Original Article

A study of gentamicin level in CSF of the pediatric patients with meningitis

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Abstract

Introduction: Paediatric clinical pharmacology is well established in western countries, but in our country. Bioavailability of a drug is altered in paediatric age group especially due to many variable factor, like, larger body surface in proportion to body-wt., changes in haematocrit values and phases of maturation of organs like kidney, liver etc. Hence clinical response, to a drug would depend on varieties of factors and, would decide the ultimate outcome in, especially, a sick child. **Aims and Objectives:** To Study Gentamicin level in CSF of the Pediatric Patients with Meningitis **Methodology:** This was prospective clinical trial at tertiary care hospitalthe children admitted in pediatric ward of a general hospital constituted the material for the present study. Only those children, for whom diagnostic L.P. was considered necessary on admission, were included in this study and hence no child was subjected to L.P. only for the purpose of this study. Out of the selected children, those who did not have any clinical and laboratory evidence of intracranial infections, constituted the group of normal children. Whereas those, who had clinical and Laboratory evidence of intracranial infections, constituted the another group under study. Both the group of children was subjected for similar work-up. Total 28 children were included into the study. **Result:** In Children Without Meningitis There are wide fluctuations is the serum concentration at $1_{1/2}$ hrs. C.S.F. did not show any detectable concentration of drug. Fluctuation in serum concentration same as in group one. Most of the children show detectable concentration of drug in C.S.F. Serum levels after 5 doses have shown marked variation. None of them had any detectable level in C.S.F. **Conclusion:** Presence of detectable in c.s.f. is in marked variation. With absence of detectable levels in children without meningitis. This does show the effect of altered blood-brain barrier in meningitis

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INTRODUCTION

Paediatric clinical pharmacology is well established in western countries, but in our country. Bioavailability of a drug is altered in paediatric age group especially due to many variable factors, like, larger body surface in proportion to body-wt., changes in hematocrit values and phases of maturation of organe like kidney, liver etc. Hence clinical response, to a drug would depend on varieties of factors and, would decide the ultimate outcome in, especially, a sick child. Though introduction of newer antibiotic has led to control of infection to a larger extent in western countries, even there, neonatal infections, in particular, meningitis, has proved to be difficult to treat, and this is probably due to altered pharmaco-kinetics in new born and small infants. Several reports in the west have stressed poor permeability of antibiotics like gentamicin across blood-brain barrier, even when such antibiotics are largely depended upon in clinical practice. Gentamicin in the commonly used antibiotic, especially in septicemia and severs infections. Even in India. Contrary to various pharmacokinetic studies, clinician often gets satisfactory response to this drug in meningitis. It is one of the most important aminoglylosides. The three components of gentamicin have similar antibacterial activity. It was the first antibiotic effective against pseudomonas. Apart from its

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action mainly against gm-ve bacteria, it has wide spectrum. It is effective against pseudomonas, e coli, enterobacter, staphylococcus aureus, group a streptococci, h. influenza, proteus. The drug is more effective in alkaline medium. Absorption, distribution and excretion[1]: The drug is poorly absorbed from gastrointestinal tract, so it has to be administeredparentally. The optimal clinical benefits, from treatment of infections caused by organisms sensitive to gentamicin, can be obtained only if the dose used provides a therapeutic, but not toxic level in the blood. Gentamicin is not appreciably metabolised in the body, so the principal determinants of the level in plasma, attained with any given dose, are the absorption, binding and excretion of the drug. The major route of administration of gentamicin from body is through the kidneys. About 25-30%[2,3] of the drug is bound to plasma proteins. There is wide[3]individual variation of peak levels of serum gentamicin, T ½ and elimination rates. These results do notcorrelate with dose of the drug. Hematocrit values, and hence individual monitoring is very important in assessment of therapy. The fluctuations are so wide that with a single dose of 2-3 mgms/kg. body wt. of the durg in normal indivisuals may give peak levels varying from 5-14 ug/ml. The doses4.9based on body wt. Do not produce uniform peak concentration, but those based on body surface area (BSA) do so. This is because, ECF varies greatly with body wt. but it does not with BSA. Postulated that binding to other cells acts in conjunction with or independent of RBC mass. Roughly, half-life is 2 hr sand effective concentration persiste for 6-8 hrs. The following table shows[4] peak concentrations when the drug is given as per body wt.

