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Medication use in the neonatal intensive care unit

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Abstract

Objective—We provide an update on medication use in infants admitted to the neonatal intensive care unit (NICU) in the United States and examine how use has changed over time.

Study Design—We performed a retrospective review (2005–2010) of a large prospectively collected administrative database.

Result—Medications most commonly administered during the study period were ampicillin, gentamicin, caffeine citrate, vancomycin, beractant, furosemide, fentanyl, dopamine, midazolam, and calfactant (56–681 exposures per 1000 infants). Those with the greatest relative increase in use included azithromycin, sildenafil, and milrinone. Medications with the greatest relative decrease in use included theophylline, metoclopramide, and doxapram.

Conclusion—Medication use in the NICU has changed substantially over time, and only 35% of the most commonly prescribed medications are FDA-approved in infants.

Keywords

pharmacotherapy; trends over time

Introduction

Infants in the neonatal intensive care unit (NICU) are exposed to a large number of medications, most of which are not labeled for use in infants because clinical trials for

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Drs. Hsieh, Hornik, and Clark have nothing to disclose.

safety, dosing, and efficacy of drugs are lacking in this population.[1] Hospitalized infants are often excluded from clinical trials due to ethical concerns and difficulties with recruitment.[2] Furthermore, these hospitalized infants in the NICU are more likely to be pre-term, with greater proportions exhibiting renal and hepatic dysfunction. These characteristics are often exclusion criteria for many clinical trials. As a result, clinicians are forced to prescribe medications for purposes outside of their licensed indications (i.e., off-label use).[3–5]

Previous investigators described medication use in the NICU through 2005.[6] However, clinical practice and prescribing patterns change over time as clinical trial data and new Food and Drug Administration (FDA) labeling information become available. The aims of this study were (1) to provide the most recent description of current prescribing practices in the NICU and (2) to examine changes in prescribing practices over time.

Methods

Study population

We obtained demographic, outcome, and medication administration data from infants discharged from 305 NICUs managed by the Pediatrix Medical Group from 2005–2010. Data were obtained from an administrative database that prospectively captures information from daily progress notes generated by clinicians using a computer-assisted tool on all infants cared for by the Pediatrix Medical Group. Information is collected regarding maternal history and demographics, physical exam findings, medications, laboratory results, culture results, diagnoses, and other aspects of clinical care. We excluded infants admitted after day of life 120, and all vitamins (except vitamin A), nutritional supplements, vaccines, eye drops, and topical medications.

Definitions

We used counts and proportions to describe medication use by 3 different methods. Total medication courses (frequency or raw count) represented the number of times a unique medication name was reported in the database. Exposure was defined as the number of unique medication names that were reported for each patient. Days of use was defined as the total number of days each medication was administered in the entire database. For example, if a medication was prescribed to 2 patients once and to 1 patient twice for a duration of 2 days each time, the medication would be reported as: exposure=1+1+1=3; course=1+1+2=4; days=(1*2)+(1*2)+(2*2)=8. In addition, medication exposures in extremely low birth weight (ELBW, <1000 g birth weight) infants and in infants who died prior to NICU discharge were determined.

The change in frequency of medication administration between 2005 and 2010 was described by both absolute and relative change. Relative increases in medication use were limited to medications with ≥1/1000 infant exposures in 2005, and relative decreases in medication use were limited to medication with ≥1/1000 infant exposures in 2010. We conducted the analysis using STATA 12 (College Station, TX). This study was approved by the Duke Institutional Review Board.

Results

Study population and counting method

A total of 450,386 infants were discharged during the study period, and 29,336 (6.5%) were ELBW infants. The median birth weight of the study population was 2490 g (25^{th}, 75^{th} percentile: 1830, 3191), and the median gestational age was 35 weeks (33, 38). The median length of hospitalization was 10 days (5, 21), and 56% of the infants were male. Overall mortality was 2.4%, which was similar to the previous study (2.7%).

