Poor Formulation Information in Published Pediatric Drug Trials

Joseph F. Standing, MPharm, MRPharmS*‡; Zahra F. Khaki*; and Ian C. K. Wong, MSc, PhD, MRPharmS*§§

ABSTRACT. **Objective.** The International Conference on Harmonisation Steering Committee recommends that appropriate formulations be used in pediatric drug trials. However, a lack of formulation research and/or economic constraints means that appropriate formulations are not always used. It is important for investigators who report the results of pediatric drug trials to provide sufficient information on the formulation and method of administration to ensure that the results can be reproduced in other clinical studies (reliability) and, more important, implemented in clinical practice (validity). The objective of this study was to evaluate whether pediatric formulation information was adequately reported in recent published trials of oral medicines that included children who were younger than 12 years.

**Methods.** Studies that were published between July 2002 and June 2004 in 10 highly cited journals (5 pediatric and 5 general medicine) were hand-searched and data were extracted independently by 2 reviewers according to a protocol. Papers that reported oral medication studies that included children who were younger than 12 years were classified as containing adequate, some, or no information on drug formulation.

**Results.** Of 3992 papers reviewed, 76 fulfilled the inclusion criteria. Only 28 (37%) gave adequate information for the study to be reproduced accurately, and 20 (26%) did not state the formulation used. When the formulation was reported, only 37 (49%) studies used a pediatric formulation (liquid, chewable tablet, granules). No significant differences between pediatric and general medical journals were seen, and no single journal consistently met the criteria for adequate information.

**Conclusion.** Highly cited journals seem to permit inadequate formulation information in pediatric drug trials that they publish, impairing their validity and reliability. Authors should provide full formulation information in all pediatric clinical trial reports. *Pediatrics* 2005; 116:e559–e562. URL: www.pediatrics.org/cgi/doi/10.1542/peds.2005-0327; clinical trial, literature review, pediatrics, child (under 12 years), dosage forms, pharmaceutical preparations.

Many children who are younger than 12 years are unable to swallow tablets whole even when given specific training.1 Despite this, children are often given tablets or capsules because of a lack of appropriate pediatric formulations.2 Splitting tablets can cause dose inaccuracies.3,4 Crushing or splitting some tablets, or opening capsules, destroys their release properties3 and can impair bioavailability as a result of chemical instability at varying gastrointestinal pHs. Although the chemical stability of matrix-based tablets may not be affected by crushing,3 the resulting powder is often mixed with food or beverages, potentially affecting drug absorption.5 For dosing accuracy and patient compliance, the International Conference on Harmonisation Steering Committee recommends that appropriate formulations be used in pediatric drug trials.6 Unfortunately, because of a lack of formulation research and/or economic constraints, crushed tablets are often used instead of appropriate liquid formulations in pediatric drug trials. In these situations, subsequent pharmacokinetic studies need to be conducted to demonstrate that this method of administration adequately delivers the drug; otherwise, such trials lack validity and reliability.7 A concept paper entitled “Guidance on Formulations of Choice for the Pediatric Population” produced by the European Medicines Agency suggested that it is necessary to identify the gaps in our knowledge that require additional research on pediatric formulations.8 Published drug trials, particularly in highly cited journals, are important sources of information to inform research and disseminate knowledge to pediatric health professionals.9 For applicability in clinical practice, it is essential that detailed information on drug formulation and administration be provided, especially when the medicine is unlicensed. Systematic review of published drug trials in highly cited journals provides an appropriate starting point to identify evidence gaps in pediatric formulations that are used in clinical trials. Our objective was to evaluate whether pediatric formulation information was reported adequately in recent published trials of oral medicines that included children who were younger than 12 years.

