appeared equally effective in controlling blood-pressure. In this series the fall of pressure in the supine position was no more pronounced with one drug than with the other. A higher proportion of patients were free from side-effects on methyl dopa than on guanethidine.

It is concluded that methyl dopa, though far from ideal, is as potent in reducing blood-pressure as previous drugs, and has the advantage of less frequent and less troublesome side-effects.

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Transplacental Passage of Ampicillin

T. E. BLECHER,* M.B., M.R.C.P.ED., M.C.PATH.; W. M. EDGAR,† M.A., M.D., M.C.PATH.

H. A. H. MELVILLE,‡ M.B., F.R.C.S.ED., M.R.C.O.G.; K. R. PEEL,‡ M.B., CH.B., M.R.C.O.G.

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Bacterial infection has been recently reported to account for 56% of deaths in England and Wales following abortion and for 5% of maternal deaths after the 28th week of pregnancy (Walker *et al.*, 1963). Butler and Bonham (1963) reported pulmonary infection as a primary necropsy finding in 13.3% of neonatal deaths in the first week of life, and considered that the majority of cases were of intrauterine origin.

There is some evidence available as to the value of antibiotics both in the treatment of maternal and foetal infections and in their prophylaxis. Smith *et al.* (1956), for example, found that combined therapy with streptomycin and oxytetracycline, given before delivery in cases of presumed intra-partum infection, reduced the perinatal mortality and the incidence of puerperal pyrexia. Leberherz *et al.* (1963), on the other hand, in a controlled trial involving 1,896 cases of premature rupture of the membranes found that demethylchlortetracycline, given by mouth after the membranes had ruptured, did not appear to reduce perinatal mortality due to infection, though the maternal morbidity rate was approximately half that in the control group. Anderson *et al.* (1962), studying congenital pneumonia, suggested certain absolute indications for antibiotic therapy during labour, and Theobald (1959) recommended that antibiotics should be given routinely after artificial rupture of the membranes, though neither he nor Anderson *et al.* give any further evidence to demonstrate the effectiveness of antibiotics used as they describe.

In reviewing the evidence, consideration must be given to the suggestion that factors other than bacterial invasion may produce inflammatory changes in the placenta, the membranes, and possibly also in the foetus (Bourne, 1962).

We decided to investigate whether ampicillin would cross the placenta to reach the amniotic fluid and foetal circulation in effective concentrations. Ampicillin has a wide spectrum of activity, is well absorbed after oral administration, and has a low incidence of side-effects in both adults and children

(Rolinson and Stevens, 1961; Brown and Acred, 1961; Knudsen *et al.*, 1961; Stewart *et al.*, 1961; Elliott *et al.*, 1964).

We have been able to find only one published report concerning the transplacental passage of ampicillin—namely, that of Elliott *et al.* (1964), who assayed ampicillin in amniotic fluid from four patients, and found only minimal concentrations.

Methods

The specimens tested included amniotic fluid and maternal sera obtained at the time of amniotomy or amniocentesis and maternal and foetal sera obtained at the time of delivery from many of the foregoing patients and from a small group of patients who were given ampicillin therapeutically during labour.

Ampicillin was given by mouth to 38 patients, in whom surgical induction of labour by low amniotomy was indicated on standard obstetric indications, in a dosage of 500 mg. six-hourly for five days. Specimens of amniotic fluid were obtained between three and one-quarter and five and three-quarter hours after the third dose of ampicillin. A mid-stream specimen of amniotic fluid was collected via a Currie catheter into a sterile container. In a further four patients, who had Rhesus antibodies, amniocentesis was performed in order to determine the bilirubin concentration in the amniotic fluid (Bevis, 1953; Walker, 1957). These four patients also were given 500 mg. of ampicillin six-hourly and amniocentesis was performed about four hours after the third dose. In all cases a specimen of maternal venous blood was taken at the same time as the specimen of amniotic fluid was collected.

At delivery, samples of cord blood and maternal blood were collected from the first group of patients and from three further patients who were given ampicillin in the same dosage for therapeutic reasons during labour. The number of doses of ampicillin given by the time delivery had taken place ranged from two to 13.

Amniotic fluid and sera were stored at 4° C. Specimens which could not be assayed within 24 hours of collection were

* Department of Pathology, St. Luke's Hospitals, Bradford. Present address: Haematology Department, Royal Infirmary, Bristol.

† Consultant Pathologist, Bradford Group of Hospitals.