We identified 1,655,397 unique medication courses for 229 medications. The mean number of medication courses per infant was 4 (1, 14) for the entire cohort and 17 (2, 45) for ELBW infants. There were minimal differences in the rankings of medications when calculated by the 3 methods. Therefore, only exposures were reported for Tables 2 through 6. The 10 most commonly reported medications, by exposure, in the NICU were ampicillin, gentamicin, caffeine citrate, vancomycin, beractant, furosemide, fentanyl, dopamine, midazolam, and calfactant (Table 1). For ELBW infants, the 10 most commonly reported medications by exposure were gentamicin, ampicillin, caffeine citrate, vancomycin, furosemide, dopamine, beractant, indomethacin, fentanyl, and albuterol (Table 2). FDA approval status for the medications most commonly used in the ELBW population is also shown in Table 2.

Medication use between 2005 and 2010

Drugs with the greatest relative increase in medication exposure from 2005 to 2010 included azithromycin, sildenafil, milrinone, ibuprofen, linezolid, cefoxitin, methadone, vitamin A, hyaluronidase, and poractant alpha (Table 3). Those with the greatest absolute increase in medication exposure from 2005 to 2010 included poractant alpha, vitamin A, ibuprofen, fluconazole, piperacillin/tazobactam, lansoprazole, methadone, morphine, meropenem, and nitric oxide (Table 4). Medications appearing on both lists included ibuprofen, methadone, and vitamin A.

Medication decreases between 2005 and 2010

Drugs with the greatest relative decrease in medication exposure from 2005 to 2010 included theophylline, metoclopramide, doxapram, aminophylline, epoietin alpha, imipenem +cilastatin, ranitidine, sodium polystyrene sulfonate, and bethanechol (Table 5). Those with the greatest absolute decrease in medication exposure from 2005 to 2010 included metoclopramide, ranitidine, ampicillin, cefotaxime, indomethacin, epoietin alpha, beractant, gentamicin, dopamine, and calfactant (Table 6). Medication use in ELBW infants is shown in Tables 7–10.

Discussion

Of the most commonly reported medications identified in our study, only 35% are FDA-approved in the newborn. From 1997–2010, 28 drugs had 24 FDA labeling changes in neonates. Only 2, famotidine and linezolid, were among the top 100 medications (#62 and #100, respectively). Such off-label drug use is concerning because, frequently, little is known about the drugs' potential side effects and adverse events; furthermore, dangerous

errors may be made in adjusting adult doses and formulations for infants and children. In fact, off-label drug use is associated with increased adverse drug reactions,[7] and the incidence of death and injury associated with adverse drug events in infants and children is likely substantially higher than what is actually reported.[8]

Several factors may have influenced the changes in medication use observed over time. An increasing number of studies investigating safety and pharmacokinetic properties of specific molecules have led to a better understanding of their effects in the target population. For example, emerging evidence has demonstrated the effectiveness of fluconazole prophylaxis in preventing invasive *Candida* infection in ELBW infants at high risk of invasive candidiasis.[9–11] In addition, the dosing of fluconazole has been described for both treatment and prophylaxis.[12] This increased understanding of the dosing, safety, and efficacy around fluconazole use likely accounts for the increase in its use (ranked 4th in absolute increase and 18th in relative increase).

On the other hand, little evidence exists for the efficacy of metoclopramide use for gastroesophageal reflux disease (GERD) in infants, which showed the second largest relative decrease in use between 2005 and 2010. A 2006 systematic literature review of metoclopramide for GERD in infants aged 0 to 23 months identified 4 studies that reported adverse effects of therapy, including irritability, dystonic reactions, drowsiness, oculogyric crisis, emesis, and apnea.[13] In 2009, the FDA required manufacturers to add a box warning to their drug labels about the risk of metoclopramide's long-term or high-dose use: chronic use of metoclopramide has been linked to tardive dyskinesia even after therapy has been discontinued.[14] During the time period of our study, Pediatrix Medical Group implemented a new electronic module dedicated to clinical quality improvement initiatives,[15] the success of which can be observed with the decrease in anti-reflux medication use.[16] Even with the decrease in metoclopramide use, however, metoclopramide was one top 20 most commonly used medications in the NICU.

