Original Investigation

Drug Labeling and Exposure in Neonates

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IMPORTANCE Federal legislation has led to a notable increase in pediatric studies submitted to the Food and Drug Administration (FDA), resulting in new pediatric information in product labeling. However, approximately 50% of drug labels still have insufficient information on safety, efficacy, or dosing in children. Neonatal information in labeling is even scarcer because neonates comprise a vulnerable subpopulation for which end-point development is lagging and studies are more challenging.

OBJECTIVE To quantify progress made in neonatal studies and neonatal information in product labeling as a result of recent legislation.

DESIGN, SETTING, AND PARTICIPANTS We identified a cohort of drug studies between 1997 and 2010 that included neonates as a result of pediatric legislation using information available on the FDA website. We determined what studies were published in the medical literature, the legislation responsible for the studies, and the resulting neonatal labeling changes. We then examined the use of these drugs in a cohort of neonates admitted to 290 neonatal intensive care units (NICUs) (the Pediatrix Data Warehouse) in the United States from 2005 to 2010.

EXPOSURE Infants exposed to a drug studied in neonates as identified by the FDA website.

MAIN OUTCOMES AND MEASURES Number of drug studies with neonates and rate of exposure per 1000 admissions among infants admitted to an NICU.

RESULTS In a review of the FDA databases, we identified 28 drugs studied in neonates and 24 related labeling changes. Forty-one studies encompassed the 28 drugs, and 31 (76%) of these were published. Eleven (46%) of the 24 neonatal labeling changes established safety and effectiveness. In a review of a cohort of 446 335 hospitalized infants, we identified 399 drugs used and 1 525 739 drug exposures in the first 28 postnatal days. Thirteen (46%) of the 28 drugs studied in neonates were not used in NICUs; 8 (29%) were used in fewer than 60 neonates. Of the drugs studied, ranitidine was used most often (15 627 neonates, 35 exposures per 1000 admissions).

CONCLUSIONS AND RELEVANCE Few drug labeling changes made under pediatric legislation include neonates. Most drugs studied are either not used or rarely used in US NICUs. Strategies to increase the study of safe and effective drugs for neonates are needed.

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Neonates, typically defined as infants up to 28 days of age, are at high risk of catastrophic drug-related adverse events. Their unique physiology prevents successful extrapolation of pharmacokinetic data from older patients, and appropriate dosing for most therapeutic agents used in neonates is unknown.[1] Despite neonatal medicine's history of catastrophic adverse events resulting from inadequate study of drugs prior to their widespread use,[2-5] the majority of drugs used in neonates have not undergone sufficient study to receive Food and Drug Administration (FDA) labeling that is safe and effective when applied to this population.[6-10]

Since 1997, a combination of pediatric incentives and requirements has significantly increased pediatric drug research and development and stimulated an increase in pediatric labeling.[11-14] The legislation encompassing these initiatives was permanently reauthorized in 2012.[15] A large number of pediatric labeling changes have resulted from these policies[16]; however, approximately 50% of drug product labeling has insufficient information on the safety, efficacy, or dosing appropriate for use in children.[17]

We analyzed the effect of recent pediatric initiatives on neonatal studies and labeling. We determined whether studies conducted under pediatric legislation included neonates, if there was a labeling change that included neonates, and the types of neonatal labeling changes made (eg, if safety and effectiveness were established). We also identified the proportion of neonates in a large cohort of hospitalized infants that was exposed to the drugs studied in neonates.

Methods

FDA Review

We reviewed the pediatric resources on the FDA website for studies submitted between 1997 and 2010, including (1) the pediatric labeling changes database, (2) medical, statistical, and clinical pharmacology reviews, (3) pediatric medical and clinical pharmacology summaries, and (4) reviews posted at Drugs@FDA,[16,18-20] to identify pediatric studies and labeling changes that included neonates. We defined a neonate as any infant 28 postnatal days of age or younger. In cases where we could not identify the exact postnatal age, we included the review and labeling change if it referred to an infant younger than 1 postnatal month, zero for the lower limit of ages (eg, 0 years of age), or newborn. We identified all drugs with pediatric studies that included neonates, the indication studied, the number of pediatric studies for each drug including neonates, the number of those studies published, the number of neonates studied if specified, the legislation responsible for the study, and whether the drug was approved for use in neonates for the indication studied. We compared the studies identified in FDA reviews with the medical literature (MEDLINE) to determine the proportion of studies identified in the reviews that were published.

