Paracetamol could be useful in the treatment of patent ductus arteriosus in the very-low-birth-weight infant

El paracetamol podría ser útil en el tratamiento del ductus arterioso persistente en el recién nacido de muy bajo peso

Dear Editor,

Patent ductus arteriosus (PDA) is frequently found in preterm newborns and its incidence increases with lower gestational age (GA), rising up to 60% in neonates of gestational ages 26 weeks and less. Clinically, it is associated with an increase in morbidity and mortality, including pulmonary oedema and haemorrhage, intraventricular haemorrhage (IVH), necrotising enterocolitis (NEC), bronchopulmonary dysplasia (BPD) and retinopathy of prematurity. The treatment of PDA includes fluid restriction, diuretics, nonselective cyclooxygenase (COX) inhibitors (indomethacin or ibuprofen) and, if all these fail, surgical closure. Recently, several authors have proposed the use of paracetamol for pharmacological closure of PDA if traditional medications fail or are contraindicated. As far as we know, there is no evidence on the use of paracetamol for this purpose in extremely preterm newborns in Spain. We present the cases of two patients with haemodynamically significant ductus (hsPDA) with contraindications for the administration of ibuprofen in which we tried alternative treatment with paracetamol before surgical closure.

Cases (Table 1)

1. Twin, female, second-born at 26^{0-7} weeks of GA with a birth weight of 720 g. Prenatal corticosteroids administered. Delivery by urgent caesarean section due to placenta praevia. Apgar score: 6/8. Noninvasive ventilation until 14 h of life, when intubation and surfactant administration were required, with good response. Reintubation 12 h later due to clinical deterioration and NEC. Two days later a hsPDA, anaemia and thrombocytopenia were detected. Consent was obtained from parents and treatment with intravenous (IV) paracetamol initiated. A control echocardiogram showed a closed ductus and normal haemodynamic parameters. Normal liver function. The patient evolved favourably and she was discharged at a postnatal age of 72 days.

2. Neonate, female, born at 23^{5-7} weeks of GA with a birth weight of 690 g. Chorioamnionitis. Prenatal corticosteroids (partial course). Vaginal delivery with cephalic presentation. Apgar score: 3/5. Intubated and given a dose of surfactant at birth. Mechanical ventilation and vasoactive medication since admission. On day 6, a hsPDA was diagnosed. Intravenous ibuprofen was initiated (one dose) and, with the verbal

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Table 1  Characteristics of patient ductus arteriosus at initiation of treatment and outcomes.

<table>
<thead>
<tr>
<th>Age at initiation of paracetamol</th>
<th>Outcome</th>
<th>Dose and duration of paracetamol</th>
<th>Contraindication for ibuprofen</th>
<th>Reverse diastolic flow ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>3rd day</td>
<td>Initial improvement</td>
<td>15 mg/kg/6 h × 48 h</td>
<td>No</td>
<td>2</td>
</tr>
<tr>
<td>7th day</td>
<td>Reopening</td>
<td>15 mg/kg/6 h × 72 h*</td>
<td>1 dose</td>
<td>1.9</td>
</tr>
<tr>
<td>14th day</td>
<td>Surgical closure</td>
<td>7.5 mg/kg/6 h × 48 h</td>
<td>Yes</td>
<td>2.3</td>
</tr>
</tbody>
</table>

* hsPDA persistence up to 2 weeks after birth.
consent of parents, switched to IV paracetamol due
to thrombocytopena and grade III IVH. The follow-up
echocardiogram (9th day) showed a small and haemo-
dynamically non-significant ductus arteriosus. The PDA
reopened at 11 days. Surgical closure was performed
the next day with poor outcome: abdominal distension,
septic appearance. The infant died 2 days post surgery.

Approximately three years ago, Hammerman et al²
published their initial experience with pharmacological closure
of PDA with oral paracetamol in 5 patients. In the index
patient, a newborn with 26 weeks of GA, paracetamol was
administered for a different indication at 2¹/₂ weeks of life
and it was observed that a hsPDA that had not responded to
two courses of ibuprofen had suddenly closed two days later.
Following this, another four neonates of 26–29 weeks of
GA in whom treatment with ibuprofen was contraindicated
or had failed were treated with paracetamol. All patients
showed either closure or a significant reduction in the size
of the ductus 48h after administration of paracetamol, and
full closure in one week. On the basis of this first experience,
other authors have used oral or intravenous paracetamol
to treat PDA in small series of patients. A review of these
studies has been recently published by Allegaert et al.³

The main concern raised by these studies has to do with
the lack of data on the pharmacokinetics and pharmacody-
namics of paracetamol in extremely preterm newborns and
the safety of its use in this population. There is also con-
siderable controversy regarding the dosage used, which is
double the dose used for analgesia in term newborns. The
mechanism of action of paracetamol is not fully understood
either, and in many of the published cases its use followed
the administration and failure of ibuprofen, so it is not pos-
tive to know whether there was a synergistic effect between
the two medications.

In the only randomised study conducted to date,⁴ 80
patients completed the course of treatment. The efficacy in
the pharmacological closure of PDA was similar for ibupro-
fen (77.5%) and paracetamol (72.5%) administered by the
oral route, and both drugs proved to be safe.⁴ These are
relevant findings, since COX inhibitors, despite having a suc-
cess rate of 70–85%, are not free from side effects, such as,
oliguria, gastrointestinal perforations, impaired platelet
aggregation, hyperbilirubinaemia, etc. Ibuprofen has also
been associated with an increased risk of BPD.⁵

In summary, although further prospective, controlled
and appropriately designed studies are needed to establish the
safety, efficacy and optimal dosage of paracetamol for the
treatment of PDA in extremely preterm infants, these last
experiences appear promising, at least in cases where tradi-
tional drugs fail or are contraindicated, and when avoiding
surgery is deemed reasonable.

References

   JA, Figueras Aloy J, Grupo SEN1500. Morbimortalidad en recién
   nacidos al límite de la viabilidad en España: estudio de base
2. Hammerman C, Bin-Nun A, Markovitch E, Schimmel MS, Kaplan
   M, Fink D. Ductal closure with paracetamol: a surprising new
   to induce ductus arteriosus closure: is it valid? Arch Dis Child.
   Oral paracetamol versus oral ibuprofen in the management of
   patent ductus arteriosus in preterm infants: a randomized con-
   meta-analysis of indomethacin versus ibuprofen versus placebo
   for PDA in preterm infants. Arch Dis Child Fetal Neonatal Ed.

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Obesity in Oviedo: Prevalence and time trends from 1992 to 2012²,+++  
Obesidad en Oviedo: prevalencia y tendencias
temporales de 1992 a 2012

Dear Editor,

Spain has one of the highest prevalences of childhood overweight and obesity in Europe. The frequency of excess

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weight has increased considerably between 1985 and 2000, although it seems to have stabilised in the past 10 years.¹

In order to fight this emerging epidemic, we need to mon-
tor the secular trends of obesity by means of population studies or surveys. This surveillance must be done in refer-
ce to standardised consensus definitions of terms such as obesity, overweight and normal weight specific for age and sex.²

We analysed the trends in overweight and obesity in chil-
dren 5–14 years of age over three sequential time intervals
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