Indomethacin treatment in small versus large premature infants with ductus arteriosus

Comparison of plasma indomethacin concentration and clinical response

T F YEH, J LUKEN, D RAVAL, A THALJI, I CARR, R S PILDES

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SUMMARY An analysis of clinical response and plasma indomethacin concentration was performed on 10 small (<1000 g) and 12 large (>1000 g) premature infants who had symptomatic ductus arteriosus and required intravenous indomethacin therapy (0.3 mg/kg per day). The postnatal age, daily fluid intake, and cardiopulmonary status of the two groups at time of study were comparable.

The small premature infants had a significantly lower peak plasma indomethacin concentration and lower concentration in the first four hours after infusion, and lower plasma concentration time integral than that of the larger premature infants. There was a significant difference between the groups in proportion of response (2/10 vs 9/12) after one dose of indomethacin; this difference was not seen after two to three doses. The results of the study suggest that small premature infants do respond to indomethacin treatment, but compared to the larger infants may require repeated doses.

Poor or transient response to indomethacin in the closure of ductus arteriosus in premature infants of very low birthweight has been reported by some investigators but not by others. Various hypotheses have been suggested for these contradictory observations. One reason for the lack of response may be related to the day of postnatal age when indomethacin was administered because the closure of ductus arteriosus by indomethacin has been shown to be age dependent. The other reason for the inadequate response in small premature infants had been postulated to be because of inadequate development of the smooth muscle in the ductus wall. Recently, Brash et al. showed a relation between plasma indomethacin concentration and ductus constriction and suggested that some failure of indomethacin treatment may be related to a low plasma concentration. The purpose of the present study was to see if there were any differences in clinical response and plasma indomethacin concentration between the small and large premature infants.

Subjects and methods

Serial assays for plasma indomethacin were performed in 22 premature infants who were enrolled in a double-blind study and received indomethacin because of the presence of a significant ductus arteriosus. The diagnosis of ductus arteriosus was made if the pulses were bounding and if there was the characteristic systolic or murmur continued into diastole at the left upper sternal border. The criteria for inclusion in the study were: firstly evidence of a significant degree of clinical cardiovascular dysfunction or an echocardiographic left atrial/aortic root dimension (LA/Ao) ≥1.3 and secondly the absence of certain non-cardiopulmonary complicating factors. These factors included: (1) total serum bilirubin 171 μmol/l (>10 mg/100 ml), (2) BUN 7-14 mmol/l (>20 mg/100 ml), (3) shock, (4) intracranial haemorrhage, (5) necrotising enterocolitis, and (6) haemorrhagic disease. After establishment of an intravenous line, each infant received 0.3 mg/kg birthweight of indomethacin sodium. There was no difficulty in infusing the drug completely in 15 seconds in each case. Infants were examined daily and if
a murmur was still present, another dose was administered up to a maximum of three doses. Therefore, all infants received at least one dose, but a smaller number received two doses and yet a smaller number, three doses. Doses were repeated at intervals of about 24 hours. All infants received 65 ml/kg per day on the first postnatal day; this was increased to approximately 150 ml/kg per day by 1 week of age. On the day before the study, and throughout the study period, the fluid intake was kept constant, with 120 ml/kg per day or 150 ml/kg per day if the infant was on phototherapy. The plasma indomethacin concentration was measured during the first 24 hours after the first dose of indomethacin. Blood samples were obtained at a half, two, four, 12, and 24 hours after infusion of indomethacin. Assay of indomethacin was performed by the electron capture gas chromatographic method. The plasma concentration × time integral or the "area" under the plasma concentration time curve was calculated from time zero to 24 hours after drug infusion using a planimeter (Compensating Polar Planimeter, Keuffel and Esser, Co., Morris-town, New Jersey). Using clinical and echocardiographic assessments, a designation of "successful response" or "failure to respond" was assigned on the basis of information available 24 hours after drug administration. A successful response was defined by the disappearance of the murmur of ductus arteriosus and an improvement in the echocardiogram. All others were designated as failures.

The infants were divided into two groups. Group 1 consisted of 10 infants whose birthweights were less than or equal to 1000 g; group 2 consisted of 12 infants whose birthweights were greater than 1000 g. We evaluated statistical differences between the groups using the independent Student's t test or χ² analysis when appropriate.

