Eur J Clin Pharmacol (2010) 66:87–95
DOI 10.1007/s00228-009-0722-8

PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

Drug utilisation on a preterm and neonatal intensive care unit in Germany: a prospective, cohort-based analysis

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Received: 12 May 2009 / Accepted: 16 August 2009 / Published online: 16 September 2009

Abstract
Purpose This study aims to describe the drug use on a Neonatal Intensive Care Unit (NICU) at a University Children's Hospital in Germany, to investigate the licensing status of the drugs used and to conclude critical areas in neonatal intensive care to support prioritisation of future research.
Methods An 11-month, prospective cohort study was conducted on the NICU at the University Children's Hospital Erlangen, Germany. All products prescribed during the study period were analysed whether or not the SPC contains information on term and preterm neonates.
Results A total of 183 patients (102 male) with a mean gestational age of 33.6 weeks (minimum=24, maximum=42) were included. The mean length of hospitalisation was 19.4 days (minimum=2, maximum=167). On average, patients received 11.1 drugs (minimum=0, maximum=46). The majority of prescriptions were accounted for by antibiotics (n=515), which were received by 90% of all patients, followed by CNS drugs (n=448) and respiratory drugs (n=306). Of all the different drugs prescribed (n=102) only 38% had information regarding their use in patients aged less than 1 month in their SPC. Analgesics and cardiovascular drugs were prescribed frequently, but without having information for use in neonates. Seventy percent of all patients and 100% of very preterm infants received at least one of these drugs.
Conclusions Treatment strategies on a preterm intensive care unit are complex and little information is available for the drugs used. Analgesics and cardiovascular drugs are of major concern. Efforts will have to be made to conduct well-designed and powered studies in this vulnerable population.

Keywords Drug utilisation · Preterm · Neonates · Neonatal intensive care unit · Unlicensed · Off-label

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Background

Neonates and in particular preterm and very preterm neonates belong to the most vulnerable population. Very preterm neonates initially have to survive whereas older neonates are often admitted to the NICU because of congenital diseases and peri- or post-natal complications. Organ immaturity and consequently difficulties adapting to extra-maternal life are reasons for very preterm neonates being often multi-morbid and in need of intensive and complex medical care. Consequently, they are exposed to high numbers of drugs, putting them at higher risk of adverse drug reactions.

In recent years, major advances have been made in the pharmacological treatment of pre-term neonates, the average number of drugs administered per infant in neonatal

intensive care units has been increasing over the last 40 years [1]. Survival of very preterm newborns has improved; thus, clinicians face more patients with complications in this group and strategies to reduce long-term morbidity have to be developed [2].

Although it has been shown that patterns of drug utilisation in neonatal intensive care are changing dynamically [1, 3], current data on drug utilisation patterns in neonatal intensive care units are limited [3, 4].

Initiatives in the US and in Europe as well as at the WHO level aim to promote research in the paediatric population [5–8]; however, recent research indicates that a large number of drugs used in neonatology are still unlicensed or off-label [9].

We conducted this study to:

1. Quantify the drug use on a neonatal intensive care unit (NICU) specialised in preterm infants at a University Children's Hospital in Germany
2. To identify drugs most frequently used
3. To investigate the extent of information available for this population in the Summary of Product Characteristics (SPC).
4. To conclude critical areas in neonatal intensive care to support prioritisation of future research

Subjects and methods

Study cohort

Data have been collected over an 11-month period (December 2004 to October 2005). Within the study period all patients admitted to the Neonatal Intensive Care Unit (NICU) at the University Children's Hospital Erlangen, Germany were included in the study population. Patients who stayed at the ward for less than 24 h have not been included. Once patients have been discharged or transferred to other wards, e.g. Neonatal Observation Ward and other hospitals, no further data have been collected. The study has been approved by the local Ethics Committee of the Medical Faculty of the University Erlangen-Nuremberg.

Data collection

From all patients demographic data, e.g. date of birth, weight at birth and gestational age, and all drug prescriptions on the ward, were prospectively recorded. Medicines given prior to presentation at the ward, e.g. in the delivery room, were retrospectively taken from the patient record (in-house referrals) or discharge letter (transferred patients).

