Interaktionsdatabasen

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Aim

The purpose of the interaktionsdatabasen is to make treatment with medicines more efficient and safe. It contains complete and up-to-date knowledge of the possible undesired effect of the individual drugs when given in combination.
This document aims to describe the technical circumstances to be taken into account when using interaction information from the database.

Contents

The database describes approx. 4000 interactions between registered drug substances and selected herbal remedies, foods, vitamins and minerals. The description consists of a literature review, one of class effects and a description of each interaction, its degree of documentation and clinical significance as well as recommendation regarding the practical handling of the interaction.

Data

XML document containing all available interaction information (section 4.4 of the original danish doc).

Information

Documentation

More than 12,000 scientific articles have been reviewed and evaluated as the basis for the interaction database.

Definition of interaction

An interaction is only described as a relationship between only two drug substances (as knowledge about interactions implying more than 2 is sparse and non-existent),

There are also descriptions between groups of drug substances called class effects (*klasseeffekt*). If there are 6 substances in one drug group and 4 substances in another drug group, then there is a theoretical possibility to find 24 different combinations of two random substances from the two drug groups. However, it is only possible to find a few of these combinations described in the scientific articles.

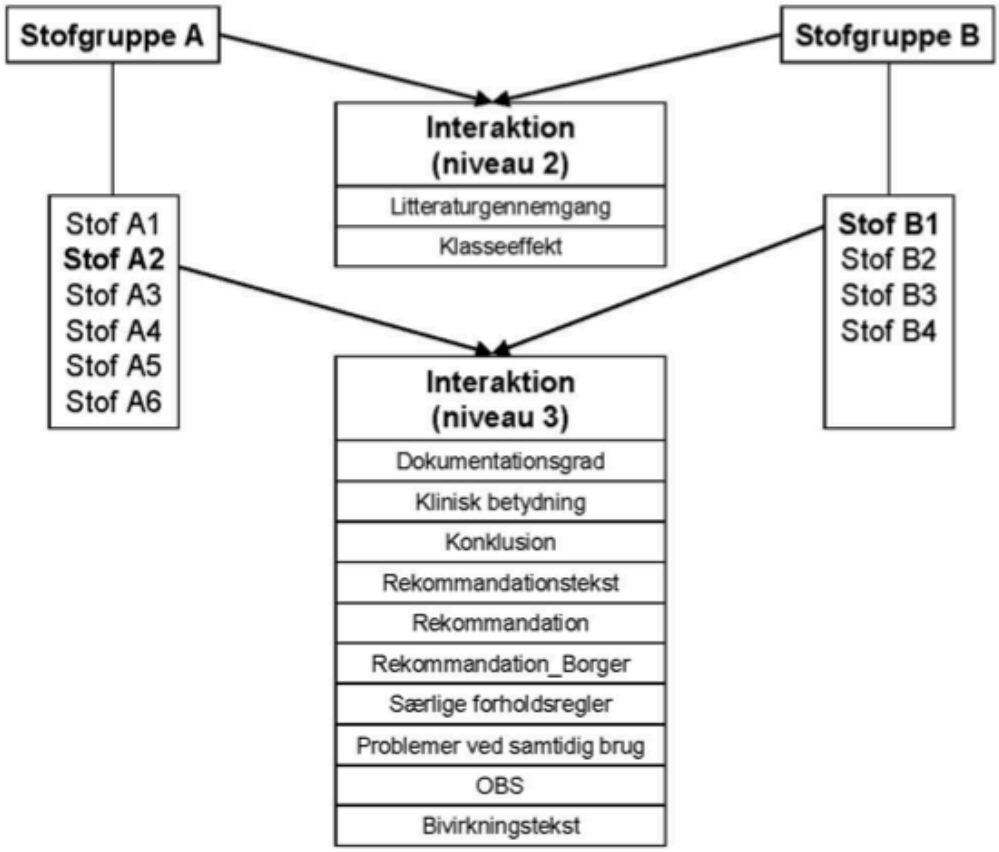
The drug-drug substance combinations are described as follows in level 3 "**Niveau3**":

- Dokumentationsgrad (Documentation)
- Klinisk betydning (Clinical significance)
- Konklusion (Conclusion)
- Rekommandationstekst (Recommendation text)
- Rekommandation

- Særlige forholdsregler (special precautions)
- Problemer ved samtidig brug (Problems with simultaneous use)
- Bivirkningstekst (Side effect)

The drug group combinations interactions is described as follows in level 2 "**Niveau2**":

- Litteraturgennemgang (Literature review)
- Klasseffekt (Class effect)



Figur 1: Sammenhængen mellem niveau 2 og niveau 3 for en interaktion.