**METHODS**

We hypothesized that pediatric clinical drug trials that are reported in highly cited journals would describe full information
on the drug formulation used. The 5 most cited journals in pediatrics and general and internal medicine categories were chosen; journals that were excluded contained mainly review articles or specialist areas of pediatrics. Included journals were hand-searched to identify papers that were published between July 2002 and June 2004 and reported oral medication studies that included children who were younger than 12 years. The papers were identified and analyzed independently by 2 reviewers (Z.K. and J.S.) according to a protocol. The following data were extracted: drug formulation, manufacturer, and for tablets/capsules whether there was an account of how the dose was administered. Reports were classified as containing adequate, some, or no information:

- Adequate: formulation and manufacturer stated; when formulation was a tablet/capsule, an account of whether children were able to swallow the dose whole or how dose was administered
- Some information: formulation or manufacturer stated; when formulation was a tablet/capsule, no account of whether children were able to swallow the dose whole or how dose was administered
- No information: no mention of the formulation or the manufacturer

Discrepancies were resolved by both reviewers' rereading the papers and reaching a consensus. \( \chi^2 \) was used to test the differences between pediatric and general medical journals in the proportion of articles that met the criteria for adequate information.

**RESULTS**

The 5 general medicine journals were *New England Journal of Medicine, Journal of the American Medical Association, Lancet, Annals of Internal Medicine,* and *British Medical Journal.* The 5 pediatric journals were *Pediatrics, Pediatric Research, Journal of Pediatrics, Archives of Diseases in Childhood,* and *Acta Paediatrica.* A total of 3992 papers were reviewed; 76 fulfilled the inclusion criteria. Reports were classified as containing adequate, some, or no information (Table 1). Only 46 (61%) of the papers stated the manufacturer of the medication. No significant difference between pediatric and general medical journals was observed (Pearson \( \chi^2 \) \( P = .92 \)), and no single journal consistently met the criteria for adequate information.

**DISCUSSION**

Pediatric drug formulation reporting in recent, highly cited, peer-reviewed journals was largely inadequate. Only 28 (37%) publications provided adequate information for the study to be reproduced accurately, and 20 (26%) did not state the formulation used at all. When the formulation was reported, only 37 (49%) studies used a pediatric formulation (liquid, chewable tablet, granules), suggesting that the International Conference on Harmonisation guidelines are often overlooked. That there was no significant difference in the use of an appropriate formulation between pediatric and general medical journals and that no single journal consistently met the criteria for adequate information suggest that inadequate formulation information in pediatric drug trial reports is a widespread problem.

One of the core principles in reporting any scientific research is to provide enough information for the experiment to be repeated (reliability) or trans-

**TABLE 1.** Analysis of Identified Papers

<table>
<thead>
<tr>
<th>Journal Type</th>
<th>Medicine, General and Internal, n (%; ( n = 25 ))</th>
<th>Pediatric, n (%; ( n = 51 ))</th>
<th>Total, n (%; ( n = 76 ))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formulation information</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adequate*</td>
<td>9 (36%)</td>
<td>19 (37%)</td>
<td>28 (37%)</td>
</tr>
<tr>
<td>Some information†</td>
<td>15 (60%)</td>
<td>22 (43%)</td>
<td>37 (49%)</td>
</tr>
<tr>
<td>No information‡</td>
<td>1 (4%)</td>
<td>10 (20%)</td>
<td>11 (14%)</td>
</tr>
<tr>
<td>Formulation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tablet/capsule</td>
<td>10 (40%)</td>
<td>9 (18%)</td>
<td>19 (25%)</td>
</tr>
<tr>
<td>Liquid</td>
<td>9 (36%)</td>
<td>23 (45%)</td>
<td>32 (42%)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (12%)</td>
<td>2 (4%)</td>
<td>5 (7%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>3 (12%)</td>
<td>17 (33%)</td>
<td>20 (26%)</td>
</tr>
<tr>
<td>Tablet/capsule</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Administration details§</td>
<td>1 (4%)</td>
<td>4 (8%)</td>
<td>5 (7%)</td>
</tr>
<tr>
<td>Manufacturer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stated</td>
<td>19 (76%)</td>
<td>27 (53%)</td>
<td>46 (61%)</td>
</tr>
<tr>
<td>Not stated</td>
<td>5 (20%)</td>
<td>22 (43%)</td>
<td>27 (36%)</td>
</tr>
<tr>
<td>Unclear‖</td>
<td>1 (4%)</td>
<td>2 (4%)</td>
<td>3 (4%)</td>
</tr>
</tbody>
</table>