National Review

We assembled a cohort of neonates (infants up to 28 days of age) from 2005 to 2010 using a deidentified data set that included infants discharged from 290 neonatal intensive care units (NICUs). The 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. From the daily notes, data were extracted, deidentified (in compliance with the Health Insurance Portability and Accountability Act of 1996), and consolidated into the Pediatrix BabySteps Clinical Data Warehouse. The "medications" and "demographics" tables were used for our analysis. We included all neonates. We used standard summary statistics to describe drug use. We searched the drug list for drugs that were identified in the FDA review to determine the exposure among neonates. The Duke University institutional review board designated this study as exempt because of the deidentified nature of the data. The FDA institutional review board exempted the national review from Research Involving Human Subject Committee review.

Results

We identified 28 drugs with 41 studies resulting in 24 labeling changes (including addition of pharmacokinetic information) that included neonates (**Table**). Of the 28 drugs, 16 had studies conducted under the incentive, 3 under the requirement, and 9 were conducted under both. Between 1997 and 2010, as a result of the pediatric initiatives, a total of 406 pediatric labeling changes were made.[16] Twenty-four (6%) of the 406 pediatric labeling changes included new neonatal information (Table and **Figure**; note that linezolid received 2 labeling changes). Fourteen (50%) of the drugs were for infectious diseases, including 8 antiviral drugs, 4 topical ophthalmic antibiotics, 1 antifungal, and 1 antibiotic. The remaining drugs included 5 for gastroesophageal reflux disease, 3 anesthetics, 3 cardiovascular drugs, 1 analgesic/antipyretic, 1 pulmonary drug, and 1 volume replacement. The majority of the studies identified in the FDA review were published in the medical literature (31 of 41; 76%).

Eleven of 24 labeling changes (46%) including new neonatal information also included an approval for use in neonates: 4 for human immunodeficiency virus (HIV) (didanosine, lopinavir/ritonavir, nevirapine, and stavudine), 3 for anesthesia (remifentanil hydrochloride, rocuronium bromide, and sevoflurane), and 4 for other conditions (Table). Thirteen of the 24 neonatal labeling changes (54%) included the statement "safety and effectiveness have not been established": acetaminophen IV, caspofungin acetate, emtricitabine, esomeprazole magnesium, lamivudine, lansoprazole, linezolid, nelfinavir mesylate, nitric oxide, pantoprazole sodium, ranitidine, sotalol hydrochloride, and valganciclovir hydrochloride (Table).

Five of the products studied in neonates did not obtain a neonatal labeling change. Prior to 2007, it was possible to enroll children in studies and not have any information from the study included in labeling. Moxifloxacin ophthalmic had a pediatric labeling change, but no neonatal information was added; no pediatric labeling change was made for bivalirudin, ciprofloxacin ophthalmic, gatifloxacin ophthalmic, or ofloxacin ophthalmic.

Table. Drugs and Studies Including Neonates Under Pediatric Legislation Between 1997 and 2010