Similarly, although ranitidine remained in the top 15 most commonly used medications in both the NICU, it experienced the second largest absolute decrease in medication use from 2005 to 2010. During this time, data were published linking the use of H2 blockers to necrotizing enterocolitis (NEC) in very low birth weight (<1500 g birth weight) infants (odds ratio = 1.71 [95% confidence interval: 1.34–2.19]).[17]

In addition, medications that have increased in use may have their own risks and adverse effects. There has been a decrease in third-generation cephalosporin use after their use was associated with increased risk of *Candida* infections.[18] This decrease corresponded with an increased use of piperacillin-tazobactam (ranked 5th in absolute increase and 14th in relative increase) and meropenem (ranked 9th in absolute increase and 13th in relative increase). These agents may carry similar risks given their broad spectrum of antimicrobial activity.

The introduction of newer and potentially safer medications may also drive changes in medication use. For example, indomethacin has been the conventional treatment for patent ductus arteriosus (PDA) in premature infants. In April 2006, the FDA approved ibuprofen lysine for closure of clinically significant PDA in premature infants because studies have

shown ibuprofen to be safer and equally as effective as indomethacin.[19] Subsequently, there has been a rise in the use of ibuprofen (3rd largest absolute increase in medication use) and a fall in indomethacin use (5th largest absolute decrease in medication use). However, in spite of these changes in prescribing patterns, indomethacin is still a commonly used medication in the ELBW infants (ranked 8th).

One of the most common complications of premature birth is bronchopulmonary dysplasia (BPD),[20] and up to 20% of infants with BPD develop pulmonary hypertension. As a result, sildenafil, approved for pulmonary hypertension in adults, has increased in use since 2005 (2nd greatest relative increase). However, the FDA recently recommended against the use of sildenafil in children ages 1 though 17 for the treatment of pulmonary arterial hypertension. This recommendation was based on a recent long-term pediatric clinical trial showing that children taking a high dose of sildenafil had a higher risk of death when compared to children taking a low dose, and that the low dose of sildenafil was not effective in improving exercise ability.[21]

The strengths of our study include the use of a large, representative cohort, as well as daily documentation of medication prescriptions for infants in the NICU. Our study is limited by the use of administrative data for the analysis. These data are not from a prospective clinical trial that has undergone the scrutiny of independent monitoring, but rather are derived from prospectively collected electronic documentation.

In summary, we identified the most commonly reported medications used in the NICU and how medication use has changed over time. Frequent studies of medication use patterns should be conducted to facilitate optimal prioritization of drug studies in infants. As many of the drugs used in the NICU are used off-label and have not been adequately studied in this population, these data are useful for researchers and NIH in setting research priorities.

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Table 1

Medications most commonly used in the NICU

Rank	Medication	Exposure*	Courses*	Days of use*
1	Ampicillin	681	709	3069
2	Gentamicin	676	785	3521
3	Caffeine citrate	156	199	3908
4	Vancomycin	91	150	987
5	Beractant	82	91	103
6	Furosemide	81	171	668
7	Fentanyl	70	86	677
8	Dopamine	62	77	327
9	Midazolam	61	71	679
10	Calfactant	56	66	72
11	Metoclopramide	54	63	706
12	Ranitidine	52	62	591
13	Poractant alpha	51	56	61
14	Morphine	51	62	527
15	Cefotaxime	43	53	316
16	Acetaminophen	43	48	241
17	Indomethacin	39	50	121
18	Phenobarbital	38	48	427
19	Albuterol	27	35	611
20	Epoietin alpha	26	30	631
21	Lorazepam	25	28	290
22	Hydrocortisone	25	32	290
23	Tobramycin	24	34	189
24	Erythromycin	24	25	103
25	Dobutamine	20	23	78
26	Dexamethasone	20	30	159
27	Fluconazole	19	23	321
28	Clindamycin	17	19	128
29	Palivizumab	17	17	24
30	Acyclovir	16	16	82
31	Vitamin A	15	15	363
32	Insulin	14	17	73
33	Ursodeoxycholic acid	14	18	259
34	Lansoprazole	14	15	106
35	Spironolactone	14	17	251
36	Chlorothiazide	12	16	230

