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Detecting Adverse Drug Reactions on Paediatric Wards

Intensified Surveillance Versus Computerised Screening of Laboratory Values

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Abstract

Background: Adverse drug reactions (ADRs) contribute significantly to patient morbidity and mortality, as well as to costs for healthcare systems. Our aim was to evaluate the type and incidence of ADRs in a paediatric hospital population, comparatively ascertained by two different methodological approaches.

Methods: Our prospective study enrolled all patients admitted to two of the general children wards (46 beds) and the paediatric intensive care unit (6 beds) at the HELIOS Klinikum Wuppertal teaching hospital in Germany, over the study period of 3 months. We used two methods to detect ADRs. The intensified surveillance system relied on a trained physician conducting ward rounds and assessing patient charts. The computer-assisted screening of pathological laboratory parameters used values slightly below or above the age-specific normal range as a trigger signal for a potential ADR, which was subsequently assessed by trained personnel.

Results: By applying both methods simultaneously we observed that 14.1% of children experienced an ADR while they were hospitalised and 2.7% of children were admitted to hospital because of the ADR. Intensified surveillance resulted in the detection of 101 ADRs in 11.9% of patients, predominantly presenting with gastrointestinal symptoms, skin and CNS disorders; computer-assisted screening identified 45 ADRs in 5.7% of patients, mainly with drug-induced blood dyscrasia and liver damage. Furthermore, the ADRs detected by the intensified method were more severe, affected younger children and showed a closer causal attributability to the reaction than the ADRs observed by the computerised method. The spectra of drugs involved were similar, with the anti-infectives being suspected most frequently. The sensitivities of the intensified surveillance system and the computerised surveillance screening came to 67.2% and 44.8%, respectively, with computer-assisted screening having a specificity of 72.8%. The mean positive predictive value of the pathological laboratory values under surveillance by computer-assisted screening was 18.6%. Approximately 25% of ADR-related drugs administered were used for off-label indications.

Conclusion: Using the published literature for comparison, we found that ADRs occur as frequently in paediatric patients as in adult patients. Intensified surveillance and computerised surveillance applied in the paediatric setting show substantial differences in their detection specificities. A higher number of and more

severe ADRs can be detected by intensified surveillance than by computerised surveillance, but require higher personnel resources.

Background

Adverse drug reactions (ADRs) contribute significantly to morbidity, mortality and hospitalisation costs in industrialised countries.[1-3] Recent meta-analyses indicate a frequency of inpatient ADRs in adult medicine of 10.9%, with 4.7% of patients being admitted because of an ADR;[3] corresponding figures in paediatric patients are 9.5% and 2.1%, respectively.[4] The ADR frequency in the published paediatric studies ranges between 5.6% and 16.8%[5-8] for inpatients and between 0.6% and 4.1% for ADR-induced hospital admissions,[9,10] which reflects the different populations and different ADR detection methodologies. Although in adult medicine several methods of ADR detection have been tested and implemented,[11-15] in paediatrics only a few methodological approaches have been applied. However, children are considered to be particularly susceptible to ADRs due to physiological changes during growth, the need for weight- or body surface area-adapted drug doses and the limited communication abilities. In addition, data on safety and optimal use of many drugs in paediatric patients are limited.[16] This situation often forces paediatricians to prescribe drugs that are unlicensed or outside the terms of their product license ('off-label'),[17] which seems to be associated with a higher risk for ADRs.[18]

The aim of the following prospective study was to estimate the incidence of ADRs in hospitalised children. A ward-based comprehensive monitoring of clinical signs and symptoms suggestive for ADRs was performed and compared with a computer-assisted screening of pathological laboratory values that are potentially associated with ADRs. Only a few comparative methodological approaches have been published so far.[12,19,20]

Methods

Patients

This prospective study was carried out in the Department of Pediatrics at the HELIOS Klinikum Wuppertal teaching hospital of the University Witten/Herdecke, Germany. All patients admitted to two of the general children wards (46 beds) and the paediatric intensive care unit (ICU) [6 beds] were included. Patients on the oncological ward, as well as out-patients, were excluded.

The comprehensive collection of ADRs was conducted over a 13-week period (91 days) between February and May 2001, whereas the computer-assisted surveillance – because of technical problems – was feasible only over an 80-day period from March to June 2001 with an overlapping period of 52 days.