Pediatric Labeling Change Date	Generic Name or Proper Name (Biologics)	Trade Name	Indication Studied	No. of Studies Published/ Total No. of Studies (n = 31/41)	No. of Neonates Studied[a] (N = 3215)	Indicated for Use in Neonates? (N = 24)	Legislation	No. of Neonates Exposed to Drug[b]	Exposure/ 1000 Neonates in 290 NICUs
				FDA Review				**National Review**	
Dec 27, 2007	6% Hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection	Voluven	Plasma volume substitute for hypovolemia	1[21]/1	?[c] (41[d])	Yes	Requirement	0	0
Nov 2, 2010	Acetaminophen IV	Ofirmev injection	Pain management, reduction of fever	2/3	47	No; neonatal PK information added to label; safety and efficacy not established in children <2 y	Requirement	28	0
None	Bivalirudin	Angiomax	Anticoagulant for procedures for congenital heart disease	2/2	10	No labeling change	Incentive	0	0
Jul 29, 2008	Caspofungin acetate	Candidiasis	Empirical therapy for presumed fungal infections in febrile, neutropenic patients; candidemia and certain *Candida* infections; esophageal candidiasis; invasive aspergillosis in patients who are refractory to or intolerant of other therapies	1/1	18	No; limited PK data in neonates and infants <3 mo insufficient to establish a safe and effective dose of caspofungin in the treatment of neonatal candidiasis; safety and efficacy have not been established in those <3 mo	Incentive and requirement	107	0.2
None	Ciprofloxacin ophthalmic	Ciloxan	Bacterial conjunctivitis	0/1	?[c]	No labeling change	Incentive	9	<0.1
Apr 1, 2002	Didanosine	Videx	HIV	1[22]/1	10	Yes; in neonates ≥2 wk	Incentive	0	0
Dec 22, 2006	Emtricitabine	Emtriva	HIV	0/1	22	No; neonatal PK information added to labeling; safety and efficacy have not been established in those <3 mo	Incentive	0	0
Jun 18, 2009	Esomeprazole magnesium	Nexium	GERD	1[23]/1	26	No; neonatal PK information added to labeling; safety and efficacy not established in those <1 y	Incentive and requirement	0	0
Jun 6, 2002	Famotidine	Pepcid	GERD	2[24,25]/2	12	Yes	Incentive	1646	3.7
Apr 1, 2004	Fenoldopam mesylate	Corlopam	Reduction of blood pressure	0/1	2	Yes; in neonates >2 kg	Incentive	0	0
None	Gatifloxacin ophthalmic solution	Zymar	Bacterial conjunctivitis	0/1	171	No	Incentive	0	0
Oct 8, 2002	Lamivudine	Epivir	HIV	2[26,27]/2	36	No; neonatal PK information added to labeling; safety and efficacy not established in those <3 mo	Incentive	8	<0.1
Oct 28, 2008	Lansoprazole	Prevacid	GERD	1[28,29]/1	24	No; neonatal PK information added to labeling; safety and efficacy not established in those <1 y	Incentive and requirement	2374	5.3
May 12, 2005 and Dec 19, 2002	Linezolid	Zyvox	Infections due to susceptible organisms; CNS infections to susceptible organisms	2[30,31]/3	At least 43[15,16]	1. Yes for infections due to susceptible organisms 2. No for CNS infections to susceptible organisms; neonatal PK information added to labeling	Incentive		
Jun 20, 2008	Lopinavir/ritonavir	Kaletra	HIV	1[32]/1	10	Yes, in neonates ≥14 d	Incentive and requirement	0	0
Apr 15, 2003	Moxifloxacin	Vigamox	Bacterial conjunctivitis	1[33]/1	209	No; no neonatal information in labeling; safety and efficacy not established in those <1 y	Incentive	119	0.3
Mar 19, 2004	Nelfinavir mesylate	Viracept	HIV	1[34]/1	31	No; neonatal PK information added to labeling; safety and efficacy not established in those <2 y	Incentive and requirement	0	0

(continued)

Table. Drugs and Studies Including Neonates Under Pediatric Legislation Between 1997 and 2010 (continued)

