Risk and pharmacoeconomic analyses of the injectable medication process in the paediatric and neonatal intensive care units

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Abstract

Objective. To analyse safety risks in injectable medications. To assess the potential impact and pharmacoeconomic aspects of safety tools.

Design. The injectable drug process was prospectively assessed using a failure modes, effects and criticality analysis. Criticality indexes were estimated based on their likelihood of occurrence, detection probability and potential severity. The impact of 10 safety tools on the criticality index was calculated and extrapolated to all drugs injected daily. Yearly costs for a reduction in criticality by 1 point (= 1 quali) per day were estimated.

Setting. Paediatric and neonatal intensive care units in a University Hospital.

Participants. Two paediatric nurses, a neonatologist, three hospital pharmacists.

Interventions. Qualitative and quantitative risk assessment.

Main Outcome Measures. Failure modes, criticality indexes, cost-efficacy ratios.

Results. Thirty-one failure modes identified, with the mean of their entire criticality indexes totalling 4540. The most critical failure mode was microbial contamination. The following gains were predicted: 1292 quali (46 500 per day by extrapolation) from ready-to-use syringes, 1201 (72 060) by employing a clinical pharmacist, 996 (59 780) from double check by nurses and 984 (59 040) with computerized physician order entry. The best cost-efficacy ratios were obtained for a clinical pharmacist (1 quali = 0.54 euros), double check (1 quali = 0.71 euros) and ready-to-use syringes (1 quali = 0.72 euros). Computerized physician order entry showed the worst cost-efficacy ratio due to a very high investment costs (1 quali = 22.47 euros).

Conclusion. Based on our risk and pharmacoeconomic analyses, clinical pharmacy and ready-to-use syringes appear as the most promising safety tools.

Keywords: paediatrics, risk assessment, FMECA, hospital pharmacy services, cost-efficacy analysis, intensive care

Introduction

Medication errors are causing significant harm to hospitalized patients with high economic implications; the risk is particularly high in intensive care units [1]. Although medication errors and adverse drug events (ADEs) have received substantial attention in adults, relatively few published reports have addressed this issue in children. Information on paediatric medication use, particularly in neonates, is often lacking [2]. Paediatric patients need weight-based dosing, which necessitates more calculations than for adults [3]. In addition, the range of licensed medications in appropriate dosage forms is limited, thus often requiring complex dose and dilution calculations before administration. Previous studies have identified an error rate of 13–84% in hospitals when preparing and administering intravenous drugs to infants and children [4–6]. Dose calculations are a common contributor to medication errors, with a factor 10 error being among the most common
Design

A FMECA was performed by a multidisciplinary team (two specialized nurses, a neonatologist and three hospital pharmacists) [12]. The analysis focused on the entire medication process of injectables, from prescription to administration, with a special attention to preparation and administration steps.

FMECA risk analysis. A brainstorming strategy was used to determine all possible ways the injectable medication process might fail. Each team member had to write down all risks and possible failures they could envisage. These suggestions were then assembled and organized during a common discussion to become the failure modes. An Ishikawa’s diagram was built to organize them step by step (Fig. 1).

Three frequently used drugs with different characteristics were chosen as models for injectables: gentamicin for antibiotics and other common injectables; morphine for analgesics and narcotics; dopamine for vasoactive and monitored drugs. The likelihood of occurrence of each failure mode for each model drug was classified from 1 to 10, the severity of the potential effect for the patient from 1 to 9 and the probability to detect the failure from 1 to 9. The evaluation was carried out according to standardized tables, taking care to remain coherent in ranking similar events [12]. Scores were obtained by consensus quotation in the team. In particular, occurrence was supported by data from the systematic critical incident reporting of the two ICUs. The criticality index of each failure mode was calculated by multiplying the frequency, severity and detection scores, yielding a minimum of 1 and a maximum of 810. The top 10 critical failure modes were determined by ranking the mean criticality indexes of the three model drugs.