* Formulation and manufacturer stated; when formulation was a tablet/capsule, an account of whether children were able to swallow the dose whole or how dose was administered was given.
† Formulation or manufacturer stated; when formulation was a tablet/capsule, no account of whether children were able to swallow the dose whole or how dose was administered was given.
‡ No mention of the formulation or manufacturer.
§ Account of whether children were able to swallow the dose whole or how dose was administered was given.
‖ Drug company sponsored study, but there was no direct indication that they supplied the medication.
<table>
<thead>
<tr>
<th>Age of Patients, y</th>
<th>Drug</th>
<th>No. of Patients in Study</th>
<th>Administration Details Provided</th>
<th>Formulation</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (neonates)</td>
<td>Levothyroxine</td>
<td>47</td>
<td>Yes</td>
<td>Tablets mixed with water; 37.5-μg, 62.5-μg treatment arms used half-tablets</td>
<td></td>
</tr>
<tr>
<td>0 (neonates)</td>
<td>Vitamin A</td>
<td>11619</td>
<td>No</td>
<td>Did not state how capsules were administered</td>
<td></td>
</tr>
<tr>
<td>0.23–0.31</td>
<td>Amodiaquine</td>
<td>291</td>
<td>Yes</td>
<td>Tablets crushed and suspended in water</td>
<td>Amodiaquine sparingly soluble in water, no suspending agent used, 5 mg/kg or 10 mg/kg measured by spoon; accurate dosing very unlikely</td>
</tr>
<tr>
<td>0.25–1</td>
<td>Omeprazole</td>
<td>30</td>
<td>Yes</td>
<td>Microsphere-containing capsules</td>
<td>Capsules emptied into teaspoon of “applesauce”: constituents and chemical properties (pH) will differ between “applesauce” manufacturers</td>
</tr>
<tr>
<td>0.5–16</td>
<td>Nelfinavir</td>
<td>193</td>
<td>Yes</td>
<td>Tablets or powder</td>
<td>&lt;25-kg group: 6 of 15 could swallow tablets; others given powder. 25-kg group: 28 of 30 swallowed tablets; others given powder.</td>
</tr>
<tr>
<td>0.5–16</td>
<td>Warfarin</td>
<td>8</td>
<td>No</td>
<td>Tablets</td>
<td>0.3-mg/kg dose rounded to nearest whole tablet; no information on whether patients could swallow dose whole</td>
</tr>
<tr>
<td>1–5</td>
<td>Prednisolone</td>
<td>217</td>
<td>No</td>
<td>Capsules</td>
<td>No information on whether capsules opened or swallowed whole</td>
</tr>
<tr>
<td>1–10</td>
<td>Chlorproguanil-dapsone</td>
<td>1850</td>
<td>Yes</td>
<td>Tablets</td>
<td>No information on how tablets administered; author states dose accuracy is greater with tablets than liquids?</td>
</tr>
<tr>
<td>2–13</td>
<td>Efavirenz</td>
<td>17</td>
<td>No</td>
<td>Capsules</td>
<td>One patient unable to swallow capsule; was given the dose by opening the capsule and mixing with “grape jelly”</td>
</tr>
<tr>
<td>3–18</td>
<td>Olpadronate</td>
<td>34</td>
<td>No</td>
<td>E/C tablets</td>
<td>No information on whether children were able to swallow the dose whole; important as crushing will compromise enteric coating</td>
</tr>
<tr>
<td>3–40</td>
<td>Nicotinamide</td>
<td>552</td>
<td>No</td>
<td>M/R tablets</td>
<td>No information on whether children were able to swallow the dose whole; important as crushing may destroy M/R properties</td>
</tr>
<tr>
<td>5–56.7</td>
<td>Itraconazole</td>
<td>39</td>
<td>No</td>
<td>Capsules</td>
<td>No information on whether included children were able to swallow the dose whole</td>
</tr>
<tr>
<td>5–67</td>
<td>Dihydroartemisinin-trimethoprim-piperaquine</td>
<td>514</td>
<td>No</td>
<td>Tablets</td>
<td>No information on whether included children were able to swallow the dose whole</td>
</tr>
<tr>
<td>6–12</td>
<td>SCI381</td>
<td>584</td>
<td>No</td>
<td>M/R capsules</td>
<td>No information on whether children were able to swallow the dose whole; important as opening capsules may destroy M/R properties</td>
</tr>
<tr>
<td>6–17</td>
<td>Sertraline</td>
<td>376</td>
<td>No</td>
<td>Tablets</td>
<td>No information on whether children were able to swallow the dose whole</td>
</tr>
<tr>
<td>6–18</td>
<td>Azithromycin</td>
<td>251</td>
<td>No</td>
<td>Tablets</td>
<td>No information on whether included children were able to swallow the dose whole</td>
</tr>
<tr>
<td>6.2–13.7</td>
<td>Vitamin D</td>
<td>20</td>
<td>No</td>
<td>Tablets</td>
<td>No information on whether children were able to swallow the dose whole</td>
</tr>
<tr>
<td>9–17</td>
<td>Dimethyl glycine</td>
<td>5</td>
<td>No</td>
<td>Capsules</td>
<td>No information on whether children were able to swallow the dose whole</td>
</tr>
<tr>
<td>13.6 ± 2.6</td>
<td>Folic acid</td>
<td>36</td>
<td>No</td>
<td>Tablets</td>
<td>No information on whether children were able to swallow the dose whole</td>
</tr>
</tbody>
</table>

