DRUG LABORATORY TEST INTERACTIONS IN CLINICAL PRACTICE

Improving laboratory test interpretation by creating awareness

Jasmijn A. van Balveren - Schasfoort

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DRUG LABORATORY TEST INTERACTIONS IN CLINICAL PRACTICE

IMPROVING LABORATORY TEST INTERPRETATION BY CREATING AWARENESS

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CONTENTS

CHAPTER 1

GENERAL INTRODUCTION

One of the main tasks of the clinician is to provide a correct diagnosis, which is needed for further medical decision making. Laboratory testing is often performed in the diagnostic process.

For a correct diagnosis, laboratory testing must be of high quality. Furthermore, the test results should add meaningful information and need to be correctly interpreted in the context of the individual patient (1). If these conditions are not met, diagnostic errors might be a consequence with unnecessary extra (hospital) revisits, diagnostic tests, and possibly inappropriate therapy and potential harm to patients. Unfortunately, diagnostic errors are common. The best estimates indicate that all of us are likely to experience a meaningful diagnostic error in our lifetime (2–4).

QUALITY OF LABORATORY TESTING

In the laboratory of clinical chemistry and haematology, chemical components and cells in body fluids, such as blood and urine are measured and evaluated. The laboratory needs to have a quality management system to facilitate correct test-ordering, specimen collection, analysis and reporting of results. All these aspects of laboratory testing are part of the so-called brain-to-brain loop: a concept introduced 50 years ago. The introduction of this concept led to a system to identify and classify errors associated with laboratory test performance. Errors have since been classified as pre-analytic, analytic, and post-analytic (5).

Nowadays, the analytical phase is highly optimized and there is a focus shift to further optimize the pre- and post-analytical phase. In particular, the interpretation of test results, as part of the post-analytical phase, needs improvement. Laboratory test interpretation is becoming more complicated, especially for non-laboratory professionals (6). The use of diagnostics is expanding and test panels are becoming increasingly complex. Currently, there are over 40,000 different In Vitro Diagnostic products available for a wide range of medical conditions (7). Given the increasing demand for healthcare attributable to the aging population in most developed countries and the growing incidence of chronic diseases, as well as technological advances, this number is expected to increase even further (8) and thus also the risk of diagnostic errors.

DRUG LABORATORY TEST INTERACTIONS

One of the sources of diagnostic errors is the presence of drug-laboratory test interactions (DLTIs).There are two main categories of DLTIs: analytical and physiological interactions (9,10).

Analytical interactions are in vitro processes. In these cases, the interactions between drugs and laboratory tests disturb the analytical process in the laboratory, which may have an important negative clinical impact, as laboratory test results may not reflect the clinical situation of the patient. These analytical interactions should be avoided by using an alternative assay, or erroneous test interpretations should be eliminated by warning systems. An example of an analytical drug test interaction is an erroneously high glucose level that can occur in continuous ambulatory peritoneal dialysis (CAPD) patients, because some glucose test strips cannot distinguish glucose from other sugars, such as icodextrin or maltose. These sugars can be present in CAPD fluid with improper administration of insulin as a result (11).

Physiological interactions are in vivo processes, in which drugs affect patients' laboratory test results. Test results may reveal an intended or unintended effect of a drug. Intended effects of drugs will generally not result in diagnostic misinterpretation, for example, an elevation in free thyroxin levels due to thyroid hormone replacement therapy. In contrast, unintended effect of drugs often can lead to diagnostic confusion. A clear example of an unintended effect of drugs is an elevated level of chromogranin A, which is indicative of the activity of a neuroendocrine tumour, but may also be the result of the frequently prescribed proton pump inhibitors. Case reports describe expensive imaging with no abnormalities and a normalized chromogranin A level after the discontinuation of the proton pump inhibitor (12). This example illustrates that unnecessary discomfort and expenditure could have been avoided if this unintended physiological interaction had been recognized in an early stage.

The clinical impact of DLTIs was already recognized and underlined in the early seventies (10,13,14), but it is still difficult to recognize DLTIs in daily clinical practice. Since there are so many interactions, it is impossible for healthcare professionals to consider all these possible interactions when interpreting laboratory test results of each individual patient.

The number of unique DLTIs described in the literature is substantial with about 50,000 DLTIs (10). The DLTI literature is fragmented and the clinical effect of a DLTI can be ambiguous. To prevent time-consuming searches in the literature, several DLTI databases with available literature have been developed. However, these databases may not be practical in daily clinical practice for several reasons, such as the lack of clinical relevance of interactions or the lack of a clear conclusion about the drug effect on a laboratory test result. Therefore, the Dutch Society of Clinical Chemistry and Laboratory Medicine created a new DLTI database with a summary of the literature and a conclusion of the effect of an interaction (15) (Figure 1) . The content of the database is revised regularly and expanded with new DLTIs.

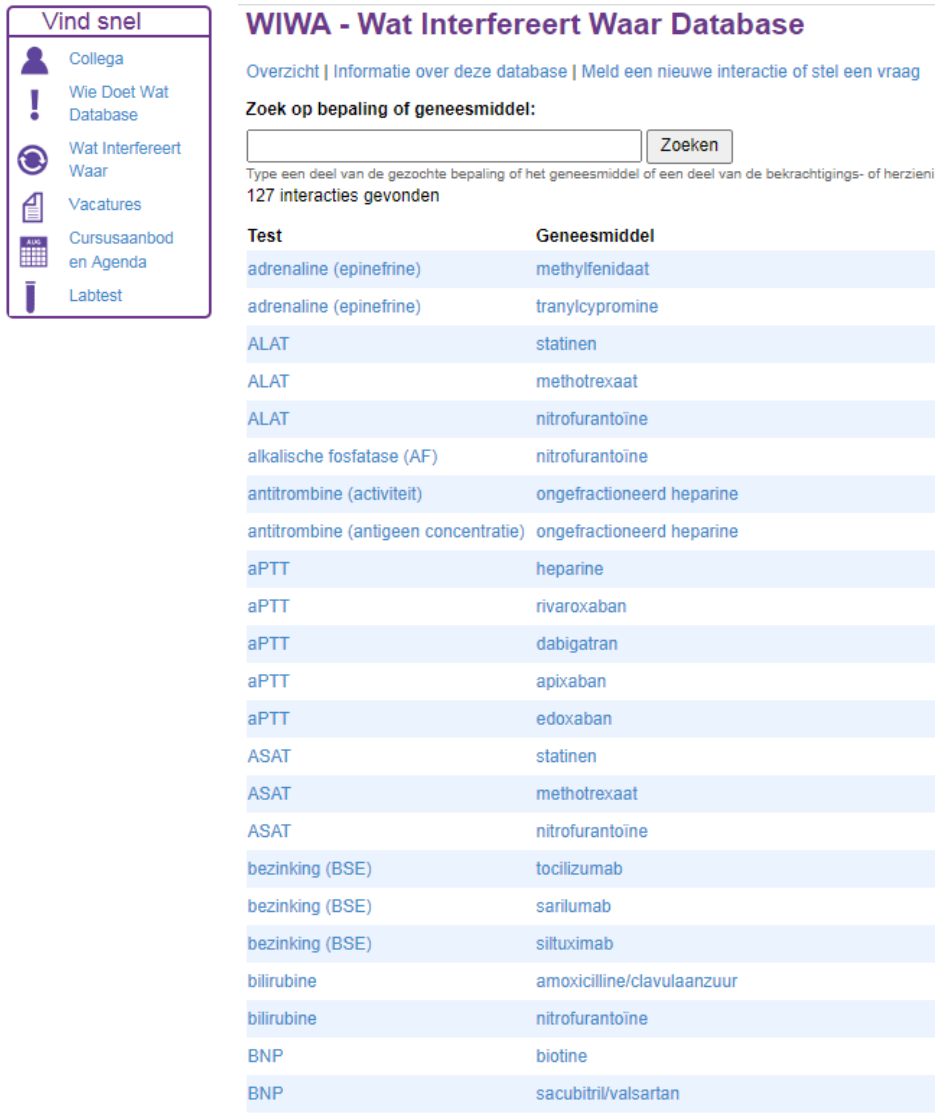

FIGURE 1: screenshot (21-12-2021) of the DLTI database of the Dutch Society of Clinical Chemistry and Laboratory Medicine. Left: fast link on homepage to DLTI database called 'What interacts where', right: opening page of database with search function to a specific interaction.

