Prescription of drugs not appropriate for children in a Pediatric Intensive Care Unit

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Abstract

Objective: To assess the extent of use of drugs not appropriate for children in prescriptions issued in a tertiary pediatric intensive care unit (PICU), according to FDA standards.

Methods: Observational cross-sectional study. The prescriptions issued to all patients admitted to the PICU at Hospital de Clínicas de Porto Alegre, Brazil, over a six-week period were assessed. Patients’ age, sex, weight, prior disease, reason for admission to the PICU and pediatric index of mortality (PIM) were recorded, as were all drugs prescribed, their indications, presentations, doses, frequencies and means of administration. Adequacy for prescription of drugs in three pediatric age ranges was defined according to USA Food and Drug Administration (FDA) approval classification, based on the USP DI 2001 drug reference database.

Results: Data were obtained in the months of July and August 2002, on different days, for six consecutive weeks, based on prescriptions issued to 51 patients in 54 admissions to the PICU. Median patient age was 10.5 months; 61% of patients were male. Two thirds of patients (65%) presented prior disease. 87% of admissions were due to clinical reasons, of which 57% were respiratory complaints. A total of 747 prescription items were registered, with prevalence of 10.5% for non-approved uses and 49.5% for off-label uses. No statistically significant difference was found in the distribution of prevalence of irregular prescription either by the three age ranges or by level of severity of disease at admission (according to PIM risk categories).

Conclusion: The high prevalence of prescription of drugs not appropriate for children confirms, in the Brazilian context, the inadequate and inadvertent use of drugs either not approved or off-label for PICU use. This demonstrates the need to encourage further studies on the quality, efficacy and safety of drugs for pediatric use.


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Manuscript received Feb 27 2003, accepted for publication Jun 17 2003.
As a result of probable ethical limitations related to drug research in children during past decades, more than 50% of the drugs prescribed for pediatric patients in the USA are unlicensed or “off-label” for use with children. In our environment it is suspected that the rate of usage of drugs which are “not appropriate for children” with pediatric patients is also elevated, especially in hospitals.

The concept of drugs which are “not appropriate for children” involves a variety of conditions, and results in an overlapping of related nomenclatures. The references consulted provide grounds for concluding that the term unlicensed covers drugs which have not been approved for use in general, have not been approved for use with children, are contra-indicated for use with children, are manufactured or modified at the hospital or for which there is no specific dosage for children. The term off label refers to drugs which are prescribed in a different manner to that described in their instructions, in terms of age group, dosage, frequency, presentation, route of administration or indications for use with children.

In some countries there are reports of elevated prevalence of the use of unlicensed or off-label drugs with children, equally at pediatric surgeries, internment units and pediatric intensive care units, in an unjustifiable manner or even due to ignorance of these peculiarities on the part of those prescribing.

Often the prescription and use of these drugs with pediatric patients are based on extrapolations from the doses and/or modifications of formulae used with adults, completely ignoring the differences between children and adults, and subject patients risks of unproven efficacy and unevaluated side-effects.

It is more than 30 years since Shirkey recognized the existence of a serious dilemma in the standardization of pediatric drugs, calling them “therapeutic orphans”. During the last decade in particular, the Food and Drug Administration - FDA and the American Academy of Pediatrics’ Committee on Drugs, both North American and both internationally recognized, have made innumerable initiatives attempting to stimulate research approval and standardization of drugs for use with children.

The objective of this study is to evaluate the extent of the use of drugs which are “not appropriate for children” in the prescriptions at a tertiary Pediatric Intensive Care Unit (PICU) according to standards established by the FDA.

Patients and Methods

This was an observational, cross-section study based on evaluation of prescriptions made for patients admitted to the PICU at the Hospital de Clínicas in Porto Alegre, during a six-week period where a different day was monitored each week. The population studied comprised all patients interned at the PICU on each of the monitored days throughout the study period. Patients who remained in ICU for prolonged periods or whose prescriptions had already been evaluated during previous weeks were excluded. Prescriptions of crystalloid solutions, parenteral nutrition, and blood products and oxygen were not considered.

The variables assessed included age, sex, weight, body surface area, previous morbid diseases, the reason for admission to the PICU, pediatric index of mortality (PIM), all prescribed drugs and the indications for their prescription along with their respective presentations, dosages, frequencies and routes of administration.