E/C indicates enteric coated; M/R, modified release.
ferred into clinical practice. The most surprising re-
sult of this study was that highly cited journals did
not routinely state the form, manufacturer, and ad-
ministration details of drugs in drug trials that in-
cluded children. When this information is not pro-
vided, the reliability of any findings is brought into
question. When the formulation was stated, tablets or cap-
sules were often used without giving any adminis-
tration details (Table 2). If details of how the drug
was administered are given, then pediatricians and
pediatric pharmacists will know that by repeating
this method, similar results can be expected. How-
ever, that none of the papers that described tablet
 crushing gave any supporting pharmacokinetic data
suggests that authors are unaware of the potential
impact on bioavailability. The outcomes in such
studies lack validity unless data are supplied to
show that adequate drug levels are achieved.

The use of excipients (ingredients used to promote
physical/chemical/microbial stability and palatabil-
ity) was not addressed specifically in our study, al-
though it is widely recognized that some can be
harmful when given to children. It therefore is
important that the manufacturer be stated so that the
formulation and its excipients can be identified. This
may facilitate the explanation of any unexpected ad-
verse reactions, and pediatric pharmacists will know
where to obtain the product that produced the trial
results. Obtaining the same formulation is especially
important when the medicine is unlicensed, as unlike
licensed preparations, unlicensed preparations are
not tested for bioequivalence, meaning that bioavail-
ability can and does differ between different formu-
lations of the same drug. It therefore is of some
concern that fewer than two thirds of analyzed pa-
pers gave the drug manufacturer.

Many published drug trials that included children
had doubtful reliability and validity because the
amount of drug absorbed was neither tested nor
reported. When such studies are published in highly
cited journals, it perpetuates the myth that children
come to no harm when inappropriate formulations
are used. This review should prompt authors and
journal editors to provide full formulation informa-
tion in future pediatric drug trials.

CONCLUSIONS

Highly cited journals often provide inadequate
formulation information in pediatric drug trials that
they publish, impairing their validity and reliability.
The reporting of formulation information needs to be
improved in future drug trials that include children.

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