Rank	Medication	Exposure*	Courses*	Days of use*
37	Aminophylline	12	13	165
38	Ceftazidime	12	15	99
39	Alprostadil	12	12	22
40	Nitric oxide	11	12	82
41	Piperacillin/tazobactam	11	15	115
42	Epinephrine	11	12	25
43	Amoxicillin	11	12	72
44	Metronidazole	11	13	97
45	Oxacillin	10	14	67
46	Nafcillin	9.0	11	66
47	Amphotericin B products	8.9	11	99
48	Amikacin	8.8	12	77
49	Vecuronium	8.5	9.8	33
50	Ibuprofen	8.3	11	35
51	Cefazolin	7.5	8.1	27
52	Meropenem	7.0	8.9	82
53	Simethicone	6.9	7.2	59
54	Levothyroxine	6.7	7.2	157
55	Fluticasone	6.7	8.1	170
56	Budesonide	6.6	7.6	153
57	Phenylephrine	6.6	7.3	29
58	Omeprazole	6.5	7.0	64
59	Epinephrine racemic	6.3	7.4	20
60	Cefepime	6.1	7.7	58
61	Pancuronium	6.1	6.8	22
62	Famotidine	5.3	6.2	62
63	Methadone	5.2	6.1	86
64	Digoxin	5.1	5.7	28
65	Chloral hydrate	5.0	5.5	28
66	Penicillin G	4.7	4.9	38
67	Naloxone	4.3	4.4	4.7
68	Pentobarbital	4.3	4.7	49
69	Prednisone/prednisolone	4.2	5.2	47
70	Aluminum/magnesium hydroxide	4.2	4.7	27
71	Theophylline	4.1	5.0	102
72	Filgrastim	3.8	4.4	13
73	Hydrochlorothiazide	3.7	4.5	61
74	Rifampin	3.6	3.8	36
75	Propranolol	3.4	3.7	15

Rank	Medication	Exposure*	Courses*	Days of use*
76	THAM acetate	3.1	4.0	5.2
77	Imipenem+cilastatin	3.0	3.3	29
78	Milrinone	2.9	3.0	15
79	Hyaluronidase	2.8	2.9	3.1
80	Bumetanide	2.8	3.8	26
81	Hydralazine	2.5	2.8	28
82	Surfactant (unknown type)	2.4	2.6	3.9
83	Captopril	2.3	2.6	24
84	Beclomethasone	2.1	2.8	32
85	Adenosine	2.1	2.5	4.0
86	Acetazolamide	2.1	3.7	24
87	Sodium polystyrene sulfonate	2.1	2.3	5.3
88	Diazepam	2.0	2.4	28
89	Zidovudine	1.9	2.0	15
90	Cephalexin	1.9	2.0	9.5
91	Ceftriaxone	1.8	1.8	5.7
92	Ipratropium	1.7	1.9	42
93	Dornase Alpha	1.6	2.2	16
94	Sulfamethoxazole+trimethoprim	1.6	1.8	16
95	Enalapril	1.5	1.8	13
96	Cefoxitin	1.5	1.6	4.9
97	Doxapram	1.4	2.0	25
98	Fosphenytoin	1.4	1.6	10
99	Sildenafil	1.4	1.6	27
100	Linezolid	1.3	1.6	14

* Units for courses, exposure, and days of use, per 1000 infants.