The criteria adopted to determine if prescriptions were appropriate were based upon FDA approval classifications, using the USP DI 2001 catalogue as a reference. A Brazilian standard was not employed because ANVISA (National Agency for Sanitary Vigilance - Agência Nacional de Vigilância Sanitária), which regulates drugs nationally does not have a similar catalogue. Three classes of drug were defined: (a) “approved” - drugs that have been approved for use with children, including all drugs approved for use with pediatric patients; (b) unlicensed - drugs which have not been approved for use with children, including drugs that have not been approved in any way, have not been approved for use with children, are contra-indicated for use with children or have no specified dosage for children; (c) off-label - drugs that have not been standardized for use with children (in terms of patient age, daily dose, number of doses per day, route of administration, presentation or indications as prescribed), thus including drugs prescribed in a different manner to that advised by pharmacological data compendia in terms of age, daily dosage, number of doses per day, presentation, route of administration or indications for use with children.

Age groups that were considered as pediatric were: (a) from 1 to 24 months; (b) from 2 to 12 years and, (c) from 12 to 18 years. The PIM score is one of the most frequently used severity indices in Pediatric ICUs, taking into account just eight, easily measured variables, and having good predictive power.

The study was approved by the Ethics and Research Commission of the HCPA. The requirement for informed consent was waived and the authors signed an undertaking to preserve confidentiality and to use the data collected solely for purposes of scientific publication.

Data was tabulated using an Excel spreadsheet. A descriptive analysis of the results was performed as was a comparison of prevalence across groups according to their characteristics using the chi-square test at a significance level of 0.05.

Results

The data for the study was collected during the months of July and August 2002, on different days of the week for six weeks consecutively. It was based upon the prescriptions made for 51 patients over 54 admissions to the PICU. The age of the patients varied from 1 month to 13 years, giving...
a median of 10.5 months, with 61% being male. Two-thirds of the patients (65%) presented previous conditions and 87% of admissions were for clinical reasons: 57% respiratory, 11% neurological, 11% gastrointestinal, 7% cardiovascular, 7% renal and 7% for other reasons.

Seven hundred and forty-seven prescription items were recorded, giving an average of 14 items per patient. Observed prevalence across all prescribed items were: 40% approved drugs, 10.5% unlicensed drugs and 49.5% off-label drugs. All of the 51 patients were prescribed at least one off-label drug and 88% of them at least one unlicensed drug.

The distribution of prescription prevalence by patient age group for the three classes of drug is shown in Table 1. There are no statistical differences between them. Prescriptions were not evaluated when made for patients less than one month old.

**Table 1 - Distribution of prescription prevalence by patient age group for the three classes of drug**

<table>
<thead>
<tr>
<th>Drug class</th>
<th>1-24 months (n = 31)</th>
<th>2-12 years (n = 17)</th>
<th>&gt; 12 years (n = 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approved</td>
<td>204 (47.0)</td>
<td>112 (44.0)</td>
<td>26 (42.5)</td>
</tr>
<tr>
<td>Unlicensed</td>
<td>55 (13.0)</td>
<td>26 (10.0)</td>
<td>8 (13.0)</td>
</tr>
<tr>
<td>Off-label</td>
<td>173 (40.0)</td>
<td>116 (46.0)</td>
<td>27 (44.5)</td>
</tr>
<tr>
<td>Total items</td>
<td>432</td>
<td>254</td>
<td>61</td>
</tr>
</tbody>
</table>

(\(\chi^2 = 2.65; \text{ gl} = 4; p = 0.616\)).

The distribution of prevalence by patient severity index at admission, according to PIM risk categories, for the three drug classes is shown in Table 2. There are no statistical differences.

The 747 prescription items were made up of 131 different drugs or pharmacological presentations. The most frequently occurring drugs are listed in Table 3.

The “not appropriate for use with children” drugs are listed in Table 4. The most common form of that use was related to dosage, in 50% of the patients, followed by the frequency of administration, in 28% of the patients.

