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Incompatibilities in paediatric intensive care – pitfalls in drug information

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Drug incompatibilities can lead to loss of effectiveness of drugs or to increased risk for undesirable effects that can even be life-threatening. Especially children are at high risk. Databases are an important source of information in routine care to avoid incompatibilities. However, they were supposedly developed considering drugs for use in adults. Thus, we analysed to what extent databases are appropriate for the identification of incompatibilities in intravenous (i.v.) drug therapy in paediatric intensive care. We analysed the information provided by two databases (Database A and B) on all pairs of two drugs prescribed to be administered via the same i.v. access line in a university paediatric intensive care unit during the study period of 50 days. A total of 50 different i.v. drugs was prescribed in 318 different combinations (drug pairs). We found information on (in)compatibilities in 23.0 % (73/318) in Database A and in 31.1 % (99/318) in Database B. Only in 11.0 % (35/318) of the drug pairs, both databases provided information. Considering those drug pairs, in 17.1 % (6/35) Database B indicated compatibility whereas Database A indicated incompatibility. Compatibility information delivered by databases on drugs used in paediatric intensive care is incomplete, heterogeneous, and partly contradictory. Thus, an increased awareness on the strengths and limitations of different databases is necessary to avoid patient harm.

1. Introduction

Drug incompatibilities bear the risk for severe patient harm: 26 % of all detected incompatibilities in an intensive care unit were classified as life-threatening (Tissot et al. 1999). Physicochemical drug-drug incompatibilities can occur in the fluid containers or infusion lines when intravenous (i.v.) drugs are co-administered (Trissel 2012). Precipitation and the formation of complexes can lead to loss of effectiveness and even to considerable risks if conglomerates are not retained by filters. Technically, drug-drug incompatibilities can be prevented by administering intravenous drugs separately (Bentley et al. 2015). In routine care, however, administering each drug separately is frequently impossible due to the large number of intravenous drugs and the limited venous access, particularly in children. In the literature, numerous analytical studies deal with the topic of potential (in)compatibilities in the combination of intravenous drug preparations – both for administration via a Y-piece and for combination in infusion bags (Kanji et al. 2010; Newton 2009). Based on those data, databases were developed in order to deliver tailored drug information to prevent incompatibilities in routine drug administration. So far, most database evaluations refer to adult patients (Bertsche et al. 2008, 2010; Marsilio et al. 2016), or were restricted to a limited selection of drug combinations used in paediatric intensive care (De Giorgi et al. 2010). Since the diseases in children differ considerably from those in adults, the therapies used in paediatric intensive care units (ICU) differ considerably from those commonly used in adult ICU patients. In addition, a considerably higher proportion of off-label use has to be taken into account comparing the paediatric with the adult setting (Gore et al. 2017; Jobanputra et al. 2015). A particular problem for children is resulting from a very limited number of i.v. lines. All these aspects have led to the question to what extent commercial databases supposedly designed for use in adults are appropriate for the identification of incompatibilities in i.v. drug therapy in paediatric ICU patients. For this purpose, we analysed the combinations of drugs prescribed in our paediatric ICU. We investigated two different i.v. compatibility databases frequently used in clinical settings for their completeness and conformity of the given information. This way, we intended to find out whether these routinely used systems are appropriate to identify incompatibilities and, thus, to effectively prevent them.

2. Investigations and results

2.1. Setting and study design

We performed an exploratory study in a university paediatric intensive care unit (Leipzig University Hospital). A clinical decision support system, databases, unit dose, or a unit-based pharmaceutical service were not implemented on a regular basis in the unit. The study period was 50 days. We assessed data of all patients who were prescribed at least two drugs for i.v. administration at one day. In the further analysis of the databases, we included all prescriptions of patients with at least two i.v. drugs to be given *via* the same access line at the same day. There was no other inclusion criterion. We did not perform any intervention during the study period. The study was approved by the Ethics Committee at the Medical Faculty, Leipzig University, Germany, according to The Code of Ethics of the World Medical Association (Declaration of Helsinki). The informed consent of the patients was not required (in accordance with the statutory requirements), because only routine data were assessed. We did not perform any additional medical examinations or interventions.

2.2. Data analysis

We assessed all combinations of two drugs prescribed to be administered *via* the same i.v. access line. For those combinations and the individual drugs involved in the combinations, we performed an anal-

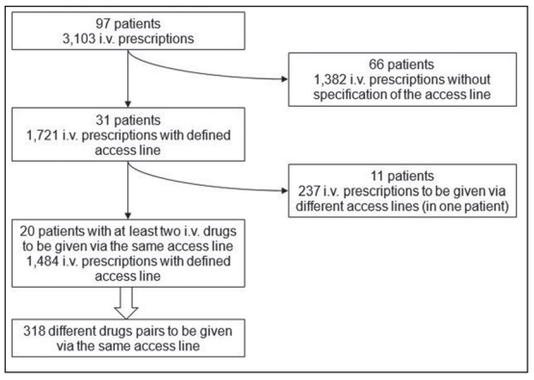

Figure: Flowchart of assessed patients and i.v. prescriptions

ysis of the information provided by two databases commonly used in routine care in paediatric ICUs. As there are different possibilities to co-administer drugs, we chose Y-piece administration as the standard for the database analysis. A Y-piece is a device in the shape of the letter Y that connects two incoming lines (e.g. from two different drug containers) into one outgoing line to the patient. We did so to reflect a quite realistic setting, as Y-piece administration is very frequent. Furthermore, incompatibilities occurring in Y-piece administration will even more likely happen if the drugs are mixed in the same container. To avoid overrepresentation of prescriptions for patients staying a long time at the hospital, we considered every different drug-drug combination only once in total, unless stated otherwise.

