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Frequency of dosage prescribing medication errors associated with manual prescriptions for very preterm infants

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SUMMARY

What is known and objective: **The risk of dosage Prescription Medication Error (PME) among manually written prescriptions within 'mixed' prescribing system (computerized physician order entry (CPOE) + manual prescriptions) has not been previously assessed in neonatology. This study aimed to evaluate the rate of dosage PME related to manual prescriptions in the high-risk population of very preterm infants (GA < 33 weeks) in a mixed prescription system.**

Methods: **The study was based on a retrospective review of a random sample of manual daily prescriptions in two neonatal intensive care units (NICU) A and B, located in different French University hospitals (Dijon and La Reunion island). Daily prescription was defined as the set of all drugs manually prescribed on a single day for one patient. Dosage error was defined as a deviation of at least ±10% from the weight-appropriate recommended dose.**

Results and discussion: **The analyses were based on the assessment of 676 manually prescribed drugs from NICU A (58 different drugs from 93 newborns and 240 daily prescriptions) and 354 manually prescribed drugs from NICU B (73 different drugs from 131 newborns and 241 daily prescriptions). The dosage error rate per 100 manually prescribed drugs was similar in both NICU: 3·8% (95% CI: 2·5–5·6%) in NICU A and 3·1% (95% CI: 1·6–5·5%) in NICU B ($P = 0·54$). Among all the 37 identified dosage errors, the over-dosing was almost as frequent as the under-dosing (17 and 20 errors, respectively). Potentially severe dosage errors occurred in a total of seven drug prescriptions. None of the dosage PME was recorded in the corresponding medical files and information on clinical outcome was not sufficient to identify clinical conditions related to dosage PME. Overall, 46·8% of manually prescribed drugs were off label or unlicensed, with no significant differences between prescriptions with or without dosage error. The risk of a dosage PME increased significantly if the drug was included in the CPOE system but was manually prescribed (OR = 3·3; 95% CI: 1·6–7·0, $P < 0·001$).**

What is new and conclusion: **The presence of dosage PME in the manual prescriptions written within mixed prescription systems suggests that manual prescriptions should be totally avoided in neonatal units.**

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WHAT IS KNOWN AND OBJECTIVE

Medication error has been defined as a non-intentional omission or failed activity related to the medication use system, which can be the cause of, or increases the risk, of an adverse event.[1] Medication errors may occur at each step of the drug management pathway, but are especially frequent at the prescription step, resulting in a prescribing medication error (PME).[2–12]

The reported rates of PME among prescriptions written for children have ranged between 4·2 and 30·1 per 100 handwritten prescriptions.[2–10] Patients in neonatal intensive care units (NICU) have a particularly high risk of PME,[11–13] and dosage error has been described as the most frequent type of PME in infants.[2,7,12,14,15]

Computerization of the prescription process is currently the main solution proposed to decrease the risk of PME.[4,16] Its efficacy has been demonstrated in patients of all ages,[16,17] and one study reported that the computerized physician order entry (CPOE) decreased the PME rate from 13% to 0% in NICU.[18] However, many circumstances in NICU with CPOE, like the development of new drugs, new recommendations, emergency situations or individual physicians' reluctance to use CPOE, may result in some handwritten prescriptions. The risk of PME among handwritten prescriptions within such 'mixed' prescribing systems has not been previously assessed in neonatology. To investigate these issues, we performed a retrospective survey of dosage PME in two French NICU that used a mixed prescription system. The study was limited to very preterm infants with gestational age (GA) below 33 weeks, a very vulnerable group at increased risk of dosage PME.[11,12,18]

METHODS

Definitions

Manual prescription was defined as any drug prescription which was not obtained from a CPOE and included handwritten prescriptions and/or prescriptions written on a computer in free text.

Dosage error was defined as a deviation of at least ±10% from the weight-appropriate recommended dose.[18] *A severe dosage error* was defined according to the European Pharmacovigilance Guide-

lines[19] according to the following criteria: (i) an error that was fatal or likely to result in a life-threatening event, or resulted in (ii) a significant, important or permanent disability, (iii) hospitalization or prolonged hospitalization, or (iv) an abnormality or birth defect, or finally (v) was judged as 'significant' by a physician. The severity of dosage errors was blindly assessed by a senior neonatologist (JBG) to characterize the seriousness of the resulting potential risk to the patient.[19]

Daily prescription was defined as the set of all drugs prescribed on a single day for one patient.

Mixed prescription system was defined as a system where, in the same NICU, some prescriptions were produced using CPOE but some others were manual.