Results

As would be expected, not only the mean birthweights but also the gestational ages were significantly (p<0.01) lower in group 1 infants (837-8 g, range 709 to 1000 g; 29-5 weeks, range 26 to 32 weeks) as compared with group 2 infants (1391-8 g, range 1162 to 1621 g; 32-1 weeks, range 31 to 35 weeks).

The clinical characteristics and cardiopulmonary status of the infants at the time of study are shown in Table 1. There was no significant difference between the groups in postnatal age, cardiopulmonary status, and daily fluid intake, indicating that the two groups were comparable other than for birthweight and gestational ages.

Comparisons of the plasma indomethacin concentration between the two groups of infants are shown in Table 2. Infants in group 1 had significantly lower peak indomethacin concentration and lower indomethacin concentration at a half, two, and four hours after infusion, as compared with those of group 2 infants. Similarly, group 1 infants had significantly smaller plasma concentration × time integral calculated from time zero to 24 hours after infusion, as compared with that of group 2 infants.

Table 3 shows the number of infants who responded and did not respond to indomethacin therapy. Two infants in group 1 and nine in group 2 responded to one dose of indomethacin with closure of the ductus arteriosus. This difference, in proportion of response between the groups, was statistically significant (p<0.05). After two to three doses of indomethacin, however, the proportion of response between the two groups was comparable. Group 1 infants received an average of 2.0±0.6 doses (mean±SD) whereas group 2 infants received 1.2±0.4 doses (p<0.01).

Table 1 Clinical characteristics and cardiopulmonary status at time of study

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (&lt;1000 g)</th>
<th>Group 2 (&gt;1000 g)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total No.</td>
<td>10</td>
<td>12</td>
<td>NS</td>
</tr>
<tr>
<td>Postnatal age (days)</td>
<td>10±1±2</td>
<td>9±3</td>
<td>NS</td>
</tr>
<tr>
<td>Fluid intake (ml/kg/per day)</td>
<td>130±3±13±3</td>
<td>130±3±10±5</td>
<td>NS</td>
</tr>
<tr>
<td>Cardiopulmonary status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of assisted ventilation</td>
<td>8</td>
<td>9</td>
<td></td>
</tr>
</tbody>
</table>

Table 2 Comparison of serum indomethacin concentration between infants with birthweights ≤1000 g and those with >1000 g

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (&lt;1000 g)</th>
<th>Group 2 (&gt;1000 g)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak indomethacin concentration (μg/ml)</td>
<td>972±3±132±9</td>
<td>1307±3±182±1</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Indomethacin concentration (μg/ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>½ hour</td>
<td>964±3±319±2</td>
<td>1230±3±295±8</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>2 hours</td>
<td>675±3±225±3</td>
<td>1124±3±268±8</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>4 hours</td>
<td>615±3±305±3</td>
<td>965±3±296±4</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>12 hours</td>
<td>555±3±335±2</td>
<td>763±5±223±8</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>24 hours</td>
<td>419±1±351±9</td>
<td>446±3±180±3</td>
<td></td>
</tr>
<tr>
<td>∫₀ CT (μg/ml per h)</td>
<td>15±1±5±1</td>
<td>20±6±4±8</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Table 3 Number of infants who responded and did not respond to indomethacin therapy

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (&lt;1000 g)</th>
<th>Group 2 (&gt;1000 g)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responded</td>
<td>2</td>
<td>9</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>
Indomethacin treatment in small versus large premature infants with duc-
tus arteriosus

Table 3 Number of infants who responded and did not respond to
indomethacin: successful response defined by disappearance of
murmur of duc-
tus arteriosus and improvement of cardiopulmonary status

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of successful responses:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>After one dose</td>
<td>2/10</td>
<td>9/12</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>After two to three doses</td>
<td>6/8</td>
<td>3/3</td>
<td>NS</td>
</tr>
<tr>
<td>No. of failing responses</td>
<td>2/10</td>
<td>0/12</td>
<td>NS</td>
</tr>
</tbody>
</table>

Discussion

Indomethacin has been shown to be effective in the
closure of the duc-
tus arteriosus.9 12 13 Emphasis has recently been focused on small premature infants with
respiratory distress syndrome, not only because they have a high incidence of duc-
tus arteriosus,14 but also because they have a high risk of developing bron-
chopulmonary dysplasia. Unfortunately, the ductus response to indomethacin in small premature infants
has not always been successful; some infants did not respond,2 whereas others responded only transiently.1