Electronic signalling systems or so-called clinical decision support systems (CDSS) could potentially offer a solution to the problem of unrecognized DLTIs. CDSS is already implemented in other processes in the laboratory of clinical chemistry and haematology, such as test ordering (16) and notification of life threatening conditions (17). In other medical departments CDSS is also being used, such as in pharmacy to monitor drug-drug interactions (18–20). A similar CDSS may send automatic messages about DLTIs based on algorithms, which use data from pharmacy and laboratory data systems.

SCOPE OF THIS THESIS

DLTIs potentially disturb the diagnostic process with possible harm to patients. The aim of this thesis was twofold: [1] examine the incidence and impact of a subset of DLTIs and [2] study a proof of concept of real-time monitoring of DLTIs in daily practice using CDSS.

Chapter 2 provides an inventory of the literature about the clinical utility of CDSS for DLTI recognition. Chapter 3 describes the implementation of a CDSS for DLTI monitoring in three hospitals. To build and design new algorithms or so-called 'clinical rules' in a CDSS for the detection of DLTIs, a database in which interactions are systematically described and validated is needed. The DLTI database from the Dutch Society of Clinical Chemistry and Laboratory Medicine (NVKC) was the basis of the clinical rules in this implementation study. The desired output from CDSS was automated DLTI alerts as part of the laboratory test report, of which an example is shown in Figure 2. The frequencies of the reported DLTI alerts were examined.

Low calcium (1.94) and low magnesium (0.66) could be caused by pantoprazole 80 mg.			
Urea	16.8(H)	mmol/L	2.5 – 4.6
Creatinine	48(L)	µmol/L	64 – 104
Estimated GFR	>90	ml/min	>90
Sodium	144	mmol/L	135 – 145
Potassium	4.0	mmol/L	3.5 – 4.8
Chloride	106	mmol/L	97 – 107
Calcium	1.94 (L)	mmol/L	2.15 – 2.60
Magnesium	0.66 (L)	mmol/L	0.7 – 1.10

FIGURE 2: example of a laboratory test report accompanied by an automatic drug laboratory test interaction alert. In this case: hypocalcaemia and hypomagnesemia caused by a prescribed proton pump inhibitor (pantoprazole).

The technical validity of the clinical rules is important, but an assessment of the clinical utility is equally or even more important. Obtaining insight in the clinical utility of specific DLTI messages yields useful information to refine DLTI clinical rules and is an important prerequisite for its introduction in clinical care. Therefore, the clinical utility of DLTI alerts to clinicians and specialists in laboratory medicine was examined using six clinical cases (chapter 4 and 5). Pharmacists were also consulted, since they use the results of laboratory tests to give an advice in the dosage of a specific drug.

Chapter 6 describes the results of a medical record study about the clinical impact of an unrecognized interaction between chromogranin A, a marker for neuroendocrine tumours, and proton pump inhibitors, a frequently prescribed drug. Earlier case reports described unnecessary extra diagnostics as a consequence of this missed DLTI (12). However, the prevalence and consequences of this unrecognized DLTI was not yet systematically examined in a large cohort of patients. Patient records from two large teaching hospitals and one university medical centre were examined.

Finally, in chapter 7, the results of this thesis are summarized and further implications and future perspectives of CDSS for DLTI monitoring are discussed.

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CHAPTER 2

IMPACT OF INTERACTIONS BETWEEN DRUGS AND LABORATORY TEST RESULTS ON DIAGNOSTIC TEST INTERPRETATION – A SYSTEMATIC REVIEW

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ABSTRACT

Intake of drugs may influence the interpretation of laboratory test results. Knowledge and correct interpretation of possible drug-laboratory test interactions (DLTIs) is important for physicians, pharmacists and laboratory specialists. Laboratory results may be affected by analytical or physiological effects of medication. Failure to take into account the possible unintended influence of drug use on a laboratory test result may lead to incorrect diagnosis, incorrect treatment and unnecessary follow-up.

The aim of this review is to give an overview of the literature investigating the clinical impact and use of DLTI decision support systems on laboratory test interpretation.

Particular interactions were reported in a large number of articles, but they were fragmentarily described and some papers even reported contradictory findings. To provide an overview of information that clinicians and laboratory staff need to interpret test results, DLTI databases have been made by several groups. In a literature search, only four relevant studies have been found on DLTI decision support applications for laboratory test interpretation in clinical practice. These studies show a potential benefit of automated DLTI messages to physicians for the correct interpretation of laboratory test results. Physicians reported 30- 100% usefulness of DLTI messages. In one study 74% of physicians sometimes even refrained from further additional examination. The benefit of decision support increases when a refined set of clinical rules is determined in cooperation with health care professionals. The prevalence of DLTIs is high in a broad range of combinations of laboratory tests and drugs and these frequently remain unrecognized.

INTRODUCTION

Diagnostic tests, such as laboratory analysis of body fluids, represent an important part of today's healthcare. The use of diagnostics is expanding and tests are becoming increasingly complex. Therefore, diagnostic test interpretation is becoming more complicated and diagnostic errors more common (1,2). There is a shifting role for laboratory specialists towards support and consultation of physicians for the interpretation of laboratory test results (3-5). One of their roles will be to eliminate harm from diagnostic errors and thereby improve the safety and quality of diagnostics. The Society to Improve Diagnosis in Medicine (SIDM) was established in 2015 to catalyse the changes necessary to reach this goal (6). It is important for all stakeholders to acknowledge the need for diagnostic expertise, to counterbalance policy makers that tend to focus on volume, efficiency and cost reduction in laboratory medicine, rather than quality and clinical effectiveness (7).
A common source of diagnostic error is the lack of knowledge of drug-laboratory test interactions (DLTIs). Misinterpretation of test results may lead to a delayed or erroneous diagnosis, unnecessary extra diagnostic tests or therapy which may harm patients.
Drugs frequently influence physiological in vivo processes and thereby affect the patients' laboratory test result. A drug may have an intended or unintended effect on a laboratory test result (8). Intended effects of drugs on laboratory test results are not the focus of this review, because it will normally not lead to diagnostic confusion. Moreover, the reason to request laboratory tests often is to monitor drug therapy, i.e. an elevation in free thyroxin levels and a reduction of thyroid stimulating hormone levels due to levothyroxine treatment.