Study design and population

The study compared the rate of dosage PME identified, through a retrospective review of the manual part of daily prescriptions in two NICU (referred to as hospitals 'A' and 'B') located in two French university hospitals (NICU A and NICU B; Dijon (France) and La Reunion Island, respectively). The CPOE systems in NICU A and B were home-made and different, but in both NICU, some prescriptions were still written manually. In NICU A (18 beds), the CPOE had been operating for more than 12 years, indicating dosage, solvent and dilution for 80 drugs. In NICU 'B' (10 beds), the CPOE had been operating for more than 10 years, indicating dosage and dilution for 60 drugs.

The following clinical characteristics of the infants were recorded in medical files for each daily prescription: gender, admission date and discharge date, GA, birthweight. The available data on each daily prescription included: date of prescription; weight and age at the day of the prescription. Data recorded for each drug manually prescribed were as follows: the International Nonproprietary Name; unitary dose and daily dose; the presence or absence of the drug in the CPOE software; the statutory situation: licensed, unlicensed, off-label; the status of the prescribing physician (senior, fellow, resident, other). In case of PME, the corresponding medical file was reviewed.

The summary of product characteristics [Vidal® dictionary] was used as the reference to establish the recommended unitary and daily dosage for licensed drugs. For unlicensed or off-label drugs, the Paediatric Dosage Handbook® was used.[20] The binary outcome variable was the presence of the dosage PME for at least one manually prescribed drug included in a given daily prescription.

The study was limited to manual prescriptions in preterm infants with GA below 33 weeks and hospitalized in the two NICU between January 2006 and December 2009. Sample size calculation was based on the results of a pilot study in NICU A. This pilot study reviewed 409 daily prescriptions with at least one drug prescribed manually and suggested a frequency of about six dosage PME per 100 manual parts of daily prescriptions. Based on this frequency, we calculated that about 250 manual parts of daily prescriptions in each of the two NICU will have to be sampled to obtain 80% power to detect a 6% difference between the respective rates of errors with the Fisher's exact test at the two-tailed $\alpha = 0{\cdot}05$. This sample size ensured also an adequate precision of the estimated frequency of dosage errors in each of the two NICU. For example, assuming that the frequency of dosage errors is close to 6%, the 95% confidence interval will estimate the frequency with a precision of about ±3·2%. Therefore, a sample of all daily prescriptions (overall 15,620 in NICU A and 6791 in NICU B) allowed a random selection of 240 daily prescriptions with a manual part in NICU A and 241 in NICU B.

Statistical analyses

Distributions of continuous variables were summarized with means and standard deviations (SD), and for qualitative variables, the frequency distributions were reported. Characteristics of infants, and their prescriptions, in the two NICU were compared using Student's *t*-tests or Kruskal–Wallis tests for continuous variables, and chi-square or Fisher's exact tests for categorical variables.

Multivariable logistic regression analyses were employed to identify infant and prescription characteristics associated with dosage PME for manually prescribed drugs. The binary dependent variable was the presence of the dosage PME for at least one drug in the manual part of a mixed daily prescription. The variables initially considered as possible risk factors for dosage PME were: GA, birthweight, weight on the prescription day, total duration of hospitalization, time elapsed between admission and prescription, total number of drugs included in the manual part of the prescription, prescribing physician level (senior, fellow, resident, other), use of unlicensed/off-label drugs and a binary variable indicating if at least one of the manually prescribed drugs was included in the CPOE system. Initially, all the aforementioned variables were included as independent variables in the multivariable logistic model. Then, backward elimination procedure was employed to select statistically significant ($P < 0{\cdot}05$ for the two-tailed model-based Wald chi-square test) variables into the final model. For each selected covariate, the adjusted odds ratio (OR) and the 95% confidence intervals were reported. First-order interactions were systematically tested and removed from the model if they did not reach the significance level.

All hypotheses were tested using two-tailed tests at a 0·05 significance level. All statistical analyses were performed using SAS 9.2 (SAS Institute, Cary, NC, USA).

The study was approved by the French Data Protection Agency (Commission Nationale Informatique et Liberté, CNIL).

RESULTS

The analyses were based on the assessment of 676 manually prescribed drugs from NICU A (58 different drugs from 93 newborns and 240 daily prescriptions) and 354 manually prescribed drugs from NICU B (73 different drugs from 131 newborns and 241 daily prescriptions).

As compared to NICU A, newborns in NICU B had lower GA (28·4 ± 1·8 vs. 29·0 ± 2·0 weeks; $P < 0{\cdot}05$), lower birthweight (1103 ± 321 vs. 1255 ± 394 g; $P < 0{\cdot}01$) and longer duration of hospitalization (37·9 ± 22·6 vs. 31·9 ± 22·2 days; $P < 0{\cdot}05$).