Data regarding the following were not collected: continuous intravenous infusions, e.g. glucose or chloride, total parenteral nutrition and oxygen administration. All drugs prescribed have been documented by product name (according to the Hospital drug list), generic name and ATC Code.

Assessment of licensing status

All products prescribed during the study period were analysed whether or not any information regarding their use in patients aged less than 1 month was provided within the Summary of Product Characteristics (SPC, Fachinformation in Germany). If no information was given the drug was classified as off-label for the study population. Drugs that were imported and chemicals prepared into a formulation within the hospital pharmacy were classified as unlicensed [10]. Since prescribing in Germany is mainly done generically, the SPCs from the products supplied from our hospital pharmacy at the time of the study were analysed.

Statistical analysis

Patients were classified as very preterm (24th–27th week of gestation), preterm (28th–36th weeks of gestation) or term–infant (≥ 37th week of gestation). Preterm infants were subgrouped according to their gestational age as shown in Table 1. Drug prescriptions have been analysed on a high-level and chemical level of the WHO Anatomic Therapeutic Chemical classification system [11]. The total number of different drugs administered to each patient and exposure rates for each drug group and individual drugs were calculated using SPSS 14.0.

Results

Patients' descriptives

A total of 183 patients, comprising 55.7% (102) male and 44.3% (81) female were included. The mean gestational age was 33.6 weeks (median=34, SD±4.66, minimum=24, maximum = 42). The majority of patients (100, 54.6%) were preterm infants; 31.1% (57) were term infants and 14.2% (26) were very preterm infants.

Approximately 20% of the patients were transferred from another hospital. The majority of these patients (56.8%) were term infants followed by very preterm infants (32.4%).

In total, 10 out of all patients admitted to the study ward died during their stay at the ward (6) or within 6 months of the study (3). One patient died 3 h after he was admitted to the ward. Two of the patients were term infants.

On average, patients stayed at the ward for 19.4 days (median=11, SD±24.65, minimum=2,maximum=167) before discharge or transfer to other wards.

Table 1 Demographics of the study population

	Very preterm neonates	Preterm neonates			Term neonates	Total
	24–27 weeks' gestation	28–30 weeks' gestation	31–33 weeks' gestation	34–36 weeks' gestation	≥37 weeks' gestation	
Number of patients	26	22	39	39	57	183
Birth weight (g)	830	1,372	1,777	2,431	3,065	2,134
SD	±248.9	±430.6	±438.7	±609.1	±556.5	±935
Length of hospital stay (days)	38.8	25	13	17	14	19.3
SD	±34.4	±24.4	±15.1	±21.7	±22.3	±24.6
Survival (%)	96.2	100	92.3	92.3	96.5	95.1
Percentage of patients u/o drug	100	86.40	51.30	61.50	68.40	69.90
Number of drugs/u/o drugs	20/9	11/3	7/2	10/4	10/4	11/4
SD	±11.5/±5.3	±6.5/±2.8	±6.9/±3.3	±10.0/ ±5.1	±8.5/ ±5.0	±9.6/ ±5.0
Number of prescriptions (total)	498	244	278	387	571	1,978
Percentage of prescriptions u/o	41.6	24.2	26.3	33.6	36.6	34.3

SD: standard deviation score, u: unlicensed, o: off label

Approximately 30% of patients hospitalised in Erlangen stayed between 1 and 5 days on the study ward, whereas about the same proportion (29.7%) of patients transferred from another hospital stayed between 11 and 20 days.

Not surprisingly, very preterm infants stayed longest, e.g. 38.5% of patients in this group were treated for more than 40 days on the ward. A summary of patient demographics is given in Table 1.

Medication/drug prescriptions

A total of 1,978 drugs have been prescribed to 181 patients, e.g. 99% of all patients received at least one drug. The mean number of drugs administered to the patients was 11.1 (median=8, SD±9.56, minimum =0, maximum=45). The majority of patients (35.5%) received between 0 and 5 drugs, 25 patients (13.7%) had 20 or more different drugs prescribed, with 40 being the highest number received by 2 patients.

According to the ATC classification system anti-infectives for systemic use ($n=515$) and drugs for the central nervous system ($n=478$) have been prescribed most often, followed by drugs for the respiratory system ($n=306$).

