THE PLACE OF ORAL PENICILLIN IN PAEDIATRICS

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In the treatment of sick children the disadvantages of a drug which can be administered only by injection are serious. This applies particularly to wasted infants in the throes of a severe infection. Here the minimum of handling is almost as important as the drug.

In February, 1947, it was decided to start an investigation at the Children's Hospital, Birmingham, to determine the reliability of penicillin given by mouth in infancy. Two papers had already appeared in this country. Henderson and McAdam (1946) recorded the results of this method of administration to thirty-seven infants. However, only nine of them were over one month old. When a dose of 10,000 units was used, bacteriostatic serum levels persisted as long as six hours, while 100,000 units produced a serum concentration persisting as long as fifteen hours. Buchanan (1946) determined the results of administering a dose of 4,000 units per pound of expected body weight per day divided up so that it could be administered before feeds. Satisfactory results were claimed in the twenty-five infants investigated, but again they were mostly under the age of one month. Further work at the same school has shown that it is only in premature infants and in the first month of life that consistently reliable serum levels can be obtained with this dose (Guthrie and Montgomery, 1947).

During the course of this work, several publications have appeared. Husson (1947) has investigated the serum levels in twenty-two infants up to the age of five months following a dose of 20,000 units orally. In every case he was able to demonstrate a serum level of at least 0.06 units after an interval of three hours. Suchett-Kaye and Latter (1947) treated twenty-five children suffering from pneumonia with oral penicillin. Their ages ranged from three months to two years. The doses used varied from 10,000 to 40,000 units at three- to four-hourly intervals. In only six of the thirteen estimations performed at three hours after the dose was a bacteriostatic level recorded. Despite this, good clinical results were obtained in all but the four most seriously ill cases. One of these was infected with a penicillin-resistant organism. Hoffman et al. (1948) have performed an extensive

survey of this problem in children from infancy up to the age of twelve years. Forty-two infants up to the age of one year suffering from respiratory-tract infections were treated with oral doses of 20,000 units three-hourly. In six of them no level was recorded at an interval of three hours, and in five it was only 0.03 unit. The problem has been tackled in older children, but all workers agree that the results obtained are less reliable and the serum levels less sustained than in infancy even with the use of massive doses. Markowitz and Kuttner (1947) gave 50,000 units before breakfast to twenty children up to the age of twelve years. The serum levels in no case persisted longer than two hours. Further, there was an unaccountable variation in the levels obtained in the same individual on successive days with the same dose. Reisman et al. (1947), using a dose of 100,000 units, did not obtain any better result. A case of bacterial endocarditis responding to oral penicillin has been recorded (Burke et al., 1946). This was a girl of eleven years who received 100,000 units three-hourly for fourteen days.

There is complete uniformity of opinion that the drug should be given on an empty stomach in order to ensure maximum absorption. The use of buffered solutions now receives little support. Stewart and May (1947) show that an aqueous unbuffered solution gives the best result. Further, their investigations demonstrate that unless the pH of the gastric secretion falls below a level of 3, it exerts no destructive action on penicillin. They also found that in some cases the administration of glucose with the drug increased the maintenance of the serum level.

Method of Assay

The best results were obtained using the micro-method described by Fleming and Smith (1947). Human plasma was found more satisfactory than horse serum in making up the 'His Serum water' since it was less liable to become turbid following sterilization. Phenol red was used as indicator and gave the best end point. As test organism the Oxford strain of *Staphylococcus aureus* 209 was employed. It showed a complete inhibition of growth in a concentration of 0.0135 I.U. per ml.

British standard penicillin supplied by the National Institute for Medical Research. Since some of the cases received sulphonamides as well as oral penicillin, it was necessary to determine the sensitivity of the organism to this group of drugs. Addition of sulphadiazine to a human serum containing penicillin up to a maximal concentration of 16 mg. per 100 ml. did not affect the estimation of the penicillin concentration. Controls were also performed by adding para-aminobenzoic acid in one or two cases where the babies were receiving both drugs. In no case was there any significant alteration in the reading obtained. It was concluded that with this strain of organism the presence of sulphonamides could be ignored.