Sr. No	Age	Peak concentration after 1mg/kg dose	Dose necessary to produce mean concentration 4-6 ug/ml.
1	1-5 yrs.	1.58 ug/m1.	2.5 mgm/kg.
2	5-10 yrs	2.03 ug/ml	2.0 MGM/KG
3	More than 10 yrs.	2.81 ug/m1	1.5 mgm/kg

But uniform peak concentration of 4-6 ug/m1 can be achieved after administration of 60 mgs/m2 of body surface area. The peak concentration is at 60 min after intramuscular administration and 5 min. after intravenous administration. Pharmacokinetics of Gentamicin in newborn [5,6,7,8:]Predictable serum levels were seen with higher dose of 6-8 mg/kg. body wt. these levels are safe. Pharmacokinetics,[7] after intramuscular and intravenous infusion slowly over 20 min, was same. C.S.F. concentration was dependant on dose. Time after administration and degree of meningeal inflammation. Peak levels in C.S.F. after intramuscular infection is 1-2 ug/m1. This concentration in C.S.F. may be sub therapeutic especially in severe infection. In order to attain higher concentrations Above MIC for the organism, intrathecal or intraventricular injection of gentamicin has been tried. This is able to attain very high concentration of the drug in C.S.F such pharmacological data has also been supplemented by correlation with clinical studies. It has been shown that children with meningitis, if given daily intrathecal injection of gentamicin for first 2-3 days along with parenteral gentamicin. Recovery from meningitis is prompt. Dr. George G. Jackson[9] *et al* were the first investigator to study this agent before 1962. Simultaneously klein[9] *et al* l also studied the various aspects of the drug. And they quoted the experience of treatment of a case of pseudomonas meningitis, in infant treated with gentamicin. In this atudy, daily estimation of gentamicin in C.S.F. and serum done show ½ the serum in C.S.F. Later on Newman *et al*[10] studied this drug in respect to the treatment of intracranial infections. John M. Leedom[11] *et al* have described their experience in the treatment, of 5 infants of meningitis, with gentamicin. They too recommend the use of intrathecal or intraventricular administration of the drug in the dose of 0.5-1.0mg/day. George *et al* have used this drug in 5 patients of intracranial infections and they concluded that though permeation through the blood-brain barrier was better in presence of inflammation, the levels achieved in C.S.F. are below MIC and so intrathecal administration in necessary. Likewise the passage of the drug across the blood-brain barrier has been studied in patients and normal individuals by cox *et al*[12]. Haris *et al*[16] reviewed the literature in respect of passage of the drug across thr blood-brain barrier and treated sixteen patients of meningitis, with occasional intrathecal, and intramuscular, administration of l mg/day drug with favorable response. Mathies *et al*[13] have treated 20 patients with Gentamicin in the dose of 3 mg/kg body wt. in 3 divided doses, in combination with other drugs. Robert *et al*[14] have tried the drug in their thirteen patients of meningitis and ventriculitis by intrathecal and intramuscular route. They measured the levels of the drug in C.S.F. after lmg/day administration of Gentamicin, intrathecally and 2 mg/kg body wt./day intramuscular administration of drug. So the literature lindicates following observations. A level of 4 – 6 ug/ml in serum is regarded as optimal for treatment of various infections. In the adults it is given in the dose of 3mg/kg body wt. but in children this is very low dose as compared to adults when body surface area is used to calculate dose. So it is recommended that 2.5 mg/kg/8 hrs. may be used in neonates.