Overall, the drug most often prescribed is phytomenadione/vitamin K ($n=163$) followed by the antibiotics piperacillin ($n=147$) and tobramycin ($n=146$).

The majority of drugs showed highest exposure rates in very preterm infants (Table 2).

Anti-infectives

Among anti-infectives tobramycin ($n=146$) and piperacillin ($n=147$) were the drugs most often prescribed. Very preterm infants also frequently received vancomycin, cephalosporins and carbapenems.

Approximately 81% of all patients were treated with penicillins and 79.8% received an aminoglycoside antibiotic, e.g. tobramycin. Among the group of patients born between the 28th and 30th weeks of gestation 100% were treated with these drugs respectively (Table 2).

Cardiovascular drugs

Cardiovascular drugs comprising predominantly catecholamines and diuretics were mainly given to very preterm infants. Dobutamine was seen most frequently ($n=58$). The most frequently used diuretic was furosemide (total exposure rate 21.3%). However, very preterm neonates more often received spironolactone (46.2%) and hydrochlorothiazide (42.3%; Table 3).

Central nervous system drugs

Central nervous system drugs comprising anaesthetics, analgesics, anti-epileptics and psycholeptic drugs, e.g. diazepam and midazolam, showed a high number of prescriptions ($n=448$), but with a total exposure rate of only 60.7%.

All four therapeutic groups showed highest exposure rates in very preterm neonates (Table 3).

Piritramide was the analgesic prescribed most often in general ($n=56$, 31% exposure rate) and in very preterm infants ($n=16$, 61% exposure rate). Metamizole ($n=43$) was the second most frequently administered analgesic, but more often to patients born during a later period of gestation. Paracetamol was prescribed rarely. In general,

Table 2 Exposure rates (in percent) for anatomical levels of the ATC classification by gestational age

	Total	Very preterm infants	Preterm infants			Term infants
		24–27 weeks' gestation	28–30 weeks' gestation	31–33 weeks' gestation	34–36 weeks' gestation	≥37 weeks' gestation
Anti-infectives for systemic use	90.7	96.2	100	82.1	84.6	94.7
Blood and blood-forming organs	90.7	69.2	100	94.9	92.3	93
Nervous system	60.7	96.2	54.5	35.9	56.4	66.7
Anaesthetics	44.8	73.1	31.8	30.8	43.6	47.4
Analgesics	37.7	65.4	18.2	12.8	43.6	45.6
Anti-epileptics	33.9	76.9	36.4	7.7	25.6	36.8
Psycholeptics	52.5	92.3	40.9	30.8	51.3	54.4
Respiratory system	60.1	84.6	90.9	48.7	56.4	47.4
Alimentary tract and metabolism	53	76.9	72.7	41	48.7	45.6
Cardiovascular system	44.8	88.5	50	30.8	28.2	43.9
Musculo-skeletal system	39.3	69.2	40.9	20.5	38.5	38.6
Sensory organs	9.8	23.1	9.1	10.3	5.1	7
Systemic hormonal preparations, excluding sex hormone	9.3	34.6	0	5.1	2.6	8.8

only four different analgesic drugs were used on a preterm intensive care unit.

Respiratory system

Of the respiratory drugs that were given to 60.1% of all patients, theophylline (n=95) and caffeine citrate (n=38) were most frequently given, followed by surfactant (n=35).

Surfactant was received by 50% of patients born between the 28th and 30th weeks of gestation and 38.5% of very preterm infants respectively.

Among the very preterm infants born in the University Hospital Erlangen (14), 71.4% (10) received surfactant (either Alveofact® or Curosurf®).

Eighty-nine and a half percent of the patients treated with caffeine also received theophylline intravenously prior to orally applied caffeine, whereas only 35.8% of the patients initially treated with theophylline received caffeine later on.

Unlicensed/off-label drug prescriptions

A total of 102 different drugs corresponding to 135 products were analysed. Sixty-three (62%) did not have any information regarding their use in patients less than 1 month old, accounting for 34% of all medication prescribed. Among those, 4 (6.3%) were classified as unlicensed, i.e. 2 were prepared in the hospital pharmacy (caffeine and calcium gluconate) and 2 were imported (indomethacin/ibuprofen iv). The remaining 59 drugs were classified off-label. One hundred percent of anaesthetics and analgesics were found to have no information regarding use in neonates/preterm neonates. On the other hand, 7 out of 15 antibiotics used and 2 out of 6 cardiac drugs (dobutamin and alprostadil) were found to have no information, accounting for 66.3% of all prescriptions in this group (Fig. 1; Table 4).