Table 2

Medications most commonly used in extremely low birth weight infants

Rank	Medication	Exposure*	FDA-approved in ELBW infants
1	Gentamicin	896	Yes
2	Ampicillin	881	No
3	Caffeine citrate	704	No
4	Vancomycin	559	Yes
5	Furosemide	495	No
6	Dopamine	425	No
7	Beractant	339	Yes
8	Indomethacin	334	Yes
9	Fentanyl	322	No
10	Albuterol	241	No
11	Calfactant	240	Yes
12	Midazolam	236	Yes
13	Hydrocortisone	215	No
14	Cefotaxime	214	Yes
15	Ranitidine	212	No
16	Metoclopramide	195	No
17	Morphine	194	No
18	Fluconazole	191	No
19	Dexamethasone	176	No
20	Vitamin A	174	No

*Per 1000 infants.

Table 3

Greatest relative increase in exposure between 2005 and 2010 (≥1/1000 infant exposures in 2010)

Rank	Medication	% Change	Exposure (2005)*	Exposure (2010)*
1	Azithromycin	2900	0.1	3.0
2	Sildenafil	1050	0.2	2.3
3	Milrinone	900	0.4	4.0
4	Ibuprofen	650	1.4	11
5	Linezolid	500	0.4	2.4
6	Cefoxitin	350	0.4	1.8
7	Methadone	158	3.1	8.0
8	Vitamin A	152	8.3	21
9	Hyaluronidase	107	1.5	3.1
10	Poractant alpha	101	32	63
11	Meropenem	100	4.5	9.0
12	Piperacillin/tazobactam	97	6.2	12
13	Cefepime	70	4.6	7.8
14	Famotidine	60	4.7	7.5
15	Lansoprazole	58	9.8	16
16	Fluconazole	44	14	21
17	Diazepam	44	1.6	2.3
18	Nitric oxide	42	8.9	13
19	Cefazolin	38	6.3	8.7
20	Prednisone/Prednisolone	36	3.9	5.3

*Per 1000 infants.

Table 4

Greatest absolute increase in exposure between 2005 and 2010

Rank	Medication	Exposure increase*	Exposure in 2005*	Exposure in 2010*
1	Poractant alpha	32	32	63
2	Vitamin A	13	8.3	21
3	Ibuprofen	9.1	1.4	11
4	Fluconazole	6.4	14	21
5	Piperacillin/tazobactam	6.0	6.2	12
6	Lansoprazole	5.7	9.8	16
7	Methadone	4.9	3.1	8.0
8	Morphine	4.8	49	54
9	Meropenem	4.5	4.5	9.0
10	Nitric oxide	3.7	8.9	13
11	Milrinone	3.6	0.4	4.0
12	Cefepime	3.2	4.6	7.8
13	Lorazepam	3.0	23	26
14	Azithromycin	2.9	0.1	3.0
15	Metronidazole	2.9	8.4	11
16	Famotidine	2.8	4.7	7.5
17	Acyclovir	2.4	16	18
18	Cefazolin	2.4	6.3	8.7
19	Sildenafil	2.1	0.2	2.3
20	Linezolid	2.0	0.4	2.4

*Per 1000 infants.

Table 5

Greatest relative decrease in exposure between 2005 and 2010 (≥1/1000 infant exposures in 2005)

Rank	Medication	% Change	Exposure (2005)*	Exposure (2010)*
1	Theophylline	−84	6.9	1.1
2	Metoclopramide	−84	88	14
3	Doxapram	−74	2.3	0.6
4	Aminophylline	−73	20	5.4
5	Epoietin alpha	−66	42	15
6	Imipenem+cilastatin	−63	4.8	1.8
7	Ranitidine	−61	80	31
8	Sodium polystyrene sulfonate	−61	3.1	1.2
9	Bethanechol	−59	2.2	0.9
10	Indomethacin	−58	61	26
11	Cefotaxime	−56	67	29
12	Amphotericin B products	−53	12	5.5
13	Ipratropium	−52	2.7	1.3
14	Ceftazidime	−51	17	8.5
15	Acetylcysteine	−47	1.7	0.9
16	Oxacillin	−46	12	6.4
17	Dobutamine	−46	26	14
18	Ceftriaxone	−46	2.4	1.3
19	Rifampin	−45	4.2	2.3
20	Palivizumab	−42	20.5	11.9

*Per 1000 infants.