				FDA Review				National Review	
Pediatric Labeling Change Date	Generic Name or Proper Name (Biologics)	Trade Name	Indication Studied	No. of Studies Published/ Total No. of Studies (n = 31/41)	No. of Neonates Studied[a] (N = 3215)	Indicated for Use in Neonates? (N = 24)	Legislation	No. of Neonates Exposed to Drug[b]	Exposure/ 1000 Neonates in 290 NICUs
Jun 24, 2008	Nevirapine	Viramune	HIV	1[35]/1	?[c] (36[d])	Yes, in neonates ≥15 d	Requirement	21	<0.1
Dec 21, 2010	Nitric oxide	INOmax	Prevention of bronchopulmonary dysplasia	3[36-38]/3	2180	No; information on neonatal clinical trials and adverse reactions was added to labeling	Incentive	4929	11
None	Ofloxacin ophthalmic	Ocuflox	Bacterial conjunctivitis	0/1	?[c]	No labeling change	Incentive	4	<0.1
Nov 12, 2009	Pantoprazole sodium	Protonix	GERD	1[39]/1	68	No; neonatal PK information was added to labeling; safety and efficacy not established in those <5 y	Incentive and requirement	39	<0.1
Oct 22, 1999	Ranitidine	Zantac	GERD	1[40]/1	12	No; information on neonatal clinical trials was added to labeling	Incentive	15 627	35
Mar 8, 2004	Remifentanil hydrochloride	Ultiva	Maintenance of anesthesia	1[41,42]/1	?[c] (60[d])	Yes	Incentive and requirement	0	0
Aug 28, 2008	Rocuronium bromide	Zemuron	Adjunct to general anesthesia	0/2	28	Yes	Incentive and requirement	37	<0.1
Mar 30, 2001	Sevoflurane	Ultane	General anesthesia	1[43]/1	?[c] (180[d])	Yes	Incentive	0	0
Oct 1, 2001	Sotalol hydrochloride	Betapace	Arrhythmia	2[44-46]/2	9	No; information on PK and PD in children aged 3 d to 12 y was added to labeling; safety and efficacy not established in pediatrics	Incentive	58	0.1
Mar 29, 2002	Stavudine	Zerit	HIV	2[47]/3	223	Yes	Incentive	0	0
Aug 28, 2009	Valganciclovir hydrochloride	Valcyte	Treatment of congenital CMV	1[48]/1	24	No; information on PK, PD, and safety was added to labeling	Incentive and requirement	0	0

Abbreviations: CMV, cytomegalovirus; CNS, central nervous system; FDA, Food and Drug Administration; GERD, gastroesophageal reflux disease; HIV, human immunodeficiency virus; NICU, neonatal intensive care unit; PD, pharmacodynamic; PK, pharmacokinetic.

[a] The number of neonates studied includes all neonates who participated in the study, including those receiving placebo or comparator. Six product reviews/summaries did not contain the precise number of neonates studied.

The number of neonates studied ranged from 1 to more 200.

[b] n = 25 384/446 335. This is the number of neonates who received at least 1 drug.

[c] Represents that the number of neonates could not be determined.

[d] The total number of pediatric participants in the study.

We found that 22 of 28 drugs (79%) clearly specified the number of neonatal participants in the review, summary, or labeling; 6 of 28 (21%) provided only the number of pediatric participants in a pediatric age range (eg, 0-3 months) and ranged from 1 to more than 200 neonates. The largest proportion of neonates was enrolled in 3 studies of inhaled nitric oxide for the prevention of bronchopulmonary dysplasia (2180 of 3215; 68%); this drug failed to prevent bronchopulmonary dysplasia.

In the Pediatrix database, we identified 399 drugs prescribed to 446 335 hospitalized neonates. Of the 28 drugs studied, the gastroesophageal reflux drugs were used most often (Table): ranitidine was the drug used most often (n = 15 627 neonates; 35 exposures per 1000 neonates), lansoprazole was third (n = 2374 neonates; 5.3 per 1000 neonates), and famotidine was fourth (n = 1646 neonates; 3.7 per 1000 neonates). Inhaled nitric oxide was the second most used drug overall, with 4929 neonates exposed (11 per 1000 neonates).