Ten tools to improve safety were chosen empirically (Table 1). Their potential benefit on the criticality indexes of the three model drugs was again assessed by the FMECA method.

The term ‘quali’ (plural: quali) was created to allow a convenient transposition from the notion of criticality to the quality gain in the medication process. One quali was defined as a reduction of the criticality index by one point. Quali for the top 10 critical failure modes were compared between the different safety tools analysed.

Generalization for economic estimate. As required in economic analyses, an extrapolation to the use of all daily injectable drugs was performed for each safety improvement tool (see Table 1), using data compiled during a large survey performed during the year 2003 in the same units [13]. On average, 7 patients with 8 drugs per day were hospitalized in the PICU and 14 patients with 3 drugs in the NICU (overall a total of 98 drugs per day). About 60 drugs were used as injectables.

Cost analysis. Cost analysis was performed from a hospital perspective. The required investment in euros per year was calculated for each tool (at the time of publication: 1 euro = 1.50 CHF = 1.43 USD = 130.90 JPY). Only direct costs were considered. Only medical supplies such as syringes, needles, in-line filters, face masks, etc. were taken into account.
for simple additional measures of asepsis, intermediate dilution, in-line filters and vials of dilution. Additional human resources were necessary for double check by nurses and clinical pharmacist. The nurse’s double-checking time at each potential failure point was estimated at 20 s [14]. The total time for all injectable drug checks was converted into euros using the local wages scale (100% salary for nurse with intermediate level of experience = 45 000 euros per year). The daily time requirements for a clinical pharmacist for both units were estimated to 50% (half-salary for pharmacist with intermediate level of experience = 40 000 euros per year). The tasks considered for the clinical pharmacist were (i) to check the correct use of drugs by nurses through specific though not systematic interventions concerning preparation (respect of concentration; of solvent; etc.) and administration (detection of physicochemical incompatibilities; check the flow rate according to concentration of the solution, etc.) and (ii) audits of the drugs stock (organization; fridge, etc.). For the CPOE, initial investment costs and maintenance costs during 1 year were estimated at 1 million euro and 300 000 euros, respectively. The estimations of initial investment and maintenance costs have been provided by the head of medical informatics’ team of the hospital. These costs are specific for a system to be used in the intensive care environment (adults and children), but cover the whole cost of the electronic patient record (not only the CPOE). For HFLA, the estimated costs included an initial investment plus the cost of aseptic preparations in the units. We estimated that 15 drugs could be provided in ready-to-use syringes (CIV AS), and we calculated the costs of development (3620 euros by drug), as well as their production cost (1.21 euros per syringe), based on our previous experience. The drug planner induced no costs [15].

Cost-efficacy analysis. The cost in euros required for an improvement of one quali per day was calculated for each safety improvement tool by dividing the investment per year by all yearly quali (extrapolation from all daily injected drugs).

Sensitivity analysis. A sensitivity analysis was performed to evaluate the influence of variations in estimated parameters on total costs (Table 1).

Results

The medication process of injectables was split up into five major steps, prescription, transcription, preparation, administration and storage. A total of 31 failure modes were determined during the brainstorming sessions (Fig. 1).
The criticality indexes calculated from the frequency, severity and detection scores estimated by the team for each failure mode are summarized in Table 2. The average sum of all criticality indexes was 4540. Among the model drugs, gentamicin totalized the greatest sum of criticality index, followed by morphine and dopamine. The most critical failure mode (mean criticality index = 432) was microbial contamination during the preparation of medicines. The top 10 critical failure modes concerned mainly preparation (5 failure modes), followed by administration (4) and transcription (1). Top failure modes for preparation were microbial contamination (432), dosage errors (343), dilution errors (312), labelling errors (224) and selection errors (171). Top failure modes for administration were physicochemical incompatibilities (330), wrong flow rate (317), selection error (208) and drug given twice (194). The failure mode during transcription was poor writing and reading (235).