Working method

Resources and DDI references

Drug interactions in Interaktionsdatabasen are selected according to the descriptions found in these 3 sources :

- Micromedex (www.smi.dk)
- Hansten (www.drugfacts.com)
- PubMed (http://www.ncbi.nlm.nih.gov/PubMed/)

In addition, interaktionsdatabasen also includes interactions described in:

- Produktresumeer (Sundhedsstyrelsen)
- Medicin.dk (Infomatum A/S)

Maintenance and updates

The interaktionsdatabasen includes interactions that are:

- Pharmacokinetic and
- Based on human data

It will not be included if:

- Expected and/or less significant pharmacodynamic interactions or,
- In-vitro interactions and animal experiments

The content of the database is updated on the basis of monthly systematic literature searches from the Royal library. The literature searches are made in the PubMed and Embase databases based on specially defined keywords and search criteria.
The maintenance and updates is carried out by professionals consisting in 2 academic staff and 2 students in collaboration with specialists in clinical pharmacology.

Sections

Interaction: LEVEL 1 / NIVEAU 1

PubMed abstracts assessed according to the design, dose, number of subjects, statistics and relevance.

Interaction: LEVEL 2 / NIVEAU 2

Overall literature review of the relevant studies described in level 1 with references.
The description of an interaction is indicated as accurately as possible.

Interaction: LEVEL 3 / NIVEAU 3

Conclusion on drug-drug interaction.
The description of level 3 interaction is based on level 1 and level 2 and must be read as an independent text.
Furthermore, assessment of the degree of documentation, clinical significance and recommendation and possible recommendation text.

Documentation degree (Dokumentationsgrader)

- Veldokumenteret: well-documented. At least 2 (from different centers) human controlled studies and/or (before and after) studies on relevant individuals with single or multiple dose (steady state) in terms of either significant kinetic or dynamic changes.
- Dokumenteret: documented. A human controlled study and/or (before and after) single or multiple dose (steady state) study in the form of either significant kinetic or dynamic changes.
- Begrænset dokumenteret: limited documented. Either more than 2 case reports with relevant before and after kinetics or dynamics.
- Ringe dokumenteret: 1-2 case reports.

Clinical significance (Kliniske betydninger)

- Udalt: clinically pronounced/physiological effect with either significant altered therapeutic response or frequent occurrence of serious adverse reactions.
- Moderat: clinically moderate/physiological effect with either slightly altered therapeutic response, or rare occurrence of more serious side effects. Serum concentration

changes, which in other experiments have been closely associated with the above mentioned phenomena.

- Ringe: unchanged or not significantly altered biological response with fewer and easier side effects - or serum concentration changes, which in other studies have not shown significant changes in the biological response.
- Mulig: Possible. Pharmacokinetic changes which are not accompanied by known adverse reactions or changes in the biological response, or solely results from in vitro studies that can not be associated with clinical/physiological endpoints.
- Ingen: None. Neither kinetic or physiological/clinical changes.
- Uafklaret: Undetected. Kinetic or physiological/clinical changes that can not be estimated based on the available documentation.

Recommandations (Rekommandationer)

6 types:

1. Kombinationer bør undergås: forbidden.
2. Kombinationen kan anvendes med dosisjustering: Combination can be used with dose adjustment. Examples:
    a. Dose of X should be reduced/increased
    b. Dose reduction of X may be required depending on the effect/side effects or concentration measurements
3. Kombinationen kan anvendes med forskudt indtagelsestidspunkt: The combination can be used with a delayed ingestion date. Examples:

. A should be taken X hours before/after B

a. A and B should be taken at X hour interval

4. Kombinationen kan anvendes under visse forholdregler: The combination can be used under certain precautions. Example:

. Frequent control of substance X's effect/adverse effect on initiation and discontinuation of combination therapy.

5. Kombinationen kan anvendes: The combination can be used.

CYP Information

Cytochrome P450 Monooxygenases (CYPs) are responsible for the Phase I of the detox process.
There are 57 human CYP enzymes. About 12 liver CYPs are responsible for the removal of the majority of drugs and toxins. These 12 CYP enzymes cover about 93% of the clinical drug metabolism. Among these, CYP3A4, CYP1A2, CYP2D6, CYP2C9 and CYP2C19, in particular, process nearly 60% of all clinical drugs.
Although they are detox enzymes, their activity can actually convert less toxic molecules into more toxic active products. These then need to be further detoxified by Phase II enzymes.
For example, CYP1A1 can activate cancer-causing agents, and CYP2E1 can activate several liver toxins and contribute to alcoholic liver damage.
Many health boosting supplements and herbs actually decrease CYP activity, and thereby reduce the activation of cancer-causing agents.
Based on SNP polymorphisms of CYP enzymes people have distinct drug responses.
The different types of drug responses are termed as: poor, intermediate, extensive and ultrarapid.
Apart from our genes, our health and the food we eat can also greatly affect CYP enzyme function.
[Ref: https://selfhacked.com/blog/cyp-enzymes-interact-supplements-related-genes/]
ID_CYP_Equality b8a5c098-7ced-4bec-9598-2cd85fbd7eba
CYP_Equality_Text Inducers
ID_CYP_Egenskab e537071a-8d03-4d86-aad8-2d48f02b276e