Seventy percent of all patients received at least one unlicensed/off-label drug (mean=4 per patient, minimum=0, maximum=24). All very preterm infants (100%) received at least one of these drugs (mean=9, minimum=2, maximum = 20; Table 1).

Discussion

This study provides for the first time a detailed overview of the population and the pharmacological treatment given on a neonatal intensive care unit specialised in pre-term neonates in a German University Hospital. Analysing a total of 1,978 prescriptions our data confirm that treatment strategies in this setting are very complex. In particular, very preterm neonates are exposed to a large amount of different drugs; however, for most of the drugs little information regarding their use in this population is available.

We also showed that drug utilisation patterns in very preterm infants are different compared with newborns with a higher gestational age.

In general, our study population represents the clientele of a specialised NICU in Germany, which is shown in the high rate of patients transferred from other hospitals (20.2%; of which 56.8% were term infants and 32.4%

Table 3 Exposure rates (in percent) of most often prescribed drugs (ATC chemical level) according to different gestational ages

Drug for week of gestation =24–27			Drug for week of gestation =28–30			Drug for week of gestation =31–33			Drug for week of gestation =34–36			Drug for week of gestation ≥37		
n=26	Number	Incidence	*n*=22	Number	Incidence	*n*=39	Number	Incidence	*n*=39	Number	Incidence	*n*=57	Number	Incidence
Midazolam	21	80.8	Phytomenadione	22	100.0	Phytomenadione	37	94.9	Phytomenadione	36	92.3	Phytomenadione	52	91.2
Phenobarbital	20	76.9	Piperacillin	22	100.0	Piperacillin	31	79.5	Piperacillin	31	79.5	Piperacillin	47	82.5
Vancomycin	20	76.9	Tobramycin	22	100.0	Tobramycin	31	79.5	Tobramycin	31	79.5	Tobramycin	45	78.9
Theophylline	19	73.1	Theophylline	19	86.4	Theophylline	16	41.0	Midazolam	19	48.7	Midazolam	29	50.9
Fentanyl	17	65.4	Colecalciferol	14	63.6	Caffeine	12	30.8	Theophylline	18	46.2	Fentanyl	24	42.1
Tobramycin	17	65.4	Surfactant	11	50.00	Colecalciferol	12	30.8	Fentanyl	16	41.0	Theophylline	23	40.3
Vecuronium	17	65.4	Caffeine	10	45.4	Dobutamine	11	28.2	Vecuronium	15	38.5	Phenobarbital	21	36.8
Dobutamine	16	61.5	Vancomycin	10	45.4	Midazolam	11	28.2	Piritramide	14	35.9	Vecuronium	21	36.8
Imipenem and cilastatin	16	61.5	Imipenem and cilastatin	9	40.9	Fentanyl	10	25.6	Metamizole sodium	13	33.3	Metamizole sodium	20	35.1
Phytomenadione	16	61.5	Midazolam	9	40.9	Vecuronium	8	20.5	Omeprazole	11	28.2	Sodium fluoride, Combinations	20	35.1
Piperacillin	16	61.5	Dobutamine	8	36.4	Surfactant	7	17.9	Vancomycin	11	28.2	Diazepam	17	29.8
Piritramide	16	61.5	Phenobarbital	8	36.4	Piritramide	5	12.8	Sodium fluoride, Combinations	10	25.6	Furosemide	17	29.8
Diazepam	15	57.7	Acetylcysteine	7	31.8	Epinephrine	4	10.3	Phenobarbital	10	25.6	Piritramide	17	29.8
Caffeine	14	53.8	Fentanyl	7	31.8	Heparin	4	10.3	Furosemide	9	23.1	Dobutamine	15	26.3
Colecalciferol	14	53.8	Vecuronium	7	31.8	Imipenem and cilastatin	4	10.3	Diazepam	8	20.5	Omeprazole	15	26.3
Fluconazole	13	50.0	Oxymetazoline	6	27.3	Sodium fluoride, Combinations	4	10.3	Dobutamine	8	20.5	Vancomycin	14	24.6
Spironolactone	12	46.2	Diazepam	4	18.2	Nystatin	4	10.3	Esketamine	8	20.5	Esketamine	12	21.0
Acetylcysteine	11	42.3	Fluconazole	4	18.2	Omeprazole	4	10.3	Metronidazole	8	20.5	Imipenem and cilastatin	9	15.8
Hydrochlorothiazide	11	42.3	Ipratropium bromide	4	18.2	Oxymetazoline	4	10.3	Acetylcysteine	7	17.9	Ipratropium bromide	9	15.8
Ipratropium bromide	11	42.3	Piritramide	4	18.2	Vancomycin	4	10.3	Imipenem and cilastatin	7	17.9	Paracetamol	9	15.8

