

# THERAPY OF SYMPTOMATIC PATENT DUCTUS ARTERIOSUS IN PRETERMS USING MEFENEMIC ACID AND INDOMETHACIN

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## ABSTRACT

*Mefenemic acid (MA) was given in three doses of 2 mg/kg/dose at 12 hourly intervals in 16 cases clinically suspected of having symptomatic patent ductus arteriosus (PDA). All babies were  $\leq 35$  weeks gestation (mean 30.1 weeks) and weighed  $\leq 1700$  g at birth (mean 1320 g), the mean age of administration of MA being 16 days. Of the 16 cases, two did not respond to therapy. One non-responder was subsequently shown to have an endocardial cushion defect without PDA on 2-D Echo and Doppler study. The other was 29 days old at the initiation of therapy. In one case, the ductus reopened after an initial closure, however, it closed on repeating a second course of the drug.*

*Thirty preterms ( $\leq 34$  weeks) who were earlier treated with three doses of indomethacin (0.25 mg/kg/dose) formed the comparative study group. The closure rate of PDA on treatment with indomethacin was 70% and that with MA was 93.3% ( $p > 0.05$ ). Two neonates treated with MA and two treated with indomethacin had feeding intolerance and vomiting, perhaps attributable to the drug therapy. We recommend the use of MA for closure of symptomatic PDA in preterms, especially in those cases where indomethacin is not tolerated or when minute titration of its dosage is impracticable.*

**Key words:** Patent ductus arteriosus, Preterms, Mefenemic acid, Indomethacin.

Patent ductus arteriosus (PDA) is the commonest heart lesion in preterms(1). The ductus normally closes during transition from fetal to extrauterine circulation, failure of which may be due to numerous factors(2,3). A significant shunt across the PDA produces hemodynamic stress to the immature left ventricle, contributing to increased morbidity and mortality in the sick neonate(2). Orally administered indomethacin which has an established role in the treatment of PDA(1,2,4-7) has its limitations and contraindications(2,5,8,9). Mefenemic acid (MA), a drug belonging to the same group of non-steroidal anti-inflammatory drugs (NSAID's) as indomethacin has been tried as an alternative modality for treatment of PDA(10,11). We present our experience of the use of MA and indomethacin in the management of symptomatic PDA.

## Material and Methods

During a period of one year from April 1990 to March 1991, 16 cases suspected of having symptomatic PDA were treated with MA (Group A) in three doses of 2 mg/kg/dose at 12 hourly intervals, and analyzed prospectively. Case records of the previous 30 consecutive cases treated with indomethacin (Group B) from January 1988 to March 1990 were retrospectively analyzed, compared with present data, and

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formed the control group. Indomethacin available as 25 mg capsules was dissolved in 10 ml distilled water and three doses of 0.25 mg/kg/dose (0.1 ml/kg of a freshly prepared solution) were given at 12 hour intervals. This procedure was resorted to as a sensitive weighing scale was not available to measure small fractions (0.25 mg) of indomethacin powder and dilutions with vehicles such as lactose powder can be erroneous.

Neonates were diagnosed to have symptomatic PDA based on the following criteria(4,7,12,13):

- (i) Systolic or continuous murmur (Grade II or more) in left infraclavicular region.
- (ii) Presence of at least three of the following:
  - (a) basal tachycardia ( $>170/\text{min}$ )
  - (b) bounding brachial and femoral arterial pulses
  - (c) hyperdynamic left ventricular impulse
  - (d) tachypnea ( $>70/\text{min}$ )
  - (e) other evidence of cardiac failure, e.g., tender palpable liver  $>3$  cm below the costal margin and crepitations on chest auscultation.
- (iii) Cardiomegaly defined as cardiothoracic ratio  $>0.6$ .

In three cases, a 2-D Echo and Color Doppler study was done to confirm the diagnosis of PDA. Details of delivery records, birth weight, gestation, clinical observations and relevant investigations, mode of therapy, side effect and outcome was recorded in all cases. All patients also received intravenous furosemide 1 mg/kg/dose 12 hourly with fluid restriction in

addition to the above drugs. Blood levels of MA and indomethacin were not estimated. Criteria of success included reversal of findings noted for the diagnosis of PDA.

All babies receiving MA or indomethacin had a complete blood count, platelet count, prothrombin time, blood urea and urine examination done before and after therapy. Serum electrolytes and serum bilirubin were done if indicated. All neonates were observed closely for the presence of oliguria, bleeding diathesis and gastrointestinal signs. Statistical evaluation of data to compare the two groups was done by the paired 't' test.

