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Ampicillin and gentamicin in the treatment of fetal intrauterine infections

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Antimicrobial agents are frequently used in pregnancy in cases of suspected amnionitis, prolonged rupture of membranes or fetal intrauterine infections.

SMITH et al. [13] considered that the criteria of intrapartum infection was persistent fetal tachycardia (160/min or above) and maternal pyrexia (98.6 ° F or above).

Prevention or treatment of fetal intrauterine infections demands whenever possible optimum use of antibiotics, according to the sensitivity test. The optimum clinical results are obtained by the administration of the appropriate antibiotic, which reaches an adequate level in the amniotic fluid and cord serum.

Due to the increasing use of ampicillin and gentamicin for fetomaternal infections and prophylaxis [6, 10, 16], we investigated the concentration of these antibiotics in the maternal serum, amniotic fluid and cord serum. The observed levels were compared with the minimal inhibitory concentration of the offending pathogens in the amniotic fluid and cord serum in cases of fetal intrauterine infections.

1 Material and methods

Sixty healthy pregnant women, between 36–40 weeks gestation, were investigated. The ages of the

Curriculum vitae

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women were from 20 to 40 years. The weight ranged from 50–60 kg. All of them delivered with cesarean section for obstetrical reasons.

Thirty of the women were given 500 mg of sodium ampicillin and the remaining 30, 80 mg of gentamicin intramuscularly. Maternal serum determinations of the antibiotics were carried out in the same women at various intervals, while the concentration of the drugs in the amniotic fluid and cord serum was performed once at the time of delivery. A total of 379 determinations were done.

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Blood was drawn from the maternal circulation and umbilical cord. Serum was separated according to standard techniques. Amniotic fluid was taken during cesarean section. The samples were immediately centrifuged at 3,000 r.p.m. for 10 minutes and kept frozen at -20°C in sterile test tubes until assayed.

Assays of antibiotic levels were carried out by agar diffusion method employing a strain of *Staph. aureus* A.T.C.C. No 25923 (American Type Control Collection) for ampicillin and *E. coli* N.C.T.C. No 1346 for gentamicin.

Women with ruptured membranes or taking antibiotics other than ampicillin or gentamicin were excluded from the study.

2 Results

Ampicillin levels in maternal serum varied from 0.30 ± 0.02 to 7.88 ± 0.25 $\mu\text{g/ml}$, with a peak level 1 hour after the intramuscular injection. (Tab. I, Fig. 1).

In the amniotic fluid mean peak concentrations of 5.67 ± 0.14 $\mu\text{g/ml}$ were found 6 hours after the administration of the drug. During peak time concentration of ampicillin in the maternal serum was found higher than in the amniotic fluid. Statistically a very significant difference was found, when tested with t-student test ($p < 0.001$).

Mean peak concentration of ampicillin in the cord serum was found to be 2.37 ± 0.16 $\mu\text{g/ml}$, 2 hours after the injection, falling to a mean level of 0.45 ± 0.09 $\mu\text{g/ml}$, 6 hours after the administration of the drug. During peak time, levels of the antibiotic in the maternal serum were found to be higher

Fig. 1. Maternal serum, amniotic fluid and cord serum ampicillin concentration ($\mu\text{g/ml}$) after one single intramuscular injection (500 mg).

than in the cord serum. Statistical analysis showed that there was a very significant difference ($p < 0.001$). Peak levels of the antibiotic in the amniotic fluid exceeded those in the cord serum, with a very significant difference ($p < 0.001$).

The highest levels of ampicillin in the amniotic fluid appeared considerably later than in the maternal or cord serum, while the maximum level of the drug in the cord serum appeared one hour later than in the maternal serum.

Levels of gentamicin in the maternal serum ranged from 0.48 ± 0.10 to 5.62 ± 0.26 $\mu\text{g/ml}$, with a peak 30 minutes after the administration of the antibiotic (Tab. II, Fig. 2).

Amniotic fluid concentration of gentamicin, reached the highest value 6 hours after the injection of the antibiotic followed by a decline. The levels were still high 2 hours later (3.54 ± 0.05 $\mu\text{g/}$

Tab. I. Maternal serum, amniotic fluid and cord serum ampicillin concentration ($\mu\text{g/ml}$) after one single intramuscular injection (500 mg).