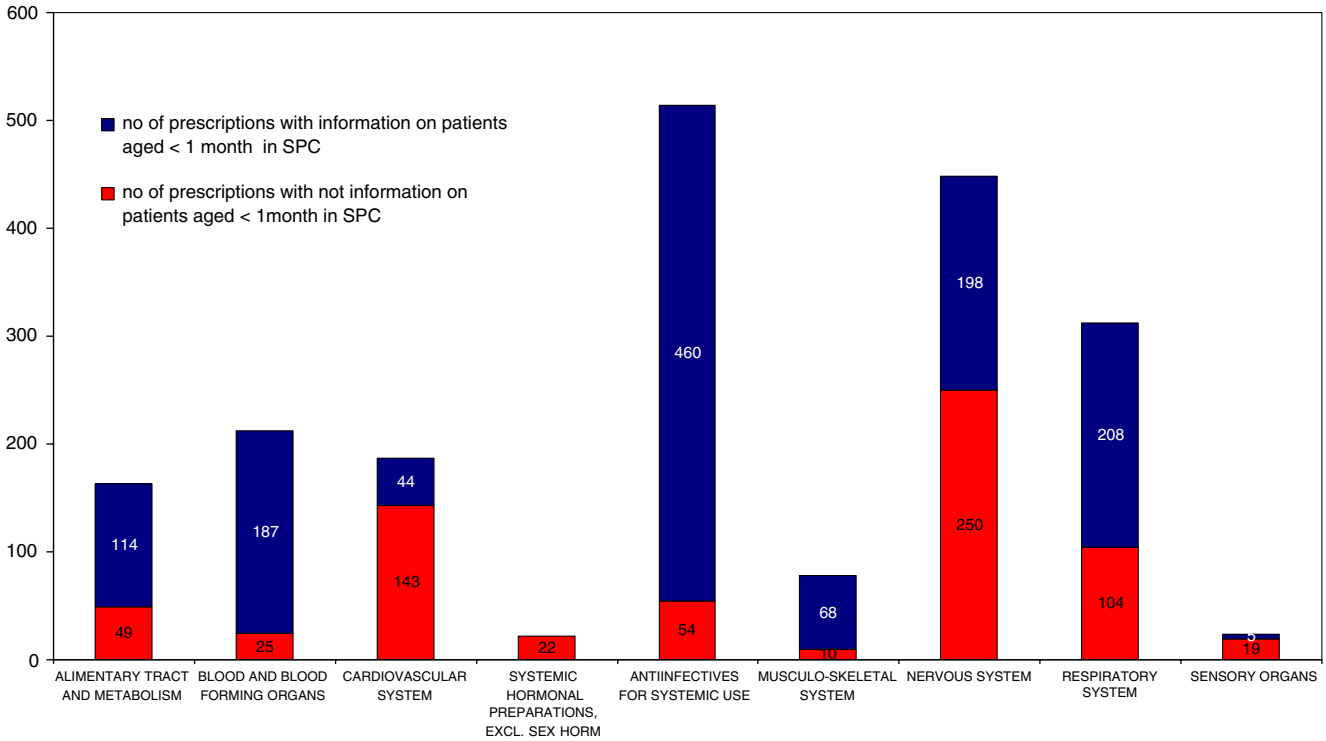

Fig. 1 Proportion of licensed and unlicensed/off-label prescriptions per ATC level

were very preterm infants). This is also reflected in the length of hospital stay, with an average of 19.4 days. A similarly high number (15.4 days) was reported by Du et al. who conducted their study in an intramural ward in the USA [1].

