A preliminary study on pharmacokinetics of oral indomethacin in premature infants in north India

P.K. Sharma, S.K. Garg & A. Narang*

Departments of Pharmacology & *Paediatrics, Postgraduate Institute of Medical Education & Research, Chandigarh, India

Received February 17, 2003

**Background & objectives:** Patent ductus arteriosus (PDA) is a frequent complication in premature infants. Intravenous indomethacin is the standard mode of medical therapy and has been shown to be efficacious in closing the ductus. In our setup, oral indomethacin is being regularly used for medical treatment of suspected or clinically diagnosed PDA. Non-availability of the parenteral preparation and lack of information regarding the pharmacokinetic disposition of indomethacin in the premature infants in north Indian population led us to conduct this pharmacokinetic study with oral indomethacin.

**Methods:** Twenty premature infants with gestational age 30.3±0.3 wk and birth weight, 1209.8±39.5 g; admitted to the neonatal unit of the Nehru Hospital, Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh were enrolled in the study. Indomethacin was administered in a single oral dose of 0.2 mg/kg and blood samples were collected through an indwelling vascular catheter at 0 and 1, 2, 4, 8 and 12 h after administration of indomethacin. Plasma indomethacin concentrations were assayed by spectrofluorometric technique.

**Results:** Large interindividual variability was observed for peak plasma concentrations (C\text{\text{max}}; 137.9±14.0 ng/ml), elimination half-life (t\text{1/2 el}; 21.4±1.7h) and area under the plasma concentrations time curve (AUC\text{0-}\infty; 4172±303 ng.h/ml) in these infants. Variables like birth weight, and sex did not have any significant effect on indomethacin pharmacokinetics. However, the plasma t\text{1/2 el} of indomethacin was significantly (P<0.01) larger in older infants (gestational age >30 wk) in comparison to younger ones (gestational age ≤30 wk). There was a negative correlation between gestational age and elimination t\text{1/2} (r = -0.77).

**Interpretation & conclusion:** In conclusion, indomethacin pharmacokinetics showed a wide variability in premature infants. In view of these findings it can be suggested that infants of smaller gestational age are at greater risk of cumulative toxicity if more than one dose of indomethacin is given. With advancing age, metabolism as well as elimination of drug is faster that may require modification in indomethacin dose to achieve therapeutic response. These preliminary results may be of use in designing future pharmacokinetic studies of oral indomethacin in preterm neonates on a larger sample.

**Key words** Indomethacin - infants - patent ductus arteriosus - pharmacokinetics

Patent ductus arteriosus (PDA) is a vascular shunt connecting the left pulmonary artery and aorta usually near the origin of the left subclavian artery. The incidence of persistent PDA varies inversely with post-conceptional age affecting more than 40 per cent of very low birth weight infants. Premature infants have a higher prevalence of persistent patency of the ductus arteriosus but the
closure of this foetal channel although delayed often occur spontaneously.

Indomethacin, a non-steroidal anti-inflammatory drug (NSAID) is used to treat the condition, and is effective in closing the PDA. However, there are frequently associated side effects on the cerebral, renal and mesenteric circulations. A typical treatment regimen for haemodynamically significant PDA involves the intravenous administration of 0.1 to 0.2 mg/kg every 12 h for three doses. The mechanism of action involved presumably is inhibition of the cyclo-oxygenase mediated production of vasodilatory prostaglandins. Several studies on the pharmacokinetics of indomethacin using oral as well as intravenous preparations in premature infants with PDA are reported. To the best of our knowledge, so far no data on the pharmacokinetic disposition of oral indomethacin in premature infants with PDA are reported. Due to the non-availability of the parenteral preparation in our country, oral indomethacin is being used on a regular basis to treat PDA. However, at present we have no facilities in our paediatric setting to assess PDA closure, therefore kinetic information could not be translated into effect (i.e., ductal closure) if at all achieved.

Hence, this study was designed and conducted solely to characterize the pharmacokinetic profile of oral indomethacin in premature infants with suspected or clinically diagnosed PDA.