Figure. Neonatal Labeling Changes Under Legislation From 1997 to 2010 and Exposure of Neonates to Drugs With a Neonatal Indication

406 Pediatric labeling changes
→ 381 No neonatal labeling
24 Neonatal labeling changes[a]
→ 13 Not indicated in neonates
11 Neonatal indication
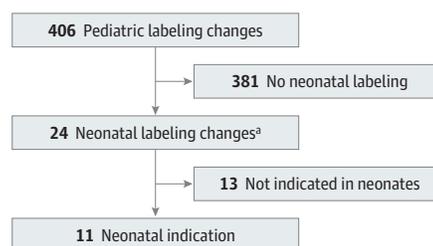
[a] There are 24 neonatal labeling changes involving 23 drugs. Linezolid has 2 labeling changes.

Thirteen of the 28 drugs studied in neonates were not used in the Pediatrix neonatal population (6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection, bivalirudin, didano-

sine, emtricitabine, esomeprazole magnesium, fenoldopam mesylate, gatifloxacin ophthalmic solution, lopinavir/ritonavir, nelfinavir, remifentanil, sevoflurane, stavudine, and valganciclovir).

Eight of 28 were used in fewer than 60 neonates per drug (acetaminophen IV, ciprofloxacin ophthalmic, lamivudine, nevirapine, ofloxacin ophthalmic, pantoprazole, rocuronium, and sotalol). Seven were used in more than 60 neonates per drug (caspofungin, famotidine, lansoprazole, linezolid, moxifloxacin, nitric oxide, and ranitidine). Of the 11 drugs with a neonatal indication, 7 were never used in the Pediatrix neonatal population: 6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection, didanosine, fenoldopam, lopinavir/ritonavir, remifentanil, sevoflurane, and stavudine. The other 4 drugs were used infrequently: famotidine, 3.7 per 1000 neonates; linezolid, 0.9 per 1000 neonates; and nevirapine and rocuronium, both less than 0.1 per 1000 neonates (Table).

The majority of labeling changes occurred prior to 2008 (18 of 28 drugs; 64%). Ten (36%) of the drugs received labeling changes in the latter 3 years of the study period (2008-2010). Of these, 2 of the 10 were in the top 3 drugs used in the NICU (lansoprazole: n = 2374 and inhaled nitric oxide: n = 4929; both with no efficacy established).

Discussion

Neonates are an understudied population. Several factors are considered before neonatal studies can be performed: there must be a public health benefit, and the studies must be feasible, ethical, and sufficient to support dosing, safety, and efficacy. Nearly 40% (11 of 28) of the drugs involving neonates pursuant to pediatric legislation between 1997 and 2010 were deemed safe and effective in neonates. Most of these were drugs used to treat infectious diseases (eg, didanosine, lopinavir/ritonavir, and nevirapine), as well as anesthesia drugs (eg, remifentanil and rocuronium). Of the infectious disease drugs, the majority were for HIV. Although neonatal HIV has been almost eradicated from the United States, it is critical to study HIV drugs because it remains a problem in developing countries.

Thirteen drugs studied received a labeling change stating that "safety and effectiveness have not been established" (Table). This is not surprising because neonates are a challenging population to study. There is considerable variability in drug metabolism and physiology within the neonatal population, which influences the pharmacokinetics, pharmacodynamics, safety, and efficacy of medications. Neonates are typically enrolled in pharmacokinetic/pharmacodynamic, safety, and dose-finding studies first; once an appropriate dose is established, safety and efficacy studies may be done. The sample size for most neonatal studies is very small because of the limitations inherent to these trials, including low study consent rates for parents of vulnerable infants; limited blood volume available to conduct pharmacokinetic studies; lack of pediatric population pharmacokinetic/pharmacodynamic analysis expertise; difficulties associated with timing of blood samples in critically ill infants; lack of availability of sensitive drug con-

centration assays from very small-volume specimens (eg, dried blood spots); and lack of robust clinical end points.[49]