Significant differences were also recorded for infant weight on the day of prescription (1186 ± 342 vs. 1312 ± 478 g; $P < 0{\cdot}01$); time elapsed between admission and prescription (17·8 ± 16·1 vs. 24·7 ± 20·5 days; $P < 0{\cdot}0001$); number of manually prescribed drugs in daily prescriptions (1·5 ± 1·1 vs. 2·8 ± 1·8; $P < 0{\cdot}0001$); number of unlicensed/off-label drugs in the manual part of daily prescriptions (0·5 ± 0·3 vs. 1·2 ± 0·8; $P < 0{\cdot}01$); number of manually prescribed drugs in daily prescription with at least one drug in the CPOE system (0·5 ± 0·2 vs. 2·1 ± 1·7; $P < 0{\cdot}0001$).

The status of the prescribing physician was also different in the two NICU, with 77% of residents in NICU A, compared with a majority of senior physicians (55%) in NICU B.

We identified a total of 36 daily prescriptions with at least one dosage error among manually prescribed drugs (25 in NICU A and 11 in NICU B). In NICU A, there were 24 prescriptions with one dosage error and one with two dosage errors. In NICU B, there were 11 prescriptions with one dosage error. The dosage error rate per 100 manually prescribed drugs was similar in both NICU: 3·8% (95% CI: 2·5–5·6%) in NICU A and 3·1% (95% CI: 1·6–5·5%) in NICU B ($P = 0·54$).

Among all the 37 identified dosage errors, overdosing was almost as frequent as the underdosing (17 and 20 errors, respectively). Potentially severe dosage errors occurred in a total of seven prescriptions (four in NICU A and three in NICU B) and represented 19% of all dosage errors. The medical files neither recorded the dosage PME nor gave sufficient information to associate clinical outcome to the PME.

Table 1 shows, for all drugs prescribed in the two NICU, the distribution of drug classes, according to the Anatomical Therapeutic Chemical Classification (ATC) System, and the corresponding frequency of dosage errors. Interestingly, the 'bloods and blood-forming organs' class accounted for one half of all dosage errors observed in NICU A (13 of 26), whereas it was never observed in NICU B. The drugs in the 'bloods and blood-forming organs' class, for which dosage errors were detected in NICU A included: sodium bicarbonate, potassium chloride, sodium chloride, cyanocobalamine, epoetine beta, vitamin K, 5% glucose and iron. Dosage error for the other ATC classes was similarly distributed in the two NICU (Table 1).

In NICU A, univariate comparisons of manual daily prescriptions with ($n = 26$) and without ($n = 214$) dosage medication error showed significant statistical difference for: total duration of hospitalization (56·9 [32·7] vs. 46·6 [27·5] days; $P < 0·05$); time elapsed between admission and prescription (36·2 [21·1] vs. 23·3 [20·0] days; $P < 0·001$); total number of drugs prescribed in a daily prescription (both CPOE and manual) (6·3 [2·4] vs. 4·7 [2·3]; $P < 0·001$); number of manually prescribed drugs in daily prescription (4·3 [2·1] vs. 2·6 [1·7]; $P < 0·0001$); at least one of the manually prescribed drug also available in the CPOE (7·7% vs. 45·8%; $P < 0·01$).

No significant difference was observed for birthweight, weight at the time of prescription, GA below 28 weeks, residents as prescribing physicians and off-label/unlicensed drugs.

In NICU B, univariate comparisons of manual daily prescriptions with ($n = 11$) and without ($n = 230$) dosage medication error showed significant statistical differences for weight on the prescription day (1078 [310] vs. 1279 [358]; $P < 0·05$); at least one of the manually prescribed drug also available in the CPOE (73% vs. 30%; $P < 0·05$). No significant difference was observed for other variables.

Overall, across the two NICU, 46·8% of manually prescribed drugs were off-label or unlicensed, with no significant differences between prescriptions with or without dosage error.

The multivariable logistic regression analysis, with backward elimination of non-significant covariates, identified only one significant independent risk factor for dosage error in the manual daily prescriptions: the risk of dosage error increased significantly if the manually prescribed drug was also present in the CPOE system (OR = 3·3; 95% CI: 1·6–7·0; $P < 0·001$). Adjustment for the number of manually prescribed drugs included in the prescription did not modify this result.