Hours after dose	Maternal serum		Amniotic fluid		Cord serum	
	n	$\bar{X} \pm \text{SD}$	n	$\bar{X} \pm \text{SD}$	n	$\bar{X} \pm \text{SD}$
1	30	7.88 ± 0.25			8	1.10 ± 0.10
2	22	6.04 ± 0.15	9	1.46 ± 0.10	8	2.37 ± 0.16
4	30	2.01 ± 0.16	6	2.53 ± 0.10	7	1.31 ± 0.10
6	23	0.93 ± 0.11	8	5.67 ± 0.14	7	0.45 ± 0.09
8	25	0.30 ± 0.02	7	5.17 ± 0.13		

n number of determinations, $\bar{X}$ mean concentration, SD standard deviation.

Tab. II. Maternal serum, amniotic fluid and cord serum gentamicin concentration ($\mu\text{g/ml}$) after one single intramuscular injection (80 mg).

Hours after dose	Maternal serum		Amniotic fluid		Cord serum	
	n	$\bar{X} \pm \text{SD}$	n	$\bar{X} \pm \text{SD}$	n	$\bar{X} \pm \text{SD}$
1/2	35	5.62 ± 0.26			8	0.25 ± 0.09
2	30	2.50 ± 0.31	9	0.55 ± 0.14	7	1.68 ± 0.10
4	25	1.76 ± 0.14	7	1.78 ± 0.14	7	0.94 ± 0.09
6	24	0.95 ± 0.08	8	5.17 ± 0.27	9	0.32 ± 0.10
8	25	0.48 ± 0.10	7	3.54 ± 0.05

Fig. 2. Maternal serum, amniotic fluid and cord serum gentamicin concentration ($\mu\text{g/ml}$) after one single intramuscular injection (80 mg).

ml). Maternal serum levels of gentamicin during peak time were found to be higher than those of the amniotic fluid, but the difference was not significant. ($p > 0.1$). Gentamicin levels in the cord serum varied from 0.25 ± 0.09 to $1.68 \pm 0.10 \mu\text{g/ml}$, with a peak level 2 hours after the administration of the drug. Maternal peak serum levels of gentamicin, observed 30 minutes after the administration of the antibiotic, were significantly higher than those of the cord serum ($p < 0.001$). Concentration of gentamicin in the amniotic fluid was higher than in the cord serum, also with a very significant difference ($p < 0.001$).

3 Discussion

Although there is little information on placental penetration by drugs, practically all drugs used in obstetrics have been found to cross the placenta barrier to some degree [9, 11].

In the present study we found that both ampicillin and gentamicin passed the placenta.

Placental transfer of ampicillin into fetus and amniotic fluid has been studied by many authors

[3, 4, 17]. BLECHER et al. [3] have found that ampicillin peak levels in the amniotic fluid are higher than those of the fetal serum. The authors attribute this difference to the partial excretion of ampicillin from the fetal kidney. Our results also show that gentamicin peak levels in the amniotic fluid are significantly higher than those of the cord serum.

MCCALLUM and GOVAN [8] studied the most common types of bacteria found in cases of premature rupture of the membranes and prolonged labor. They found *E. coli*, *Str. faecalis* and *Proteus sp.* present in 60 per cent, 37.5 per cent and 11.2 per cent, respectively. They also found *Str. viridans* in 23.7 per cent and non-haemolytic streptococci in 8.7 per cent. Other authors [6] report the predominance of the Gram negative organisms in cases of intrauterine infections.

Our results in correlation with the studies of BEAR et al. [1] and ROLINSON and STEVENS [12] showed that the concentration of ampicillin in the maternal serum and amniotic fluid 1/2–2 hours and 6–8 hours, respectively, after medication, would be sufficient to inhibit: *Staph. non-PCN-ase producer*, *Streptococci* (Group A, B, G, viridans, as well as many strains of faecalis), *Listeria monocytogenes*, certain strains of *E. coli* and *Proteus mirabilis*.

Levels of ampicillin in the fetal serum, during peak time, were found to be lower than those of the amniotic fluid. However these would be sufficient for the inhibition of *Staph. non-PCN-ase producer*, *b-hemolytic Streptococci* (Group A, B, G), *Str. viridans*, certain strains of *Str. faecalis* and *List. monocytogenes*, but not against *E. coli* and *Proteus mirabilis*. [1, 12]

Tab. III. Sensitivity of bacteria to ampicillin.