On the other hand, such observations were not reported by other studies.5 8 12 13 These inconsistent
findings may arise from the differences between the studies in postnatal age of the infants, route, and
doses used in drug administration, and in the definition of successful response. It is also possible
that the duc-
tal muscle in small premature infants is, indeed, inadequate, which can be attributed to
the failure of duc-
tal closure. The present study indicates that small premature infants do respond to
indomethacin, but may require more doses than large premature infants if indomethacin is given at 24 hour
intervals. This characteristic response in small premature infants may be related, at least in part, to their
lower plasma concentration of indomethacin.

Since we do not have complete pharmacokinetic data on all infants, the lower plasma indomethacin
concentration in small premature infants can only be speculated upon. It is known that small premature
infants have large extracellular fluid space15 which may account for the large volume of distribution.
Variation in serum protein concentration among the infants may also contribute to the variation of volume
distribution since indomethacin is highly bound to serum protein.16 Small premature infants with lower
serum protein concentration will enable more to dif-
fuse out of the vascular compartment to other body fluid and tissue, lowering plasma concentration.

Brash et al. 8 showed a positive relation between the duc-
tus response and the plasma concentration of
indomethacin at 24 hours after infusion. The same
authors reported that 32 of 38 successful responses
were associated with plasma levels above 250 μg/ml at
24 hours after infusion. Our study was not conducted
to define the therapeutic level and our data do not
clarify the question of target concentration or minimal
exposure time above which the duc-
tus closure will occur. Seven infants in our study, however (four
in group 1 and three in group 2, postnatal age ranging
from 5 to 10 days), whose indomethacin concentra-
tions at 24 hours were greater than 250 μg/ml, did not
show evidence of response and required additional
doses before the duc-
tus closed. On the other hand,
one infant (1318 g) whose indomethacin concentration
at 24 hours was <250 μg/ml showed evidence of duc-
tal closure. Given the relatively small numbers, our
findings and those of Brash et al. 8 are not inconsistent
and do not contradict the idea that duc-
tus closure is related to plasma indomethacin concentra-
tion. It is likely that an indomethacin concentration dependent
response would probably be represented by a con-
tinuum for each individual, with variation between
individuals that seems to widen as more experience
accumulated. It would be unwise to assume that
infants with plasma indomethacin concentra-
tion >250 μg/ml will have a good response; some obvi-
ously will not. Some of these small premature infants
may require higher concentrations of indomethacin or
require longer duration of exposure time to the drug
than large infants. Further study is needed to define
the therapeutic level of indomethacin in small prema-
ture infants.

Recently, Mahony et al. 5 performed a double-blind
controlled study of prophylactic indomethacin
therapy in premature infants with subclinical duc-
tus arteriosus. The authors reported a positive initial
response in all 10 infants ≤1000 g based on clinical
judgment. It is difficult to interpret the differences
between their study and ours. All infants in Mahony’s
study did not have major left to right shunts, nor did
they have echocardiographic changes in left atrium/aorta
to the time of the study, while in our study,
all infants had a ratio of ≥1:3 and had cardiovascular
distress.9 Mahony evaluated the initial response during
the first 24 hours after the third dose of indomethacin,
based on clinical judgment, while in
our study the response was judged by clinical and
echocardiographic criteria and was evaluated after
each dose of indomethacin. Furthermore, their
infants were younger (2-9 days) than ours. It is possi-
ble that small premature infants with substantial left
to right shunts may not respond to indomethacin
treatment as effectively as those with a subclinical
ductus arteriosus occurring at an earlier postnatal
age.

There may have been other factors responsible for
the poor response to indomethacin, for example the
inadequate muscular tissue in the duc-
tal wall, as sug-
gested by Danilowicz et al. 7 or a primary histological
anomaly of the ductus wall with unfragmented subendothelial elastic laminae as suggested by Gittenberger-de Groot. We did not evaluate those hypotheses but our results suggest that the inadequate response in our small premature infants may be related, at least in part, to the low plasma indomethacin concentration and low plasma indomethacin concentration time \times \text{integral}.

References


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Indomethacin treatment in small versus large premature infants with ductus arteriosus. Comparison of plasma indomethacin concentration and clinical response.

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