An elevated level of chromogranin A can be indicative of activity of a neuroendocrine tumour. However, as an example of an unintended effect of a drug, this may also result from the administration of frequently prescribed proton pump inhibitors (PPIs). PPIs stimulate enterochromaffin cells which results in elevated levels of chromogranin A. Case-reports describe expensive imaging with no abnormalities and a normalized chromogranin A level after discontinuation of the PPI (9). This example illustrates that unnecessary discomfort and expenditure could have been avoided if this unintended physiological interaction had been recognized promptly. Another example is an elevated creatinine level in patients using trimethoprim. By inhibiting creatinine secretion, trimethoprim can lead to an elevation in serum creatinine independently of any changes in Glomerular Filtration Rate (GFR) (10). This factitious creatinine elevation impacts on GFR estimation and may, in certain cases, erroneously lead to the conclusion of an impaired kidney function.

In some cases the interactions between drugs and laboratory tests disturb the analytical process in vitro, which may have an important negative clinical impact, since affected

laboratory test results may not reflect the clinical situation of the patient. These analytical interactions should be avoided by using an alternative assay or erroneous test interpretation should be eliminated by warning systems. An extreme example of the danger of an analytical drug-test interaction is an erroneously high glucose level that can occur in continuous ambulatory peritoneal dialysis (CAPD) patients, because some glucose test strips cannot distinguish glucose from other sugars (e.g. icodextrin, maltose) that can be present in CAPD fluid (11). The improper administration of insulin has resulted in fatal consequences in a number of these cases.

Yao et al. investigated the presence of DLTIs in all labels of single ingredient Food and Drug Administration (FDA) approved drugs (8). Only analytical interactions were included in the search. A total of 134 out of 1368 labels (9.8%) were positive for an interaction with at least one laboratory test. Thirty-one labels indicated that the drug does not interfere with laboratory tests. All the other labels did not contain information about DLTIs, indicating that studies about DLTIs have been lacking for most drugs.The number of DLTIs described in the literature is substantial with a number of about 50.000 (12). Therefore, the application of a knowledge-based electronic expert system with concise and evidence-based DLTI information seems necessary. A knowledge-based expert system may send automatic messages about interactions based on the combination of data from pharmacy and laboratory data systems. Pharmacists already make extensive use of computerized clinical decision support with and without using laboratory test results. These expert systems use clinical rules to monitor drug therapy, to alert on possible interactions or side effects of drugs. Laboratory results are also routinely used to adjust dosage of medication, for instance in patients with impaired kidney function (13). These pharmacological decision support systems have proven to be beneficial and are still improving (14). Vice versa, expert systems could also use clinical rules for laboratory test interpretation based on pharmacological data in the department of clinical chemistry, but such systems are not yet available in today's clinical practice.

Decision support applications are based on algorithms. To build DLTI algorithms, relevant information about interactions is conditional. Information about DLTI can be found in literature, but is very fragmentarily described and sometimes even contradictory effects are reported, i.e. the effect of a drug on a laboratory test may result in both an increase or decrease of measured values (15, 16). Therefore, several DLTI databases have been introduced to provide an overview of interactions and the corresponding available literature (8, 17). Databases were published by the U.S. Library of Medicine (18), the American Association of Clinical Chemistry (AACC) which was based on the work of of Young et al. (12, 19), the Swedish Society for Clinical Chemistry in collaboration with the National Corporation of Pharmacies, which was based on the work of Tryding et al.(20, 21) Multirec (22) and the First DataBank MedKnowledge (23).

The aim of this review is to give an overview of the literature investigating the clinical impact and use of DLTI decision support applications on laboratory test interpretation and discuss future developments.

METHODS

A systematic literature search was conducted to collect studies investigating the impact and use of DLTI decision support applications on interpretation of laboratory test results. Studies were extracted from PubMed and the Cochrane library using the key words 'drug test interaction', 'drug interference', 'DLTI', 'drug laboratory test effect', 'DLE', 'laboratory test interaction' and 'decision support' or 'laboratory computer'. The search was limited to studies in humans and in the English language. Both ambulant and hospitalized patients were included in the reviewed study population. No specific study characteristics were excluded with the exception of case reports. Related articles and quoted articles from relevant articles were also reviewed. The search period ended July 2018. We also summarized available DLTI databases, which were found in the references of the conducted systematic literature search.

RESULTS

With the search strategy and the key words described above, 139 articles were found. Thirty-five articles were about decision support applications for drug prescribing. Nine articles described decision support applications in other medical departments. Eleven articles described drug-drug interactions and three articles a specific drug-laboratory test interaction. Sixty articles did not deal with drugs, laboratory tests or interactions at all. Three articles were about our topic of interest: DLTI decision support in laboratory test interpretation (24-26). One other relevant article (27) was selected, which was found in the references of a related article (8). These four qualifying studies are summarized in table 1.

Friedman et al. introduced an automatic reporting system of possible drug-test interactions in a university hospital in 1978 (27). The system was able to recognize more than 20.000 possible interactions adopted from the drug-test interaction file from the National Institute of Health. This DLTI database contained a complete overview of the literature per interaction, but these interaction reports did not always contain a clear conclusion about the drug effect on a laboratory test result (28). For a period of 16 months, the system searched the digital health records from patients for abnormal laboratory test results and drugs that were administered to the patient. It then searched

the DLTI database and printed reports for each patient indicating all possible DLTI. Four different departments participated: internal medicine, surgery, gynaecology and the intensive care unit. Most DLTIs were found in the intensive care unit. The drugs most frequently causing interaction messages were furosemide, hydrochlorothiazide, acetaminophen and penicillin. The laboratory tests most frequently reported in interaction messages were the white blood cell count, haemoglobin, potassium and glucose. Physicians reported that the system had both educational and clinical value. Of the interaction messages, 30% were found to be useful and in 4% of all reports this resulted in changes in patient's management. In addition to interviewing physicians, 186 patient records were selected randomly by the research staff to review the interactions. Almost half of the messages concerned a possible idiosyncratic toxic effect (e.g. aplastic anaemia or hepatitis) or a toxic dose dependent effect. However, no evidence of toxicity was found in the patient record. In approximately one third of cases an alternative explanation was found for the deviated laboratory test result. Approximately 20% of the interaction messages were categorized as clinically relevant: the interaction was the most probable explanation of the deviated test result. From the review by the expert panel of patient reports, it was concluded that in 0.1% of cases physicians altered their therapeutic strategy because of the interaction message.

Groves and Gajewski (24) described a comparable DLTI system as used by Friedman et al. (27). The technical aspects of the system were described extensively, but the clinical usefulness of the DLTI messages was not reported.

In 1983, McNeely described an approach to implement automatic interpretative comments on specialized laboratory test results (25). Comments about potential drug interference were also included, but specifications of these comments were not described. The clinical usefulness of DLTI information was only briefly mentioned: clinicians reported to 'enjoy' the provided drug interference data.

More recently, Grönroos et al. proposed a computerized DLTI decision support application and described the basic terms of the concept (29-31). This application was examined by Kailajärvi et al. on practical usefulness and appreciation by physicians during 10 months in 26 wards of a university hospital (26). Thirty-four drugs and 18 hormone tests were included, resulting in a total of 48 possible DLTIs. These interactions were all classified as clinically relevant and were well-documented in the literature. They all reflected an undesired effect of a drug. The system would only send a DLTI message when the onset and duration of the interaction were in concordance with the administration date of the drug and test result.

