D.

were attained at two hours (Table 2). This concentration did not depend on age (Table 3). At six hours the concentration had dropped to negligible levels. Children with gastro-enteritis tended to have lower peak blood levels than children with other disorders (Table 4). This result was statistically significant ($p < 0.01$). Doubling and quadrupling the dosage appeared to have a like effect on the peak blood levels (Table 5), similar to other penicillins.

Liquor Amnii Concentrations. In one specimen the level obtained was 0.12 µg./ml. with no apparent inhibition of activity in undiluted fluid. However, in the remaining three specimens, no activity could be found until dilution was carried out. Then minimal (< 0.1 µg./ml.) concentrations could be found.

Cerebrospinal Fluid Levels. In five children, with no meningeal disorder, no ampicillin activity could be detected at any time between one and six hours after oral dosage. In one child with mild mumps meningoencephalitis, a minimal concentration (0.01 µg./ml.) was found.

The child who had undergone brain surgery showed an initial level of 0.68 µg./ml. cerebrospinal fluid. This level after ampicillin dosage declined *pari passu* with the decline in blood concentration of the fluid.

Ventricular fluid from the case of *Esch. coli*

TABLE 4

EFFECT OF GASTRO-ENTERITIS ON BLOOD LEVELS (µg./ml.) OF AMPICILLIN AFTER DOSE OF 12.5 mg./kg.

	Time After Dose			
	1 hr.	2 hrs.	4 hrs.	6 hrs.
Cases with gastro-enteritis	2.07 ± 1.69	1.96* ± 1.34	1.03 ± 1.37	1.16 ± 2.21
Others	2.39 ± 1.44	4.0 ± 2.7	1.47 ± 1.20	0.78 ± 1.00

* Statistically significant at 5% level.
Figures are group means with S.D.

TABLE 5

EFFECT OF DOUBLING AND QUADRUPLING DOSE OF AMPICILLIN ON BLOOD LEVELS

	Time After Dose			
	1 hr.	2 hrs.	4 hrs.	6 hrs.
Blood level (µg./ml.)	Dose, 25 mg./kg.			
		3.58 ± 2.12	2.15 ± 1.33	
Blood level (µg./ml.)	Dose, 50 mg./kg.			
	7.12 ± 1.22	7.99 ± 2.74	4.71 ± 1.77	1.66 ± 0.42

Figures are group means with S.D.

meningitis showed levels ranging from 0.09 to 0.6 µg./ml. This latter level was attained during regular six-hourly dosage (50 mg./kg./day).

Minimal Inhibitory Concentrations. The gastro-intestinal pathogens tested were surprisingly resistant to the effects of ampicillin: only 73% were sensitive to concentrations of 3.12 µg./ml. (Table 6). Of particular interest was the relative resistance of various serotypes of pathogenic *Esch. coli*. The salmonella group were the least resistant.

In Vivo Efficacy in Gastro-enteritis. The results of this trial have been assessed by two criteria: the relief of symptoms, and clearing from the bowel of pathogens. Accordingly the patients have been analysed in two main groups: those from whom no bowel pathogen was isolated, and those with an established bacterial infection. A further subdivision into grades of severity on admission was made for purposes of comparison. The treated and control groups were reasonably congruous for age, severity of disease and type of organism isolated. The distribution of the cases is shown in Table 7.

The results were submitted to statistical analysis by the fourfold table method, with Yates correction for small numbers. Statistical significance was accepted at the 5% level.

Compared with the similar untreated controls,

TABLE 6
ASSESSMENT OF SENSITIVITY *IN VITRO*

Organism	No. Tested	Minimum Inhibitory Concentrations (µg./ml.)					
		25 µg.	12.5 µg.	6.25 µg.	3.12 µg.	1.56 µg.	0.78 µg.
<i>Salmonella typhimurium</i> ..	33				17	14	2
<i>S. newport</i> ..	3				1	1	1
<i>S. bovis morbificans</i> ..	2			1	1		
<i>S. potsdam</i> ..				1			
<i>S. saint paul</i> ..	2			1	1		
<i>S. oranienburg</i> ..	1					1	
<i>S. adelaidae</i> ..	1						1
<i>S. enteritidis</i> ..	1					1	
<i>Sh. sonnei</i> ..	13	11 greater than 25 µg./ml., 3 insensitive	1	6	2	1	
<i>Sh. flexneri</i> ..	1	Insensitive				1	1
<i>Esch. coli</i> (7) ..							
O 26 B6					1		
O 11 B4				1			
O 55 B5	7	Insensitive					
O 111 B4				1			
O 6			1	1			
O 26				1			
O 127					1		

TABLE 7
GASTRO-ENTERITIS TRIAL: DISTRIBUTION OF PATIENTS BY GRADE OF SEVERITY AND TYPE OF DISEASE

	Grade 1 (mild)	Grade 2 (moderate)	Grade 3 (severe)	Total
No pathogen isolated	23	16	19	58
Pathogen isolated	14	8	8	30
Total ..	37	24	27	88

children with no bowel pathogen did not fare better symptomatically when treated with ampicillin at any time after admission. This applied to all grades of severity of the disease. Similar results pertained to the mildest grade of gastro-enteritis associated with an isolated bowel pathogen. However, in the combined data for moderate and severe disease of this type, at the fourth and sixth day of treatment, the ampicillin group tended to do better symptomatically. The trend failed to gain statistical significance ($0.2 > p > 0.1$) (Table 8). A similar trend to earlier clearing of stool pathogens was observed in the more severe grades (Table 9).

On analysing the results by grouping according to variety of organisms, a trend to earlier symptomatic and bacteriological cure in the salmonella group emerged (Table 10).