Material & Methods

Twenty premature newborns with suspected or clinically diagnosed PDA admitted consecutively to the neonatal unit of the Department of Paediatrics, PGIMER, Chandigarh between February to October 2002 fulfilling the following inclusion criteria i.e., gestational age ≤32 wk; haemodynamically stable (systolic and diastolic blood pressure within normal limits adjusted for gestational age, normal heart rate); and the presence of indwelling vascular catheter were enrolled. Infants with congenital malformations; documented infection; clinical bleeding tendency; thrombocytes count<60000/mm\(^3\), oliguria (<1 ml/kg/h) during the preceding 8 h and hyperbilirubinaemia that required exchange transfusion were excluded from the study. Prior to the study written informed consent was obtained from the parents and the ethics committee of the institute approved the study protocol.

Medication and dose: Each infant received indomethacin at a dose of 0.2 mg/kg body weight in pure powder form (Indian Drug Pharmaceutical Ltd., India) mixed with milk and administered through a nasogastric tube.

Study procedure: The pharmacokinetic parameters of the single oral dose of indomethacin were determined after the drug was administered. Blood samples each of 0.6 ml were collected through an indwelling arterial catheter at time 0 and at 1, 2, 4, 8, and 12 h after drug administration. All samples were collected in heparinized test tubes, and were immediately centrifuged for 10 min at 900 g. Plasma was separated and stored at -20°C until assayed for indomethacin using spectrofluorometric technique.

Analysis of data: Data were analysed using open one compartmental model. The pharmacokinetic parameters for single dose oral indomethacin in premature infants were calculated as follows:

Peak plasma concentration (C\(_{\text{max}}\)) and time to reach the peak plasma concentration (T\(_{\text{max}}\)) were calculated from the actual plasma data. Rate constant for plasma drug elimination i.e., K\(_{\text{el}}\) was calculated by regression analysis of the monoexponential declining line of the log of plasma drug concentration versus time graph, while elimination half-life (t\(_{1/2}\) el) was obtained from the formula, t\(_{1/2}\) el = 0.693/K\(_{\text{el}}\). Area under the plasma drug concentration versus time curve for indomethacin (AUC\(_{0-12h}\)) was calculated by trapezoidal rule. Extension of the AUC data to infinity was done by dividing the last observed concentration of drug in plasma by the elimination rate constant (K\(_{\text{el}}\))

Statistical analysis: All values are presented as mean±SE. Comparison between the groups was done by two tailed unpaired Student’s t-test and P<0.05 was considered significant. Correlation between t\(_{1/2}\) el and gestational age was done by Pearson correlation analysis.
Results

The infants had mean birth weight of 1209.8±39.5 g (range=900-1545 g) and mean gestational age of 30.3±0.3 wk (range=27-32 wk). Fig. shows the plasma indomethacin concentrations at different time intervals following single oral dose of 0.2 mg/kg. There was a tendency for slow disappearance of the indomethacin from the plasma. The indomethacin levels appeared in plasma at 1 h in all except three babies and were detectable till 12 h. The mean plasma $t_{1/2}$ of indomethacin was calculated to be 21.4±1.7 h with elimination rate constant ($K_{el}$) of 0.036±0.014 h. The peak plasma concentration ($C_{max}$) achieved was 137.9±14.0 ng/ml and time to reach peak level ($T_{max}$) was 3.8±0.6 h. Mean $AUC_{0-\infty}$ was calculated to be 4172±303 ng.h/ml. To assess the influence of gestational age, gender and birth weight on the pharmacokinetic disposition of indomethacin in these babies, we divided them into two groups based on these variables for comparison (Table). A significantly ($P<0.01$) higher elimination $t_{1/2}$ of indomethacin was seen in infants with gestational age of ≤ 30 wk as compared to babies of >30 wk, indicating a faster elimination with increasing age. No significant difference was observed in any of the pharmacokinetic parameters between male and female infants. However, $t_{1/2}$ and $AUC_{0-\infty}$ were slightly higher in male babies. Similarly, birth weight did not affect any of the kinetic parameters significantly. A negative correlation was found between gestational age and elimination half-life ($r = -0.77$).

Discussion

Several studies have been conducted that have addressed the disposition of indomethacin in neonates\textsuperscript{7-12,16,17}. Analysis of their results reveals that there is great deal of variability among neonates with regards to the disposition of indomethacin.