Table 1. Drugs prescribed to very preterm infants in two NICU according to the ATC system and corresponding frequency of dosage errors

Drug classes	Number of drugs (Number of dosage errors)	
	NICU A Mixed system	NICU B Mixed system
Alimentary tract and metabolism	91 (3)	29 (0)
Blood and blood-forming organs	255 (13)	30 (0)
Cardiovascular system	80 (1)	36 (0)
Dermatological	0 (0)	0 (0)
Systemic hormonal preparations, (excluding sex hormones and insulin)	20 (1)	8 (1)
Anti-infective drugs for systemic use	39 (3)	54 (3)
Nervous system	95 (5)	53 (5)
Respiratory system	75 (0)	21 (0)
Sensory organs	0 (0)	0 (0)
Various	21 (0)	123 (2)
Total	676 (26)	354 (11)

DISCUSSION

According to the National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP), medication error (ME) is defined as a preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the healthcare professional, patient or consumer.[21] The present study only considered dosage ME because these were reported as the most common type of medication error in many studies[2,7,12,14] and were easy to identify in a retrospective chart review. The study also focused on very preterm infants (GA < 33 WG) as a highly vulnerable group, where dosing errors are both especially dangerous and relatively frequent.[11,12,18] Indeed, rapid post-natal changes in body weight and drug metabolism (absorption, distribution, kidney and liver elimination)[11,12,18] make the very preterm infant at high risk of drug side effects and dosage errors as neonatal prescription has to be precisely tailored to the birthweight, body weight at time of prescription, GA, post-natal age and associated clinical conditions.[20]

In this study, the rate of dosage error per 100 prescribed drugs was similar in NICU A and B (3·8% and 3·1%, respectively). Muñoz Labián *et al.*,[22] who reviewed 100 manual prescriptions of newborns admitted to intensive or intermediate care units, found a similar dosage error rate (4%). Pallas *et al.*[23] reported 39·5% of incorrect handwritten prescriptions in a third level neonatal unit with 11·1% of dosage errors.

In our study, overdosing errors were as frequent as underdosing errors, but other studies have given discrepant results. For instance, Folli *et al.*[2] found mostly overdosing errors whereas Cordero *et al.*[18] found that overdosing represented only one-third of all dosage errors. It is worth noting that the frequency of potentially severe dosage ME that we found among manual prescriptions delivered within a mixed prescription system (15·4% and 27·3% of all dosage errors in NICU A and B, respectively) was as high as the 19·5% observed among the exclusively handwritten prescriptions in a study by Fortescue *et al.*[4]

To the best of our knowledge, there has been only a single published study on medication errors among children in a mixed

system.[24] Maat *et al.*[24] reviewed 1577 prescriptions of children between 0 and 18 years, excluding patients receiving intensive care. The authors reported that the risk of dosage ME for free text prescriptions was five times higher than for standardized computerized prescriptions.[24] The present study was not designed to compare manual prescription and CPOE, but it demonstrated that dosage ME associated with manual prescriptions were not eliminated in a mixed prescription system. Furthermore, dosage ME were not recorded in the medical files, thus suggesting that they were not detected during hospitalization.

Children and particularly neonates frequently need off-label or unlicensed drugs. Carvalho *et al.*[25] demonstrated that the prevalence of off-label/unlicensed drugs was higher in preterm infants below 35 weeks and in those with high severity scores. We confirmed this, finding as close to 50% of manually prescribed drugs were off-label or unlicensed in this study. As repeatedly stated in the literature, the need for rigorous assessment of drugs through clinical trials is mandatory, especially in the very preterm infants, with marked immaturity of both metabolism and renal excretion of drugs.

This study failed to identify most of the factors usually associated with increased risk of dosage ME, presumably because it focused on a subpopulation limited to very preterm neonates. For instance, we did not find a statistical difference in birthweight between the very preterm infants with or without dosage errors, although a small birthweight has been associated with the most fragile patients who had an increased risk of dosage errors.[12,16,23]

In this study the unique independent risk factor for dosage error for a manually prescribed drug was the presence of the drug in the CPOE system. This finding may suggest that physicians have a reduced experience with manual prescribing of drugs usually prescribed by the CPOE system of their NICU.

Limitations of this study include the fact that only two NICU participated and that the retrospective review did not allow us to obtain accurate information about indication of treatment and the clinical consequences of dosage PME. However, other studies reported similar incidence of dosage errors for manually prescribed drugs, and the results for the two NICU were generally consistent.

WHAT IS NEW AND CONCLUSION

This study showed similar rate of dosage ME among manual prescriptions received by very preterm newborns in two NICU that used a mixed prescription system. This rate was comparable to those reported by many studies for exclusively handwritten prescriptions. Therefore, the CPOE does not prevent the risk of dosage error in the residual manual prescriptions.

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