Intensified Surveillance System

Children were assessed daily (except at weekends) for the presence of any suspected ADR by a trained physician who participated in ward rounds and questioned the attending paediatrician, nurses, patients and their parents. Furthermore, medical and nursing records were examined for notes that raised suspicions of a potential ADR, such as changes in medication. Data collection was supervised by an experienced clinical pharmacologist (P.T.), with whom all ADRs were discussed. Documentation of patients with suspected ADRs was performed on an MS Excel worksheet (Microsoft, version 7.0), including initials, gender, age, weight and height, date of admission and discharge, admission diagnosis, ADR description (duration and time of occurrence, severity, treatment), suspected drug(s) and co-medication (dose, route and duration of administration, causality with regard to the ADR). Furthermore, the primary source of information (nurses, paediatricians, patients, their parents, medical records) was recorded.

Computerised Surveillance of Pathological Laboratory Values

By assessing similar studies in internal medicine[12] and neurology,[20] laboratory parameters that could indicate an ADR were defined (table I and table II). Values slightly below or above the

Table I. Physiological laboratory values giving rise to a laboratory filter signal (LFS)[a]

Physiological parameter	LFS
White blood cell count	<0.8 × LLN
Platelet count	<0.5 × LLN and >1.25 × ULN
Haemoglobin level	<0.9 × LLN
Eosinophil count	>1.25 × ULN
AST or ALT level	>1.5 × ULN
Alkaline phosphatase level	>1.25 × ULN
Total bilirubin level	>1.5 × ULN
Creatinine level	>1.25 × ULN
Creatine kinase level	>1.5 × ULN
Blood glucose level	<0.9 × LLN and >1.25 × ULN
Sodium level	<0.9 × LLN
Potassium level	<0.8 × LLN and >1.25 × ULN
Lactate level	>1.0 × ULN

a Indications have been given relatively because of age-dependently varying limits.

ALT = alanine aminotransferase; **AST** = aspartate aminotransferase; **LLN** = lower limit of normal; **ULN** = upper limit of normal.

age-specific normal ranges of the hospital's laboratory were considered as trigger signals for a potential ADR. Since there are – in contrast to adults – no defined ranges where pathological laboratory values are considered to be indicative of a potential ADR (e.g. 2-fold elevations in liver enzyme levels according to the Council for International Organizations of Medical Sciences [CIOMS] criteria[21]) for paediatric patients, we chose the gap between normal range and ADR-trigger arbitrarily; however, this value was always close to the normal range and was chosen by considering the cut-off point where paediatricians would normally react. The computer-based monitoring system generated a daily list of 'laboratory filter signals' (LFSs), including the patient's name, medical record number and date of event. Regular (three times weekly) checks of these filtered laboratory values were performed by the department of clinical pharmacology. The cause of each LFS value was evaluated by reviewing each patient's medical chart and contacting the attending paediatrician. Initials and demographic data of patients showing LFSs, as well as other relevant information (e.g. LFSs, diagnoses, considerations concerning the causality of the LFS), were entered into a relational database (Microsoft Access 97). Once there was a suspicion of an ADR, information about the ADR (nature/type, intensity, course/outcome, treatment, preventability) and up to three suspected causative or interacting agents (dose, route of administration, duration of treatment, attributability to the LFS) were documented, as well as the total number of drugs administered. Again, all suspected cases were discussed with a paediatrician and supervised by a clinical pharmacologist.

Classification of Adverse Drug Reactions (ADRs) and Medications

ADRs were defined according to the WHO definition.[22] ADRs due to drugs used in an off-label manner were included,[22] whereas prescribing and dispensing errors were excluded. The sources of information for the verification of potential drug adverse effects were the manufacturer's summary of product characteristics (German 'Fachinformation')[23] and the most recent edition of the quarterly updated Micromedex database.[24]

Causality assessment was performed according to the WHO classification scheme, considering chronological and symptomatological aspects, as well as other potential causes.[22,25] For ethical reasons no active rechallenge was performed, but rechallenge information was used when available. Only 'possible', 'probable' and 'definite' ADRs were taken into consideration.

The severity of verified ADRs was classified using a severity score ranging from grade 1 to 5 as follows: severity of '1' denoted an ADR without physical or psychological impairment; '2' an ADR with slight physical or psychological impairment;

Table II. Drug monitoring concentrations giving rise to a laboratory filter signal (LFS)

Drug	LFS
Digoxin	>2.2 μg/L
Digitoxin	>25 μg/L
Gentamicin	>12 mg/L
Vancomycin	>40 mg/L
Theophylline	>20 mg/L
Carbamazepine	>12 mg/L
Phenobarbital (phenobarbitone)	>45 mg/L
Primidone	>15 mg/L
Ethosuximide	>120 mg/L
Phenytoin	>25 mg/L
Valproic acid (sodium valproate)	>150 mg/L

'3' an ADR with moderate physical or psychological impairment that requires action to be taken; '4' an ADR with severe physical or psychological impairment, with the necessity of therapeutic intervention and intensive care; and '5' an ADR with lethal progress. Since ADRs with a severity grade of 3–5 necessitated therapeutic interventions, they were analysed together in comparison with ADRs of severity grade 1 and 2. Furthermore, we classified ADRs as type A or B reactions as described by Rawlins.[26]

Classifications of affected organ systems and ADR associated drugs were performed following WHO standards ('system organ class' [SOC] and 'anatomical therapeutic chemical' [ATC] classification systems). In order to classify drug use as being off-label, we used the German official summary of product characteristics (SPC).[23] We defined off-label use in a very strict way as follows: (i) as any use of the drug outside the licensed age range; and (ii) if the use was clearly outside the range of given indications.