## Result

A total of 46 patients treated from January 1988 to date (30 with indomethacin and 16 with MA) for suspected PDA were analyzed. Comparative summary of both groups is shown in *Table I* and details of patients treated with MA (Group A) are provided in *Table II*. In one neonate from Group A and three from Group B the PDA reopened after initial response and a repeat course of the same drug successfully closed the PDA. While 14 out of 16 patients given MA responded to therapy, one patient with birth weight of 1100 g and 28 weeks gestation (Case No. 1) who was treated at the age of 29 days did not respond. The other failure (Case No. 11) was shown on 2-D Echo and Doppler study to have an endocardial cushion defect without PDA. Hence, a favorable response was noted in 14 out of 15 (93.3%) cases treated with MA. Twenty one patients out of 30 (70%) treated with indomethacin responded. Mean age of treatment with MA was 16 days (range 4-45) and in 6 cases MA was effectively used after 15 days of life. Two cases in Group A, expired of

**TABLE I—Comparison of Salient Features of Patients Treated with Mefenemic Acid (Group A) and Indomethacin (Group B)**

Feature	Oral mefenemic acid (Group A)	Oral indomethacin (Group B)
Number of patients	16	30
Period	April 1990-March 1991	January 1988-March 1990
Mean age (and range) of treatment in days	16 (4-45)	10.2 (4-22)
Mean birth weight (g)	1320 g	1230 g
Mean gestation (weeks)	30.1	28.6
Dosage (mg/kg/dose)	2 mg × 3 doses 12 hourly	0.25 mg × 3 doses 12 hourly
Method of administration	Suspension (Ponstan-Parke Davis) 10 mg/ml 0.2 ml/kg/dose	25 mg capsule dissolved in 10 ml distilled water. Administered after shaking at 0.1 ml/kg/dose
Efficacy	93.3% ( $p > 0.05$ )	70%
Expired	$n = 2$	$n = 5$

**TABLE II—Summary of Salient Features of Group A**

Case No.	Birth weight (g)	Gestation (weeks)	Age at MA therapy (days)	Outcome with reference to PDA closure
1	1100	28	29/34 (repeat)	Failure
2	1450	32	15/30 (repeat)	Success after initial failure
3	1100	30	5	Success
4	1200	30	4	Success
5	1400	32	45	Success
6	1150	29	31	Success. PDA presence and closure confirmed on 2-D echo
7	1250	30	18	Success
8	1700	35	4	Success
9	1200	31	6	Success
10	1500	33	10	Success
11	1600	35	5/8 (repeat)	Failure. 2-D echo and color Doppler showed no PDA
12	1200	28	8	Success
13	1600	33	19	Success. PDA presence and closure confirmed on 2-D echo
14	1000	27	10	Success
15	900	27	10	Success
16	1400	32	28	Success

MA—Mefenemic acid.

sepsis. Five cases in Group B expired, 3 of sepsis, one following an intracranial bleed and the other following gastrointestinal bleed. None of the patients given MA had any major side effects. Two cases in each group developed feeding intolerance which resolved spontaneously.

## Discussion

Although the rate of spontaneous closure of PDA in preterms is 20-30%, with oral indomethacin it ranges from 60-90%(2,3-7,14). As intravenous indomethacin was not available, an oral preparation in the form of Indocid capsule (25 mg) was used. In absence of a sensitive electronic weighing scale we had to prepare a fresh suspension of this powder in distilled water. As this powder is not well soluble in water, its exact dosage as a solution perhaps is unpredictable and inaccurate. The unused suspension was discarded and a fresh solution prepared for each subsequent dose. Towards the end of the trial period with indomethacin we came across two patients, one who developed an intracranial bleed and the other a massive gastrointestinal bleed soon after initiating indomethacin therapy. Both these had thrombocytopenia without DIC, an observation which has been documented earlier(2,6,15). Since the hematological parameters of both these were normal before onset of treatment we felt that indomethacin might have led to this catastrophe leading to death. Recent data documents changes in blood flow to the brain and the gut in patients treated with indomethacin(16,17).

Mefenemic acid (MA) has recently been found to be effective for closure of PDA by Shimada *et al.*(10,11). However, there have been few other clinical trials on the use of MA for PDA closure, and none

so far in Indian literature. It is available as a readymade suspension and hence the exact dose can be easily administered. MA like indomethacin belongs to the group of NSAIDs and is a cyclo-oxygenase inhibitor preventing conversion of arachidonic acid to  $\text{PGE}_2$ , thus preventing patency of PDA(18,19). Given orally it reaches a peak plasma level within two hours of administration and has a half life of three to four hours. Though uncommon, it can cause gastrointestinal complications like hemorrhage and ulcers, abnormal hepatic and renal functions and rarely hemolytic anemias and agranulocytosis(18,19).

On using MA we did not encounter any major side effects though two babies did develop feeding intolerance and vomiting, which was also seen in two patients treated with indomethacin. A total of 93.3% of patients in our series responded to MA treatment confirming its efficacy. 2-D Echo and Color Doppler were done in three cases only. Of these, in one (Case No. 11) the lesion was diagnosed to be an endocardial cushion defect without PDA. In two patients (Case No. 6 and 13) we proved the presence and closure of PDA after MA therapy on 2-D Echo and Doppler study. From this experience we feel that all future trials on pharmacological closure of PDA should preferably include the use of 2-D Echo and Doppler studies for the diagnosis of patency and proof of subsequent closure of the ductus, to prevent false positive and false negative diagnosis and also to rule out ductus dependant lesions before starting therapy.

Although MA therapy appeared more effective (93.3%) than indomethacin (70%) for closure of PDA in our series, this difference was not statistically significant ( $p > 0.05$ ). This study although not blinded was over a small period of time

and was conducted under the supervision of the same physicians, and the neonatal care offered by us had not changed over this period in relation to the management of this particular problem. Our initial experience with MA therapy, although small (15 cases) suggests that MA is effective, perhaps safer, and certainly easier to administer. Hence, we suggest that further comparative double blind trials be carried out with larger number of patients.

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## NOTES AND NEWS

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