Short Communication

Jean-Daniel Hecq*, Irene Krämer and Jean Vigneron

European Databases on Stability and Compatibility of Injectable Medicinal Products in Europe

<https://doi.org/10.1515/pthp-2019-0012>

Received May 24, 2019; revised September 06, 2019; accepted September 07, 2019

Abstract: In hospitals, the majority of medication therapy is administered intravenously. Especially, in intensive care units, simultaneous use of various injectable drugs is a common practice. Drug incompatibilities have been reported to be associated with up to 60 % of all serious and life-threatening adverse drug events. Several databases are used by hospital pharmacists to answer the questions of (in)compatibility of co-administered injectable drugs. The objective of this article is to present the European databases on compatibility and stability of injectable drugs. According to a questionnaire which was sent to the National Hospital Pharmacy Associations of the 28 countries of European Community there are three national databases available in EU countries which are in alphabetical order, Belgium, France and Germany. The Belgian database is dedicated to injectable medications, is updated and distributed annually in French language on a USB key. STABILIS® is an international database giving information with pictograms translated into 29 languages. This database contains also monographs of non-injectable drugs. The internet-based ADKA STABIL-Datenbank is focused on anticancer drug therapy, listing detailed datasets in German language on stability and compatibility including the references.

Keywords: electronic database, injectable drugs, compatibility, chemical stability

Introduction

In hospitals, the majority of medication therapy is administered intravenously. About 30 to 50 % of inpatients are treated by intravenously administered medications [1]. Recently, Fekadu et al. reported that 50 %, 32 % and 13 % of patients are prescribed two, three or four injectable drugs, respectively, to be administered at the same time [2]. Especially, in intensive care units, simultaneous infusion of various injectable drugs is a common practice when patients require multiple products to be administered at the same time and have limited i.v. access. This leads to the question of drug-drug and drug-infusion compatibility. Already twenty years ago, Belgado et al. reported that 17 % of questions received by hospital pharmacists are related to i.v. drug compatibility [3]. Moreover, drug incompatibilities are associated with up to 60 % of all serious and life-threatening adverse drug events [4].

Caring about stability and compatibility of i.v. medication prior to and during administration may not be the favorite interest of many pharmacists. However, no other health care professionals are as qualified or as obligated to effectively apply their training and experience and the abundance of published data to this aspect of patient care [5].

Several databases are used as information sources by hospital pharmacists to answer the questions of (in)compatibility of co-administered injectable drugs. The world-wide most well-known sources are Trissel's Handbook on Injectable Drugs and Trissel's 2 Clinical Pharmaceutics Database. When seven i.v. drug compatibility references were evaluated by using requests from a US-drug information center, the highest-performing references were provided in Trissel's 2 database [6].

The objective of this article is to identify European databases specified on compatibility and stability of i.v. preparations, and to introduce them.

Method

National Hospital Pharmacy Associations of the 28 countries of European Community were contacted, and asked

*Corresponding author: Jean-Daniel Hecq, Department of Pharmacy, CHU UCL Namur | Site Godinne, Avenue Therasse, 1, 5530 Yvoir, Belgium, E-mail: Jean-daniel.hecq@uclouvain.be

Irene Krämer, University Medical Center Johannes Gutenberg-University Mainz, 55131 Mainz, Germany, E-mail: irene.kraemer@unimedizin-mainz.de

Jean Vigneron, Meurthe et Moselle, Centre Hospitalier Universitaire de Nancy, rue du Morvan, Vandoeuvre, 54511 Meurthe et Moselle, France, E-mail: j.vigneron@chru-nancy.fr

for the existence of a national database on stability and (in)compatibility of injectable drugs, the name of the authors or the working group, the number of drugs, data and references contained in the last edition. Identification of a database was followed by contacting the authors in order to receive further information.

Results

From 28 national associations contacted, ten responses were received. Three countries reported that a national database is available. This is, in alphabetical order, Belgium, France and Germany. The respective authors or coordinators are: Professor Jean-Daniel Hecq (B), Doctor Jean Vigneron (F) and Professor Irene Krämer (G), the name of the databases are “Stabilité des médicaments injectables en perfusion / stabiliteit van geneesmiddelen voor intraveneuze infusie”, Stabilis®, and ADKA STABIL-Datenbank, Stabil®-Liste.