Investigation of Absorption

The absorption of penicillin from the alimentary tract of forty infants has been investigated and sixty-three serial estimations of serum penicillin levels undertaken. The first experiment consisted in giving a single large dose and watching the fate of the penicillin in the serum at hourly intervals. In some cases a similar dose was injected on the following day for comparison. The results are set out in table 1. For a period of three hours the levels following injection are very much higher than those after oral administration. Subsequently, if the levels are observed over a further period of five hours, there is little to choose between the two methods.

The next problem was to find a method of oral administration which would ensure a sustained level sufficient to deal with virulent infections by penicillin-sensitive organisms. Instructions were given that penicillin in aqueous solution of a strength of 20,000 units per ml. should be administered in $\frac{1}{4}$ to $\frac{1}{2}$ oz. of the feed by spoon immediately before the feed. There was very little difficulty in persuading the majority of babies to take the drug. The addition of a little sugar sometimes helped. There is an element of chance about the administration of any drug by mouth to a small baby, and this is reflected in a few of the results. They are recorded in table 2.

In the first six cases small doses were used as advocated by previous workers. It was considered that a sustained level of not less than 0.04 units per ml. was advisable to deal with severe infections. By this standard these doses are clearly inadequate. In two cases, 2 and 5, the effect of giving between three and four times the dose was tried. Excellent sustained levels were obtained. Since both these babies were under two months old, it was decided to try giving proportionately large doses to older ones. Up to the age of six months satisfactory absorption from the intestinal tract was recorded in twenty-seven babies with three exceptions. Case 7 received too small a dose. It was learned subsequently that the age and not the weight of the baby should be the guiding factor. Case 15 was suffering from a very severe attack of enteritis; the stools were watery and offensive, and contained some

TABLE 1
A COMPARISON OF ORAL AND INTRAMUSCULAR ADMINISTRATION

No.	Age	Weight (lb.)	Dose	Hourly serum levels (units per ml.)								Remarks
				1	2	3	4	5	6	7	8	
1	5 m.	14½	Oral 100,000	0.16	0.16	0.16	0.08	0.04	0.04	0.03	0	
2	2 m.	10	I.M.	1.20	1.20	0.32	0.08	0.03	0.03	0		
			Oral 100,000	0.08	0.32	0.64	0.32	0.16	0.04	0.03	0	
3	3 wk.	7½	I.M.	2.50	1.20	1.20	0.64	0.16	0.16	0.08		
			Oral 7,000	0	0.04	0.04	0.04	0.03	0.03	0.03	0.03	
			Oral 50,000	0.64	0.32	0.32	0.64	0.64	0.64	0.16	0.32	
4	3 wk.		I.M.	M	M	1.20	0.64	0.64	0.32	0.16	0.08	
			Oral 100,000	0.32	0.64	0.32	0.16	0.04	0	0		
5	5 m.	9½	I.M.	M	M	M	0.64	0.08	0.04	0.04		
6	9 m.	12	Oral 100,000	0.32	0.64	0.08	0.08	0.04	0.04	0.03	0	
			Oral 100,000	0.64	0.32	0.32	0.04	0.03	0.03	0.03	0	Mixed feeding
7	2½ m.	7	I.M.	2.50	0.64	0.16	0.08	0.04	0.03	0.03	0	
			Oral 50,000	0.08	0.08	0.08	0.08	0.04	0.04			Pyloric stenosis

M indicates a level of over 1.2 units per ml.