**Generalization for economic estimate**

In a total of 4540 criticality points averaged between the model drugs (272 400 criticality indexes per day by extrapolation), we expected to gain 1292 quali (46 500) with CIVAS, 1201 (72 060) with a clinical pharmacist, 996 (59 780) with double check by nurses, 984 (59 040) with CPOE, 555 (23 296) with in-line filters, 457 (12 348) with vial of dilution, 408 (17 122) with HFLA, 170 (4590) with intermediate dilution, 144 (6192) with simple additional measures of asepsis and 98 (951) with the drug planner.

The differences in quali of each safety tool for the top 10 critical failure modes are shown in Fig. 2. For the most critical failure mode (microbial contamination), the expected gain in quali varied from 0% with in-line filters to 53% with double check by nurses. The expected gain in quali for the second critical failure mode (dosage errors) varied from 0% with in-line filters to 37% with double check by nurses. The expected gain in quali for the third critical failure mode (dilution errors) varied from 0% with in-line filters to 32% with double check by nurses.

**Table 1** The 10 safety tools, their associated costs, the percentage of injectable drugs injected daily affected by each safety tool, the extrapolated number used to multiply mean criticality index, and the parameters for sensitivity analysis, together with their estimated variation

<table>
<thead>
<tr>
<th>Safety tool</th>
<th>Associated costs</th>
<th>Percentage of affected injectable drugs (normalized per day)</th>
<th>Extrapolated number to multiply mean criticality index (max = 60)</th>
<th>Sensitivity analysis: parameters with estimated variations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current situation</td>
<td>No costs</td>
<td>100%</td>
<td>60</td>
<td>Free</td>
</tr>
<tr>
<td>Computerized physician order entry</td>
<td>Initial investment and maintenance</td>
<td>100%</td>
<td>60</td>
<td>−964 800 euros on mean cost per year = initial investments written off after 5 years</td>
</tr>
<tr>
<td>Double check by nurses</td>
<td>Human resources</td>
<td>100%</td>
<td>60</td>
<td>±5 s spent for a check</td>
</tr>
<tr>
<td>Clinical pharmacist</td>
<td>Human resources</td>
<td>100%</td>
<td>60</td>
<td>±10 years of experience</td>
</tr>
<tr>
<td>Ready-to-use syringes</td>
<td>Development &amp; production costs</td>
<td>60% could be prepared as ready-to-use syringes</td>
<td>36</td>
<td>±0.31 euros on price of a syringe (R &amp; D)</td>
</tr>
<tr>
<td>Vial of dilution</td>
<td>Medical supplies</td>
<td>45% concerned by a withdrawal of a small volume (&lt;0.5 ml)</td>
<td>27</td>
<td>±0.42 euros on price of a vial</td>
</tr>
<tr>
<td>Intermediate dilutions</td>
<td>Medical supplies</td>
<td>45% concerned by a withdrawal of a small volume (&lt;0.5 ml)</td>
<td>27</td>
<td>No variation</td>
</tr>
<tr>
<td>In-line filters</td>
<td>Medical supplies</td>
<td>70% administered via a central line</td>
<td>42</td>
<td>±2 in-line filters used by day (filters blocked; number of patients or central line)</td>
</tr>
<tr>
<td>Simple additional measures of asepsis</td>
<td>Medical supplies</td>
<td>72% not ready-to-use</td>
<td>42</td>
<td>No variation</td>
</tr>
<tr>
<td>Horizontal laminar airflow hood in the unit</td>
<td>Initial investment and medical supplies</td>
<td>72% not ready-to-use</td>
<td>42</td>
<td>−7236 euros on mean cost per year = initial investments written off after 5 years</td>
</tr>
<tr>
<td>Drug planner</td>
<td>No costs</td>
<td>16% administered at unusual dosing interval (e.g. every 18 h)</td>
<td>10</td>
<td>free</td>
</tr>
</tbody>
</table>