2.3. Description of the databases

In our analysis, we assessed two databases: Kompatibilität im Katheter – KiK 4, oData, Rastede, Germany (Database A, access *via* AiDKlinik® Arzneimittel-Informations-Dienste, Dosing GmbH, Heidelberg, Germany), and King®Guide to parental admixtures, Internet edition, King Guide Publications, Inc., Napa, California, USA (Database B).

Database A contains brand names approved in Germany. The contents derive from the summaries of product characteristics, literature (e.g., Trissel: Handbook on Injectable Drugs), and laboratory results. Drug combinations fall into three risk categories:

- possibly critical (conflicting reports or batch-dependent incompatibility),
- problematic (available data not satisfactory),
- incompatible under any circumstances (several documented instances of incompatibility).

Database A does not include information on compatible combinations.

Database B contains active ingredients and solvents with a focus on drugs approved in the USA. The contents derive mainly from original literature. Database B provides the following three categories:

- incompatible (documented incompatibility),
- conflicting reports (contradictory data),
- compatible (established finding).

As normal saline is the standard solvent in the study unit, we chose normal saline for our analysis as well as "unspecified solvent" meaning data deriving from combining finished products or if a solvent was not specified in the original article.

2.4. Results

We assessed a cumulative total of 3,103 i.v. prescriptions in 97 consecutive patients admitted to a paediatric ICU of a university hospital during the 50 days study period (Fig., Table 1). Considering every prescription per patient once, we performed the database analysis based on 246 prescriptions with a total of 50 different i.v. drugs prescribed in 318 different combinations (drug pairs). On 6 drugs, no information was provided at all by Database A, and no information was available for 9 drugs in Database B (Table 2). Database A principally contained information on both individual drugs in 89.3 % (284/318) of the drug pairs, Database B in 64.5 % (205/318). However, we found information on (in)compatibilities only in 23.0 % (73/318) in Database A and in 31.1 % (99/318) in Database B of all drug pairs. The 5 most frequent drugs involved in incompatibilities are shown in Table 3, the respective combinations in Table 4. In Database A, information was available exclusively on incompatibilities and was classified into three risk categories: 1.0 % (3/318) possibly critical, 5.0 % (16/318) problematic, and 17.0 % (54/318) incompatible under any circumstances. In contrast, Database B also included compatibility information in 20.4 % (65/318) of the drug pairs. Of all drug pairs, 6.6 % (21/318) were declared as to be incompatible. 1.9 % (6/318) of the drug pairs fell in the category conflicting reports and for 2.2 % (7/318), different other specific data were provided in Database B. Only in 11.0 % (35/318) of the drug pairs, both databases provided information. Of those drug pairs, 17.1 % (6/35) were categorised as compatible in Database B but incompatible in Database A.

3. Discussion

I.v. drug incompatibilities can lead to ineffective or harmful therapy. Appropriate information to prevent incompatibilities is therefore required at the point of care. Even though several commercially

Table 1: Characteristics of assessed patients

Characteristic	Value
Number of patients (m/f) [n]	97 (50/47)
Median age (Q25/Q75; min/max) [years]	4.0 (1.1/9.4; 0.02/18.9)
Median number of days of treatment per patient* (Q25/Q75; min/max) [n]	3 (2/7; 1/50)
Median number of i.v. drugs per patient per day (Q25/Q75; min/max) [n]	4 (2/7; 1/17)
Diagnosis leading to admission**	
Diseases of the respiratory system [n]	18
Surgery [n]	17
Certain infectious and parasitic diseases [n]	11
Injury, poisoning and certain other consequences of external causes [n]	10
Diseases of the nervous system [n]	8
Diseases of the ear and mastoid process [n]	7
Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified [n]	6
Miscellaneous [n]	20

*during the study period
**according to ICD-10 except of surgery

Table 2: I.v. drugs not available in databases A and B. The frequency of involvement of those drugs in different combinations is shown

Database A		Database B	
Drug	Frequency [n]	Drug	Frequency [n]
Levetiracetam	12	Metamizole	35
Octreotide	10	Potassium canrenoate	34
Thiamine	7	Levomepromazine	12
Acetazolamide	2	Ambroxol	14
Epinephrine	2	Clemastine	11
Methylthioninium	2	Levothyroxine	11
		Esketamine	3
		Methylthioninium	2
		Piritramide	2

Table 3: Top 5 drugs involved in incompatibilities according to Databases A (category "incompatible under any circumstances") and B (category "incompatible")

