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Clinical Relevance of Drug-Drug Interactions

A Structured Assessment Procedure

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Abstract

Introduction: Computerised drug interaction surveillance systems (CIS) may be helpful in detecting clinically significant drug interactions. Experience with CIS reveals that they often yield alerts with questionable clinical significance, fail to provide relevant information on risk factors for the adverse reaction of the interaction and fail to detect all significant drug interactions. These problems highlight the importance of transparency and selectivity in choosing the drug interactions to be included in CIS. In The Netherlands, the Working Group on Pharmacotherapy and Drug Information is responsible for maintenance of the CIS of the Royal Dutch Association for the Advancement of Pharmacy (KNMP).

Methods: The Working Group developed an evidence-based procedure for structured assessment of drug-drug interactions and revised all drug interactions in the CIS accordingly.

Results: For every drug interaction four core parameters were assessed: (i) evidence on the interaction; (ii) clinical relevance of the potential adverse reaction resulting from the interaction; (iii) risk factors identifying patient, medication or disease characteristics for which the interaction is of special importance; and (iv) the incidence of the adverse reaction. On the basis of this assessment the drug-drug interactions for inclusion in the CIS were selected. After revision of the drug combinations in the KNMP-CIS, the Working Group judged 22% of the combinations to be not interacting and another 12% to be interacting but not requiring action.

On the basis of this assessment the subset of drug combinations for which interaction alerts are generated and the information on management of a drug interaction alert for users of the CIS were adapted. When an alert is generated by

the CIS, the user of the system is supplied with comprehensive information on the four core parameters, the mechanism of the interaction and critical information for management of the interaction for the individual patient.

Discussion: This structured procedure offers the possibility for transparent and reproducible assessment of the clinical relevance of drug interactions.

Conclusion: A CIS selectively generating interaction alerts based on this assessment may help in realising the goal of good clinical practice and may offer a methodology to further increase drug safety.

Background

The quality of pharmacotherapy is highly dependent on the process of choosing a drug in relation to the nature of the disease. In the process of choosing the optimal pharmacotherapeutic strategy, factors like route of administration, dose, contraindications, the potential for adverse drug reactions and costs play an important role. The possibility of a drug influencing the safety or efficacy of another drug (a drug-drug interaction) is an additional variable in making the optimal choice for pharmacotherapy.

Drug interactions increase morbidity and mortality and may lead to hospital admission.[1-4] In primary healthcare, 9–70% of patients are reported to be exposed to drugs with the risk of a drug interaction, with 1–23% of these interactions being of major relevance.[5-10] A French study reported an incidence of 27 per 10 000 prescriptions with contraindicated drug interactions in an ambulatory outpatient population.[11] During hospital admission the number of drug interactions per patient increases, with potential clinically relevant drug interactions occurring in 1 of 70 prescriptions.[12,13]

Many sources of information on drug interactions are available for healthcare providers, ranging from the summaries of product characteristics and product leaflets to text books and internet sites (e.g. www.gsm.com, www.epocrates.com, www.fda.gov, www.arizonacert.org).[14-16] However, knowledge of an interaction between two drugs is no guarantee for timely recognition of the interaction or for taking the appropriate action to prevent the risk of an adverse outcome.[17,18] Unless there are major advances in our understanding of drug-drug interactions, our ability to appropriately apply this information to specific patients will lag far behind.[19,20]

Computerised drug interaction surveillance systems (CIS) may be helpful in detecting and preventing drug interactions of clinical significance.[21] However, many pharmacists and doctors experience that these systems yield a large number of drug interactions with questionable or unclear clinical significance, fail to provide identifiable patient and medication risk factors, fail to detect all relevant drug interactions and include a variable set of interactions.[18,22-25] These shortcomings lead users to be uncertain about the quality of the system and to ignore drug interaction alerts.[23,25] Furthermore, one study shows that interpretation of drug interaction signals without clear information on the background and clinical relevance leads to discrepancies in the perception of the seriousness of the interactions.[26]

These problems stress the importance of transparency and selectivity in choosing the drug interactions to be included in a CIS. The Working Group on Pharmacotherapy and Drug Information is responsible for the maintenance of the CIS of the Royal Dutch Association for the Advancement of Pharmacy (KNMP). In this 22-member multidisciplinary Working Group, internists, general practitioners, pharmacists, hospital pharmacists, clinical pharmacologists and (a member of) The Netherlands Medicines Evaluation Board are represented. The Working Group recently developed a procedure for the structured assessment of drug-drug interactions. On the basis of this assessment, drug interactions are selected for inclusion in the KNMP-CIS, which has widespread use by general practitioners and (hospital) pharmacists.