**FMECA risk analysis**

The criticality indexes calculated from the frequency, severity and detection scores estimated by the team for each failure mode are summarized in Table 2. The average sum of all criticality indexes was 4540. Among the model drugs, gentamicin totalized the greatest sum of criticality index, followed by morphine and dopamine. The most critical failure mode (mean criticality index = 432) was microbial contamination during the preparation of medicines. The top 10 critical failure modes concerned mainly preparation (5 failure modes), followed by administration (4) and transcription (1). Top failure modes for preparation were microbial contamination (432), dosage errors (343), dilution errors (312), labelling errors (224) and selection errors (171). Top failure modes for administration were physicochemical incompatibilities (330), wrong flow rate (317), selection error (208) and drug given twice (194). The failure mode during transcription was poor writing and reading (235).
critical failure mode, i.e. microbial contamination, five safety
tools allowed a gain in quali. The greatest improvement of
384 quali was obtained with CIVAS whereas intermediate
dilution was associated with a loss of quali (−72). Six safety
tools gained quali for the second most critical failure mode,
dosage errors during preparation. For the third most critical
failure mode, the wrong flow rate, almost none of the pro-
posed tools allowed a significant safety improvement.

Cost-efficacy ratio

Cost in euros per year and associated gain in quali for each
tool are represented in Fig. 3. The 10 tools are laid out in four
quadrants, according to yearly costs gained per quali and total
quali gained. Intervals were calculated with the sensitivity
analysis. The best cost-efficacy ratio were obtained for a clini-
cal pharmacist (1 quali = 0.54 euros), for double check by
nurses (1 quali = 0.71 euros) and for CIVAS (1 quali = 0.72
euros). The CPOE showed the worst cost-efficacy ratio due to
the very high investment costs (1 quali = 22.47 euros).

Discussion

Our work confirms that FMECA is a feasible tool for a
proactive assessment of the injectable medication process in
the PICU and NICU, even before the occurrence of adverse events. As most medication errors are multifactorial, an FMECA was particularly useful in that it allowed consideration of the global medication process. Such errors are difficult to study and FMECA is a novel approach to predict the most cost-effective interventions.

Figure 2 Top 10 of failures modes and comparative gain or loss of quali for each safety tool (mean CI = mean criticality index).

Figure 3 The 10 safety tools are laid out in four quadrants, according to yearly costs to gain 1 quali per day and total quali gained per day. Intervals were calculated with a sensitivity analysis.
These would then need to be tested and measured in PICUs and NICUs.

Unlike other reports, we voluntarily did not focus exclusively on prescriptions by examining also the preparation and administration steps, which are seldom investigated in the literature [16]. Prox et al. [17] for instance analysed and classified drug administration errors but did not include errors occurring during the preparation step. However, such specification appears to make sense, since errors at the administration stage have been found to be the most common ones in paediatric patients [18].

In our current work, microbiological contamination during preparation was the most critical failure mode. A similar result was found in a recently published large multi-centre audit of six European hospital departments [19]. Aseptic procedures required for the safe preparation of intravenous drugs were frequently violated by staff, often unaware of the potential harm. CIVAS offer a safe alternative to reduce microbiological contamination and dilution errors and avoid drug wastage. An earlier development of ready-to-use vancomycin syringes for our NICU was very satisfying [20]. HFLA alone was unable to significantly reduce risks of microbiological contamination as it requires qualified operators, standardized protocols and a quality control procedure to be efficient.

The difficulties encountered when preparing infusions from concentrated stock solutions in intensive care units are highlighted in the literature [21, 22]. To further improve preparation in paediatrics, the most critical step in this FMECA, we have begun studying the safest procedure with the best accuracy for solutions prepared by three different techniques: (i) small volumes withdrawn as currently, (ii) intermediate dilutions and (iii) standardized vials of dilution.