“Stabilité des médicaments injectables en perfusion / stabiliteit van geneesmiddelen voor intraveneuze infusie”, Pr J-D Hecq, Belgium

In 1981, a special interest group (SIG) of the Belgian Association of Hospital Pharmacist was formed to collect data concerning the physical and chemical stability of most used IVD.

The 1st edition of a «Guide for the administration of drugs by infusion» was published in the same year. Stabilities, compatibilities and incompatibilities with intravenous solutions or other IVD were described for 20 IVD. A new edition was distributed in 1987 and followed by 3 up-dated versions. In December 1991, the 1st of eleven editions of a new manual entitled “Stability of injectable drugs in infusion” was launched. This manual summarizes stability data only. The number of reviewed drugs amounts to 195. The latest printed version contained more than 500 pages. In 2000, the publication of a more practical electronic version on CD-Rom started.

In order to compile the database, the contents of 26 national and international journals were monthly systematically reviewed by visiting the websites. This method replaced gradually the consultation of university libraries. Pubmed is screened weekly. Alerts are encoded in Google and in ResearchGate with keywords. Books and other electronic databases are also consulted regularly. In some cases,

authors are contacted directly. The 2018 edition comprises 52.755 data sets on the stability and (in)compatibilities of 567 drugs alone or in binary, ternary or quaternary mixtures in different types of containers, based on 3.261 references. Interactions with containers and extractions of plasticizers are also mentioned. A review of the stability after microwave freeze-thaw treatment and in peritoneal dialysis solution supplements the review. Reading different databases may lead to conflicting data. The physico-chemical factors influencing the stability of the i.v. preparations and the criteria for judging the quality of a publication are given in detail.

The 2019 USB key is the 18th electronic version published. It is the result of 37 years of literature review and contributes to the knowledge of stability of IVD by Belgian hospital pharmacist and the quality of patient care. This database may also help compounding units for the determination of validity of batch preparation of ready-i.v. preparations, based on long-term stability studies at 5 ± 3 °C or at -20 °C [7].

Stabilis, Dr J. Vigneron, France

Stabilis was established in 2001 in CDROM format. Stability information is given by using pictograms translated in different languages. The first edition was translated into 5 languages. A second edition was published in 2003 and a third edition in 2006 with 24 languages and the database moved to a website www.stabilis.org in 2008. Currently, information is given in 29 languages.

The database provided initially information on injectable drugs with the stability in solutions, in admixtures, information on the factors influencing stability (pH, container, solvent, temperature, concentration) and incompatibilities. Monographs of non-injectable drugs were added since 2013 (oral solutions, eye-drops, aerosols, capsules, etc).

The information “level of evidence” was implemented in 2015 for monographs of anticancer drugs and then extended to antifungal, antivirals and some antibiotic drugs. Since 2016 the function “table of incompatibilities” allowed the users to create individual tables of incompatibilities. This functionality is especially useful for patient groups where many injectable drugs are used regularly (hematology, intensive care units). In 2018, a unique functionality named “research teams” was created, where research teams from universities and hospital pharmacies involved in research on stability and compatibilities of drugs are presented. Currently (March 2019), the database presents a list of 612 teams including 147 teams still active (at least one publication since 2016). The function is also

interactive and allows users to provide stability study ideas when data are not available in the literature.

In 2018, the functionality “Posters” was initiated where posters are listed dealing with stability and compatibilities and presented on international congresses. 248 posters are currently available coming from 15 countries which can be downloaded by the users.

In 2019, web-links were included presenting mainly other databases and guidelines to perform stability studies useful for users involved in research.

Currently, the database contains 789 monographs including 461 injectable drugs. Summary lists are also available on stability data like list of drugs stable in different containers (PVC, polyolefin, EVA, etc) or incompatibilities in various solvents (0.9 % sodium chloride, 5 % dextrose and even rarely used solvents like Ringer lactate or 3 % sodium chloride).