In The Netherlands, tracking of virtually complete prescription data is possible since patients usually register with only one pharmacy and local pharmacies keep a computerised, detailed record of all delivered prescriptions. For this reason electronic medication surveillance for the complete drug use profile of the individual patient is possible.

In this manuscript we describe the procedures for structured assessment of drug-drug interactions and the translation of this assessment to the CIS of the Working Group on Pharmacotherapy and Drug Information in The Netherlands. Furthermore, we present the results of the revision of the complete KNMP-CIS on the basis of these assessments.

Structured Assessment of Drug Interactions

Goals

To develop a system for structured assessment of drug interactions it is important to define the goal of drug interaction alerts. The Working Group defined this goal as "timely recognition of the opportunity to intervene in drug use in order to prevent an undesired effect as a result of a combination of drugs". This definition clearly states that a drug interaction alert is only useful when an intervention is necessary and possible, e.g. prescribing and/or dispensing an alternative drug, dose adjustment or adjusted monitoring of drug effects. The Working Group stated that users of the CIS should be presented with drug interaction alerts requiring a potential intervention, accompanied with appropriate information on the relevance for their individual patient and with a clear proposal for potential interventions. Furthermore, the assessment procedure should facilitate quick updates of the CIS when new drug interactions are recognised or new information on existing drug interactions is published.

Core Dataset

For the assessment of drug interactions the Working Group defined four core parameters:

1. Evidence on the drug interaction.
2. The clinical relevance of the potential adverse reaction resulting from the drug interaction.
3. Risk factors: the drug interaction may be of special importance in patients with the specific risk factor.
4. Incidence of the adverse reaction in patients given the combination of the drugs.

When assessing these four parameters for every potential drug interaction, a complete and transparent set of information is collected that can be used as the basis for management of the drug interaction. Information on these parameters is collected and prepared by pharmacists from the Scientific Institute for Pharmacists in The Netherlands and presented to the Working Group every 6 weeks. On the basis of these four core parameters clinical relevance is discussed in a multidisciplinary way by the Working Group.

Evidence

The first suggestions that a drug interaction exists often comes from the registration file and summary of product characteristics of newly registered drugs. The importance of structured research on drug interactions in the preregistration phase is stressed by the Note for Guidance on the Investigation of Drug Interactions, which gives guidelines for conducting studies on drug interactions.[27] Despite this research, problems arise in gaining insight into the background information to assess the clinical relevance of these drug interactions. Evidence on the drug interaction may be theoretical or the evidence may be derived from clinical research that is not published and therefore not freely accessible (i.e. data on file). In assessing the clinical relevance of newly registered drugs the standard operating procedure of the Working Group is to ask the registration holder of the drug for detailed information on the drug interaction, as well as searching a standard set of sources:

- drug interaction text books;[14,15]
- PubMed database;[28]
- Excerpta Medica database (EMBASE);[29]
- Iowa Drug Information System (IDIS);[30]
- European Public Assessment Reports (EPARs).[31]

Table I. Quality of evidence

0	Pharmacodynamic animal studies; *in vitro* studies with a limited predictive value for the human *in vivo* situation; data on file
1	Incomplete, published case reports (no re- or de-challenge, presence of other explaining factors for the adverse reaction)
2	Well documented, published case reports; retrospective analyses of case series
3	Controlled, published interaction studies in patients or healthy volunteers with surrogate endpoints
4	Controlled, published interaction studies in patients or healthy volunteers with clinically relevant endpoints
–	Posters and abstracts from scientific meetings: 0 or 1, depending on the information provided. When the information of the poster or abstract is not published in a peer-reviewed journal within 3 years after the scientific meeting, this information is re-categorised as 0
–	Information from the Summary of Product Characteristics/European Public Assessment Reports (EPAR): 0, 1 or 2, depending on the information provided[31]
–	Retrospective case series: 2 or 3, depending on the information provided

Once papers have been selected as potential sources of evidence on the drug interaction, the Working Group uses a five-category scale to assess the quality of the evidence for a drug interaction as defined in table I.[32] When no evidence on the drug interaction is found, this is scored as absent.