CYP_Egenskab_Tekst P-glycoprotein substrate inhibitor
ID_CYP_Equality 53527659-aed1-413b-b457-b97c40097214
CYP_Equality_Text substrate
ID_CYP_Equality f2d4fa63-2a9d-47f9-9505-c74e441ea9bd
CYP_Equality_Text inhibits

CYP information in Interaktionsdatabasen can be retrieved from table Niveau3:
CYP_DATA

1. **ID_CYP_Navn**: ID CYP Name
2. **ID_CYP_Egenskab**: ID CYP Properties
    1. Inducer
    2. P-glycoprotein substrate inhibitor
    3. Substrate
    4. Inhbitor
3. **ID_CYP_Kilde**: ID CYP Source
    1. Bidstrup & al., 2003
    2. Scandinavian Medical Information
    3. www.lmk.dk
    4. P450
    5. gentest.com
    6. Unger & Kashina, 2003

How to extract information

The XML-Document

Bilag/Appendix 7.1 and Henholdsvis bilag/Annex 7.2 and a database schema in bilag/Appendix 7.3.

Steps:
Python package: xml.etree.ElementTree

- **ID_Rekommendationstekst** (Table NIVEAU3)
    - Tekst (Table REKOMMENDATIONER)
- **ID_Stof1/ID_Stof2** (Table NIVEAU3)
    - Navn (Table STOFFER)
    - **ID_Substans** (Table SUBSTANSER)
        - From ID_Substans map to **ID_Præparatgruppering** (Table PRAEPARATGRUPPERINGER)
        - Substansnavn (Table SUBSTANSER)
    - **ID_Præparatgruppering** (Table PRAEPARATGRUPPERINGER)
        - **ID_Praeparat** map to **Praeparatidentifier** (Table PRAEPARATER)

From **Praeparatidentifier** map to Lægemiddelstyrelsen ListeOverGodtkendteLaegemidler.txt (https://laegemiddelstyrelsen.dk/da/godkendelse/godkendelse-af-medicin/lister-over-godkendte-og-afregistrerede-laegemidler/saadan-bruger-du-listen-over-godkendte-laegemidler/).

From STOF -> SUBSTANS -> PRÆPARAT -> DrugID -> ATC code

1. Missing mappings from STOF to Substans (pro.medicin.dk, www.whocc.no). See unmapped_stof.tsv:
    a. See drive manual_interaktionsdatabasen sheet for the manual addition of codes or manual_unmapped_stof.tsv.
    b. A total of 17 (methylthioniniumchlorid proveblue, amantadin, artemether, artesunat, empaglioflozin, encainid, grapefrugtjuice, influenzavirus A, kamilleblomst, ledipasvir, linagliptin, lorcainid, lumacaftor, lumefantrin, ombitasvir, primaquin and sacubitril).
2. Collapse stof - substans - atc kode to stof - atc kode.
3. A total of 69 missing mappings from stof to atc kode (unmapped_stof_substans.tsv). Manual addition of codes (See drive manual_interaktionsdatabasen or manual_unmapped_stof_substans.tsv).
4. A final total of 7 substances were excluded from the analysis (removed_stof.tsv):
    a. Ginseng
    b. Grapefrugtjuice
    c. Hvidtjørnfrugt (Crataegus L. spp.)
    d. Ingefær
    e. Kamilleblomst
    f. Laropiprant
    g. Schizandra
5. Removal of duplicates (A,B) = (B,A) in the previous files
6. Assign a number and color to collapse the different recommendations
    a. [0] [red] Kombinationen bør undgås.
    b. [1] [red] Kombinationen bør undgås. Se klasseeffekt.
    c. [5] [green] Kombinationen kan anvendes.
    d. [2] [yellow] Kombinationen kan anvendes under visse forholdsregler.
    e. [3] [yellow] Kombinationen kan anvendes med dosisjustering.
    f. [4] [yellow] Kombinationen kan anvendes med forskudt indtagelsestidspunkt.