The most often retrieved monographs are those of anticancer drugs called by 36 % of the users, followed by antibiotics called by 21 % of the users. 15 anticancer monographs are in the list of the 20 most utilized monographs. Concerning the drug usage forms, 91 % of the users open a monograph of injectable drugs, 12 % of oral solution and 2 % of eye-drops.

Monographs were initially compiled for medicinal products marketed in France, then marketed in Europe and now worldwide.

Stabilis is freely accessible. Information is mainly (70 %) retrieved in Europe, with 23 % of users coming from France, followed by Spain and Germany, 15 % in America (the first three countries being Brazil, Mexico and Columbia), 5 % in Asia (mainly Vietnam and Japan), 5 % in Africa and Middle East, and 5 % in Oceania.

Stabilis software has been updated and continuously developed since the very beginning. New functions are currently under development concerning in particular physical compatibilities [8, 9]

ADKA STABIL Datenbank (plus Stabil® Liste), Pr I. Krämer, Dr J. Thiesen, Germany

In the late 1980s, centralized pharmacy-based production of ready-to-administer cytotoxic preparations was implemented in German hospitals. Information regarding the physical and chemical stability of the ready-to-administer preparations was needed in order to declare a valid in-use stability date on the product label and to ensure a safe use on the wards. Literature regarding physico-chemical stability of the preparations was especially searched by the pharmacy staff of the University

Hospital in Mainz. The relevant primary and secondary literature was searched and all available data about stability and compatibility of cytotoxic drugs were recorded. Because information was lacking or rudimentary, a working group was founded in that institution starting experimental studies. Up to 2019, the research team studied the physico-chemical stability of 27 active substances with antineoplastic activity.

In order to share the information with the increasing number of German hospital pharmacies entering the field of centralized cytotoxic preparation, the compiled data were first published in 1989 in a printed version called STABIL-Liste®. In the beginning updated versions were printed every four years and afterwards every second year because of the rapidly increasing number of licensed products and information. Background information about the methods of literature research, evaluation of the literature and the compilation of data records was published for the 7th edition in 2015. In 2019, the 9th edition containing data of 126 different cytotoxic drugs and the first edition in English language will be published. The STABIL-Liste® comes as a ring binder with film laminated, yellow colored, heavy-weight paper usable in clean rooms. In German speaking countries the binder is also known as ‘Gelbe Liste’ (‘yellow list’) or Krämer Liste. Comprised information is given on the physico-chemical stability of cytotoxic drugs after first opening of the concentrates or after reconstitution, and after further dilution with recommended vehicle solutions and compatible container material. The physico-chemical in-use stability data given in the table, represent intervals recommended by the authors after sound review and evaluation of the available literature or results of own experimental studies. Additional fields contain the available information on compatibility and incompatibility of cytotoxic preparations with other injectable drugs used in oncology patients.

In 1999, the STABIL-database, containing detailed facts and references on stability and compatibility of cytotoxic drugs, was published in electronic format. Two editions were available as CD-ROM. Since 2019, the electronic database is available as an internet-based-version, named ADKA STABIL-Datenbank. The electronic database was re-designed and is integrated in the ADKA Arzneimittel-Info-Datenbank (ADKA (German Society of Hospital Pharmacists) Drug Information Module). Currently, the database contains 148 monographs of cytotoxic and supportive drugs based on 1015 different publications and sources, resulting in 2761 stability-datasets and 3771 in-/compatibility-datasets. In each monograph the reasonable in-use stability intervals, evaluated by the authors, are presented as well as the underlying datasets

and the reference literature. In each dataset information is given in note form on the stability interval, percentage rate of remaining drug content, storage temperature, concentration of the active drug substance, solvent used for reconstitution (if applicable), vehicle solution, container material, pH, light influence and the bibliographic data of the reference. In the compatibility datasets information about the analytical method used and the test results are specified. Thereby, the database allows users to retrieve appropriate information to a specific question regarding compatibility or stability, e. g. when very high or low concentrations of the active drug substance, specific or deviant vehicle solutions or deviant solvents are to be assessed.