‡ Department of Obstetrics, St. Luke's Hospitals, Bradford.

discarded, because in preliminary observations it was found that antibiotic activity sometimes diminished with storage. Largely for this reason fewer results appear in the series in which specimens were obtained at delivery than in the first series of specimens taken at amniotomy.

Technique of Assay

Ampicillin assays were carried out by the cup-plate method as described by Knudsen *et al.* (1961), with slight modifications. The test organism was *Sarcina lutea* (A.T.C.C. 9341). Each solution was placed in eight wells in a large assay plate, which was incubated at 37° C. for 18 hours. The diameters of the inhibition zones were then measured and the mean diameter calculated for each solution. The ampicillin content of the test solution was then read off from graphs constructed from the zone series of standard solutions, which were included on every plate. It was found that if the amniotic fluids were diluted 1 in 5, the maternal sera 1 in 4, and the cord sera 1 in 2 the zones they gave fell within, or close to, the range of those given by the standard solutions. These dilutions were therefore used throughout the investigations.

The diluent used for both standards and specimens was 4% bovine albumin in M/20 phosphate buffer, pH 7.0, as described by Knudsen *et al.* (1961). Some preliminary experiments showed that there was no significant difference in the zone sizes obtained with solutions consisting of (a) diluent, (b) amniotic fluid, and (c) amniotic fluid diluted 1 in 5 with diluent, when the same amount of ampicillin was added to each.

Other preliminary experiments with amniotic fluid showed that there appeared to be no carry-over of the antiseptic (chlorhexidine) used routinely at amniotomy, in that amniotic fluid from patients who had not been given antibiotics showed no antibacterial activity.

Results

The concentrations of ampicillin found in specimens have been plotted against the time interval between the patient receiving the last dose of ampicillin and the specimen being taken.

Ampicillin Levels in Maternal Sera at Time of Amniotomy or Amniocentesis (Fig. 1, A)

There is a general downward trend in ampicillin concentration with increasing time interval after the last dose. These results appear comparable with those obtained by Knudsen *et al.* (1961) and Bunn *et al.* (1962) with sera taken at certain specified times after a single oral dose of 500 mg.

Ampicillin Levels in Amniotic Fluid (Fig. 1, B)

The values ranged between 0.42 $\mu\text{g./ml.}$ and 5.1 $\mu\text{g./ml.}$, but unlike the maternal-serum levels these results show no tendency to be lower with increasing time after the last dose.

With only two exceptions the levels of ampicillin were found to be higher in the amniotic fluid of individual patients than in the respective maternal serum taken at the same time. Omitting these two exceptions the ratio of concentration in amniotic fluid to concentration in corresponding maternal serum ranged from 1.3:1 to 15.5:1, with a mean of 3.9:1. However, the time interval between the last dose of ampicillin and the specimens being taken was, in all cases, such that the concentrations of maternal serum would be expected to have fallen well below their peak levels.

Ampicillin Levels in Maternal Sera at Time of Delivery (Fig. 2, A)

The highest levels in the maternal sera were found at two to three hours after the last dose. There were also some low values at this time which may have been due to impairment of absorption from the gut during labour.

Ampicillin Levels in Cord Sera (Fig. 2, B)

The levels found ranged from 0.24 $\mu\text{g./ml.}$ to 2 $\mu\text{g./ml.}$ In 14 of the 23 cases (61%) the level in the cord serum was less

FIG. 1.—(A) (bottom). Concentration of ampicillin in maternal serum collected at time of amniotomy or amniocentesis, plotted against time since last dose. (B) (top). Concentration of ampicillin in amniotic fluid plotted against time since last dose. Dots represent specimens taken at amniotomy. Open circles represent specimens taken at amniocentesis.

FIG. 2.—(A) (bottom). Concentration of ampicillin in maternal serum collected at time of delivery, plotted against time since last dose. (B) (top). Concentration of ampicillin in cord serum plotted against time since last dose. Dots represent cases in which amniotic fluid has been previously collected. Open circles represent cases in which ampicillin was given for therapeutic reasons.

than that in the respective maternal serum. There was no correlation between the concentrations found and the total number of doses of ampicillin received up to the time of delivery.

Discussion

These findings differ from those of Elliott *et al.* (1964), who collected amniotic fluid from four patients two hours after a single oral dose of 750 mg. of ampicillin. In one of their four cases ampicillin was found in the amniotic fluid in a concentration of 0.12 $\mu\text{g./ml.}$ and in the other three cases there were only minimal amounts (less than 0.1 $\mu\text{g./ml.}$).