TABLE 1: Characteristics and results of reviewed studies

Study	Country	Study period	Included departments (n)	Included DLTIs (n)	Way of reporting to physicians	Evaluation of messages	Effect of DLTI message on medical management
Friedman et al. (1978)	United States	16 months	4	>20.000	Printed reports, no manual filter	Questionnaires to 40 physicians, review by expert panel of effect of interaction messages in 186 patient reports	4% changes in medical management (questionnaire results) 0.1% changes in management (according to documented evidence review)
Groves and Gajewski. (1978)	United States	NR	NR	>20.000	Printed and digital reports alongside laboratory test results	NR	NR
McNeely (1983)	Canada	3 months	NR	NR	NR	Polls to general practitioners and specialists	Specialists report to 'enjoy' being provided with drug interference data
Kailajärvi et al. (2000)	Finland	10 months	26	48*	Printed and digital reports alongside laboratory test results, automatic and manual filter by laboratory physician	Questionnaires to 23 physicians	74% of physicians consider changes in medical management

NR: Not Reported; * (only endocrinological tests)

In the study period, 3.845 hormone test results were produced. Of all hormone test results, 11% were accompanied by a DLTI message. More than 90% of the DLTI messages concerned effects on thyroid stimulating hormone, parathyroid hormone and free thyroxin. Twenty-three internal medicine physicians were surveyed and considered the messages useful. In addition, these alerts had caused 74% of the physicians to sometimes refrain from additional further examinations. Apart from these two studies, no further research was found about DLTI decision support applications in clinical practice.

DISCUSSION

In this review, we searched for literature about the impact and use of DLTI decision support applications on laboratory test interpretation by health care professionals.

A total of four reports were found. Two of the studies have shown a high prevalence of DLTIs in hospitalized patients (up to 43% of all patients, depending on which ward (27) and up to 11% of endocrinological test results (26)). The potential beneficial effects of automated DLTI warning messages for health care professionals who interpret laboratory test results is significant (26, 27).

The clinical benefit was determined from a limited retrospective evaluation of patient records in one study (27), and surveys with physicians in three studies (25-27). One study only briefly mentioned positive feedback from specialists about DLTI information (25). In the other two studies, physicians reported 30%- 100% of DLTI messages to be useful (26, 27). These differences in reported usefulness could be explained by differences in study design. Kailajärvi et al. included 48 interactions with common laboratory tests and drugs (26) whereas Friedman et al. studied more than 20.000 interactions, including interactions with less frequently requested laboratory tests and drugs (27). Furthermore, in the study of Kailajärvi et al., the messages were automatically selected based on predefined usefulness criteria and thereafter, judgement by the laboratory specialist before sending the DLTI messages to the responsible physician, while the other study did not apply any selection.

There are several DLTI databases, which are useful for healthcare professionals when they suspect a possible DLTI, but a disadvantage of such databases is that physicians have to actively suspect an interaction before they consult a database. This disadvantage is eliminated when decision support applications are introduced. The available DLTI databases can be used for automated decision support, but there are some important limitations. In some databases the clinical relevance of interactions is lacking, or literature is listed but not summarized. Also, some databases do not contain information on the degree, duration and incidence of the effect or of risk factors (such as age or gender) and often cited literature is not up to date. Databases should ideally contain a summary and a conclusion of the available literature and should be updated continuously (32).
Research showed the added value of decision support applications to alert health care professionals on possible DLTIs, but the effectiveness of such a system increases when a refined set of clinical rules is determined in cooperation with health care professionals who use the system (26, 27). These refined clinical rules are needed to prevent excessive numbers of DLTI messages and consequently so-called 'alert fatigue' of physicians (33). Although the benefit of DLTI decision support was already shown in the past (27), it is not widely implemented today. To implement a DLTI decision support tool, an accessible DLTI database is crucial. Moreover, in a DLTI decision support system, current drugs and laboratory tests have to be uniformly registered and coded in a digital patient record and data exchange between the systems must be realised. An example of the structure of the conditional data exchange is shown in figure 1. Finally, a proper connection between the patient records of different healthcare professionals (i.e. physician and pharmacists) is a requirement for a complete overview of possible interactions.

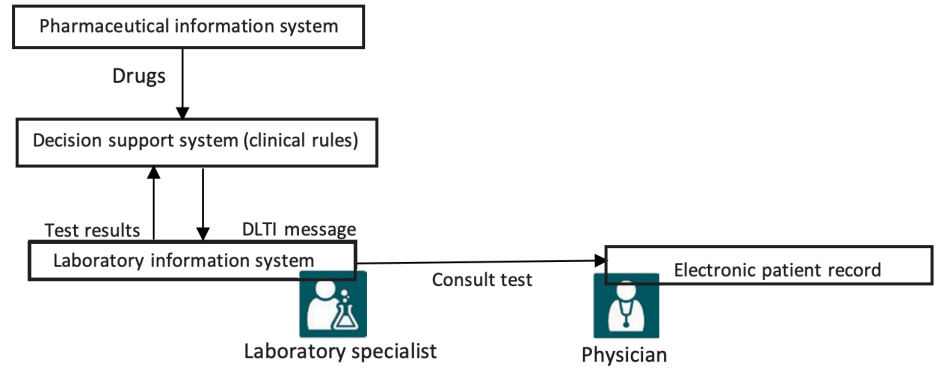

FIGURE 1: Conditions needed for automated DLTI decision support.

Awareness of DLTIs is essential for correct interpretation of laboratory test results and consequently correct diagnosis and treatment of patients. The existing literature shows a high prevalence of DLTI in a variable range of laboratory tests and drugs. It is likely that in daily practice the prevalence of DLTI is even higher, since interactions are not systematically examined or reported. Promising new methods of interaction detection are recently published, such as data analytics examining temporal correlations between drug administration and lab value changes.(34)

A Dutch consortium of the Society of Clinical Chemistry and Laboratory Medicine (NVKC) is currently performing a multicentre pilot study to investigate the prevalence of DLTIs and the value of an automated DLTI decision support system in clinical practice. The purpose of the study is to get a proof of concept of the system, which is expected to support laboratory specialists and physicians in the correct interpretation of laboratory test results. The final goal is to reduce diagnostic errors and thereby contribute to improve healthcare.

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CHAPTER 3

REAL-TIME MONITORING OF DRUG LABORATORY TEST INTERACTIONS: A PROOF OF CONCEPT

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ABSTRACT

Objectives

For the correct interpretation of test results, it is important to be aware of drug-laboratory test interactions (DLTIs). If DLTIs are not taken into account by clinicians, erroneous interpretation of test results may lead to a delayed or incorrect diagnosis, unnecessary diagnostic testing or therapy with possible harm for patients. A DLTI alert accompanying a laboratory test result could be a solution. The aim of this study was to test a multicenter proof of concept of an electronic clinical decision support system (CDSS) for real-time monitoring of DLTIs.

Methods

CDSS was implemented in three Dutch hospitals. So-called 'clinical rules' were programmed to alert medical specialists for possible DLTIs based on laboratory test results outside the reference range in combination with prescribed drugs. A selection of interactions from the DLTI database of the Dutch society of clinical chemistry and laboratory medicine were integrated in 43 clinical rules, including 24 tests and 25 drugs. During the period of one month all generated DTLI alerts were registered in the laboratory information system.