The internet-based ADKA STABIL-Datenbank is updated continuously and always up-to-date. Subscriptions are available at the German Society of Hospital pharmacists (ADKA). Hospital pharmacies in Europe can achieve a license in combination with the ADKA Arzneimittel-Info-Datenbank. Stand-alone licenses are offered to customers others than hospital pharmacies [10].

Discussion

To our knowledge, the first manuscript on compatibilities and incompatibilities was published in 1955 [11]. Another two publications followed in 1961 [12, 13]. Three reviews appeared in 1965 [14], 1966 [15] and 1971 [16]. Two publications by Allen LW & al are probably the most cited studies regarding compatibilities in y-site injection [17, 18]. The first compilation of stability studies in textbook format was published in 1971, i. e. 'The King Guide to parenteral admixtures'. In 1977, the first edition of the internationally-known 'Handbook on injectable drugs' edited by Lawrence Trissel was published. Today, several international electronic information sources provide information on stability and compatibility of medicinal products, e. g. Trissel's 2 Clinical Pharmaceutics database, Facts and Comparisons 4.0 IV Chek, CompoundingToday.com, IV INDEX, Clinical Pharmacology IV Compatibility. The benefit of the different sources as measured by the existence of records on compatibility, the inclusion of specific concentration information for each drug in a pair, and the presence of references for the information provided is varying [6].

The same is the case for the three European databases presented here. They partially contain overlapping information and partially differing information. The reason is the differing drug market in the different countries and sometimes different formulations licensed

in different countries. Experimental studies are usually performed with the licensed products available in the countries where the authors are situated.

For the same drug-drug pair contradictory results about compatibility can be found in different databases. In this case, it is necessary to read the detailed information or even the full text of the underlying experimental study. The evaluation of the experimental study on physicochemical stability should be based on seven criteria. The most important ones are: complete description of equipment, methods, medicinal products studied; complete description of the validation procedures the analytical method; demonstration of the stability-indicating capability of the assay; statistical analysis; appropriateness of the conclusions [19].

Risk minimization in coadministration of injectable drugs remains important because polymedication is common practice in various patient groups like cancer patients, transplant patients and intensive care patients (neonatal, paediatric, adult). In recent reports, rates of compatibility varied from 9 to 42% and of incompatibilities from 15 to 68% [20–24]. Hospital pharmacists should not only answer questions regarding drug-drug compatibilities, but develop together with physicians and nurses incompatibility-reducing infusion schemes to be used in vulnerable patient groups.

The next version of the Belgian database will be available on the website of the Belgian Association of Hospital Pharmacists. New functions for the French database are currently under development concerning in particular physical compatibilities and a tool to perform stability studies. The German database will soon contain more detailed information about the filter types (also brandnames) to be used or avoided will be added to the German database.

To help the hospital pharmacists in their decision, professional interpretation and advice of stability and (in) compatibility data on the level of medicinal products could be implemented. An educational video 'How to use the database in daily practice' is in progress concerning the German database.

The French Society of Oncology Pharmacy organizes in Paris on 2 days every year since 2013 a "Masterclass on Stability Studies".

A symposium is organized for the fifth consecutive year at UCL Namur University Hospital, site of Godinne (Belgium) concerning the centralization of injectable drugs in hospital, as well as the physico-chemical stability problems and studies.

Finally, a discussion about a systematic cooperation of the three teams will be started.

Conclusion

Three electronic European databases on compatibility and stability of injectable drugs provide comprehensive information on different core areas. Apart from the international databases, specific information for medicinal products licensed in Europe, are in the focus of these databases. They are updated regularly or continuously what is useful and essential, because of the rapidly growing drug market and demand for information on safe administration. New functions are currently under development.

Conflict of interest statement: The authors state no conflict of interest. The authors have read the journal's Publication ethics and publication malpractice statement available at the journal's website and hereby confirm that they comply with all its parts applicable to the present scientific work.