Some drug interactions lack evidence from studies or case reports but have theoretical considerations as the primary basis, e.g. in cases where an analogy is suspected with another representative of the same drug class that is known to have a drug interaction. For interactions suspected to be relevant on the basis of an analogy, the Working Group requires detailed information on the mechanisms of the interaction to consider the drug interaction to be relevant. For example, the HMG-CoA reductase inhibitors ('statins') are known to have differential inhibiting effects on the cytochrome P450 enzyme system. Therefore, it is incorrect to handle the statins as a homogenous group when considering drug interactions and the cytochrome P450 system.

The Potential Adverse Reaction

The second core parameter considered by the Working Group is the clinical relevance of the potential adverse reaction from the drug interaction.

The Note for Guidance on the investigation of drug interactions defines a drug interaction as clinically relevant "when the therapeutic activity and/or toxicity of a drug is changed to such an extent that a dosage adjustment of the medication or medical intervention may be required".[27] This relevance often strongly depends on individual patient or disease characteristics. A dichotomous categorisation of the drug interaction as relevant or irrelevant is an undesired oversimplification of drug interaction assessment. To obtain a useful, transparent and reproducible result the Working Group uses a six-category scale for the seriousness of the adverse reaction of a drug interaction. The effect of the drug interaction as reported in the evidence on the drug interaction forms the basis for the classification of the effect. The categories (A–F) are in order of increasing seriousness (table II). When no effect of the drug interaction was described, e.g. because of lack of evidence, this was scored as 'unknown'. Although no strict limits could be defined to separate categories of seriousness, the following general descriptions per category proved to be useful in the assessment. For effects categorised in A or B, seriousness of the adverse reaction is minimal and clinical relevance in general is low. For effects categorised as C or D, clinical relevance may exist depending on the individual patient's risk factors for the effect. If no specific risk factors are known, these combinations in general should be considered to be clinically relevant. For categories E and F, the seriousness of the drug interaction effect is life threatening (e.g. failure of potentially life-saving therapy) or the combination is suspected to have resulted in death.

For each new adverse reaction, the Working Group discusses which category the reaction should be placed in. By categorising effects of drug interactions and using earlier classifications of adverse reactions for assessment of new drug interactions, a reproducible system of categorisation of drug interaction effects has been developed.

Some adverse reactions, such as changes in blood pressure, and changes in international normalised ratios (INRs) for patients taking oral anticoagulants, can have different gradations in seriousness. For categorisation of these effects the Working Group uses the National Cancer Institute's Common Toxicity Criteria (NCI-CTC).[33] The NCI-CTC has a six-step scale (0–5) for dividing gradual adverse reactions of drugs, which are translated into A–F in the Working Group's system.

Risk Factors

The risk of an adverse outcome from drug interactions may depend on characteristics relating to the patient (e.g. age, sex), disease (e.g. renal and hepatic function) and medication (e.g. dose, route of administration). Information on these risk factors is essential for the user of the CIS. The Working Group, while assessing the relevance of a drug interaction, gathers information on factors predictive for an adverse outcome. This information is derived from the evidence collected on the drug interaction as described previously. For this parameter the problem exists that, in the majority of potential drug interactions, information on specific risk factors for the adverse event resulting from the drug interaction is absent. However, when information is presented on risk factors this information is used in the assessment of the drug interaction and, if judged relevant, is presented to the user of the CIS.

Table II. Examples of effects per category of seriousness of adverse reactions resulting from drug interactions[a]

Category	Adverse reaction
A	Clinically irrelevant effect
	Failure of therapy with digoxin
	Ventricular premature beats, atrial ectopics
	Increase of international normalised ratio up to 4.0
B	Adverse reactions resulting from increased bioavailability of calcium antagonists of the dihydropyridine class
	Amnesia
	Fatigue
	Headache
	Nausea
C	Adverse reactions resulting from increased bioavailability of antiepileptics, ciclosporin, tacrolimus and sirolimus
	Increased risk of failure of therapy with methadone, leflunomide, iron supplementation, thyroxine and antidepressants
	Parkinsonism, tremor
	Increased risk for upper gastrointestinal bleeding
D	Adverse reactions resulting from increased bioavailability of aminoglycosides, lithium, methotrexate and digoxin
	Increased risk of failure of therapy for a serious, non-lethal disease, e.g. levodopa, methyldopa, loop diuretics
	Deep vein thrombosis
	Convulsions
E	Increased risk of failure of lifesaving therapy, e.g. antiretroviral medication, quinidine, rejection prevention (ciclosporin, tacrolimus, sirolimus)
	Prolonged QT interval
	Pulmonary embolism
	Rhabdomyolysis
	Multi-organ failure
F	Death
	Torsades de pointes, ventricular tachycardia
	Increased risk of pregnancy with risk factors for the fetus/neonate
	Bone marrow depression
	Serotonin syndrome