In the present series of 42 cases ampicillin was found in all specimens of amniotic fluid. The concentrations varied from 0.42 $\mu\text{g./ml.}$ to 5.1 $\mu\text{g./ml.}$: they were 2.5 $\mu\text{g./ml.}$ or more in 27 cases (64%), 4.0 $\mu\text{g./ml.}$ or more in 11 cases (26%), and 5.0 $\mu\text{g./ml.}$ in one instance.

These concentrations were substantially higher than those in the foetal circulation. This observation, together with the fact that in extrauterine life ampicillin is excreted in the urine in high concentration, invites the conjecture that it may reach the amniotic fluid partly via the foetal kidney. In any event it appears that ampicillin reaches the amniotic fluid only after some delay and then tends to accumulate in it.

From the studies of Rolinson and Stevens (1961), Stewart *et al.* (1961), Brumfitt *et al.* (1962), and Sutherland and Rolinson (1964) it seems that the concentrations of ampicillin reached in the amniotic fluid in nearly two-thirds of this series would be sufficient to inhibit *in vitro* *Streptococcus pyogenes*, non-penicillinase-producing strains of *Staphylococcus pyogenes*, many strains of *Proteus mirabilis*, most strains of *Str. faecalis*, and a significant proportion of strains of *Escherichia coli*—that is to say, a substantial proportion of the strains of organisms commonly encountered in intrauterine infections.

The concentrations of ampicillin found in the cord blood were substantially lower than those of the amniotic fluid. Thus in only 26% of cases were the levels above 1.25 $\mu\text{g./ml.}$ This concentration of 1.25 $\mu\text{g./ml.}$, though capable of inhibiting the highly sensitive *Str. pyogenes* and the non-penicillinase-producing strains of *Staph. pyogenes*, would, however, be ineffective against most strains of *E. coli*, many strains of *Proteus mirabilis*, and some strains of *Str. faecalis* according to the figures given by the above-mentioned workers.

Therefore, though effective concentrations were attained in the amniotic fluid and in the maternal serum, the concentrations in the foetal circulation are likely to have little effect against a high proportion of infecting organisms.

There is sufficient evidence here, however, to suggest that ampicillin might be of value in the treatment of suspected maternal and foetal infections, bearing in mind, firstly, that a higher dosage might achieve greater concentrations in the foetus, and, secondly, that many of the other antimicrobial agents available have various disadvantages or even contraindications—for example, the limited spectrum of the penicillins other than ampicillin; the danger of blood dyscrasias and of neonatal collapse (Sutherland, 1959; Lambdin *et al.*, 1960) with chloramphenicol; the foetal and possibly maternal toxic effects of the tetracyclines (Lancet, 1963; Douglas, 1963; Witkop and Wolf, 1963; Cohlan *et al.*, 1963; *Obstetrical and Gynaecological Survey*, 1964; *B.M.J.*, 1964); and the possible risk of kernicterus with certain sulphonamides (Silverman *et al.*, 1956). In addition to having a wide spectrum of activity, ampicillin has the advantages of very low toxicity, ease of administration, and of giving good levels in the amniotic fluid as well as in the maternal circulation. It is not suggested, however, that it is necessarily the drug of choice, and its precise

value or otherwise could be determined only by means of a carefully controlled clinical trial.

Summary

Forty-two women were given 500 mg. of ampicillin six-hourly by mouth. Amniotic fluid and maternal blood samples were collected at the time of amniotomy or amniocentesis, between three and a quarter and five and three-quarter hours after the third dose. Samples of maternal and cord blood were collected at the time of delivery from 23 women who received ampicillin in the same dose schedule by mouth during labour. The ampicillin content of all samples was estimated by the cup-plate method.

The drug was detected in every specimen of amniotic fluid and serum examined. In the amniotic fluid the concentrations ranged from 0.42 $\mu\text{g./ml.}$ to 5.1 $\mu\text{g./ml.}$, and were 2.5 $\mu\text{g./ml.}$ or more in 27 of the 42 cases. The concentrations found in cord serum were lower. They ranged from 0.24 $\mu\text{g./ml.}$ to 2 $\mu\text{g./ml.}$, and in 12 of the 23 specimens were 1 $\mu\text{g./ml.}$ or more.

The concentrations of the amniotic fluid and maternal serum are probably sufficiently high to be effective against a high proportion of the bacteria likely to be encountered in intra-partum infections, but the concentrations in cord serum would probably be ineffective against a significant proportion of them. Higher levels might be attained in the foetus by increasing the dose.

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