Results

Approximately 65 DLTI alerts per day were detected in each hospital. Most DLTI alerts were generated in patients from the internal medicine and intensive care departments. The most frequently reported DLTI alerts were potassium-proton pump inhibitors (16%), potassium-beta blockers (11%) and creatine kinase-statins (11%).

Conclusions

This study shows that it is possible to alert for potential DLTIs in real-time with a CDSS. The CDSS was successfully implemented in three hospitals. Further research must reveal its usefulness in clinical practice.

INTRODUCTION

It is well known that many drugs interact with laboratory test results [1]. To interpret test results correctly, it is important to be aware of drug laboratory test interactions (DLTIs). DLTIs can be the result of analytical interferences, which make test results unreliable since they do not correctly reflect the clinical situation of the patient. An example of an analytical interaction is the effect of biotin on biotin-based immunoassays, such as some troponin assays: cardiac troponin concentrations can be falsely low in patients using dietary supplements containing high levels of biotin [2]. Additionally, the interaction between drugs and laboratory test results can have a physiological cause and then does correctly reflect the clinical situation of the patient: the drug has an intended or unintended (side) effect on a test result [3]. An example of an unintended drug effect is a hyponatremia caused by serotonin reuptake inhibitors. Wrong interpretation of test results can lead to a delayed or erroneous diagnosis, unnecessary extra diagnostic tests and/or therapy with possible harm for patients and additional healthcare costs [4, 5].

The clinical impact of DLTIs was already recognized and underlined in the early seventies [6–8], but it is still difficult to recognize DLTIs in daily clinical practice. DLTIs are not always known by clinicians [9] and even if a DLTI is suspected, scientific evidence for the DLTI is hard to find. DLTI literature is fragmented and the clinical effect of a DLTI can be ambiguous. To prevent time- consuming searches in the literature, DLTI databases with available literature have been developed [10]. However, these databases may not be practical in daily clinical practice for several reasons, such as long lists of scientific articles, which have not been summarized and may even describe contradicting results. Therefore, the Dutch Society of Clinical Chemistry and Laboratory Medicine created a new DLTI database with a summary of the literature and a conclusion of the effect of an interaction [11]. The content of the database is revised and expanded regularly with new DLTIs.

A possibility to make the knowledge of a DLTI database easily accessible for clinicians in laboratory test interpretation is the use of an electronic clinical decision support system (CDSS). Since increasing amounts of data are electronically stored, including laboratory test results and prescribed drugs, implementing CDSS is the logical next step to merge these data into ready-to-use, patient specific DLTI alerts (Figure 1). A CDSS is especially useful when the alerts are available at the time laboratory results are reviewed and clinical decisions are made. CDSS is already widely implemented in pharmacy for drug monitoring [12, 13], but not for laboratory test interpretation [10]. DLTI alerts reported in real-time by CDSS could lead to a significant improvement of DLTI awareness. In a recent study we have shown that physicians are interested in the possibilities of this concept [9]. Figure 1 shows an example of how a test report can be accompanied by

a DLTI alert. The aim of this study was to apply a multicentre proof of concept of a decision support system in real-time monitoring of DLTIs in clinical practice and assess the frequency of DLTI alerts.

Low calcium (1.94) and low magnesium (0.66) could be caused by pantoprazole 80 mg.			
Urea	16.8(H)	mmol/L	2.5 – 4.6
Creatinine	48(L)	µmol/L	64 – 104
Estimated GFR	>90	ml/min	>90
Sodium	144	mmol/L	135 – 145
Potassium	4.0	mmol/L	3.5 – 4.8
Chloride	106	mmol/L	97 – 107
Calcium	1.94 (L)	mmol/L	2.15 – 2.60
Magnesium	0.66 (L)	mmol/L	0.7 – 1.10

FIGURE 1: Example of a laboratory test report accompanied by an automatic drug laboratory test interaction alert. In this case: low calcium and magnesium caused by a proton pump inhibitor.

MATERIALS AND METHODS

The study was conducted in three large teaching hospitals in the Netherlands: the Jeroen Bosch hospital (’s-Hertogenbosch), Zuyderland Medical Centre (Sittard-Geleen and Heerlen) and Medical Spectrum Twente (Enschede), hereafter hospital 1, 2 and 3, respectively.

The CDSS ‘Gaston Lab’ (version 3) from the company Gaston Medical (Eindhoven, the Netherlands) was used [14, 15]. In Figure 2 the electronic connections that were made in one of the hospitals between the CDSS and various patient records are shown. This was not universal for each hospital, since information about drugs and test results may also be stored and queried elsewhere (such as the electronic patient record). Laboratory test results and prescribed drugs with predefined codes, such as the internationally used logical observation identifiers names and codes (LOINC) for laboratory tests and anatomical therapeutic chemical (ATC) codes for drugs are used to run so-called clinical rules. These clinical rules are presented as flowcharts by a user-friendly interface (see Figure 3). In the first step of a flowchart all data are filtered with a specific criterion, for example “creatinine” or “trimethoprim”. A possible DLTI can be detected by further specifying the criterion in the clinical rule, for example “creatinine above the upper reference limit” or “trimethoprim prescribed at the time the test is performed”. All clinical rules were constructed alike.

The CDSS generated an alert of a possible DLTI based on one test result outside the reference range and one prescribed drug. The number of alerts per DLTI per hospital was recorded. To get an impression of the frequency that a drug potentially caused a test result outside reference ranges, the incidence of all generated results of a specific test within the reference range and simultaneously prescribed drug was also monitored in hospital 1. This allowed the calculation of percentage test results outside reference ranges compared to total tests with a potential interacting drug.

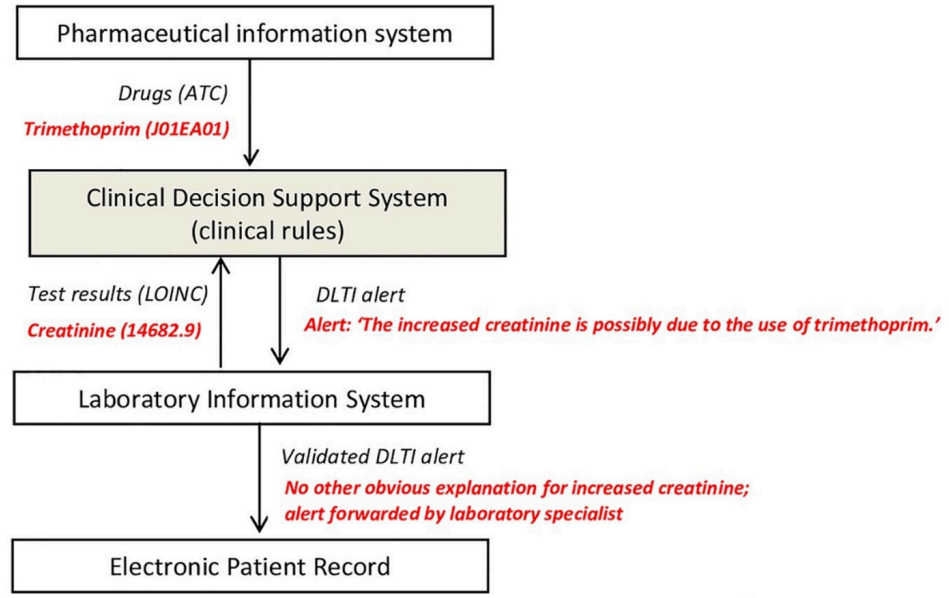

FIGURE 2: Connections of electronic decision support system (containing clinical rules) to receive real-time patient data and consequently, send DLTI messages. ATC, anatomical therapeutic chemical (drug classification system of the World Health Organization); LOINC, logical observation identifiers names and codes (universal standard for identifying medical laboratory observations, such as laboratory tests); DLTI, drug laboratory test interaction.

