How can routinely collected comedication information from phase II/III trials be used for screening of potential effects on model parameters? A case study with the oral direct thrombin inhibitor Dabigatran etexilate

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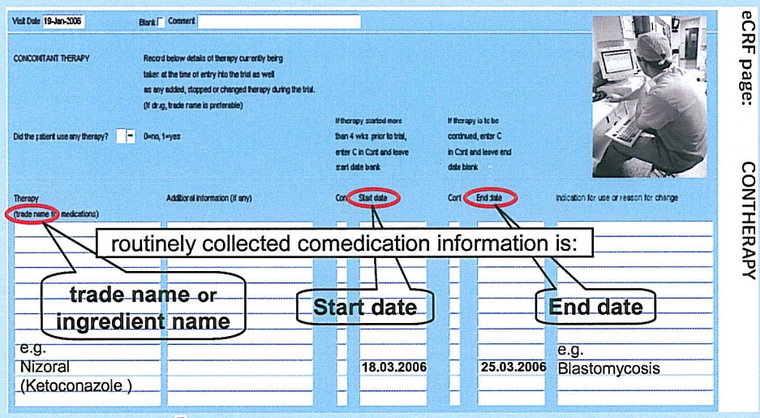
Objective

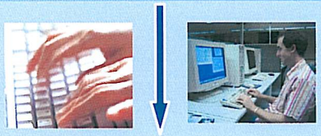
- Development of a process that allows screening for the impact of comedication(s) (CM) on model parameters using comedication information routinely collected during phase II/III.
- The process should be exemplarily applied using data from a phase II study with dabigatran etexilate.

Methods

A. Standard process for inclusion of comedication data into a NONMEM dataset

I. Concomitant Therapy (CT) information collection and coding





Regional Coding Centre (RCC) assigns a unique code to the comedication using the WHO drug dictionary (WHO-DD)

Code and dates are entered in the clinical database (e.g. O*C)

Oracle Clinical

II. Definition of Special Search Categories (SSCs)

- Comedication classes of interest might be e.g. common comedication in the target population or comedication with interaction potential.
- The comedication classes need to be defined as SSC.

Two types of SSCs are possible:

SSCs based on the Anatomical Therapeutic Chemical (ATC) classification system, e.g. ACE inhibitors

SSC: ACE Inhibitors only Mono
This SSC includes all products of the ATC class listed below:
ACE inhibitors, plain: ATC3 (C09A)
0 = no comedication taken
1 = comedication taken (based on recorded data)
2 = comedication taken (based on an assumed start and/or stop date)

SSCs based on the drug substance names e.g. all clinical relevant CYP 3A4 inhibitors

SSC: CYP 3A4 inhibitors Mono-Comb
This SSC includes all single and multiple active ingredients products of the following substances in any salt form:
Amiodarone, Cimetidine, Citrus Paradisi, Clarithromycin, Diltiazem, Eythromycin, Fluoxetine, Fluvoxamine, Indinavir, Itraconazole, **Ketoconazole**, Mibefradil, Nefazodone, Nelfinavir, Ritonavir, Saquinavir, Troleandomycin, Verapamil
0 = no comedication taken
1 = comedication taken (based on recorded data)
2 = comedication taken (based on an assumed start and/or stop date)

Notes: • Define whether single or multiple ingredient products should be included
• Define which salt forms or enantiomers should be included
• Extensive literature research is necessary for comprehensive definitions

III. Generation of SSCs via a SAS program

SSC XY study independent listing of all codes and trade/ ingredient names

A SAS program was developed that generates for each SSC the WHO-DD code numbers of all respective trade names/ingredient names.

IV. CM data extraction

- Another SAS program[1] extracts from the clinical database of a study of interest the start and stop dates for each of the trade/ingredient names of each SSCs.
- Rules for replacement are defined to deal with missing or partial start and stop dates.
- Timely overlapping comedication treatment periods for one SSC were collapsed.

CM class XY study specific listing of comedication treatment periods per SSC

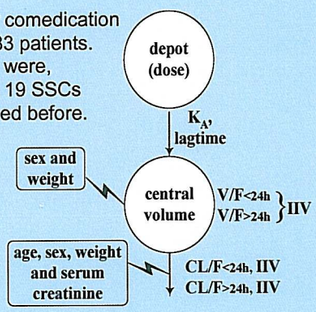
V. CM dataset assembling

ID	TIME	DAT1	TAD	AMT	DV	AGE	CRCL	CM1	CM2	CM3
1	10:52	03.12.2002	0	50	0	71	42.6	0	1	0
1	12:37	03.12.2002	1.75	0	9.5	71	42.6	0	1	0
1	15:15	03.12.2002	4.38	0	25.2	71	42.6	0	1	0
1	20:00	03.12.2002	0	50	0	71	42.6	0	1	0
1	08:30	04.12.2002	0	50	0	71	42.6	0	1	0
1	20:00	04.12.2002	0	50	0	71	42.6	0	1	0
1	08:00	05.12.2002	0	50	0	71	42.6	0	1	1
1	20:12	05.12.2002	0	50	0	71	42.6	0	1	1
1	07:59	06.12.2002	0	50	0	71	42.6	0	1	1
1	08:40	06.12.2002	0.68	0	19.8	71	42.6	0	1	1
1	11:37	06.12.2002	3.63	0	31.8	71	42.6	0	1	1
1	14:10	06.12.2002	6.18	0	25.1	71	42.6	0	1	1
1	20:00	06.12.2002	12.02	0	17.7	71	42.6	0	1	1

The SAS program compares each dataset record with the study specific listing and an identifier is assigned to all records between start and stop date +1 day for a recorded comedication defined in a SSC.

B. Application example, Dabigatran etexilate

- The dabigatran dataset from the Phase II study for comedication screening contained 7782 concentrations from 1483 patients.
- Thirty-one SSCs were defined. Of the 31 SSCs 19 were, associated with > 5% of the concentrations. These 19 SSCs were investigated using the PopPK model developed before.
- The SSCs were investigated as categorical covariates applying a standard forward inclusion/backward elimination model building strategy.



Results of comedication screening for Dabigatran etexilate

Parameter	Comedication class	Effect
CL/F < 24 hours	Opioids	17 % decreased
CL/F < 24 hours	Antacids	53 % increased
CL/F > 24 hours	Antacids	12 % increased
CL/F > 24 hours	Proton pump inhibitors	8 % increased
V/F	Antiemetics	28 % increased
V/F	Paracetamol + combinations	9 % decreased

Results:

Standard process for inclusion of comedication data into a NONMEM dataset

- The SAS code development and the literature research to define SSCs based on substance names (e.g. clinical relevant P-gp inhibitors) were time consuming.
- Once the process was defined and the standard SSCs were setup the incorporation of the comedication information into the dataset was very fast.

Application example, Dabigatran etexilate

- Three comedications had a statistically significant influence on dabigatran exposure and two on apparent volume of distribution (see table).
- The changes caused by these comedications were not considered clinically relevant because the magnitudes of the effects were minor.

Conclusions:

Standard process for inclusion of comedication data into a NONMEM dataset

- An efficient process was developed and successfully applied to include routinely collected comedication information for screening of drug-drug interactions.
- The SSCs can be applied across studies and projects.

Application example, Dabigatran etexilate

- None of the statistically significant effects were considered clinically relevant.
- None of the other CM classes investigated had a statistically significant influence on steady state exposure, indicating that they can be coadministered with Dabigatran.
- The results obtained for dabigatran were included in the proposed drug label.

Reference:

1. Chowdhury S. et al. PAGE 14 (2005) Abstr 836 [www.page-meeting.org/?abstract=836]