a Per category examples of potential effects within the category are shown. In every effect category new events are added after assessment by the Working Group.

Incidence

An interacting combination of drugs will not lead to an adverse outcome for every patient. The Working Group, while assessing the relevance of a drug interaction, gathers information on the incidence of adverse outcomes. As for risk factors, in many cases information on the incidence of the adverse outcome is lacking because of the absence of interaction studies. In these cases the user of the CSI is informed of the absence of this information.

Results of the Assessment

Based on the information on the four core parameters the Working Group assesses whether a particular combination of drugs gives an interaction (interaction: yes or no) and whether this combination of drugs has to be alerted at the moment of recognition by the CIS (action: yes or no).

Interaction: Yes/Action: Yes

A drug combination that the Working Group assesses as interacting (interaction: yes) and for which direct alerts have to be generated (action: yes) is entered in the CIS.

It is rare for the evidence to show clearly and unambiguously what the final assessment of the drug interaction should be. Consequently, it is not always clear to those who were not involved in the discussion how the Working Group was able to arrive at its recommendation. In order to address this problem, in accordance with the procedures adopted by the Scottish Intercollegiate Guidelines Network (SIGN), the Working Group has introduced the concept of considered judgement. Under considered judgement, the Working Group summarises its view of the total body of evidence on the drug interaction. This summary covers the four core parameters of the assessment process. Besides this summary, when alerting a drug interaction, the surveillance system generates a text for the user to aid in the process of managing the interaction. Four different texts are provided by the Working Group: a prescriber text, a pharmacy counter text, a hospital text and a background information text.

The prescriber text gives an alert and information for the prescribing physician. This text takes into account the possibility of prescribing an alternative medication or adjusting therapy monitoring. The pharmacy counter text gives information relevant at the moment of dispensing of the drug in the pharmacy. From our previous experience, a third text dedicated to the clinical situation (the hospital text) is provided.

Besides the prescriber, pharmacy counter and hospital text, all users of the CIS can consult a fourth text (the general background information text). This text offers information on the four core parameters as assessed by the Working Group, as well as information on the mechanism of the interaction and a short review of the literature on the interaction. Quality of evidence on the drug interaction and the seriousness of the adverse outcome are transparently translated to the user as an alphanumeric code: 0A (evidence lacking; clinically irrelevant effect) to 4F (evidence consists of controlled, published interaction studies with a clinically relevant endpoint; the adverse outcome is clinically very relevant). Together with the risk factors and the incidence of an adverse outcome, the user of the surveillance system is presented core information on the drug interaction in a transparent and concise manner in the case of an alert.

Interaction: Yes/Action: No

When the Working Group assesses a combination of drugs to be interacting (interaction: yes) but requires no action (action: no) when the combination of drugs is prescribed, this combination of drugs is entered in the surveillance system. However, the CIS will not automatically generate an alert for these interactions. Instead, these interactions are only logged by the system. Users of the CIS can create a tailor-made system; i.e. they are able to generate an alert for these combinations in their local situation, which is why these drug combinations have been entered into the interaction surveillance system.

Interaction: No

When the Working Group assesses a combination of drugs to have no interaction (interaction: no) and therefore no action is required, the drug combination will not automatically generate an alert. In these cases, users of the CIS are not able to generate an alert for the combination. In a separate drug information system published by the KNMP, the Informatorium Medicamentorum, information on these drug combinations is gathered.[34] Publication in this medium provides the opportunity for users to detect whether a drug combination has been assessed by the Working Group and provides complete information on all four core parameters.