A random selection of interactions from the DLTI database of the Dutch Society of Clinical Chemistry and Laboratory Medicine were integrated in 43 clinical rules for this study, including 24 tests and 25 drugs (Table 2). Well-established interactions between frequently prescribed drugs and/or frequently requested laboratory tests were used. Some interactions were applicable to a group of drugs (e.g. Angiotensin Converting Enzyme-inhibitors) and others only to a specific drug (e.g. trimethoprim). The DLTI database contained information about more than 43 possible DLTIs, but in the current study interactions were only included in the CDSS if the effect was well documented in the literature according to a working group of laboratory specialists of the Dutch society of clinical chemistry and laboratory medicine.

Validation of DLTI clinical rules was done with test patients of whom their drug use interacted with test results to confirm that parameters used in the definitions were linked to the correct data in the pharmaceutical and laboratory information system and electronic patient record. After this validation, the clinical rules were also validated with real-time patient data. Only patient records of in-hospital (clinical or outpatient) patients were included. The results were obtained in each hospital over a period of one month in the spring of 2019. We used descriptive statistics (N; %; mean (standard deviation); median; 5–95 percentile), using the R statistical package (version 1.2.5033).

Approval by the ethics committee was not required for this type of study. The study was funded by the Quality Foundation of the Dutch Medical Specialists (SKMS, grant number: 42678870).

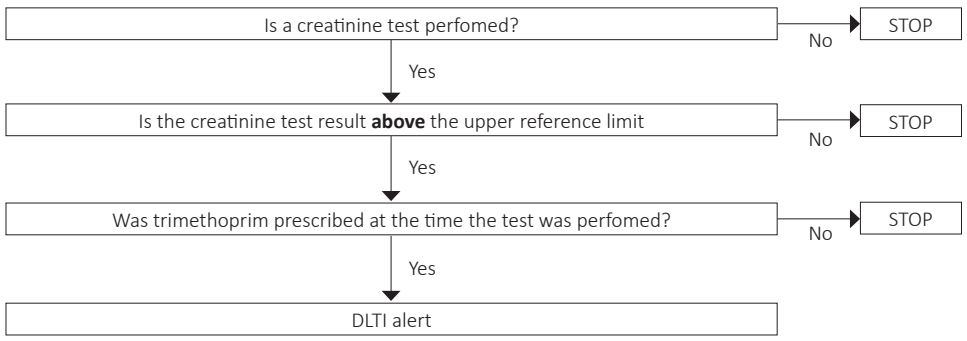

FIGURE 3: A clinical rule: creatinine and trimethoprim. DLTI, drug-laboratory test interaction.

RESULTS

We implemented the CDSS in three different hospitals and results of generated DLTIs were recorded for a period of one month. In Table 1 the demographics of all patients from the three hospitals with DLTI alerts are shown. Most DLTI alerts were generated in patients from the department of internal medicine (42%), followed by the intensive care (23%) and the department of cardiology (18%). The median age of patients with DLTI alerts was 69 years. The majority of patients with a DTLI alert was men (62%).

Table 2 shows the prevalence of DLTI alerts in the three hospitals. In each hospital, more than 2,000 DLTI alerts were generated, i.e. on average 65 DLTI alerts per day. Potassium — proton pump inhibitors was the most frequently reported DLTI alert (n=1,069, 16%), followed by potassium — beta-blockers (n=711, 11%) and creatine kinase — statins (n=699, 11%). Proton pump inhibitors also accounted for other frequently reported DLTI alerts interacting with calcium (n=542, 8%) and magnesium (n=442, 7%), as were statins interacting with aspartate aminotransferase (ASAT) (n=620, 9%) and alanine aminotransferase (ALAT) (n=569, 9%). Some DLTI alerts were rarely reported, such as neutrophil granulocytes and lithium (n=4) and chromogranin A and proton pump inhibitors (n=1).

TABLE 1: Demographics of patients with DLTI alerts (n=6,575).

Age, years	
Median (5-95 percentile)	70.0 (47–87)
Gender	
Men, %	61.6
Medical department, %[a]	
Internal medicine	41.9
Intensive care	22.5
Cardiology	17.5
Surgery	10.7
Neurology	2.8
Geriatrics	1.3
Emergency care	1.2
Gynaecology	0.5
Paediatrics	0.5
Psychiatry	0.5
Dermatology	0.4
Other	0.3

[a]Requesting physicians of hospital 2 unknown, percentages based on hospital 1 and 3. DLTI, drug laboratory test interaction.

In Table 3 DLTI frequencies from hospital 1 are shown in relationship to gender, age, total tests performed and total tests with a prescribed potential interacting drug. The frequency of performed tests was comparable in men (51%) and women. Test results with a potential interacting drug and test results with a DLTI alert were more frequently detected in men (62% vs. 54% in women). The median age of patients with performed laboratory tests was lower (65 years) than the median age of patients with laboratory test results and a potential interacting drug and test results with a DLTI alert (70 years). The test frequencies ranged from 0 (catecholamines in urine) to 12,615 (platelets).

In patients with a prescribed potential interacting drug, test results outside the reference range were counted. For six laboratory tests, results were outside reference ranges in more than 50% of all performed tests (marked in bold), such as prothrombin (in combination with vitamin K antagonists) and platelets (in combination with valproic acid).

Some tests were rarely outside the reference range with a prescribed potential interacting drug, such as platelets (heparin: 1%) and TSH (lithium: 1%).

TABLE 2: DLTI alerts issued during one month.

Laboratory test	Increase or decrease of test result	Interacting drug	Total	Hospital 1	Hospital 2	Hospital 3
ALAT	↑	Methotrexate	64	63	1	0
	↑	Statin	569	203	227	139
APTT	↑	Heparin	12	1	4	7
ASAT	↑	Methotrexate	19	14	5	0
	↑	Statin	620	183	273	164
Calcium	↓	Proton pump inhibitor	542	101	198	243
Chromogranin A	↑	Proton pump inhibitor	1	0	0	1
Creatine kinase	↑	Statin	699	225	146	328
Catecholamines[a]	↑	Methylphenidate	0	0	0	0
Conjugated bilirubin	↑	Amoxicillin/clavulanic acid	172	7	4	161
Creatinine	↑	Cimetidine	2	0	0	2
	↑	Trimethoprim	97	78	16	3
Free thyroxin	↑ and ↓	Amiodarone	12	6	4	2
	↓	Carbamazepine	1	0	0	1
	↓	Lithium	8	8	0	0
Ionised calcium	↓	Proton pump inhibitor	98	0	88	10
Lactate	↑	Metformin	27	0	19	8
Magnesium	↓	Proton pump inhibitor	442	258	108	76
Metanephrines[a]	↑	Methylphenidate	0	0	0	0
Neutrophil granulocytes	↓	Clozapine	0	0	0	0
	↓	Lithium	4	0	4	0
Platelets	↓	Amoxicillin/clavulanic acid	193	28	19	146
	↓	Glycoprotein 2b3a antagonist	0	0	0	0
	↓	Heparin (including LMWHs)	20	1	0	19
	↓	P2Y12 inhibitor	281	80	96	105
	↓	Valproic acid	22	8	8	6
Potassium	↑	ACE inhibitor	243	66	27	150
	↑	Beta blocker	711	269	135	307
	↓	Proton pump inhibitor	1,069	340	435	294
	↓	Thiazide diuretic	125	17	55	53
PT	↑	Vitamin K antagonist	55	32	0	23
PTH	↑	Loop diuretic	63	47	6	10
Sodium	↓	Immune globulins IV	4	0	4	NA
	↓	Selective serotonin reuptake inhibitor	83	24	59	NA
	↓	Thiazide diuretic	101	42	59	NA
Total bilirubin	↑	Amoxicillin/clavulanic acid	120	8	6	106
TSH	↑ and ↓	Amiodarone	23	14	2	7
	↓	Glucocorticoid	36	30	1	5
	↑	Lithium	2	1	0	1
	↑	Valproic acid	2	1	0	1
Uric acid	↑	Thiazide diuretic	22	19	3	0
Vitamin B12	↓	Metformin	3	3	0	0
	↓	Proton pump inhibitor	8	5	3	0
Total			6, 575	2,182	2,015	2,378