**Discussion**

In accordance with modern drug evaluation directives, the acquisition of licensing for a given drug or of standardization for a specific indication or a specific patient age group requires exhaustive, time-consuming research. Possibly due to commercial reasons, and, maybe as a result of not having been sufficiently pressurized or stimulated by the official drug control authorities during recent decades, the pharmaceutical industry has not been committed to the performance of clinical trials for efficacy and safety with pediatric groups in order to obtain licenses to offer its products for this segment.

Studies evaluating the prevalence of the prescription of drugs which are “not appropriate for children” within PICUs are rare. Jong et al., based on an evaluation of 2,139 courses of medication prescribed to 238 children at a Dutch PICU, found prevalence of 48% for unlicensed drugs and 18% for off-label drugs with children. Turner et al., with the same type of population, evaluated 862 prescription items, and demonstrated a unlicensed or off-label drug prevalence of 31% without making distinctions. The current study evaluated 747 prescription items and revealed a 10.5% prevalence of unlicensed drugs and a 49.5% off-label drug prevalence.

These elevated prevalence rates for drugs which are “not appropriate for children” are not exclusive to PICUs. Highly expressive prevalence rates have also been observed at other pediatric care locations. McIntyre et al., investigating general pediatric practice, found a prevalence of 0.3% for unlicensed drugs and 10.5% for off-label. Numbers which could have been higher if use that was non-standard for the indications had been investigated. Chalumeau et al., studying pediatric clinics, found that 4% of prescriptions were for unlicensed drugs and 29% for off-label (65% because of age, 23% indications, 10% dose and 7% route), with 6% being off-label for more than one reason. Turner et al. evaluated 2,013 prescription items given to 609 patients at clinical and surgical pediatric wards, observing 7% unlicensed drug usage and 18% for off-label.5

With respect of the age group of the patients in the current study, we found a higher prevalence of “not appropriate for children” drugs within the over-twelve age group (61 items for three patients), although the number of patients was low within this age group. It is possible that increasing the sample size for this age group may have altered this difference. McIntyre et al. did not find any significant difference in the prevalence of unlicensed or off-label drugs between the age groups evaluated. However, in the study by Chalumeau et al. there was a greater prevalence of off-label drugs (70%) being used with neonates, probably due to the lack of pharmaceuticals appropriately licensed for this age group or of more flexible pediatric formulations.

None of the studies consulted classified the prevalence of the prescription of drugs that are “not appropriate for use with children” in terms of patient severity. Conceivably, at PICUs, severity could be considered to justify the prescription and use of unlicensed or off-label drugs, calling the risk-benefit ratio in defense. Our study, while it did not evaluate the reasons for which professionals may prescribe drugs that are “not appropriate for use with children”, the unlicensed and off-label prescription items were evenly
distributed across the various severity groups (according to PIM risk categories) (Table 2), although the patient sample was small in the two groups containing the most serious cases (51 items in three patients and 94 items in five patients).

Studies by Turner et al.\textsuperscript{6} and Gill et al.\textsuperscript{18} into adverse events caused by drugs to interned pediatric patients, show that certain of the drugs which we have classified as unlicensed or off-label (Table 4) may be the agents responsible for the adverse reactions they observed.

It may be surprising that drugs which are frequently used in pediatric prescriptions have been classified as off-label (e.g., Paracetamol) or as unlicensed (e.g., Dipyrone). In the case of Paracetamol, the formulation as prescribed and employed at the time of study presented a low viscosity resulting in 1 milliliter being equal to 30 drops whereas in the case of the best known product on the market 1 milliliter is between 16 and 20 drops. The doctors at the unit were unaware of this peculiarity of the product dispensed by the pharmacy and were prescribing as though there were 20 drops per milliliter, leading to under-prescription of up to 50% less than intended. In this case the prescription of Paracetamol was classified as being off-label for presentation.

