Poor response to oral indomethacin therapy for persistent ductus arteriosus in very low birthweight infants

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SUMMARY Administration of oral indomethacin to treat cardiorespiratory failure in 7 low birthweight infants, after failure of conventional therapy, produced an improvement in only 2 infants. These infants had a higher birthweight than the group as a whole. Surgical ligation, rather than oral indomethacin, may be the treatment of choice for persistent ductus arteriosus in very low birthweight infants.

In view of the increasing frequency of persistent ductus arteriosus in neonatal special care units, there has been an increased interest in methods of duct closure. The recent introduction of pharmacological techniques of duct closure by means of indomethacin has led to its widespread use in this condition, in order to avoid surgical ligation as a method of treatment (Friedman *et al.*, 1976; Heymann *et al.*, 1976). However, complications from the use of such drugs have been recorded, and other theoretical risks suggested (Nadas, 1976). In addition, the initial success rate for treatment with indomethacin has not always been supported by studies from other centres (Neal *et al.*, 1977). We report our own experience with indomethacin therapy for persistent ductus arteriosus in low birthweight infants over the past 18 months.

Methods

Diagnosis of a left to right shunt through a persistent ductus arteriosus was made on clinical grounds, by the presence of a characteristic systolic murmur, together with a wide pulse pressure, radiological evidence of pulmonary plethora, and usually an increase in diameter of the cardiac shadow (Jones and Pickering, 1977). Conventional therapy with digoxin, frusemide, and restriction of fluid intake to less than 150 ml/kg per day was begun if failure occurred. Failure was defined as increasing requirement for oxygen or respiratory support, or as cardiac failure as evidenced by liver enlargement, tachycardia, and/

or excessive weight gain. Constant positive airway pressure was usually used to treat recurrent apnoea, which was a common problem if the infant was not ventilated (Robertson, 1974). If clinical improvement did not occur, surgical ligation was performed, and carried a low operative mortality (Cooke *et al.*, 1978). Nevertheless, there was frequently a reluctance to subject small infants to surgery at an early stage as prolonged supportive measures may result in spontaneous recovery, even in severe cases (Robertson, 1974).

However, if such measures include ventilation, infants may die from chronic lung disease before recovery from persistent ductus arteriosus occurs (Nelson *et al.*, 1976; Cooke *et al.*, 1978). To avoid such a situation, indomethacin therapy has been tried before ligation of the ductus in 7 infants.

After at least 48 hours of digoxin and diuretic therapy, with respiratory support as required, indomethacin was administered if no clinical improvement had occurred. 0.2 mg/kg per dose was given via a nasogastric tube at 12-hourly intervals for 3 doses. One infant (case 1) had only one dose because of pronounced oliguria. Surgical ligation was carried out if no improvement occurred after 3 doses of indomethacin.

Results

Seven low birthweight infants received treatment with indomethacin (Table). All had been ventilated for moderate to severe hyaline membrane disease, and 3 infants were still receiving ventilation at the time of treatment (cases 1, 5, and 7). Mean gesta-

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Table Course of illness treated by oral indomethacin

No.	Early illness	Gestation (wk)	Birth-weight (g)	Time murmur first heard	Time of ductus 'failure' developing	Age when indomethacin started	Result	Outcome
1	HMD	25	790	7 days	8	27	No response; oliguria 1d	Duct ligated 46d; died 127d; bronchopulmonary dysplasia
2	HMD	32	1340	11 days	21	24	No response	Duct ligated 29d; did well
3	HMD	29	1200	4 days	27	32	No change; oliguria 1d	Duct ligated 35d; did well
4	HMD	30	1120	3 days	9	16	No response	Duct ligated 19d; did well
5	HMD	28	1140	4 days	4	15	No response	Duct ligated 49d; died 69d; bronchopulmonary dysplasia
6	HMD	30	1440	8 days	21	23	Symptoms/signs reduced after 1 dose; off all therapy after 4d	Continued to do well
7	HMD	34	2080	9 days	18	21	Symptoms/signs reduced after 3rd dose; off all therapy after 4d	Continued gradual improvement complicated by bronchopulmonary dysplasia

HMD, hyaline membrane disease; d, day.

tional age was 29.7 weeks (range 25 to 34 weeks) and mean birthweight 1300 g (range 790 to 2080 g). The ductus murmur was heard at a median age of 7 days, and failure occurred at a median age of 18 days. Indomethacin was given at a median of 5 days after failure. No response was noted clinically in 5 out of 7 infants. Oliguria occurred in 2 infants, but they recovered within 24 hours. Of the 5 infants in whom indomethacin therapy failed, all had surgical ligation of the ductus, 2 died subsequently at 69 and 127 days from bronchopulmonary dysplasia, probably as a consequence of prolonged mechanical ventilation in the presence of pulmonary plethora. All the other infants survived and did well. In the 2 infants who showed a response to indomethacin (cases 6 and 7), the murmur of persistent ductus arteriosus, though reduced in intensity, persisted in both infants. Other symptoms and signs were much reduced, however, and both infants were off all treatment at 4 days after the start of indomethacin treatment. Case 7 subsequently had a recovery prolonged by chronic lung disease, but did well.

Discussion

In previous published work on the use of indomethacin in the treatment of persistent ductus arteriosus in low birthweight infants, results have been very good, with successful closure of the duct in most if not all cases (Friedman *et al.*, 1976; Heymann *et al.*, 1976); with higher doses of indomethacin than used in our unit, renal failure was common (Friedman *et al.*, 1976; Heymann *et al.*, 1976). In the series reported in this paper, only 2 out

of 7 infants avoided surgery because of a response to indomethacin therapy. In these 2 infants, the signs of persistent ductus arteriosus did not disappear completely, but supportive therapy could rapidly be discontinued. Both infants were relatively more mature and of greater birthweight than the group as a whole, and no infant of less than 30 weeks' gestation and 1400 g birthweight responded to indomethacin therapy. In the series of Friedman *et al.* (1976) all infants were over 1050 g birthweight, with an average birthweight of 1500 g, and so comparable with the 2 infants successfully treated in this series. Heymann *et al.* (1976) included several infants of below 1000 g in their group of successfully treated infants, but full details of infants in a more extensive study are not available (Heymann and Rudolph, 1977).

The time of administration of indomethacin may be important, as postnatal age and the duration of patency of the ductus may alter its response. We gave the drug relatively late, at between 11 and 28 days after the first clinical signs of the ductus appeared, at a postnatal age of 15 to 32 days. This is considerably later than the time of administration in other series such as that of Heymann *et al.* (1976). When observed at operation, the ducts that failed to close were of large diameter and thin walled, and it was not difficult to attribute the failure of closure to lack of muscular tissue in the duct wall. It is not possible to say for certain whether this was an acquired feature, but it does seem probable.

In conclusion, it seems that indomethacin may not prove useful in the treatment of very low birthweight infants with persistent ductus arteriosus, at

least at a late stage of the illness. In larger infants who develop cardiorespiratory failure secondary to persistent ductus arteriosus, a trial of indomethacin therapy may avoid the necessity of surgical ligation.

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