[a]In urine, ↑ increase of test result, ↓ decrease of test result, NA, not available: missing data due to incorrectly implemented clinical rule, frequencies >500 are marked in bold. ACE, angiotensin-converting-enzyme; ASAT, aspartate aminotransferase; ALAT, alanine aminotransferase; APTT, activated partial thromboplastin time; DLTI, drug-laboratory test interaction; IV, intravenous; LWMH, low molecular weight heparin; PT, prothrombin time; PTH, parathyroid hormone; TSH, thyroid stimulating hormone.

TABLE 3: DLTI alerts compared to total number of tests performed and potential interacting drug in hospital 1.

	Tests performed	Interacting drug	Tests with potential interacting drug	Test results outside reference values (DLTI alert)
Age, years				
Median (5–95 percentile)	65 (21–86)		70 (44–87)	70 (44–88)
Gender				
Men, %	51		54	62
Test	n		n	n (% of tests with interacting drug)
ALAT	6, 511	Methotrexate	611	63 (10%)
		Statin	1,600	203 (13%)
APTT	347	Heparin	21	1 (5%)
ASAT	4,119	Methotrexate	71	14 (20%)
Calcium	3,059	Proton pump inhibitor	1,203	101 (8%)
Catecholamines[a]	0	Methylphenidate	0	0 (0%)
Chromogranin A	3	Proton pump inhibitor	0	0 (0%)
Creatine kinase	2,876	Statin	937	225 (24%)
Conjugated bilirubin	2,177	Amoxicillin/clavulanic acid	416	7 (2%)
Creatinine	11,600	Trimethoprim	262	78 (30%)
Free thyroxin	837	Amiodarone	44	6 (14%)
		Lithium	72	8 (11%)
Ionised calcium	998	Proton pump inhibitor	0	0 (0%)
Lactate	29	Metformin	18	0 (0%)
Magnesium	2,389	Proton pump inhibitor	1,023	258 (25%)
Metanephrines[a]	24	Methylphenidate	0	0 (0%)
Neutrophil Granulocytes	5,162	Lithium	0	0 (0%)
Platelets	12,615	Amoxicillin/clavulanic acid	227	28 (12%)
		Heparin	75	1 (1%)
		Glycoprotein IIb/IIIa inhibitor	0	0 (0%)
		P2Y12 inhibitor	1,159	80 (7%)
		Valproic acid	8	8 (100%)
Potassium	8,417	ACE inhibitor	340	66 (19%)
		Beta blocker	2,959	269 (9%)
		Proton pump inhibitor	2,376	340 (14%)
		Thiazide diuretic	154	17 (11%)
PT	392	Vitamin K antagonist	32	32 (100%)
PTH	265	Loop diuretic	56	47 (84%)
Sodium	8,266	Immune globulins IV	376	0 (0%)
		Selective serotonin reuptake Inhibitor	506	24 (5%)
		Thiazide diuretic	45	42 (93%)
Total bilirubin	3,883	Amoxicillin/clavulanic acid	16	8 (50%)
		Amiodarone	37	14 (38%)
TSH	2,052	Glucocorticoids	128	30 (23%)
		Lithium	68	1 (1%)
		Valproic acid	3	1 (33%)
Uric acid	617	Thiazide diuretic	30	19 (63%)

TABLE 3. Continued

	Tests performed	Interacting drug	Tests with potential interacting drug	Test results outside reference values (DLTI alert)
Vitamin B12	655	Metformin	4	3 (75%)
		Proton pump inhibitor	43	5 (12%)
Total	77,293		15,974	2,182 (14%)

[a]In urine, percentages of test results outside reference range above 50 are bold marked. ACE, angiotensin-converting-enzyme; ASAT, aspartate
aminotransferase; ALAT, alanine aminotransferase; APTT, activated partial thromboplastin time; DLTI, drug-laboratory test interaction; PT, prothrombin time; PTH, parathyroid hormone; TSH, thyroid stimulating hormone.

DISCUSSION

The aim of this study was to demonstrate a proof of concept of a CDSS which can automatically identify DLTIs in clinical practice. We succeeded to implement the system in three large teaching hospitals where possible DLTIs were detected approximately 65 times per day per hospital.

The use of CDSS with DLTI alerts for interpretation of laboratory test results has not frequently been described [10]. A comparable study on this topic was published more than 20 years ago and in this study 11% of tests was accompanied by so-called 'drug-laboratory effect reminders' [16]. In this study a subset of interactions for endocrinological tests was examined. In our study we included DLTIs with chemical, haematological and coagulation tests.

Frequencies of DLTI alerts were different between hospitals. There were more DLTI alerts on bilirubin and amoxicillin/clavulanic acid in hospital 3 in comparison with the other hospitals. We can only speculate on the cause of these differences, such as a difference in prescription behaviour of physicians, a different hospital population or for certain DLTIs a difference in dosages of drugs prescribed by the hospitals.

Refinement of clinical rules increases the effectiveness of CDSS and is needed to prevent excessive numbers of DLTI alerts [17]. There are several considerations for refinement. First, a DLTI alert may be eliminated if there is another more likely cause of a pathological test result. This is illustrated by the interaction between parathyroid hormone (PTH) and loop diuretics. Of all PTH test results outside the reference range, 84% of test results originated from patients with a prescribed loop diuretic that may have an increased PTH due to chronic kidney disease. Another example is statins interacting with creatine kinase and ASAT. Statins may cause myopathy and disturbed liver function, resulting in elevated creatine kinase and ASAT concentrations. However, creatine kinase and ASAT are also elevated in cardiac events. Therefore, it might be a suggestion to expand clinical rules with patient characteristics, such as medical history (chronic kidney disease in the first example) or other test results (elevated concentrations of cardiac markers in the second example) to filter alerts.