The present study has shown a large inter- individual variability for various pharmacokinetic parameters and apparently high variability among

![Fig.](#) Indomethacin plasma concentrations (mean±SE) at different time points after single oral dose (0.2mg/kg) in premature infants (n=20). Values shown in the Figure are mean values at that time point.
Table. Effect of gestational age, sex and birth weight on pharmacokinetic parameters of indomethacin

<table>
<thead>
<tr>
<th>Variables</th>
<th>$C_{\text{max}}$ (ng/ml)</th>
<th>$T_{\text{max}}$ (h)</th>
<th>$t_{1/2}$ (h)</th>
<th>$AUC_{0-\infty}$ (ng.h/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age (wk)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\leq 30$ (n=10)</td>
<td>117.4±9.3</td>
<td>3.8±0.2</td>
<td>26±2.2</td>
<td>4544±387</td>
</tr>
<tr>
<td>$&gt;30$ (n=10)</td>
<td>158.4±25.4</td>
<td>3.8±0.2</td>
<td>16.7±1.6*</td>
<td>3799±457</td>
</tr>
<tr>
<td>Sex (M:F)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male (n=12)</td>
<td>139.2±18.6</td>
<td>3.83±0.16</td>
<td>22±2.5</td>
<td>4328±444</td>
</tr>
<tr>
<td>Female (n=8)</td>
<td>136±22.8</td>
<td>3.75±0.25</td>
<td>20.4±2.2</td>
<td>3937±384</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1200 (n=9)</td>
<td>128±20.6</td>
<td>3.77±0.22</td>
<td>25.1±2.85</td>
<td>4437±442</td>
</tr>
<tr>
<td>$\geq 1200$ (n=11)</td>
<td>146±19.6</td>
<td>3.81±0.18</td>
<td>18.4±1.62</td>
<td>3955±425</td>
</tr>
</tbody>
</table>

*P<0.01 compared to $\leq 30$ wk gestational age

Bioavailability of orally administered indomethacin in preterm infants is about 20 per cent, and the time to peak plasma levels later than that reported in adults$^7$. The major factors which control gastrointestinal absorption are pH dependent diffusion and gastric motility, both of which are abnormal in premature infants; adult values for gastric acidity are usually reached only after 3 yr$^{19}$. An additional factor could be the poor aqueous solubility of indomethacin, which may contribute to its incomplete and non-uniform absorption. For a variety of drugs, premature infants have a longer half-life of elimination and a lower clearance rate than in adults$^{20,21}$. The plasma elimination half-life observed in our study ranged from 9 to 43 h (mean±SE = 21.4±1.7 h), whereas it is reported to be 3-11h in adults$^{22}$. The significantly higher mean half-life of elimination in infants with gestational age $\leq 30$ wk could probably be attributed to immature renal function, resulting in decreased clearance, because a fraction of the drug is excreted unchanged and there exists relatively low levels of enzymatic activity, such as glucuronidation, O-demethylation and deacylation, needed for metabolism of the drug$^6$. A negative correlation of $t_{1/2}$ with gestational age indicates a maturational development in plasma clearance of indomethacin. In general, the hepatic clearance of drugs in newborns is one-fourth to one-half the adult value and maturation to or beyond the adult capacity occurs slowly after birth$^{23}$. In our study, we did not estimate the indomethacin plasma protein binding in individual patients, therefore its effect on the plasma concentration of indomethacin in different patients cannot be ruled out. Kwan et al$^{24}$ estimated that a substantial amount of indomethacin undergoes enterohepatic recycling and this will cause the calculated half-life of elimination to be larger than that it would be if renal and biliary excretion were not complicated by intestinal reabsorption.

Pharmacologic closures of the ductus have been reported using oral indomethacin, though with varied efficacy$^{25-27}$. These differences in response to indomethacin have been attributed to drug
instability, poor oral absorption, and age at the time of treatment and other related factors that have important bearing on indomethacin disposition. Some workers suggest poor oral absorption as a major contributing factor to the variation in treatment efficacy.

Because of the large inter-individual variability in indomethacin pharmacokinetic in neonates, it is to be established to what degree the patient characteristics influence the pharmacokinetics of drugs. The elimination half-life showed a negative correlation with gestational age. Thus, when indomethacin is administered in infants of smaller gestational age, one may anticipate longer elimination half-life and slower metabolic clearance of the drug, that can cause cumulative toxicity when more than one dose is given. In older infants metabolism and elimination of drug is faster that may require modification in the dose to achieve therapeutic response. The preliminary data obtained may be of value in designing future studies on a larger sample to confirm these findings.

References


Reprint requests: Dr S.K. Garg, Professor, Department of Pharmacology, Postgraduate Institute of Medical Education & Research, Chandigarh 160012, India