Drug	Frequency of the respective drug involved in different combinations [n]	Cumulative frequency of combinations containing the respective drug per day and patient [n]
Database A		
Pantoprazole	17	382
Furosemide	11	188
Casofungin	5	157
Potassium canrenoate	9	144
Ranitidine	4	120
Database B		
Pantoprazole	10	211
Furosemide	7	107
Ranitidine	1	95
Caspofungin	3	60
Vancomycin	2	58

Table 4: Top 5 incompatible drug combinations according to Databases A (category "incompatible under any circumstances") and B (category "incompatible")

Incompatible drug combination	Cumulative frequency of the respective drug combination per day and patient [n]
Database A	
Pantoprazole-ranitidine	95
Furosemide-pantoprazole	88
Casofungin-potassium canrenoate	51
Caspofungin-pantoprazole	46
Caspofungin-furosemide	40
Database B	
Pantoprazole-ranitidine	95
Caspofungin-furosemide	40
Furosemide-vancomycin	37
Cefotaxim-pantoprazole	35
Levofloxacin-pantoprazole	21

available databases offer such information, only limited scientific data is available about the appropriateness of such databases in the paediatric setting. Children, however, differ from adult patients in the prevailing diseases (additionally depending on the age of the child) and, consequently, in the pharmacotherapies used for treatment. Additionally, the number of i.v. lines is particularly restricted in children. Children in ICU settings are a specifically vulnerable patient group in which drug-related problems can frequently result in clinically relevant adverse events (Davis 2011; Kaushal et al 2001). Therefore, we investigated two commercially available databases for their appropriateness to identify incompatible drug combinations actually prescribed in a paediatric ICU setting and, hence, to prevent severe harm to those patients.

The data presented here show that the available databases contained the prescribed drugs in paediatric ICU patients to a varying degree. Generally, this difference could be explained by the fact that Database A with higher drug coverage originated in the same country of origin as the investigation setting. A particularly obvious difference was the lack of medicinal products containing metamizole in the country of origin of Database B. However, differences in the approval status cannot solely account for the extent of the difference between the databases. There is indication that the heterogeneity depends largely on the creators of such databases. Both databases provided information only in less than one third of the combinations actually prescribed. This value is alarmingly low and shows that many combinations relevant to paediatrics were not included, despite good drug coverage in general at least in Database A. It should be kept in mind that the content of the pieces of information differed considerably between the two databases. Especially the number of warnings on combinations categorised incompatible under any circumstances was more than twice as high in Database A compared to Database B. This difference becomes even more obvious when the actual prescription frequency reflecting routine care on the paediatric ICU is taken into account. Another difference between the databases is the kind of information provided: Database A contained only incompatible combinations, whereas the majority of information retrieved from Database B concerned compatible combinations. Especially in patients with a limited number of lumens, the information on compatible combinations is advantageous as it enables safe co-administration. Furthermore, the databases were incongruent: only 11% of the drug combinations were available in both databases at all, and in 17% of those combinations the pieces of information were even contradictory: Database A indicated incompatibility and Database B in contrast compatibility. This is likely to be caused by the heterogeneity of the methods used to determine incompatibility (Kanji et al. 2010). However, missing or contradictory information can endanger the patient's safety. In this context, it is important to note that drug-drug interactions are comparably well investigated and described in the approval documents. Based on that, drug-drug interactions have found their way into commercial databases. In contrast, regarding data on incompatibilities, the approval documents usually only recommend a separated administration *via* a different i.v. line. However, this procedure is hardly reasonable in practice due to the limited venous access in children. More sophisticated investigations on incompatibilities within future approval procedures might lead to better data consistency.

Drugs and databases used may vary from setting to setting and, thus, general conclusions should be drawn with care. However, the underlying problem of incomplete and heterogeneous information concerns settings all over the world (Gaetani et al. 2017; Leal et al. 2016) and demands solutions. Especially in the case of incompatibilities, physicians and pharmacists should not only rely on the information from a single database and should keep in mind the different strengths and limitations of the databases to obtain the best possible drug information.

The limited number of drug combinations available in both databases reflects the limited data on (in)compatibilities (Bentley et al. 2015), also due to the vast number of possible combinations. For drugs used in rare diseases, especially affecting children, clinical experience in routine care is limited and a particular risk arises from incompatibilities not yet described. Especially data considering typical drugs and drug combinations used in intensive care units are lacking or are heterogeneous (De Giorgi et al. 2010; Kanji et al. 2010). This applies even more for combinations of three or more drugs.

In conclusion, we found that databases designed to identify incompatibilities do not sufficiently consider typical drug-drug combinations in paediatric intensive care. Moreover, the information provided by the databases was partly contradictory. Missing or inappropriate information that is not adjusted to the setting can give the user a false sense of security and, thus, endanger patient safety. Thus, several different resources should be consulted to obtain comprehensive information. Consequentially, information tailored to each unit's special needs should be generated. Also, a counselling service to provide pharmaceutical expertise can serve to increase patient safety.

Conflicts of interest: None declared.

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