We found that 13 drugs studied in neonates were not used at all among more than 400 000 hospitalized neonates. One reason may be that there is a disparity between the drugs being studied in neonates (particularly HIV drugs) and the conditions of patients in the Pediatrix database; 6 of the 13 drugs studied, but not used, were for HIV or HIV complications. Four drugs failed to receive a neonatal indication, including 1 to treat HIV, so it is possible that this is the reason that clinicians chose not to use these medications. The other products were for rare conditions that are not represented in the assessed population or would be used outside of the NICU: 2 were anesthetics not used in the NICU, 1 was for a rare cardiovascular condition, and 1 was for volume replacement (Table). It is possible that, because nearly one-third of the labeling changes occurred in the last 3 years of the study period, we did not capture their use because of a delay in uptake by clinicians. However, only 3 of the 10 labeling changes during that period had "safety and efficacy established," so we would not expect the drug to be used, and 2 of the 3 were HIV drugs, a rare condition in the United States, making it unlikely that extending the national review would identify increasing use of these drugs. Many factors influence drug selection in neonates, including the current standard of care, availability of the drug in the hospital formulary, and the level of comfort using a given drug in neonates in light of the existing knowledge base.

Few hospitalized neonates were exposed to a drug approved for use in neonates as a result of federal legislation (<0.5% of all drug exposures in neonates). We found that most of the exposure to drugs was off-label for neonates; only a minority of neonates received a drug approved for use in neonates (Table). Drugs that were used most often were used off-label despite studies indicating they were not effective for the indication studied. For example, ranitidine, lansoprazole, and inhaled nitric oxide (for the prevention of bronchopulmonary dysplasia) were the top 3 drugs used in neonates (representing 91% of all drug exposures in neonates from the 28 drugs studied); however, none have FDA labeling for the indication studied because of lack of efficacy. Gastroesophageal reflux is difficult to diagnose and treat, particularly in neonates. Unfortunately, antireflux medications, such as ranitidine and lansoprazole, are associated with serious adverse effects in neonates,[50] and quality improvement efforts in the Pediatrix Medical Group have reduced exposure in this vulnerable population. Although inhaled nitric oxide use is approved in term and near-term infants for hypoxic respiratory failure, it failed to prevent bronchopulmonary dysplasia and is not recommended.[51] Thus, many neonates are exposed to drugs that are not indicated in this population, exposing them to unnecessary adverse events without the possibility of clinical benefit.

There are several potential limitations to our study. Unfortunately, we could not identify the number of neonatal participants who were in 6 studies of the drugs with publicly available information from the FDA reviews and labeling. We could not determine the clinical indication for use of drugs in the Pediatrix data. For drugs that are most often used for surgery, such as remifentanil and rocuronium, we most likely underesti-

mated the exposure because we did not capture drugs that were used in the operating room. Finally, we only include neonates who were hospitalized. For premature infants, this is most likely a representative sample. However, our database does not include outpatient neonates, such as neonates who were discharged well from the term nursery.

In conclusion, federal legislation encouraging the study of products used in the pediatric population has resulted in very few labeling changes that include new neonatal information. Studying drugs in neonates is critical; however, because of scientific and regulatory challenges, trials involving neonates are scant. The rapid physiological changes in the developing neonate affect study design and end points. Study designs and procedures that are appropriate in adults and older children may not be appropriate in neonates. Extrapolation of efficacy from adults or older pediatric populations—a tool that can sometimes be used to decrease the "trial burden" for the pediatric population—is less easily adapted to the neonate. The Pediatric Exclusivity program is voluntary. Therefore, sponsors are not obligated to perform the pediatric studies outlined in the FDA's written request. Furthermore, appropriate formulations for use in neonates may not exist. Because of these challenges of performing clinical trials in infants, few labeling changes have included infant-specific information. Novel trial designs need to be developed, and appropriate study end points must be identified and validated. Education of parents and caregivers regarding the need for studies of drugs being given to neonates will also increase trial success. The scientific and clinical research community will need to work together with the FDA to conduct essential neonatal studies.

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