TABLE 2
SERUM LEVELS OBTAINED IN CASES RECEIVING ORAL PENICILLIN AT REGULAR INTERVALS

	No.	Age	Weight (lb.)	Dose	Hourly serum levels (units per ml.)						Remarks
					1	2	3	4	5	6	
Cases receiving small doses	1	2½ m.	6½	5,000 3-hourly	0	0	0				Premature
	2	1½ m.	6½	7,000 3-hourly	0.04	0.03	0	0.03	0.03	0.03	
	3	1½ m.	6	5,000 3-hourly	0.04	0.04	0.04	0.03	0.03	0.04	
	4	2 m.	4½	7,000 4-hourly	0.04	0.04	0.03	0			Premature
	5	1 wk.	6½	5,000 3-hourly	0.04	0.04	0.04	0.04	0.03		
	6	2 m.	8	10,000 3-hourly	0.03	0.04	0.03				
Cases receiving moderate doses	7	2½ m.	5½	20,000 3-hourly	0.04	0.04	0.03	0	0.03	0.03	Premature
	8	2½ m.	7½	20,000 4-hourly	0	0.08	0.16	0	0.32	0.04	
	9	3 m.		20,000 3-hourly	0.16	0.32	0.16				Nephrosis
	10	1 m.	6	20,000 3-hourly	0.64	0.32	0.16				
	(2)	1½ m.	6½	20,000 3-hourly	0.16	0.16	0.32	0.32	0.16	0.32	
	(5)	1 wk.	6½	20,000 3-hourly	0.08	0.16	0.16				
Cases receiving large doses	11	1½ m.	7	30,000 4-hourly	0.16	0.32	0.32	0.08	0.08	0.04	
	12	2½ m.	7	40,000 3-hourly	0.16	0.16	0.08	0.08	0.16	0.32	
	13	1½ m.	5½	40,000 3-hourly	0.08	0.08	0.16	0.32	0.64	1.2	Premature
	14	4 m.	10½	40,000 3-hourly	0.64	0.64	0.64	0.32	0.64	0.64	
	15	2 m.	8½	40,000 3-hourly	0	0.03	0.03	0	0.03	0.03	Severe enteritis
	16	3 m.	11	50,000 3-hourly	0.08	0.08	0.08	0.16	0.16	0.08	
	17	5 m.	9½	50,000 3-hourly	0.32	0.16	0.08	0.64	0.32	0.16	
	18	4½ m.	9½	50,000 3-hourly	0.03	0.04	0.08	1.2	1.2	M	
	19	3 m.	7½	50,000 3-hourly	0.32	0.32	0.32				
	20	2 m.	8½	60,000 4-hourly	No level attained						Pyloric stenosis
	21	4 m.		60,000 3-hourly	0.03	0.04	0.04				
	22	3 m.	10½	60,000 4-hourly	0.64	0.32	0.16	0.16	0.64	0.64	
	23	3 m.	11	60,000 4-hourly	0.64	0.64	0.32	0.04			
	24	2 m.	8½	60,000 6-hourly	0.03	0.03	0.04	0.04	0.04	0.04	
	25	3 m.	10½	70,000 4-hourly	1.2	0.64	0.32	0.32			
	26	4 m.	10½	70,000 4-hourly	0.32	0.64	0.32		0.16	0.64	
	(2)	5½ m.	7	70,000 4-hourly	0.64	1.2	0.64	0.32			
	27	6 m.	13½	70,000 4-hourly	0.16	0.16	0.16	0.16			
	28	5 m.	12½	70,000 3-hourly	0.32	0.16	0.16	0.08			
	29	3 m.	5½	80,000 4-hourly	0.03	0	0.08	0.32	0.16		
	30	4 m.		80,000 3-hourly	0	0	0.16	0.08	0.16	0.08	
					All levels over 1.2						
					0.08	0.16	0.04	0.16	0.08	0.08	
Cases over 6 months on mixed diet	(30)	5½ m.	13	70,000 4-hourly	0	0	0.03	0.03	0		
	31	7½ m.	16½	70,000 4-hourly	0.03	0	0.03				
				100,000 4-hourly	0	0.03	0.16	0.16			
	(17)	7 m.		100,000 4-hourly	0.03	0.04	0.03	0.03			
	32	7 m.	16	100,000 4-hourly	0.16	0.04	0				
	33	8 m.	14	100,000 3-hourly	0.04	0.04	0.04	0.04	0.04	0.04	

Where the case number is enclosed in brackets, this indicates that previous investigations have been carried out on the same baby and are recorded earlier in the table.
M indicates a level of over 1.2 units per ml.

blood and mucus. Several of the other babies had relaxed, undigested stools caused by food intolerance consequent on some infection outside the alimentary tract, and yet absorbed the drug well. Case 20 suffered from pyloric stenosis with frequent vomiting. The wide variations in the levels in Cases 18 and 28 almost certainly reflect a failure in the technique of administration.