Data Analysis

Age, number of drugs administered and duration of hospitalisation are given as mean, standard deviation and median values. Incidence calculations were performed by using the hospital administrative database. Multiple hospitalisations of the same child were counted as multiple patients. ADR incidence was calculated as a percentage of patients with an ADR and, for consideration of the wide range of duration of hospitalisation, estimated as number of ADRs per 1000 patient days.

The relation between age and frequency, as well as severity, was evaluated by Fisher's exact test; the two-sided median test was applied to detect a correlation between duration of hospitalisation and occurrence of ADRs.

For each laboratory value the positive predictive value (PPV) was calculated as the percentage of LFSs indicating an ADR. Assuming that there was a complete collection of ADRs during the simultaneous application of both methods, the sensitivity and specificity of the methods were calculated. The sensitivity of each approach was defined as the percentage of ADRs that were detected with one method, as compared with the total number of ADRs observed with both methods combined. The specificity of the computer-assisted surveillance system was estimated as the percentage of patients without ADRs and without LFSs out of the total number of patients without an ADR. For statistical comparisons Stata® 7.0 (Stata Corporation 2001) was used.

Results

ADRs Detected by Intensified Surveillance

During the intensified surveillance period of 91 days, 703 patients (295 females; 42.0%) with a mean age of 4.6 ± 5.1 years (median 2.2 years) were admitted to the three wards (table III). Their mean duration of stay was 7.2 ± 13.2 days (median 5 days). The most frequent admission diagnoses were respiratory diseases 20% (respiratory infections 11%, asthma and obstructive diseases 6%), gastrointestinal diseases 10% (infectious origin 7%), neuropsychiatric disorders 8%, as well as trauma and cardio-circulatory disorders, congenital abnormalities and non-organ related infections (each 4%).

Daily surveillance revealed 101 ADRs that occurred in 84 patients (35 females 41.7%) with a

Table III. Demographic data of patients according to the method of data collection

Demographic	ISS (91 days)	CLS (80 days)
Patients admitted[a] (n)	703	636
sex (male/female)	408/295	354/282
age (yrs, mean ± SD; median)	4.60 ± 5.14; 2.19	4.97 ± 5.25; 2.39
Patients with ADR (n)	84	36
sex (male/female)	49/35	22/14
age (yrs, mean ± SD; median)	2.79 ± 4.19; 0.90	6.54 ± 5.43; 5.38
ADR frequency (%/ADRs per 1000 patient days)	11.95/23.22	5.66/12.75
age ≤1 yr	17.65[b]/27.24	3.70/6.54
age >1–5 yrs	10.58[b]/22.70	4.89/14.62
age >5–10 yrs	8.49[b]/17.51	6.32/19.23
age >10 yrs	5.97[b]/15.85	9.22/22.95

a Multiple hospitalisations of the same child were counted separately.

b Incidence and severity grade significantly dependent on age (Fisher's exact test, $p < 0.05$).

CLS = computerised alert system; **ISS** = intensified surveillance system.

mean age of 2.8 ± 4.2 years (median 0.9 years), i.e. 12.0% of all patients admitted to these wards experienced at least one ADR, which resulted in an ADR frequency of 23.2 ADRs per 1000 patient days (table III and table IV). In 13 cases the ADR was the cause for the hospital admission (1.8% of all admissions). The duration of stay in children having an ADR was 14.3 ± 27.3 days (median 9 days, 95% CI 8.0, 10.5), which was significantly longer than children without ADRs (6.3 ± 9.5 days, median 4 days, 95% CI 4.0, 4.4; $p < 0.05$). Children <1 year of age were significantly more frequently affected by ADRs (17.7%) than children >10 years of age (6.0%; $p < 0.01$). The incidence of ADRs in the ICU came to 9.2%.

The organ systems mainly affected by the 101 ADRs (table V) were the gastrointestinal tract (n = 61, 60.4%), the skin (n = 27, 26.7%), the CNS (n = 6, 5.9%) and the cardiovascular system (n = 4, 4.0%). The most frequent adverse events were diarrhoea (n = 45, 44.6%), exanthema (n = 17, 16.8%) and candidosis (n = 10, 9.9%).