Revision of the Drug Interactions in the Computerised Drug Interaction Surveillance System

On the basis of this structured assessment, in 2002–2003 the Working Group revised the complete set of drug combinations present in the KNMP-CIS. All interactions in the CIS were combinations of two drugs. Exceptions were made for the interactions concerning oral anticoagulants and antiretroviral medication since these interactions were assessed in close cooperation with the Federation of Thrombosis Services in The Netherlands and experts in the field of treatment of HIV infections, respectively. Revision of these combinations is currently ongoing.

The opportunity for voting exists in the cases where the Working Group, on the basis of a discussion on the four core parameters, could not reach consensus. For a valid vote, at least two-thirds of the members of the Working Group are required to be present, with the majority opinion accepted as the decision of the Working Group. In revising the drug interactions of the CIS this procedure did not need to be used.

Before the revision of the KNMP-CIS, the system included 244 different drug combinations. These drug interactions had been previously added to the CIS on the basis of information from the product leaflets and occasionally on the basis of results from specific drug interaction studies published in the medical literature. These drug interactions were introduced into the CIS after multidisciplinary discussion in the Working Group, although without the structured assessment that is presented in this article.

After revision according to the structural assessment, the Working Group judged 54 (22%) of these combinations not to be interactions. This subset of combinations was withdrawn from the CIS. Of the remaining 190 combinations, 30 (12% of the original 244 combinations) were judged to be interactions but not to require action. These combinations were left in the CIS, but no alert is generated when the combination is recognised. For the remaining 160 combinations (66% of the original 244 combinations), an alert is generated as soon as the combination is detected by the CIS.[1]

Discussion

We have described the procedure for structured assessment of drug interactions by the Working Group on Pharmacotherapy and Drug Information of the KNMP and the procedures for informing the users of the CIS on the interpretation of the assessment results for their individual patients.

The Working Group adopted the procedure for structured assessment of drug interactions in 2002 and revised the complete CIS accordingly. This resulted in 34% of the combinations being assessed as 'not interacting' or 'interacting but not requiring any action'. This percentage is comparable with the results of a German group that concluded that the number of alerts would be reduced by approximately 30% when drug pairs were filtered out that do not require active management as a result of minor or unspecified severity.[19]

Since the revision, all new drug interactions have been entered into the CIS only after completing the structured assessment procedure. Since 2002, expe-

1 A complete overview of the outcomes of the drug combinations assessment in the CIS is available as supplementary material from URL: http://www.adisonline.com/drs (table III, table IV and table V).

rience with the procedure shows that the major goals for the assessment procedure have been achieved. Adverse reactions are reproducibly categorised, reassessment of drug interactions on the basis of new information is a rapid process, and the structured assessment facilitates the translation of the information from the four core parameters to clinical action.

As the authors from a recently published study concluded, >75% of major drug interactions with published evidence are manageable, i.e. adverse reactions can be prevented by taking specific actions.[19] Manageability is highly dependent on facilitation of the process of adequately informing CIS users and critically selecting the combinations for which alerts are of clinical significance. A CIS specifically generating clinically significant alerts, accompanied with adequate information, may offer a tool for further optimisation of the quality of pharmacotherapy.

It is important to recognise that the quality of evidence supporting drug-drug interactions may differ between drugs registered before and drugs registered after the publication of the Note for Guidance on the Investigation of Drug Interactions, which provided guidelines for research on interactions.[27] However, public availability of the information from drug-interaction studies is important, instead of these results remaining as 'data on file' or short descriptions in the summaries of product characteristics and EPARs.

It has to be taken into account that CIS are no substitute for the information in the product leaflets. However, since information in the product leaflet is often too comprehensive to assess the relevance of a drug interaction for the individual patient, an alert from the CIS provides additional information to the text of the product leaflet.

Theoretically, information on pharmacogenetic testing, e.g. on enzyme and receptor mutations, may introduce benefits in recognising patients at increased risk of adverse reactions resulting from drug-drug interactions. However, at the moment pharmacogenetic testing is not part of routine clinical practice and is therefore not applicable. When this information becomes important in daily practice, inclusion in the assessment procedure as previously described can be easily achieved.

Conclusion

The procedure for assessment of the clinical relevance of drug interactions as described in this manuscript offers the possibility for transparent and reproducible assessment of the clinical relevance of potential interacting drug combinations. A CIS selectively generating interaction alerts based on this assessment may help in achieving good clinical practice and offers a methodology to further increase drug safety.

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