It was observed that the addition of cereals to the diet sometimes coincided with a diminution in the efficiency of the absorption of penicillin from the alimentary tract. Two cases, 17 and 30, originally absorbed the drug well, but after an interval of six weeks, during which cereals had been started, a further test was made. The falling off in absorption was definite. In all, five cases on a mixed diet

infant kidney is believed to contribute to the success achieved with oral penicillin in the early months of life.

The absorption of the drug from the alimentary tract of one or two older children was observed, using a dose of 100,000 units. The results were so unreliable that the investigation was abandoned.

As a result of this work it is claimed that penicillin may be administered orally to any infant below the age of six months as reliably as the sulphonamides, provided a big enough dose is employed and mixed feeding has not been started. It is not agreed that injection is the route of choice in severely ill babies. It is just in these cases that the full advantages of oral administration are apparent. Where there is persistent vomiting or severe enteritis parenteral administration must be employed. The relaxed undigested stools so frequently seen in the course of infection in infancy are not a contraindication to giving the drug by mouth. Further, it was found that the modification of the feed by lactic acid does not destroy the penicillin.

The size of the dose must be based on the age and not the weight of the infant. This rule applies to premature babies as well. Table 3 shows the doses employed at this hospital. These doses are given immediately before each feed. At night a double dose is given before the last feed.

Using these doses, success has been achieved not only in treating respiratory tract infection, but also in at least one case of multiple osteomyelitis which had failed to respond to the sulphonamides. In no case have any toxic manifestations been observed.

Claims have been made that oral penicillin used in the same dose as intramuscular administration will attain as good a level in infancy. Examination of the levels in some half-dozen babies under treatment with intramuscular penicillin, selected at random from different wards, shows that this is not true. These results are recorded in table 4.

TABLE 3
DOSES OF PENICILLIN BY MOUTH

Age	3-hourly	4-hourly
0-6 weeks	20,000 U	30,000 U
6 weeks-3 months	40,000 U	60,000 U
3 months-6 months	50,000 U	70,000 U

were investigated. Even a dose of 100,000 units was not sufficient to ensure an adequate serum level. It is not known if there is any real connexion between these two factors, nor can any explanation be advanced. Incubation of a solution of penicillin with a suspension of a cereal food for several hours in the laboratory failed to demonstrate any adsorption of the drug.

Case 9, a three-month-old baby suffering from the nephrotic syndrome, was of interest. It demonstrated the excellent levels which may be obtained in these cases with moderate dosage. A similar result was obtained in a boy of two and a half years suffering from the same disease. Immaturity of the

TABLE 4
BLOOD LEVELS DURING ROUTINE INTRA-MUSCULAR ADMINISTRATION

No.	Age (months)	Weight (lb.)	Dose	Hourly levels (units per ml.)							
				1	2	3	4	5	6	7	8
1	3	9	20,000 3-hourly	0.04	0.03	0.03	0.04				
2	9	17	10,000 3-hourly	0.16	0.16	0.64	0.16	0.04	0.03		
3	4	11	20,000 4-hourly	0.16	0.08	0.08	0.08	0.08	0.16	0.16	0.16
4	7	13½	30,000 3-hourly	M	0.32	M	M	0.32	0.16		
5	2½	8½	12,000 3-hourly	0.04	0.32	0.16	M	0.64			
6	7	15	30,000 3-hourly	0.64	0.32	0.16	1.2	0.32	0.16		

M indicates a level of over 1.2 units per ml.

Summary

Oral administration of penicillin is the method of choice up to the age of six months.

It is not suitable when there is severe enteritis or persistent vomiting.

Owing to the unpredictable variation in absorption, it is essential to use massive doses.

In older children the success of oral administration becomes a matter of trial and error. It is certainly to be condemned in cases of severe illness.

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