Thirty-one (30.7%) ADRs were judged to be grade 3 or 4 and two (2%) of these ADRs required intensive care surveillance. Almost all ADRs resolved within 8 days (n = 90, 89.1%). Although younger children were significantly more likely to suffer from an ADR, their ADRs were of significantly lesser severity ($p < 0.05$) [table IV]. The majority of ADRs (n = 69, 68.3%) were classed as 'probable' in the causality assessment and most of the ADRs (n = 81, 80.2%) were classified as type A reactions.

Patients with ADRs received a mean of 6.3 ± 3.2 (median 6) drugs (ICU patients received a mean of 9.5 ± 5.6 drugs, median 8). The most common groups of ADR-related drugs were anti-infectives (n = 84), including cefuroxime (n = 31), erythromycin (n = 25) and sulbactam/ampicillin (n = 14), followed by antiasthmatics (n = 15), antiepileptic drugs (n = 8) and cardiovascular drugs (n = 7). Twenty-one (20.8%) ADRs were caused by two or more interacting drugs.

The decisive information for the detection of an ADR was provided by the nurses in 31% of cases and the patient records in 30%, followed by physicians (21%), patient relatives (12%) and patients themselves (6%). By the time of our investigation 92 (91.1%) of the 101 ADRs had already been documented in the patient record.

ADR Detection by Computerised Surveillance of Laboratory Values

During this 80-day surveillance period, a total of 636 patients (282 females; 44.3%) with a mean age of 5.0 ± 5.3 years (median 2.4 years) and a mean duration of stay of 7.0 ± 13.6 days (median 4.0 days) were admitted (table III).

A total of 296 LFSs in 184 patients (28.9% of all 636 patients admitted during the surveillance period) were detected. In 148 patients an ADR could be excluded after their medical records were checked. In the remaining 36 patients, 45 ADRs could be verified (22 males, 14 females; mean age 6.5 ± 5.4 years, median 5.4 years). The overall incidence of ADRs was 5.7% or 12.8 ADRs per 1000 patient days (table III and table IV). Older children were more often affected than toddlers. The duration of stay for the children with ADRs was significantly longer than for those without: median 6 days (95% CI 4.6, 9.4) versus 4 days (95% CI 4.0, 5.0; $p < 0.05$). Five of the 45 ADRs were the reason for hospital admission (0.8% of all admissions).

Table IV. Distribution of adverse drug reactions (ADRs) according to the method of data collection

ADR characteristics	ISS (91 days)	CLS (80 days)
Total number identified	101	45
Leading to hospitalisation (% of all admissions)	1.8	0.8
Severity ≥ grade 3 (%)	35.7	22.2
age ≤1 yr	26.7[a]	0.0
age >1–5 yrs	31.8[a]	11.1
age >5–10 yrs	66.7[a]	33.3
age >10 yrs	62.5[a]	38.5
Causality (%)		
'possible'	28.7	80.0
'probable' or 'definite'	71.3	20.0
Type (%)		
type A	80.2	15.6
type B	19.8	60.0
type not attributable	0.0	24.4

a Incidence and severity grade significantly dependent on age (Fisher's exact test, p < p.p5).

CLS = computerised alert system; **ISS** = intensified surveillance system.

Table V. Comparison of ADRs detected by the intensified surveillance system and the computerised surveillance system

Affected system	% of all ADRs	ADR	Total number	Severity grade 3 or 4 (n)
Intensified surveillance system				
Gastrointestinal tract	60.4	Diarrhoea, vomiting, constipation	60	6
		Hepatomegaly	1	1
Skin and mucosa	26.7	Exanthema	17	7
		Candidosis	10	8
CNS	5.9	Dyskinetic CNS symptoms	5	4
		Apnoea	1	1
Cardiovascular	4.0	Blood pressure dysregulation	2	2
		Tachycardia	2	2
Other	3.0	Fever	1	0
		Oedema	1	0
		Anaphylaxis	1	1
Computerised surveillance system				
Blood	62.2	Leukocytopenia	10	0
		Leukocytopenia with thrombocytosis	1	0
		Leukocytopenia with thrombocytopenia	1	0
		Eosinophilia	7	2
		Thrombocytosis	6	0
		Anaemia	3	0
Liver	26.7	Elevated transaminase levels	7	2
		Elevated alkaline phosphatase levels	5	1
Other	11.1	Hyperkalaemia	1	1
		Hyperglycaemia	1	0
		Myositic AST/CK elevation	1	1
		Elevated serum creatinine level	1	0
		Elevated drug concentration	1	1

The LFSs that were related to the 45 ADRs (table V) were leukocytopenia (n = 12, 26.7%), elevated liver aminotransferase levels (n = 7, 15.6%), thrombocytosis or thrombocytopenia (n = 6, 13.3%), eosinophilia (n = 7, 15.6%), elevated alkaline phosphatase levels (n = 5, 11.1%), and anaemia (n = 3, 6.7%). The overall PPV of the LFSs was 18.6% (55 of 296 LFSs were ADR-associated), with elevated liver enzyme levels and leukocytopenia having the highest PPV of 50% and 35.3%, respectively (figure 1).