MATERIAL AND METHODS

The children admitted in pediatric ward of a general hospital constituted the material for the present study. Only those children, for whom diagnostic L.P. was considered necessary on admission were included in this study and hence no child was subjected to L.P. only for the purpose of this study. Out of the selected children, those who did not have any clinical and laboratory evidence of intracranial infections, constituted the group of normal children. Whereas those, who had clinical and Laboratory evidence of intracranial infections, constituted the another group under study. Both the group of children were subjected for similar work-up. As the microbiological method, was used for assay of Gentamicin in this study, it was very important to conform that the children had not received any other antibiotic in the recent past. Those children, who showed presence of antibiotic activity in this serum sample (so), were excluded from present study and only those who did not have any + ve^{s}o sample were finally considered for study. The selected children were weighed on proper weighing machine. Gentamicin, in the dose of 3mg/kg-body wt., was then given intramuscularly. 90 minutes after the drug administration, the blood ($s1_{1/2}$) and C.S.F. (c_1) were collected. Children, who were found to have intracranial infection, were added if necessary after the required serum and C.S.F. samples were collected 90 min. after the first injection, as the study did not necessitate any more collection of samples. Both these group of children were subjected to collection of serum samples s_0 and $S_{1½}$. And one sample of C.S.F. C1 ½.; S_0 denotes serum sample at zero hour before administration of drug and $S_{1½}$ and $_{1½}$ denote serum and c.s.f. sample respectively at 1½ hrs after drug administration. Third group of children did not have intracranial infection but necessiated further continuation of drug. In this group of children single serum and C.S.F. sample was collected after 5 doses. The specimen were sent to the laboratory immediately on collection for bio assay. Along with two serum samples and one C.S.F. sample, another sample of saline was also sent to the laboratory. All the four samples were coded. And hence laboratory personnel not only did not know to whom they belong. But also were unaware of the differentiation between S_0 and $S_{1\ ½}$ samples and C.S.F. and saline samples.

RESULTS

Total number of children in study =28, Number of S_0 positive = 4, Number of children totally analysed = 24, S_0 positive are the children where the samples of blood on admission showed the presence of some antibiotic as shown by microbiological method of assay. As this method of assay could not differentiate various antibiotics that patient may have had in the recent past. All such children were excluded from the study. Inclusion of such patients would have interfered with the interpretation of subsequent results.

Table 1: Distribution of the Children without meningitis

Sr. No	Age	Sex	S1 ½	C1 ½
1	1 ½ months	Female	2.7µg/ml	0 µg/ml
2	5 Years	Male	2.4 µg/ml	0 µg/ml
3	5 Years	Male	2.6 µg/ml	0 µg/ml
4	8 Months	Male	2.0 µg/ml	0 µg/ml
5	4 Months	Male	2.0 µg/ml	0 µg/ml
6	9 months	Male	3.0 µg/ml	0 µg/ml
7	1 ½ Months	Male	1.5 µg/ml	0 µg/ml
8	3 years	Female	1.5 µg/ml	0 µg/ml
9	1 ½ Years	Male	1.3 µg/ml	0 µg/ml
10	1 ½ Years	Male	1.0 µg/ml	0 µg/ml
11	1 ½ Years	Female	0.5 µg/ml	0 µg/ml
12	$3_{1/3}$ Years	Male	0.5 µg/ml	0 µg/ml

No. of children analysed -12 Male, Female- 5, There are wide fluctuations is the serum concentration at $1_{1/2}$ hrs. C.S.F. did not show any detectable concentration of drug.

Table 2: Distribution of the Children with Meningitis

Sr No.	Age	Sex	S1 ½	C1 ½
1	22 days	Female	4.0 µg/ml	4.0 µg/ml
2	3 years	Female	2.5 µg/ml	2.5 µg/ml
3	5 years	Female	2.5 µg/ml	2.0 µg/ml
4	5 years	Female	4.0 µg/ml	1.1 µg/ml
5	1 ½ years	Male	1.7 µg/ml	1.5 µg/ml
6	5 years	Male	5.3 µg/ml	0 µg/ml
7	1 ½	Male	1.8 µg/ml	1.0 µg/ml

No. of children analysed -7, Male -3, Female -4, Fluctluation in serum concentration same as in group one. Most of the children show detectable concentration of drug in C.S.F.

