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# Identification of relevant drug interactions in Neonatal Intensive Care Units

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## ① Objectives

Among the different types of **medication errors**, **drug interactions** may have serious consequences in **Neonatal Intensive Care Units** (NICU). However, they can be easily detected with appropriate tools, particularly in the context of a computerized prescribing system with pharmaceutical analysis.
The objective of this work was to calculate a **theoretical criticality index**, using a method inspired by the **Failure Modes, Effects and Criticality Analysis** (FMECA) method, for each drug interaction identified in NICU and to **prioritize** them by pharmacists and physicians.

## ② Methods

The study was a retrospective review of prescriptions in a French NICU.
The study included prescriptions:

- for all preterm infants with gestational age below 33 weeks of gestation
- hospitalized between January 2006 and December 2009.

For each prescription, drug interactions were evaluated with the French **Theriaque®** medication database.
The **criticality index of each drug interaction** (CI) was calculated by multiplying **occurrence** (O) , **severity** (S) and **detection** (D) **scores** (Figure 1).
The scales of each score had been built by a multidisciplinary group. Severity and detection scores were assessed by pharmacists and physician. **Intraclass Correlation Coefficients**[1] (ICC) were used to compare pharmacists and physicians scores, and a synthesis of the results was made.

$$CI_x = O_x \times S_x \times D_x$$

Figure 1 : criticality index of each drug interaction

## ③ Results

We identified **907** prescriptions with at least 2 drugs prescribed (**4605** drugs prescribed, with **109** different drugs), These prescriptions concerned **327** preterm infants. The five most prescribed drugs were : ascorbic acid + ergocalciferol + retinol + α-tocopherol (12.9 %), caffeine (11.4 %), vitamin K / phytonadione (10.4 %), sodium chloride (4.8 %), salbutamol (4.5 %).

Among the 907 prescriptions, **449** drug interactions were identified by using Theriaque®, and were categorized into **47 different drug interactions**.

The **10 most critical drug interactions** for pharmacists and physicians were detailed, and a common medical and pharmaceutical synthesis was established (Table I).

The ICC [1] of the detection was **0.75** (95% CI: 0.63-0.88), and the severity was **0.32** (95% CI: 0.08-0.56), demonstrating that physicians and pharmacists do not have the same vision of severity of drug interactions in NICU.

Table I: Results of the most critical drug interaction for pharmacists and physician. (INN: International Nonproprietary Names)

| Drug 1 INN | Drug 2 INN | Criticality index Physician | Criticality index Pharmacists | Comments about risks associated with drug interactions |
|---|---|---|---|---|
| rifampin | betamethasone | **63.8** | 12.5 | Report all associations limiting the effectiveness of corticosteroids. No means of detection biological available. |
| fluconazole | midazolam | 52.5 | 35.0 | Potential toxicity of midazolam. |
| hydrocortisone | ibuprofen | 42.5 | 11.3 | High risk with preterm infants. Detection means exist (fibroscopy , plain abdominal radiography). |
| vancomycin | amphotericin b liposome | 42.5 | 7.0 | Toxic effects may be additive. Biological analysis in the medium term only. |
| amikacin | vancomycin | 37.5 | 27.0 | Toxic effects may be additive. |
| rifampin | morphine | 35.0 | 22.5 | The decrease in the efficacy of morphine is intolerable. Pain assessment scales every 3 hours. |
| sufentanil | nalbuphine | 35.0 | 22.5 | To give information if nalbuphine is introduced after sufentanil,because there is a risk of a rapid opioid inhibition effect. |
| metronidazole | rifampin | 33.8 | 22.5 | Risk of reducing the effectiveness of antibiotics. |
| vecuronium bromure | amikacin | 33.8 | 22.5 | Exacerbation of respiratory depression. When stopping the amikacin there is a possible need to increase the dose of curare. |
| midazolam | sufentanil | 25.5 | 33.8 | Risk of hypotension. Newborns under sufentanil are intubated. |
| ciprofloxacin | hydrocortisone | 22.5 | **157.5** | No prolonged corticosteroid therapy in the neonatal period. |
| ciprofloxacin | betamethasone | 15.0 | 105.0 | No prolonged corticosteroid therapy in the neonatal period. |
| caffeine | ciprofloxacin | 4.0 | 90.0 | High therapeutic index of caffeine dosage. No caffeine dosage (unless apnea) made in clinical practice. CYP1A2 appears in the months after birth. |
| omeprazole | cyanocobalamin | 20.0 | 85.0 | In theory, no proton pump inhibitor in the neonatal period? (in our study they were prescribed between 2006 and 2009). |
| furosemide | ibuprofen | 21.0 | 52.5 | No indication of furosemide with prescription ibuprofen. |
| hydrocortisone | vecuronium bromure | 7.5 | 35.0 | Very short duration of corticosteroid therapy in the newborn. |
| spironolactone | potassium chloride | 5.0 | 35.0 | Prescribed potassium probably due to hypokalemia, Biological monitoring conducted. |

DI belonging to the top 10 of the physician
DI belonging to the top 10 of the pharmacists
DI belonging to the top 10 of the physician **AND** pharmacists

## ④ Discussion and conclusions

This work highlights the importance of **multidisciplinary** collaborations to **secure** the circuit of health products. This method can be used as a basis for future studies involving medical and pharmaceutical teams for the production of **pharmaceutical interventions**. It is easily **transferable** to other medical specialties with the same objectives.

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[1] SHROUT, P.E., FLEISS, J.L. Intraclass correlations: uses in assessing rater reliability. Psychol Bull, 1979, Mar;86, (2), 420-428.