Thirty-three ADRs (73.3%) were classified as severity grade 1, four ADRs (8.9%) were classified as severity grade 2 ADRs with mild impairment, and seven ADRs (15.6%) were assigned to severity grade 3. Only one ADR (2.2%) led to ICU treatment (severity grade 4). No ADR-related death occurred. In contrary to the intensified surveillance system, a trend towards more severe ADRs in the older children did not reach statistical significance (table IV). Thirty-six (80.0%) of the ADRs were judged as 'possible', whereas only four (8.9%) were classified as 'probable' and five (11.1%) as 'definite' in the causality assessment. Only 7 ADRs (15.6%) belonged to type A reactions, whereas the majority, 27 (60.0%), were type B reactions (table IV). Eleven ADRs (24.4%) could not be clearly assigned to one of the ADR types.

Patients with ADRs received a mean of 3.0 ± 2.8 (median 2) drugs (ICU mean of 5.8 ± 5.1, median 4.5) at the time point of occurrence of the reaction. In most cases (n = 36) one single drug was suspected for being the causative agent, in six ADRs two drugs were suspected in combination and in another three ADRs three drugs could be related. The most frequent ADR-associated drug groups were anti-

infectives (n = 35), including cefuroxime/cefotaxime (n= 10/4) and ampicillin/amoxicillin (n = 5/2), followed by anticonvulsants (n = 13) and cardiovascular drugs (n = 6). A drug-drug interaction was suspected in nine (20%) of the ADRs.

Combination of the ADR Surveillance Systems

Restriction to the overlapping period of 52 days and combination of both surveillance methods resulted in a total of 76 different ADRs in 58 (24 females; 41.4%) of 411 patients admitted to the hospital during that period (169 females; 41.1%). ADR characteristics during this overlapping period with respect to type, severity and drug causality were comparable to data shown for the separate analyses. The combined incidence of ADRs came up to 14.1% (or 32.8 ADRs per 1000 patient days), of which 11 patients were admitted because of the ADR (2.7% of all admissions). The sensitivity of the intensified surveillance system was calculated to 67.2%; in contrast, the sensitivity of the computerised approach was 44.8% with a specificity of 72.8%. In the overlapping surveillance period only four ADRs (5.3%) were detected simultaneously by both methods. These were only counted once in the respective calculations. Furthermore, another four ADRs detected by the computerised system in patients having already appeared in the intensified surveillance system were shown to be different from