Urinary Tract Infections. Brisk and sustained clearing of infection was attained in two cases in which there was no anatomical basis for the infection, and the organism was found to be sensitive to ampicillin by standard disc techniques. The remaining two cases had either an insensitive organism or

underlying congenital lesion and did not respond completely.

Pneumonia. Only the results of treatment of undoubted cases of pneumonia have been recorded. This diagnosis was arrived at in retrospect by three clinicians independently reviewing the history, physical signs, course, haematological and x-ray data; all dubious cases were discarded. The patients had the usual course of antibiotic treated pneumonia, except for one that proved to be staphylococcal in origin. Persistence of the illness, and the development of empyema after five days on ampicillin treatment were noted in this case.

Discussion and Conclusion

The results for blood levels attained correspond quite well with those reported in adults (Knudsen *et al.*, 1961). A corollary of this is the absence of age as a determining factor in the group studied. The doubling of levels with doubling of dosage is similar to that reported by Rolinson and Stevens (1961).

In common with other penicillins, ampicillin does not appear to cross into the cerebrospinal fluid at all well, but may attain therapeutic levels when the meninges are inflamed. The levels attained in amniotic fluid were disappointingly low, with the dose and time interval used. Until further data are available on this aspect, the use of ampicillin as a prophylaxis in premature rupture of the membranes does not seem advisable.

In gastro-enteritis the drug may be of some value, although this conclusion could not be given with

TABLE 8

GASTRO-ENTERITIS TRIAL: EFFECT OF AMPICILLIN ON SYMPTOMS OF PATIENTS WITH A STOOL PATHOGEN

Day after Treatment	Cumulative No. of Patients Cleared from Pathogen							
	Mild Disease		Moderate Disease		Severe Disease		All Grades of Severity	
	Drug	Placebo	Drug	Placebo	Drug	Placebo	Drug	Placebo
4	3	3	0	1	1	0	4	4
6	4	5	2	1	2	0	8	6
8	4	6	3	1	3	2	10	9
Total treated	5	7	8	3	3	5	12	15

TABLE 9

GASTRO-ENTERITIS TRIAL: EFFECTS OF AMPICILLIN ON STOOL CULTURES OF PATIENTS WITH INTESTINAL PATHOGEN

Day after Treatment	Cumulative No. of Patients Cleared from Pathogen							
	Mild Disease		Moderate Disease		Severe Disease		All Grades	
	Drug	Placebo	Drug	Placebo	Drug	Placebo	Drug	Placebo
4	2	1	3	0	2	1	7	2
6	3	2	3	0	3	1	9	3
8	3	4	3	0	3	2	9	6
Total treated	7	7	4	4	3	5	14	16

statistical backing. The small numbers in the trial tend to vitiate the results. However, a previous trial (Elliott, Maxwell and Robertson, 1961-62), comparing the activity of ampicillin and chloramphenicol in this disease, showed a slight trend in favour of ampicillin, particularly in salmonella infections. This is the group that fared better on ampicillin in the present trial.

It is unlikely that enteropathogenic *Esch. coli* infections were influenced by ampicillin since the inhibitory concentration *in vitro* required for these was high. Blood levels, however, are not a good

guide to behaviour *in vivo*. Harrison and Stewart (1961) have postulated an enterohepatic recirculation of ampicillin resulting in low concentrations in the lower ileum and colon in animals. Certainly normal humans receiving ampicillin have negligible quantities in their faeces (Stewart, Coles, Nixon and Holt, 1961).

It is of interest that the mean blood levels of ampicillin attained in children with gastro-enteritis were lower than in children without this disease, possibly implying malabsorption. In turn this might be associated with higher colonic concen-

TABLE 10

GASTRO-ENTERITIS TRIAL: RESPONSE OF SYMPTOMS AND FAECAL CULTURES TO AMPICILLIN ACCORDING TO PATHOGEN TYPE

Day after Admission	Cumulative No. of Patients Cured											
	Salmonella Group				Shigella Group				Pathogenic <i>Esch. coli</i> Group			
	Symptoms		Cultures		Symptoms		Cultures		Symptoms		Cultures	
	Drug	Placebo	Drug	Placebo	Drug	Placebo	Drug	Placebo	Drug	Placebo	Drug	Placebo
4	1	0	3	0	1	1	3	2	2	4	1	0
6	3	1	3	0	3	1	5	4	2	5	1	0
8	6	2	3	1	4	3	5	4	2	5	1	1
Total treated	6	6	6	6	4	4	6	4	2	7	2	7

trations of the antibiotic. Larger doses may well enhance this desirable effect.

The notable efficacy of this antibiotic in renal tract infections (Brumfitt, Percival and Carter, 1962) is attributable both to its spectrum of activity and to its high renal excretion (Knudsen *et al.*, 1961). Our results confirm its activity in the paediatric age-group.

Although ampicillin, being penicillinase sensitive, holds no advantage over penicillin G. in staphylococcal infections, its potential activity against *H. influenzae* (Rolinson and Stevens, 1961) is a distinct theoretical advantage.

Certainly all cases of pneumonia treated with ampicillin did well, apart from the one proven to be staphylococcal in origin. No cases of toxicity or sensitivity to ampicillin were noted in any of the children treated, with the exception of an urticarial reaction in a child with previous penicillin V. sensitivity.

Summary

Ampicillin is well absorbed in children, and

appears to share the low toxicity of other penicillins. Its activity in gastro-enteritis of bacterial origin is promising and could probably be enhanced by larger doses. Its therapeutic efficiency in renal tract and pulmonary infections appears to be satisfactory.

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