The mean number of different drugs given to our patients is 11.1 (SD ±9.56). Previously reported numbers vary between 3.7 [1] and 8.6 [12] drugs per patient [1, 9, 12, 13]. The high number in our study is explained by the specialisation of our study ward and the high proportion of very preterm and preterm infants (69%). Daniell and Darlow reported data from New Zealand, where even in 1989 the average number was already 14.5 drugs per patient in those with a birth weight less than 1,500 g [12]. In the USA, Warrier et al. found a lower number with an average of 9.9 drugs per patient given to those born at 24–27 weeks' gestation [4]. Du et al. and Del'Aera et al. report lower numbers; however, only about 50% of their study populations consisted of preterm neonates [1, 9]. The lower numbers in other studies

Table 4 Drug groups with most unlicensed/off-label prescriptions

	Number of drugs u/o/ total number of drugs	Total number of prescriptions	Percentage of u/o prescriptions
Drugs for acid-related disorders	1/1	35	100
Drugs used in diabetes	3/3	6	100
Antithrombotic agents	4/5	26	69.23
Cardiac therapy	2/6	101	66.34
Diuretics	3/4	81	87.65
Corticosteroids for systemic use	5/5	22	100
Anti-bacterials for systemic use	7/15	478	10.67
Anti-inflammatory and antirheumatic drugs	2/2	10	100
Anaesthetics	6/6	116	100
Analgesics	4/4	119	100
Anti-epileptics	3/4	73	15.1
Respiratory system drugs	5/11	312	33.3
Ophthalmologicals	5/6	24	79.17

may also be explained because they excluded all routine nursery care items such as vitamin K prophylaxis and exclusively considered patients born at the institution [1].

Antibiotics

Undoubtedly, antibiotics are the most frequently used drugs in neonatal intensive care. We observed that 90.7% of all our study patients were treated with at least one, but mostly two antibiotics. Within the group of very preterm infants 96.2% and among the preterm infants (28th–30th week of gestation) 100% of patients received antibiotic treatment. These absolute numbers are in line with the data published from another hospital in Germany by Gortner et al. where the exposure to antibiotics in preterm neonates (24–29 weeks' gestation) was 98.8% [14]. Similar high exposure numbers for antibiotics are reported from the USA [1, 4].

However, looking at individual drugs a great variation with regard to which drugs are used most frequently is apparent. Authors from the UK [15, 16], Australia [17] and the USA [13, 18] report gentamicin to be the most frequently used antibiotic. From Italy, Dell'Aera et al. [9] report amikacin and ampicillin to be the most frequently used antibiotic and Du et al. from the USA report cefotaxime to be the most common agent [1]. Our data show that in Germany tobramycin/piperacillin is the preferred antibiotic for neonates and preterm neonates. This heterogeneity indicates that empiric antibiotic treatment varies among neonatal intensive care units and countries and there are currently no consensus guidelines regarding the choice of empiric antibiotics.

This finding is not surprising; a Cochrane review comparing the antibiotic regimens for suspected late onset sepsis in newborn infants concluded that there is inadequate evidence from randomised trials in favour of any particular antibiotic regimen for the treatment of suspected late onset neonatal sepsis [19]. Consequently, the choice of antibiotic regimes to use depends upon personal experience and hospital policies rather than being guided by comparative clinical studies.

Respiratory drugs and surfactant

Chronic lung disease is the most common lung disease among premature newborns with an increasing incidence as birth weight and gestational age decrease [20]. Surfactant has been shown to be beneficial for the prevention and treatment of respiratory distress syndrome [21–24]. With its use, clinical practice has changed significantly over the last 25 years [25].

Hughes et al. reported a significant increase in surfactant administration between 1994 and 2001 in Northern Ireland [26] and Warrier et al. report from the USA that 100% of babies born at less than 23 weeks' gestation and 81% of patients born at 24–27 weeks' gestation (very preterm infants) were given surfactant [4].