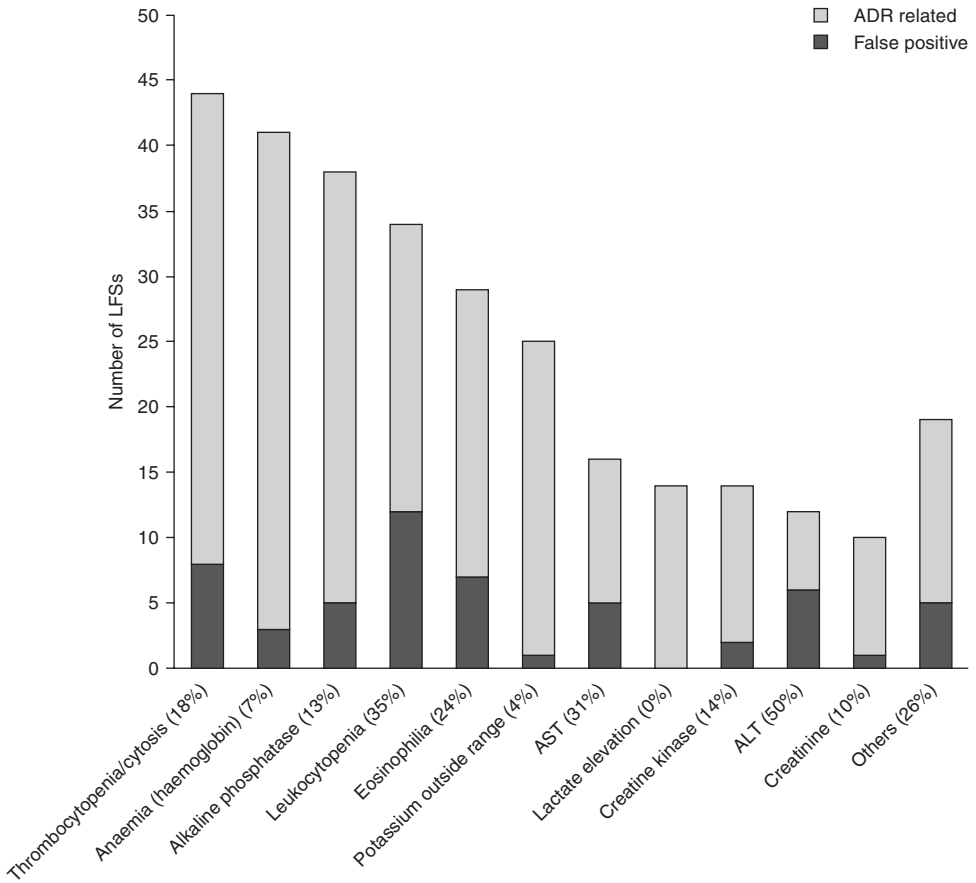

Fig. 1. Laboratory filter signals (LFSs) [n = 296] detected by computerised surveillance of pathological laboratory values. The positive predictive value (regarding LFSs pointing to an at least possible ADR) is given as a percentage in brackets. **ADR** = adverse drug reaction; **ALT** = alanine aminotransferase; **AST** = aspartate aminotransferase.

the respective ADRs that were detected by the intensified method.

With regard to all drugs identified as having the potential to result in an ADR during the whole study, in eight cases (4.5%) there was no information at all about paediatric indications in the German SPC, in 18 cases (10.1%) drugs were definitely not indicated for the age of the child treated and in an additional 18 (10.1%) cases, the paediatric labelling status was not clear from the SPC, i.e. the indicated paediatric age range did not include a lower age limit.

Discussion

A number of studies have been published,[5-10,18,19,27-37] where ADRs were evaluated in paediatric hospitals. However, to our knowledge, different methodological approaches for ADR detection in children have only been compared in one limited pilot study under very special conditions, to date.[19] To extend this approach to a more general paediatric population we conducted and compared a ward-based intensified surveillance system and a computerised alert system utilising potentially ADR-associated pathological laboratory values as described by others for the use in adult medicine.[12-15,20]

Comparison of Methodological Approaches for ADR Detection

By comparing the methods applied, we found a sensitivity of 67.2% for the ward-based monitoring and a sensitivity of 44.8% for the surveillance using pathological laboratory values. The higher sensitivity of the intensive monitoring is not an unexpected finding; similar results were obtained in a paediatric isolation ward study by Weiss et al.[19] (sensitivity of staff physicians' recognition was 50% and of laboratory findings was 40%; the percentages refer to ADRs, not to patients) and also by our group in a department of neurology (sensitivity of intensified surveillance 71.8%, computerised surveillance 45.1%),[20] as well as by Levy et al.[13] in an internal cardiopulmonary ward (sensitivity of staff physicians' recognition was 84.5%, automated laboratory surveillance was 62%). Other similar studies on internal medicine wards achieved superior sensitivity values for computerised alert systems than for 'stimulated spontaneous' or 'enhanced voluntary' reporting or retrospective chart review.[12,14] However, in these studies the ward-based monitoring was not as comprehensive as our intensive daily visits and the retrospective chart review for ADR detection, as was used in two of the studies,[12,13] relied on clinical documentation, which was frequently incomplete in terms of ADRs.[38]

The PPV of the LFSs was 18.6%, which is comparable to that reported in adult studies of 12.6%,[12] 17.6%[13] and 24.2%,[20] although these numbers certainly depend on medical specialties and underlying diseases. Because of rapid changes in certain laboratory values during the growth period, we had to adapt our detection limits carefully in each individual case to the age-specific normal range of the laboratory value under investigation. In order not to miss too many ADRs we fixed our signal limits close to the border of the normal ranges (table I and table II) and thereby accepted a lower specificity and lower PPVs of our LFS (figure 1). The relative specificity (true negative laboratory values) in our investigation came up to 72.8%. This value is as low as is shown in comparable investigations in adults with 75%,[12] 42.2%[13] and 78.9%,[20] and somewhat limits the value of pathological laboratory data as a routine ADR identification tool. Unfortunately, no number of false positive laboratory signals was given by Weiss et al.[19]