References

- Hecq JD. Centralized intravenous additive services (CIVAS): the state of the art in 2010. *Ann Pharm Fr* 2011;69:30–7.
- Fekadu T, Teweldemedhin M, Esrael E, Asgedom SW. Prevalence of intravenous medication administration errors: a cross-sectional study. *Integr Pharm Res Pract* 2017;6:47–51.
- Belgado BS, Hatton RC, Doering PL. Evaluation of electronic drug information resources for answering questions received by decentralized pharmacists. *Am J Health Syst Pharm* 1997;54:2592–6.
- Cada DJ. Preventing iv medications errors. *Hosp Pharm* 2002;37:1139.
- Hasegawa GR. Caring about stability and compatibility. *Am J Hosp Pharm* 1994;51:1533–4.
- Smith WD, Karpinski JP, Timpe EM, Hatton RC. Evaluation of seven i.v. drug compatibility references by using requests from a drug information center. *Am J Health Syst Pharm* 2009;66:1369–75.
- Hecq JD. Stabilité physicochimique d'injectables reconstitués en milieu hospitalier : 35 ans de recueil de données. *J Pharm Belg* 2017;99:32–41.
- D'Huart E, Vigneron J, Gindre I, Lider P, Demoré B. First international database of research teams in stability and compatibility of medications: an additional function in the Stabilis® database. *Ann Pharm Fr* 2018;76:436–43.
- D'Huart E, Lider P, Vigneron J, Demoré B. Evolution of the stabilis® database: creation of a level of evidence for stability studies. *Pharm Technol Hosp Pharm* 2018;3:3–12.
- Thiesen J, Sarakbi I, Krämer I. Die STABIL-Liste® 7. Auflage 2015. *Krankenhauspharmazie* 2016;37:485–96.
- Bogash R. Compatibilities and incompatibilities of some parenteral medication. *Bull Am Soc Hosp Pharm* 1955;12:445–85.
- Kirkland WD, Jones RW, Ellis JR, Schultz CG. Compatibility studies of parenteral admixtures. *Am J Hosp Pharm* 1961;18:694–9.
- Jones RW, Stanko GL, Gross HM. Pharmaceutical compatibilities of pentothal and nembutal. *Am J Hosp Pharm* 1961;18:700–4.
- Misgen R. Compatibilities and incompatibilities of some intravenous solution admixtures. *Am J Hosp Pharm* 1965;22:92–4.
- Patel JA, Philipps GL. A guide to physical compatibility of intravenous drug admixtures. *Am J Hosp Pharm* 1966;23:409–11.
- Kramer W, Ingloff A, Cluxton R. IV additive review. *Drug Intell Clin Pharm* 1971;5:211–28.
- Allen Jr LV, Levinson RS, Phisutsinthop D. Compatibility of various admixtures with secondary additives at Y-injection sites of intravenous administration sets. *Am J Hosp Pharm* 1977;34:939–43.
- Allen Jr LV, Stiles ML. Compatibility of various admixtures with secondary additives at Y-injection sites of intravenous administration sets. Part 2. *Am J Hosp Pharm* 1981;38:380–1.
- Hecq J-D, Bihin B, Jamart J, Galanti L. Criteria for judging the quality of a publication on physicochemical stability of ready to use injectable drugs. *Pharmac Technol Hosp Pharm* 2017. DOI:10.1515/ptph-2017-0012.
- Kanji S, Lam J, Johanson C, Singh A, Goddard R, Fairbairn J, et al. Systematic review of physical and chemical compatibility of commonly used medications administered by continuous infusion in intensive care units. *Crit Care Med* 2010;38:1890–8.
- Leopoldino RW, Costa HT, Costa TX, Martins RR, Oliveira AG. Potential drug incompatibilities in the neonatal intensive care unit: a network analysis approach. *BMC Pharmacol Toxicol* 2018;19:83.
- Marsilio NR, Silva D, Bueno D. Drug incompatibilities in the adult intensive care unit of a university hospital. *Rev Bras Ter Intensiva* 2016;28:147–53.
- Mendes JR, Lopes MC, Vancini-Campanharo CR, Okuno MF, Batista RE. Types and frequency of errors in the preparation and administration of drugs. *Einstein (Sao Paulo)* 2018;16:eAO4146.
- Ramanath KV, Hymavathi R. Assessment of intravenous admixtures in hospitalized patients of a rural tertiary care teaching hospital. *Am J PharmTech Res* 2012;2:533–43.