### Table 2 - Distribution of prevalence by patient severity index at admission, according to PIM risk categories, for the three drug classes

<table>
<thead>
<tr>
<th>PIM risk categories</th>
<th>&lt; 1% (n=12)</th>
<th>1-4.99% (n=17)</th>
<th>5-14.99% (n=13)</th>
<th>15-29.99% (n=3)</th>
<th>&gt; 30% (n=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approved</td>
<td>54 (42.0)</td>
<td>133 (47.0)</td>
<td>90 (48.0)</td>
<td>25 (49.0)</td>
<td>40 (43.0)</td>
</tr>
<tr>
<td>Unlicensed</td>
<td>23 (18.0)</td>
<td>32 (11.0)</td>
<td>19 (10.0)</td>
<td>2 (4.0)</td>
<td>13 (14.0)</td>
</tr>
<tr>
<td>Off-label</td>
<td>52 (40.5)</td>
<td>120 (42.0)</td>
<td>79 (42.0)</td>
<td>24 (47.0)</td>
<td>41 (44.0)</td>
</tr>
<tr>
<td>Total items prescribed</td>
<td>129</td>
<td>285</td>
<td>188</td>
<td>51</td>
<td>94</td>
</tr>
</tbody>
</table>

$\chi^2 = 8.87, \text{ gl } 8, p = 0.353$.

PIM: pediatric index of mortality, n: number of patients in each risk category, () percentage values based on the items prescribed according to the patients’ risk category.

### Table 3 - Drugs most frequently prescribed at PICU in the sample studied

<table>
<thead>
<tr>
<th>Drug</th>
<th>n. of items prescribed</th>
<th>% *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midazolam</td>
<td>56</td>
<td>7.5</td>
</tr>
<tr>
<td>Paracetamol</td>
<td>46</td>
<td>6.0</td>
</tr>
<tr>
<td>Dipyrone</td>
<td>42</td>
<td>5.5</td>
</tr>
<tr>
<td>Fentanyl and Ranitidine</td>
<td>35</td>
<td>4.5</td>
</tr>
<tr>
<td>Furosemide, Diazepan &amp; Vancomycin</td>
<td>25</td>
<td>3.5</td>
</tr>
<tr>
<td>Chloral hydrate</td>
<td>20</td>
<td>2.5</td>
</tr>
<tr>
<td>Hydrocortisone, Salbutamol and Quetamina</td>
<td>17</td>
<td>2.0</td>
</tr>
<tr>
<td>Dopamine, Cefepime, Metoclopramide and Calcium gluconate</td>
<td>16</td>
<td>2.0</td>
</tr>
<tr>
<td>Phenytoin and Potassium Chlorate</td>
<td>12</td>
<td>1.5</td>
</tr>
</tbody>
</table>

* percentage based on total number of items prescribed.

### Table 4 - Drugs most frequently prescribed at PICU in the sample studied (according to class)

<table>
<thead>
<tr>
<th>Drugs class (prevalence)</th>
<th>Most frequent drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approved (40.0%)</td>
<td>Midazolam, Ranitidine, Vancomycin</td>
</tr>
<tr>
<td>Unlicensed (10.5%)</td>
<td>Dipyrone, Ampicillin+ Sulbactam, Omeprazol</td>
</tr>
<tr>
<td>Off-label for dosage (20.0%)</td>
<td>Furosemide</td>
</tr>
<tr>
<td>Off-label for frequency (14.0%)</td>
<td>Furosemide, Metoclopramide</td>
</tr>
<tr>
<td>Off-label for age (5.0%)</td>
<td>Fentanyl, Salbutamol</td>
</tr>
<tr>
<td>Off-label for presentation (5.0%)</td>
<td>Paracetamol</td>
</tr>
<tr>
<td>Off-label for route (3.0%)</td>
<td>Phenytoin, Dexamethasone, Salbutamol</td>
</tr>
<tr>
<td>Off-label for indication (2.5%)</td>
<td>Furosemide, Ondansetron, Topical mineral oil</td>
</tr>
</tbody>
</table>
dose for children, even though its use within this segment is widespread; (c) for frequency, intravenous Metoclopramide is indicated for children as a single, allowing for repetition when necessary, which is far from the fixed intervals of 6 to 12 hours at which it is frequently employed; (d) for route, intravenous Phenytoin is only indicated for the treatment of epileptic states, however it is used for continuous anticonvulsive therapy with patients with vein access; (e) for indication, Ondansetron is recommended only for vomiting related to chemotherapy and post-op and not as an alternative for vomiting due to other causes, as it has been prescribed.