A possible remedial action for improving the efficiency of our electronic alert system is the implementation of additional clinical information like admission diagnosis, medication or antidote ordering, sudden dose variations, diagnostic findings and clinical events into computerised detection algorithms, an approach which has been published from few hospitals.[14,15] However, such a record linkage requires a sophisticated hospital information system that has been realised in only a few hospitals in Germany so far; in the US about 13% of hospitals rely completely on electronic patients' charts and in 32% the installation of such a system has begun.[39]

Frequency of ADRs

The combination of both detection methods in the respective overlapping period resulted in an ADR frequency of 14.11%, with 2.7% ADR-

induced admissions. The ADR incidence that is described for children in the literature is comparable to our findings with given ranges between 4.4% and 21.5%[5-8,18,19,27-29] and for admission rates due to ADRs between 2.0% and 4.3%.[1,9,30-32] In a recently published meta-analysis Impicciatore et al.[4] stated that the overall rate of paediatric hospital admissions due to ADRs was 2.1% and the incidence of ADRs for hospitalised children was 9.5%. In contrast to all but one[29] of the studies included in this meta-analysis, we excluded haemato-oncological patients from our considerations. Confirming our data, Martinez-Mir et al.[29] observed a similar ADR incidence in their population (children up to 2 years of age) as we did when we restricted our analysis with the combined methods' approach to a similar age group (0–5 years of age; 14.4% vs 15.5%).

With regard to age distribution, we observed a higher ADR-frequency in younger children by the ward-based monitoring, which may reflect the increased disposition of toddlers for diarrhoea and candidosis. On the other hand, the frequency of blood sampling for laboratory values may be lower in the younger age group and therefore less ADRs could be detected by LFSs in this age group. Contradictory results for the age distribution of ADRs were reported by other authors, who described decreasing,[35] unchanged[28] or increasing incidences of ADRs along with age in children.[5,7] These discrepancies may be explained by the different methodological approaches used, the different length of stay of children in different age groups and the different specialties included (e.g. no haematological diseases in our survey).

Astonishingly and unlike former findings of especially high rates of ADRs in paediatric ICUs,[33,34] but in accordance with Gill and coworkers,[35] we detected a similar or even lower ADR frequency in our ICU with 16.3% or 23.1 ADRs per 1000 patient days versus 13.9% or 34.5 ADRs per 1000 patient days on the general wards. Supposing intensified drug therapy in ICUs,[18] i.e. in our study a mean number of 6.7 drugs were given daily to each patient with an ADR on ICU versus 4.7 on the general wards, this finding contradicts the hypothesis that the risk of ADRs increases with the number of drugs applied.[5-7,18,28] One reason for our surprising observation may be the fact that the low number of patients (n = 43 children) during our observation period is not representative. Furthermore, the highly complex clinical situation on ICU may impede the causality assessment.

Characteristics of Detected ADRs

Using the intensified surveillance system we mainly found adverse gastrointestinal and skin reactions in younger children and with a rather close causal relationship. In contrast, when using the computerised surveillance system we predominantly observed alterations in blood counts and liver function tests, particularly in older children, where the causality assessment was often obscured by underlying diseases. In addition, the latter ADRs were often very mild, almost invisible clinically and of an idiosyncratic nature (rare ADRs, not dose-related), in contrast to the usual predominance of type A reactions as described in other studies[5,6,18] and also by our ward-based monitoring with only 19.8% type B reactions. By means of intensified surveillance we detected not only more, but also more severe, ADRs than by using the computerised alert system. Regarding the severity of ADRs, the meta-analysis by Impicciatore et al.[4] revealed an average of 12.3% of ADRs classified as severe, although definitions of severity were not applied using a strictly uniform definition in all of the studies. For instance, we have used 'necessity for treatment in the ICU' as a criterion for severity grade 4 ('severe'), which might be a stricter definition than 'potentially life threatening' in other studies. Accordingly, we reported a low rate of severe ADRs with 2.0% of all ADRs for the intensified surveillance system and 2.2% for the computerised surveillance system.

In our ward-based monitoring, more than 60% of all ADRs affected the gastrointestinal system, which is a higher percentage then in comparable studies that reported a maximum of 42.5%.[7] One reason for this might be the inclusion of parents as a source of information in the current study, who reported 10 of 61 gastrointestinal ADRs. However, we did not use a very strict definition for diarrhoea (two subsequent really loose stools per day), so the number of patients with antibacterial-associated diarrhoea may be relatively high. Skin manifestations including exanthema and candidosis also occurred quite frequently among the children in our study (27%) when

compared with the literature with a maximum of 25%.[35] Both, the gastrointestinal and skin ADRs were mainly attributed to anti-infective drugs, which seem to be involved in ADRs to a larger extent than in other publications, with the exception of Weiss et al.,[19] who unfortunately did not specify the different kinds of ADRs found in their study. In contrast, CNS symptoms were relatively rare among the ADRs identified using our intensified surveillance system (7%), although the literature reports higher numbers of between 14% and 22%.[6,28,29]