In contrast, Lindner et al. [3] recently showed a decrease in surfactant use when comparing its use in the late 1980s and in the early 2000s in various study sites in Germany.

In our study we found that only 38% of patients born at 24–27 weeks' gestation received surfactant. The reason for this low number might be that as a specialised centre many patients were transferred from other hospitals where surfactant had been given immediately after birth, but had not been documented in the accompanying patient records. Looking at patients born at the University Hospital Erlangen between the 24th and 27th weeks of gestation, 70% received surfactant immediately after birth or later on the ward, which is in line with the numbers reported by Lindner et al. [3].

One of the reasons for the heterogeneity of this clinical practice is that the administration of surfactant needs intubation and whether the benefits of prophylactic surfactant are superior to the risks of intubation has not been shown.

Methylxanthines are well accepted therapies for neonatal apnoea; however, adequate data on safety and efficacy are still limited. In our analysis 73.1% and 53.8% of patients born at 24–27 weeks' gestation received theophylline and caffeine respectively. Lindner et al. report similar numbers from Germany: in their study, an increase in the use of methylxanthines, e.g. theophylline and caffeine, from 56.7% to 89.4% over the period 2001–2004 was observed [3]. In contrast, Warrier et al. from the US report in the same population 41.3% theophylline and 29.7% caffeine use [4].

Unlicensed/off-label prescriptions

Previous studies in neonatal intensive care units found that about 10% (9.9–12%) of prescriptions were unlicensed and about 50% (47–79%) were off-label for age, dosage or indication [9, 15, 17, 27, 28].

The percentage of prescriptions found to be unlicensed or off-label is lower in our study (34%). This is because in contrast to other studies we only investigated the licensing status for age and not for dose and indication. However, looking at the total number of products given on our NICU we found that for 69% no information on use in neonates and preterm infants was available in the product information. Furthermore, we identified that 69.9% of all patients and 100% of very preterm infants received at least one of these prescriptions with median numbers of 4 and 9 respectively. Similar numbers are given in the literature: O'Donnell et al. reported that 80% of all patients had received at least one u/o medicine, whereas Conroy et al. indicated 90% of patients had done so [15, 17].

Surprisingly, we found that there was no information available for anaesthetics and analgesics; hence, all of them were prescribed off-label. The lack of information for these medicines in neonates and preterm neonates clearly contributes to the little prescribing seen in these patients.

However, a clear increase in the use of analgesics can be seen compared with studies from the 1980s and early 1990s. This reflects the increasing awareness that untreated pain has long-term effects such as developmental retardation and alteration [28]. Nevertheless, our data show that appropriate pain treatment is still neglected in neonatal intensive care on an NICU in Germany, which is not least due to missing data, particularly in very preterm infants.

Considerable differences in the use of analgesics are seen among the countries, e.g. whereas in our ward piritramide is the dominating opioid analgesic, the majority of other authors report morphine to be the opioid of choice. In an Australian study morphine was the second most frequently prescribed drug on an NICU; in contrast, Warrier et al. do not report any analgesics among the 15 most frequently prescribed drugs, which is in line with the Italian data from Del'Aera et al. [4, 9, 17].

Metamizole is the second most frequently used analgesic in our study; however, in the USA and many other countries it is not on the market because of its capacity to induce agranulocytosis and aplastic anaemia.

Conclusion

We provide an unique and detailed overview of the drugs used on a specialised NICU in Germany. The data show that there are many similarities, but also differences in treatment regimes compared with the few previously published studies from Germany and other countries.

In summary, this reflects the uncertainties in neonatal drug therapy due to a lack of data and confirms the need for future larger scale randomised controlled trials. A large proportion of patients are treated with non-licensed medicines, e.g. every very preterm baby on the NICU receives at least one drug for which no information on safety and efficacy is available. In particular, cardiovascular drugs, including diuretics and anaesthetics/analgesics are of major concern. The European regulatory authorities have recognised paediatric therapeutic needs and some of the drugs frequently given to very preterm infants, such as midazolam, fentanyl, dobutamine or hydrochlorothiazide, are already on their list of off-patent drugs [29]. Well-designed and powered multicentre and cross-nationality studies will have to be conducted as the key to successful improvement of drug therapy in neonates and preterm neonates in particular.

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