Table 6

Greatest absolute decrease in exposure between 2005 and 2010

Rank	Medication	Decrease in exposure*	Exposure in 2005*	Exposure in 2010*
1	Metoclopramide	−74	88	14
2	Ranitidine	−49	80	31
3	Ampicillin	−39	699	659
4	Cefotaxime	−38	67	29
5	Indomethacin	−35	61	26
6	Epoietin alpha	−28	42	15
7	Beractant	−26	93	67
8	Gentamicin	−26	684	658
9	Dopamine	−23	73	50
10	Calfactant	−20	67	47
11	Vancomycin	−17	96	79
12	Furosemide	−16	89	73
13	Aminophylline	−15	20	5.4
14	Albuterol	−12	34	22
15	Dobutamine	−12	26	14
16	Midazolam	−9.3	63	54
17	Ceftazidime	−8.7	17	8.5
18	Palivizumab	−8.6	21	12
19	Spironolactone	−6.4	17	11
20	Amphotericin B products	−6.3	12	5.5

*Per 1000 infants.

Table 7

Greatest relative increase in exposure between 2005 and 2010 in ELBW infants (≥1/1000 infant exposures in 2010)

Rank	Medication	% Change	Exposure (2005)*	Exposure (2010)*
1	Azithromycin	2050	0.4	8.6
2	Ibuprofen	1340	7.8	112
3	Sildenafil	1125	1.6	20
4	Carnitine	733	3.6	30
5	Cefuroxime	700	0.2	1.6
6	Milrinone	525	1.6	10
7	Linezolid	464	3.1	18
8	Amlodipine	291	1.1	4.3
9	Ganciclovir	236	1.1	3.7
10	Cefoxitin	219	2.7	8.6

* Per 1000 infants.

Table 8

Greatest absolute increase in exposure between 2005 and 2010 in ELBW infants

Rank	Medication	Exposure increase*	Exposure in 2005*	Exposure in 2010*
1	Vitamin A	179	93	273
2	Caffeine citrate	176	620	796
3	Poractant alpha	135	100	235
4	Ibuprofen	105	7.8	112
5	Fluconazole	95	141	236
6	Gentamicin	67	853	920
7	Fentanyl	47	295	342
8	Meropenem	45	36	81
9	Piperacillin/Tazobactam	44	45	89
10	Lorazepam	38	76	114

* Per 1000 infants.

Table 9

Greatest relative decrease in exposure between 2005 and 2010 in ELBW infants (≥1/1000 infant exposures in 2005)

Rank	Medication	% Change	Exposure (2005)*	Exposure (2010)*
1	Cromolyn	−93	2.7	0.2
2	Terbutaline	−88	3.4	0.4
3	Scopolamine	−87	4.5	0.6
4	Norepinephrine	−85	1.3	0.2
5	Metoclopramide	−79	298	62
6	Ceftizoxime	−75	1.6	0.4
7	Aztreonam	−74	3.8	1.0
8	Theophylline	−73	38	10
9	Doxapram	−70	22	6.7
10	Chlorpromazine	−69	1.3	0.4

* Per 1000 infants.

Table 10

Greatest absolute decrease in exposure between 2005 and 2010 in ELBW infants

Rank	Medication	Decrease in exposure*	Exposure in 2005*	Exposure in 2010*
1	Metoclopramide	−236	298	62
2	Ranitidine	−152	293	141
3	Epoietin alpha	−143	223	81
4	Indomethacin	−139	424	285
5	Cefotaxime	−118	282	164
6	Aminophylline	−64	94	30
7	Albuterol	−60	283	223
8	Dopamine	−57	449	392
9	Ceftazidime	−55	130	84
10	Dobutamine	−51	162	110

* Per 1000 infants.