The most cost-effective way of reducing the criticality of injectable drugs was expected for a clinical pharmacist in the NICU and PICU. Physicochemical incompatibilities during administration were one of the most critical failure modes, and its improvement was worthy of note. Our results agree with numerous publications demonstrating the benefit of a paediatric clinical pharmacist, particularly in the prescription step [23, 24]. One study reported savings of $9135 per year in a 10-bed PICU of a university-affiliated children’s hospital [25].

The use of in-line filters was proposed in order to reduce microbiological contamination of injectable medications, but there is no convincing evidence so far of their efficiency in preventing catheter-related infections [26]. The advantages of such devices are a reported reduction of phlebitis, and the elimination of air, filtration of particulate contaminants and drugs precipitates. The fact that in-line filters cannot be used with colloids and blood and may complicate drug administration by adsorption and are expensive has to be considered in the cost-efficacy analysis [27].

Some drugs with uneven administration times, such as gentamicin, are particularly prone to wrong administration times. To avoid errors in the calculation of the correct administration time, a drug planner giving the time of next injection based on the last injection may be used [15]. This simple tool can be used for all drugs with uneven injected times. Although the impact of this tool is limited, its cost is virtually zero.

CPOE improved a considerable number of failure modes, but at high relative costs. A number of publications advocate the positive impact of a CPOE on drug prescription and administration safety in paediatric inpatients [28, 29]. However, CPOE for paediatric drug management may also introduce new errors unseen with the previous paper prescription [30]. Han et al. [31] even reported an increase in mortality from 2.8 to 6.6% in a paediatric referral centre after implementation of a commercially available CPOE system. This unexpected result was only partially attributable to the new prescription tool itself, and was associated with major changes in the organization processes. Such contradictory results highlight the difficulty of a successful implementation of a CPOE, no doubt influenced by the quality and the exhaustiveness of the program itself, but also by numerous technical, organizational, cultural and human factors. CPOEs are often included in more complete electronic patient record systems, and their high costs may be justifiable as their advantages extend well beyond the specific safety issues of injectable drugs.

Overall, the two major interests of an FMECA are its simple application and the quantitative character of the evaluation made possible by combining three complementary factors. The evaluation is easy to perform and not too time-consuming. A FMECA is therefore very helpful to decide and prioritize actions to be taken. Moreover the active brainstorming and discussion necessary to find consensual benchmarks contribute to the development of a very clear and shared vision of the process organization, accounting for all the different perspectives. The structured analysis allows constructive, objective and respectful discussions. Team members noticed that they gained extensive comprehension on each other’s constraints.

The major limitation of FMECA is an unavoidable subjective component. As the team becomes larger and multidisciplinary this bias is minimized. In the current study, we obtained consensual benchmarks between all members of the team, thus guaranteeing the highest possible objectivity. To further limit variability, the scores were based on explicit criteria published earlier [12]. It should be noted that the specific mark found for a failure mode is not an essential result, as the main goal is to rank risks and compare orders of magnitude. A further limitation is that it is impossible to assess the impact of a combination of multiple failures on a specific outcome. However, the separate analysis of each failure mode is also an advantage as it leads to a deeper understanding of the risk associated to each step, thus allowing targeted improvements. The FMECA method has not been fully validated but is recommended by the Institute for Healthcare Improvement [32].

Our results on criticality of injectable medication are specific to our local situation. Conclusions may not be directly applicable to the injectable medication process in every PICU. However, the impact of some safety tools on the criticality can easily be generalized. Most of the reported
failure modes also concern other institutions and our data appear as a good starting point to locally repeat a similar evaluation of the medication process.

**Conclusion**

The use of a prospective risk analysis such as FMECA has allowed a quantitative evaluation of the safety of paediatric patients in connection with the injectable medication process. The FMECA allowed generating tools for continuous safety improvement by modelling the relative safety gain for specific tools or new developments. Based on a pharmacoeconomic analysis in our local setting, the involvement of a clinical pharmacist and the introduction of ready-to-use syringes for selected drugs have been shown to be the most cost-effective tool.

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**References**