Bacteria	Minimum inhibitory concentration ($\mu\text{g/ml}$)
Staph. non-PCN-ase producer	0.1 – 0.8
Str. Group A	0.01 – 0.05
Group B	0.04 – 0.2
Group G	0.2 – 0.4
Str. viridans	0.04 – 1.6
faecalis	1.0 – 12.5
List. monocytogenes	0.08 – 0.32
Prot. mirabilis	3.1
E. coli	5.0

Our results are in agreement with the data of BLECHER et al. [3] and show that the observed levels of the antibiotic are sufficient to inhibit a high proportion of infecting pathogens in the maternal serum and amniotic fluid, though have little effect against organisms in the fetal serum.

In the present series we obtained higher levels of gentamicin than those of YOSHIOKA et al. [16]. The above mentioned authors have found a 3.25 and 1.25 $\mu\text{g/ml}$ maximum concentration of gentamicin in the maternal and fetal circulation respectively, but they have not examined the levels of drug in the amniotic fluid.

According to our results and those reported by BLACK et al. [2] and FINLAND [7], it seems that the levels of gentamicin reached in the amniotic fluid 6 hours after the administration of the anti-

Tab. IV. Sensitivity of Bacteria to Gentamicin.

Bacteria	Minimum inhibitory concentration ($\mu\text{g/ml}$)
Staph. aureus	1.15 – 5
Str. pyogenes	2.4 – 6
E. coli	1.5 – 5
Klebsiellae	5
Pseud. aeruginosa	0.3 – 5
Proteus sp.	5 – 10
Mycoplasma sp.	5

biotic, would be effective against Staph. aureus, E. coli, Klebsiella, Pseud. aeruginosa, Mycoplasma sp. plus some strains of Str. pyogenes and Proteus sp. (Tab. IV).

The obtained levels of gentamicin in the fetal serum, 2 hours after medication, in correlation with the data of the drug during peak time would be sufficient to protect the fetus against some strains of E. coli, Staph. aureus and Pseud. aeruginosa, but not from Str. pyogenes and Proteus sp. (Tab. IV). Results of our study show that ampicillin and gentamicin reach an adequate level in the amniotic fluid and fetal circulation. These levels are effective against a high proportion of infecting pathogens [1, 2, 5, 7, 15] in cases of amnionitis, prolonged rupture of the membranes or fetal infections. However the application of these results from the in vitro study to the clinical practice must be evaluated with caution.

Summary

The optimum clinical results in the treatment of fetal intrauterine infections are obtained by the administration of the appropriate antibiotic, which reaches an adequate concentration in the fetal serum.

The pharmacokinetics of ampicillin and gentamicin were studied in 60 pregnant women. Ampicillin and gentamicin were given intramuscularly prior to cesarean section. At delivery maternal serum, amniotic fluid and cord serum antibiotic levels were tested.

Assays of the levels of antibiotic were performed by agar diffusion method using Staph. aureus A.C.T.C. 25923 (American Type Control Collection) and E. coli N.C.T.C 1346, as standard organisms.

During peak time, concentration of ampicillin in the maternal serum was found to be significantly higher than those of the amniotic fluid and cord serum ($p < 0.001$). Peak levels of the antibiotic in the amniotic fluid was also significantly higher than in the cord serum ($p < 0.001$). Our results, also showed that the determined levels of ampicillin, especially during peak time, are sufficient to inhibit in vitro, a high proportion of infecting pathogens in the maternal serum and amniotic fluid, but have little effect against organisms in the fetal serum.

Concentration of gentamicin in the maternal serum during peak time was found higher than those of the

amniotic fluid, but there was not a significant difference. Maternal serum peak levels of the drug were also higher than in cord serum, with a very significant difference ($p < 0.001$). Maximum levels of gentamicin in amniotic fluid were higher than in cord serum, also with a very

significant difference, ($p < 0.001$). Gentamicin levels in amniotic fluid and fetal serum, especially, during peak time, would be adequate to inhibit in vitro the most common pathogens, sensitive to the drug.

Keywords: Agar diffusion method, amniotic fluid, fetal serum, intrapartum infections.

Zusammenfassung

Ampicillin und Gentamycin in der Behandlung von Intrauterinen Infektionen

Zur optimalen Therapie fetaler intrauteriner Infektionen ist die Verabreichung eines geeigneten Antibiotikums angezeigt, das in wirksamer Dosis in das fetale Serum gelangt.