With the computerised surveillance system, haematotoxicity and hepatotoxicity were responsible for the majority of ADR-related LFSs. Blood count or liver function test alterations in adults were shown to be in the forefront.[12,13,20] On the other hand, other parameters, such as serum creatinine levels and electrolyte disturbances, played only a minor or no role in paediatric LFSs. As mentioned previously, the spectrum of useful laboratory parameters and their PPVs strongly depend on the patient population, with their age-related specific underlying diseases and treatment.

The method-inherent differences in the detected ADRs resulted in a very small overlap of events (5.3% of all ADRs in the overlapping period). Therefore, the combination of both systems could be considered as complementary in our setting and increased the efficiency of the ward-based monitoring. This is confirmed by the results of Weiss et al.[19]

Drugs Leading to ADRs

In our study antibacterials were the most frequently suspected drugs (intensified surveillance system 67.7%, computerised surveillance system 61.4%) followed by antiasthmatics and antiepileptics. This is in accordance with findings presented by others,[18,19,29,35-37] whereas in some reports, including those on oncological patients,[6,7,28] antineoplastics were believed to result in the most ADRs.

Unfortunately, we were not able to document all drug-prescriptions and, therefore, were not able to estimate incidences of ADRs in relation to drug use. One recent and comparable study, also excluding cytostatics and HIV drugs, showed a consistent relation between frequency of drug usage and frequency of ADRs.[29]

A particular point of concern is the off-label use of drugs in children. Turner et al.[18] showed a higher percentage of ADRs with unlicensed or off-label drugs (6% vs 3.9% in drugs used according to their license), especially concerning severe ADRs (14 of 19 involved drugs). Recently, in a French study, a higher rate of ADRs associated with off-label drug use also in paediatric outpatients was shown (relative risk 3.44).[40] Unfortunately, definitions and their application for unlicensed or off-label drug use differ in the individual studies. In our study, approximately 25% of the drugs associated with ADRs were either not labelled for the age of the patient treated or the age labelling status was unclear. Neubert et al.[41] reported a frequency of 27% for unlicensed or off-label drug use on a German paediatric isolation ward, where off-label drug use was not associated with a higher incidence of ADRs. Our figure is lower than is described in most other studies for total paediatric drug usage.[17,40,42] The reason could be our restriction to consider only the licensed age range of a drug and not its dose and frequency of administration or its exact indication. Secondly, we cannot provide data for the overall prescription of off-label drugs during the observation period. Finally, country-specific differences in licensing status, drug use and manufacturing or modification practices of the hospital pharmacies[42] have to be taken into account.[17]

Admission Diagnosis and Length of Hospitalisation

Most of our patients experiencing ADRs were admitted because of infectious or non-infectious respiratory diseases (intensified surveillance system 56.0%, computerised surveillance system 22.2%), other localised or systemic infections (intensified surveillance system 11.9%, computerised surveillance system 36.1%) and CNS affections (all but one seizure disorder) [intensified surveillance system 5.9%, computerised surveillance system 13.9%]. These numbers coincide with those of other authors,[6,7,28,35,37] whose ADR patients were also primarily admitted because of respiratory (24–36%) and infectious diseases (18–26%). Our data collection period included the late winter months with

their summit of respiratory infections, which could have accentuated our rate of antibacterial and antiasthmatic treatment, as discussed by Martinez-Mir et al.[10]

Children with ADRs had a significantly longer stay in hospital than patients without ADRs. We cannot conclude to what extent this is attributable to the ADR, since we were not able to adjust for risk factors, e.g. age, sex, type and severity of illness, comorbidity or number of drugs. In two studies in adults,[1,2] an increase in the length of hospitalisation of roughly 2 days per ADR has been calculated after appropriate adjustment. On the other hand, one study in adults showed a rise in the rate of adverse events (not only ADRs) due to prolonged hospitalisation.[43]

Conclusion

In conclusion, we were able to demonstrate an ADR frequency in children of at least a similar extent to the published values given for adults. Applied in paediatrics, the ADR surveillance methods of comprehensive ward-based monitoring and screening of laboratory values show substantial differences in their detection specificities and can act complementarily if combined. Intensive monitoring finds more and more severe ADRs than laboratory parameter monitoring, but with more expense. The latter, though being afflicted with a low PPV of its LFSs and low specificity, can still be a valuable and easily usable tool, if it is adapted to the clinical routine.

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