Turner et al. observed that off-label drug prescriptions are more frequent that unlicensed drug prescriptions in the pediatric segment. In this study the greatest off-label drug prescription prevalence occurred with respect of dose, in common with other studies. This type of prescription is probably the result of a lack of information on the part of those prescribing, which agrees with the study by Chalumeau et al. We imagine that this also occurs as a result of the available pharmacological presentations, which make the prescription of precise doses difficult.

The prescription of off-label drugs for children is often necessary. This is related to the fact that a large number of drugs currently prescribed do not have information on the label or information leaflet about doses for children. Those prescribing are thus confronted with dilemma of either prescribing drugs in the absence of sufficient information to guarantee safety or of leaving their patients without potentially effective, and sometimes life-saving, treatment. In this context, basing their decisions on the medical literature, previous experience or the opinion of specialists may be appropriate and gives a foundation to prescribing professionals. The directions which accompany drugs, while being a significant source of information about the drug and its use, is not the defining factor in appropriate prescribing and much less a substitute for medical judgement.

When the question of standardization for age is considered, the enormous variations in children’s weight from birth to 12 years of age must be taken into account. Standard practice is to adjust the dosage according to the size of the child, which leads to many prescriptions being different to the directions recommended by licences. Furthermore, often no alternative licensed drug is found for certain situations, which suggests that the origin of the problem is not the not appropriate use of the drugs by professionals, but an inadequate evaluation during the drug registration process.

The limitations of this study could be related to eventual distortions of classification, since only one, internationally recognized, source was consulted - the “USP DI 2001. Drug Information for the Health Care Professional” catalogue. Similarly, studies of this type, which are intended to provide some sort of quality control over the care afforded to patients, no matter how secret they are intended to be, never pass unnoticed by the professionals working at the unit. Thus there may be changes in prescriber behavior during the performance of the study, causing a selection bias, also mentioned by Chalumeau et al. Nevertheless, if this had occurred it could only have reduced the severity of the situation as presented. Additionally, the study traces the profile of complaints during the winter in our locale, evaluating the prescription of items which predominate during only one season and not during the rest of the year.

The FDA regulates the production, approval and marketing of drugs, not their use by doctors. New uses, dosages and indications are unlicensed by the FDA until substantial evidence has been obtained about their safety and efficacy for a given indication or age group. This process can take years or may never occur, because there is little incentive for the pharmaceutical industry to conduct trials and submit information on new uses for drugs with pediatric patients. The most frequently reported explanations for the lack of results from pediatric studies for the approval of new drugs or for new pediatric indications for already existing drugs have been: the excessive cost of trials when compared with the size of the potential market among pediatric patients; difficulty finding a sufficient number of patients to participate in studies which demonstrate statistical significance; the prolonged period over which a pediatric trial may have to be performed, thus increasing the time taken to approve important new drugs; the complexity of the ethical factors associated with research into children; the scarcity of qualified pediatric pharmacological investigators, and the fact that doctors who treat children prescribe the drugs which are available on the market without concerning themselves with the performance of studies of this nature.

In Brazil, ANVISA, an authority linked to the Health Ministry, is charged with the protection of the health of the public by means of sanitary control over the production and sale of products and services which are subject to sanitary vigilance, including drugs. One of its competencies is the authorization of the registration of drugs within national territory, based upon data and information from internationally recognized regulatory authorities. According to a survey performed by the Consumers’ Association in Britain, few drug companies are interested in performing clinical trials with children spontaneously. Changes to government legislation on drug licensing may be an alternative which would guarantee that products used with children are safe and effective. Drug legislation, originally designed to protect patients and doctors from unsafe drug use has become an obstacle to drugs which are necessary to these patients being made available.

Concluding, the elevated prevalence of prescriptions of drugs which are “not appropriate for children” confirms, in our country too, the inappropriate and inadvertent use of drugs which are untested or with presentations which are not appropriate for children in PICUs. This points to a need for well-designed and controlled studies of the quality, efficacy and safety of drugs for pediatric use in general.
The performance of high-quality studies, evaluating both the efficacy and toxicity of drugs in children from different age groups and different diseased states should be stimulated. Nevertheless, the development and evaluation of drugs which are essential for newborns, infants and children requires the collaboration of pediatricians, pharmacists the pharmaceuticals industry and the sanitary regulatory authorities.

References


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