Table 3: Distribution of the patients with Gentamicin level after 5th dose (µg/ml) Children Without Meningitis

Sr. No.	age	Sex	s	c
1	5 Years	Female	0.5 µg/ml	0 µg/ml
2	4 Years	Male	0.5 µg/ml	0 µg/ml
3	2Years	Male	5.0 µg/ml	0 µg/ml
4	8 months	Female	2.2 µg/ml	0 µg/ml
5	26 days	Male	0.5 µg/ml	0 µg/ml

Serum levels after 5 doses have shown marked variation. None of them had any detectable level in C.S.F.

DISCUSSION

With better knowledge of clinical pharmacology it has been possible to monitor drug therapy in an individual patient drug monitoring not only helps in achieving adequate concentration of the drug but also can guard against possible toxic effects. This is especially vital in

case of drug where therapeutic margin of safety is small. As an individual patient may have interaction between several pharmacokinetic variables, drug monitoring offers a fairly useful method in maintenances of adequate therapy. Several pharmacokinetic parameters have been studied in relation to a drug like Gentamicin. In of renal disease on pharmacokinetic pattern of Gentamicin, as mainly the drug is excreted via kidneys. Comparatively fewer studies have correlated the blood brain barrier in case of meningitis. Such a data is totally lacking in our population. The present study has therefore tried to assess the blood brain barrier for this drug in children with and without meningitis. The S1 ½ levels, of the drug in group one patients without meningitis, showed wide fluctuation from 0.5 to 3.0 µg/ml, 1 ½ hrs. after administration of the drug in the dose of 3 mg/kg body wt. the age group of these patients in study were between 6 weeks to 5 years. Literature mentions that there is wide individual variation of peak levels of gentamicin. Moreover the levels do notcorrelate only with the dose of the drug hematocritvalues, and so individual monitoring is important In assessment of therapy. A study by donald[15]mentions that with a single dose of 2-3 mgms/kg body wt. The peak levels varied from 5 to 14 µg/ml. moreover MIC and MBC should be done with pharmacokinetic study in individual case for assessing the therapy. The wide fluctuations may be partly because of hematocrit values, the RBCs can take up this drug and release the drug in plasma with some equilibrium. Other factor being binding of the drug to plasma proteins in the range of 25-30%. The quantum, of the drug, bound to plasma proteins also varies greatly in individuals. In out study the factors causing variation in peak concentration of the drug were not measured. Most of the children attending the general hospitals are malnourished, so the serum protein levels are low and this may affects the binding of the drug to plasma proteins, and thereby free form of the drug may be more in the plasma. In this study there were no detectable levels of the drug in c.s.f. in this group of children. This suggests that the normal blood-brain barrier doesnot allow any appreciable transfer of drug in c.s.f. the method used in the study was the microbiological assay with which it is difficults to detect smaller concentration of the drug. There is paucity in literature about the studies of the levels of the drug in c.s.f. in normal 1[12] children, even in western countries, probably because of ethical reasons. Such a data is of course not available in our country. The results of this group of children highlights marked variability in serum concentration of the drug and, also show that the drug isnot able to permeate the normal blood brain barrier. The question arises whether a drug, which fails to penetrate blood brain barrier detectable concentration. Can do so in situations where blood-brain barrier is altered as in cases of meningitis. To evaluate this aspects the second group of children with meningitis have been studied. The serum levels at 1 ½ hrs. in this group of children in the first group. Serum levels varied from 1.7 µg/ml to 5.3 µg/ml. naturally no difference in the group of children. However the c.s.f. concentration at 1 ½ hrs. Showed different pattern as compared to those in children of group I. children with meningitis demonstrated c.s.f. concentration at 1 ½ hrs., varying from 1 to 4 µg/ml, except in one child where there was no detectable level. As mentioned earlier the method used for assay was accurate only to detect levels above 0.5 mg/ml. and hence concentration below that level couldnot be judged with accuracy. Presence of detectable in c.s.f. is in marked variation. With absence of detectable levels in children without meningitis. This does show the effect of altered blood-brain barrier in meningitis.

CONCLUSION

Presence of detectable in c.s.f. is in marked variation. With absence of detectable levels in children without meningitis. This does show the effect of altered blood-brain barrier in meningitis.

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