Original Article

A study of theuraptic response to gentamycin on CSF of the Paediatric patients with meningitis

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Abstract

Introduction: 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 organs like kidney, liver etc. Hence clinical response, to a drug would depend on verities 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. **Aims and Objectives:** A Study of Theuraptic Response to Gentamycin on 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:** The ratio of S1 ½ to C1 ½ varies mostly from 1.8:1 to 1:1, only one child showed lower concentration of drug in C.S.F. with ratio of 4:1 and another child had no detectable levels of drug in C.S.F. There was no correlation between the cell count in c.s.f. and ratio of s1 ½ to c1 ½. No. of children analyzed -12, Male – 7, 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. **Conclusion:** It may be necessary to monitor serum concentration in such a way that minimal concentration be achieved to produce maximum therapeutic response without any risk of side effects.
Keywords: Gentamycin, CSF, Pediatric Meningitis.

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INTRODUCTION

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 organs like kidney, liver etc. Hence clinical response, to a drug would depend on verities 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. The three components of gentamicin have similar antibacterial activity. It was the first

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antibiotic effective against pseudomonas. Apart from its 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 administered parentally. 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 metabolized 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 not correlate 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 drug in normal individuals may give peak levels varying from 5-14 ug/ml. The doses 4.9based 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 hrs and effective concentration persisted 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* l were the first investigator to study this agent before 1962. Simultaneously klein[9] *et al* 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 study, 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 l mg/day administration of Gentamicin, intrathecally and 2 mg/kg body wt./day intramuscular administration of drug. So the literature indicates following observations.

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 necessitated 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: S1 ½ / C1 ½ Ration in Relation to C.S.F. Changes

Sr. No.	S1 ½ / C1 ½	C.S. F		
		Cytology	Sugar mg%	Protein mg%
1	1	110 cells 90% p 10% L	21 mg %	350 mg %
2	1	150 cells 40% L	42 mg %	350 mg %
3	1.25:1	60 cells 40%	96 mg %	110 mg %
4	4:1	0	57 mg	30 mg %
5	1:1	125 cells 40% p 60% L	32 mg %	250 mg %
6	-	325 cells 65% P 35% L	24 mg %	180 mg %
7	1.8:1	370 cells 30% P 70% L	48 mg %	900 mg%

The ratio of S1 ½ to C1 ½ varies mostly from 1.8:1 to 1:1, only one child showed lower concentration of drug in C.S.F. with ratio of 4:1 and another child had no detectable levels of drug in C.S.F

Table 2: 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 analyzed -12, Male – 7, 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.

DISCUSSION

With better knowledge of clinical pharmacology it has been possible to monitor drug therapy in an indivisual 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 the repentic margin of safety is small. As an individual patient may have interaction between several pharmacokinetic variables, drug monitoring offers a fairly useful method in maintainances 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 corelated the blood brain barrier in case of moningitis. 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 indivisual variation of peak levels of gentamicin. Moreover the levels donotcorelate only with the dose of the drug haematocritvalues, and so indivisual monitoring is important In assesment of therapy. A study by donald[3] metions 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 indivisual case for assessing the therapy. The wide fluctuations may be partly because of haematocrit 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 indivisuals. The ratio of serum to c.s.f. levels at 1 ½ hrs. varied from as high as 1:1 to 4:1, our results are similar to many others quoted in was tern litrerature. Klein13,16, newman[14,19,23]. Arthur[15,17,] john[19] cox[20], Riley21. Mathies22 have shown the levels of the drug in c.s.f. and their serum/c.s.f. ratio varied from 8:1 to 2:1 altered blood-brain barrier is due to inflammatory changes resulting out of infection in children with meningitis. We have tried to correlate cytological and bio-chemical changes in c.s.f. in relation to the reatio of s1 ½ and c1 ½, as these changes in c.s.f. correlate roughly with the degree of inflammation. There was no correlation between the cell count in c.s.f. and ratio of s1 ½ to c1 ½. it was observed that with higher concentration of proteins in c.s.f., the penetration of gentamicin in c.s.f. was enhanced, whereas with smaller amount of proteins in c,s,f, correlated with smaller penetration of drug across the meninges. This was exemplified by case No.4, where protein content of c.s.f. was normal (30 mg%) and this child showed s1 ½ as 4:1, it is thus felt from the present study that altered blood-brain barrier due to inflammatory changes does allow better plenetration of drug and its concentration in c.s.f. probably is correlated with protein concentration of c.s.f. and not to cell count in c.s.f. however small number of cases in present study doesnot preclude such universal statement. Only one child in this group did not show any detectable levels of drug in c.s.f., inspite of showing evidence of meningeal inflammation in term of cytobiochemical changes in c.s.f. we have no explaination for such a occurrence. The western literature doesnot make a mention of such exceptions. As we have not studied many more variable parameters that may be co-existing in a given patient. it is left to guesswork why a single patient has differed from the group. it is likely that the duration of inflammatory changes and several compensatory adjustments, that may occur naturally, may decide the ultimate penetration of the drug across blood-brain barrier. In this a study we have not tried to correlate clinical outcome with pharmacokinetic results. However in western literature they have Correlated so in studies by klein[20], newman[8, 10]. Arthur[11,12], john[11] cox[11], Riley[20] Mathies[16]. In this study we have not tried to assess the effects of intrathecal administration of drug. Considering smaller concentrations of the drug attained in c.s.f., even in children with meningitis, it has been felt that intrathecal administration, especially in first few days of treatment, may help to achieve higher concentration of drug. Long term administration of any antibiotic demande maintainance of steadly state level can be assessed only collection of several samples of blood in succession over few days. As this was not very easy. We have tried to assess serum levels of gentamicin after 5th dose, each dose of 3mg/kg body wt., given every a hrs. this is with reference of theoretical consideration that gentamicin steady state levels may be attained probably at the end of forty hours or so, though this cannot be considered as accurate atate of steady state levels. The study has shown marked variation of serum concentration from 0.5 ug/mm to 5 ug/ml. none of the c.s.f. sample have shown any detectable levels of drug even after 5 doses, of course this group comprised of children without meningitis, and this correlates well with the results in group one children. It is clear from the present study that though gentamicin doesnot cross the blood-brain barrier to appear in detectable concentration in c.s.f. in children without meningitis, it does so in children with meningitis. Is an accepted range of therapeutic efficacy. While concentration of more than 12 ug/ml are considered to be toxic. However it may be necessary to monitor serum concentration in such a way that minimal concentration be achieved to produce maximum therapeutic response without any risk of side effects. It may not be safe to consider that equal concentration in serum and c.s.f. may be necessary to achieve the optimum therapeutic response. Hence merely increasing the drug concentration in c.s.f. by addition of intrathecal administration may not be the total answer to achieve better results.

CONCLUSION

It may be necessary to monitor serum concentration in such a way that minimal concentration be achieved to produce maximum therapeutic response without any risk of side effects.

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