Ziel der vorliegenden Untersuchung war die Aufstellung einer Pharmakokinetik für Ampicillin und Gentamycin. Die Antibiotika wurden insgesamt 60 schwangeren Frauen vor dem Kaiserschnitt intramuskulär injiziert. Kurz nach der Geburt wurden die Konzentrationen im mütterlichen Serum, im Fruchtwasser und im Nabelschnurblut bestimmt. Wir verwendeten hierzu die Agardiffusionsmethode und benutzten Staph. aureus A.C.T.C. Nr. 25923 (American Type Control Collection) und E. coli N.C.T.C. 1346 als Standardmikroorganismen.

Die maximale Ampicillinkonzentration war im mütterlichen Serum signifikant höher als im Fruchtwasser und im Nabelschnurblut ($p < 0.001$). Ebenso lag die Konzentration im Fruchtwasser über derjenigen im fetalen Serum

($p < 0.001$). Wir konnten zeigen, daß die im mütterlichen Serum und im Fruchtwasser gemessenen Konzentrationen ausreichen, um eine große Zahl von pathogenen Mikroorganismen wirksam zu hemmen. Die Konzentration im fetalen Serum reichte jedoch nicht aus, sodaß wir in vitro keinen echten Hemmeffekt beobachten konnten.

Die Messung der Gentamycin-Konzentrationen ergab, daß der Peak im mütterlichen Serum höher lag als der im Fruchtwasser, ohne daß ein statistischer Unterschied gesichert werden konnte. Die mütterliche Serum-Gentamycin-Konzentration lag ebenfalls über derjenigen im Nabelschnurblut. Hier war der Unterschied hochsignifikant ($p < 0.001$). Desgleichen war die Gentamycin-Konzentration im Fruchtwasser höher als die im Nabelschnurblut ($p < 0.001$). Wir konnten aber in vitro nachweisen, daß die im Fruchtwasser und auch im Fetalserum gemessenen Konzentrationen ausreichen, um die meisten pathogenen Mikroorganismen wirksam zu hemmen, vorausgesetzt, daß sie gentamycinsensitiv sind.

Schlüsselwörter: Agardiffusionsmethode, fetales Serum, Fruchtwasser, intrauterine Infektionen.

Résumé

L'ampicilline et la gentamicine dans le traitement des infections foetales intrautérines

Les résultats cliniques optima pour le traitement des infections foetales intrautérines sont obtenus par administration de l'antibiotique approprié qui atteint une concentration adéquate dans le sérum foetal.

La cinétique de l'ampicilline et de la gentamicine a été étudiée sur 60 femmes enceintes auxquelles ces antibiotiques avaient été administrés par voie intramusculaire avant une césarienne. A l'accouchement, le niveau des antibiotiques a été mesuré dans le sérum maternel, le liquide amniotique et le sérum du cordon.

La concentration de l'antibiotique dans les échantillons ci-dessus a été mesurée par la méthode de diffusion en gélose, utilisant les souches de Staph.aureus (A.C.T.C. No 25923 – collection américaine de cultures type) et E. coli N.C.T.C. 1346, comme organismes standard.

La concentration maximum de l'ampicilline dans le sérum maternel a été trouvée significativement plus élevée que la concentration correspondante dans le

liquide amniotique et le sérum du cordon ($p < 0.001$). Les concentrations maximales de l'antibiotique dans le liquide amniotique ont été aussi significativement plus élevées que dans le sérum du cordon ($p < 0.001$).

Nos résultats indiquent également que les concentrations maximales dans le sérum maternel et le liquide amniotique sont suffisantes pour l'inhibition in vitro d'un certain nombre de bactéries pathogènes tandis que celles de l'antibiotique dans le sérum foetal restent insuffisantes.

La concentration maximum de gentamicine dans le sérum maternel s'est révélée plus élevée que dans le liquide amniotique, bien que cette différence n'ait pas atteint un degré significatif. Les concentrations maximales du médicament dans le sérum maternel ont été plus élevées que dans le sérum du cordon ($p < 0.001$), la différence ayant été cette fois significative. La concentration maximum de gentamicine dans le liquide amniotique et le sérum foetal semble suffire à l'inhibition in vitro de bactéries pathogènes les plus communs qui sont sensibles au médicament.

Mots-clés: Infections intrautérines, liquide amniotique, méthode de diffusion en gélose, sérum foetal.

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