Second, cut-off values of test results for DTLI alerts need to be considered. In this study, a DLTI alert was only reported when a laboratory test result was below or above the reference range. Cut-off values for reported DLTI alerts could also be adjusted to values that require medical treatment. For example, instead of the upper reference limit for potassium, a higher potassium value known to cause (serious) adverse effects could be chosen for an alert. Instead of static cut-off values, DLTI alerts could also be triggered on so-called delta checks, i.e. comparing current patient test results to previous results. Third, repeated DLTI alerts in the same patient are presumably less useful and could cause alert fatigue. In our study, we found the same DLTI alert several times during follow-up of hospitalized patients.

Fourth, knowledge and preferences about DLTIs of the receiving medical specialist also influence usefulness of DLTI alerts [9]. Physicians with shorter clinical experience more often appreciate a DLTI alert. Therefore, it is desirable to customize DLTI alerts per healthcare professional or department.

Finally, the timing and reporting of DLTI alerts and how these are presented to healthcare professionals should be considered. For example, a DLTI alert can be added to an individual test result or overall test report and could be shown as a pop-up or as a text below the laboratory results.

These considerations for refinement and others are part of a continuous clinical evaluation of individual alerts, which is highly recommended in CDSS development [18, 19]. One remarkable observation in our study was the un- equal distribution of DLTI alerts between men (62%) and women, while laboratory tests were performed almost equally in men and women. Drugs were only slightly more often prescribed in men (54%), thus not explaining the gap in DLTI alert frequencies between men and women. The few studies that counted DLTI alerts did not report patient characteristics such as gender [16, 20]. These findings should be confirmed in future research.

The strength of our study lies in its multicentre design. Most studies indicating a positive effect of CDSS are single-centre trials, using in-house designed decision support systems. As a result, difficulty in recognizing the value of decision support is one of the major barriers to widespread effective use of CDSS [13]. Furthermore, implementation of CDSS can be expensive and technically challenging [21, 22]. In our study, three out of six

participating hospitals failed to implement the CDSS due to a lack of resources (time and money). We experienced that cooperation on a higher (national) level is favourable to overcome implementation issues. We demonstrated that our CDSS is applicable in three different hospitals with different electronic patient records and pharmacy and laboratory information systems. The study consortium continues to improve the system and examine its effectiveness in collaboration with clinicians, including pharmacists and physicians.

In this study, we started with 43 randomly selected DLTIs as a proof of concept. However, thousands of interactions are described in the literature. More alerts for possible interacting drugs with clinical relevance should be added. The clinical usefulness of each DLTI alert must be evaluated in future research. Alerts about less known drug side effects and analytical laboratory interferences might be most relevant.

Since clinical data including laboratory test results and prescribed drugs are increasingly electronically available, a DLTI decision support tool can be more widely implemented. Increased availability of electronic data in hospitals opens many doors for technologies such as CDSS, aimed at increasing patient safety.

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CHAPTER 4

CLINICAL USEFULNESS OF DRUG-LABORATORY TEST INTERACTION ALERTS: A MULTICENTRE SURVEY

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ABSTRACT

Background

Knowledge of possible drug-laboratory test interactions (DLTIs) is important for the interpretation of laboratory test results. Failure to recognize these interactions may lead to misinterpretation, a delayed or erroneous diagnosis, or unnecessary extra diagnostic tests or therapy, which may harm patients. The aim of this multicentre survey was to evaluate the clinical value of DLTI alerts.

Methods

A survey was designed with six predefined clinical cases selected from the clinical laboratory practice with a potential DLTI. Physicians from several departments, including internal medicine, cardiology, intensive care, surgery and geriatrics in six participating hospitals were recruited to fill in the survey. The survey addressed their knowledge of DLTIs, motivation to receive an alert and opinion on the potential influence on medical decision making.

Results

A total of 210 physicians completed the survey. Of these respondents 93% had a positive attitude towards receiving DLTI alerts; however, the reported value differed per case and per respondent's background. In each clinical case, medical decision making was influenced as a consequence of the reported DLTI message (ranging from 3 - 45% per case).

Conclusion

In this multicentre survey, most physicians stated DLTI messages to be useful in laboratory test interpretation. Medical decision making was influenced by reporting DLTI alerts in each case. Alerts should be adjusted according to the needs and preferences of the receiving physicians.

INTRODUCTION

In today's healthcare, laboratory testing is becoming increasingly complex and therefore, diagnostic test interpretation more complicated. This may result in an increase of diagnostic errors, especially for non-laboratory professionals (1). A well-known cause of possible diagnostic error is the unobserved presence of drug-laboratory test interactions (DLTIs). Knowledge of possible DLTIs is important for the interpretation of laboratory test results. Failure to recognize these interactions may lead to misinterpretation, a delayed or erroneous diagnosis, or unnecessary extra diagnostic tests or therapy.

There are two categories of DLTIs: physiological and analytical interactions. Physiological interactions are in vivo processes. Test results may reveal an intended or unintended effect of a drug. Intended effects of drugs will generally not result in diagnostic misinterpretation, such as an elevated free thyroxin concentration due to levothyroxine treatment. However, unintended or side effects of drugs can often lead to diagnostic errors, such as an elevated level of chromogranin A due to proton pump inhibitors (2). Analytical interactions are in vitro processes. In these cases the interactions between drugs and laboratory tests disturb the analytical process, which may have an important negative clinical impact, since affected laboratory test results may not reflect the patient's clinical condition. An example of an analytical interaction is an elevated glucose measurement due to intravenous vitamin C therapy (3).

Thousands of interactions have been reported (4) making it seemingly impossible for healthcare professionals to take into account all these possible interactions in interpreting laboratory results of their individual patients. Electronic signalling systems or clinical decision support applications could potentially offer a solution to this problem. Due to the increasing availability of structured digital health records clinical decision support applications have collected worldwide attention, which makes it possible to apply algorithms on patient data. Especially in pharmacotherapy and laboratory diagnostics the benefit of clinical decision support is recognized and applied in multiple initiatives, such as drug monitoring, improvement in laboratory test utilization and diagnostic prediction algorithms (5-11). Since laboratory test results and prescribed drugs of individuals are noted in electronic health records, the design and implementation of DLTI algorithms could also be realised. However, implementation of clinical decision support systems can be technically challenging (12, 13).

In a recent review of the literature (14), only four relevant studies were found on DLTI decision support applications in clinical practice (15-18). These studies show a potential benefit of automated DLTI alerts to physicians for the interpretation of laboratory test results. In two of these studies, the effect of DLTI messages on treatment of patients was

evaluated with questionnaires among physicians (15, 18). In one study, 40 physicians completed a questionnaire. Of the DLTI reports 30% were judged as useful and 4% resulted in some change in patient's medical management (15). In the other study, DLTI messages for endocrinological tests were evaluated in a survey with 23 specialists in internal medicine (18). All respondents considered the alerts useful and 74% of them reported to sometimes even refrain from further additional examination. Thus, these limited study results showed a large potential improvement in laboratory test interpretation.

The aim of our study was to further examine the appreciation and clinical usefulness of DLTI alerts in clinical cases including a variety of laboratory tests according to a large group of physicians. We hypothesized that the appreciation of DLTI alerts differs between physicians due to differences in laboratory and clinical experience.

Obtaining insight into the clinical relevance of specific DLTI messages for physicians yields useful information to design optimal DLTI clinical rules in a computerized decision support application in clinical practice.

METHODS

Physicians of six teaching hospitals (see author affiliations) participated in this study. Two hospitals were large tertiary care centres directly connected to a university.

A web-based survey was designed and subsequently approved by a panel of laboratory specialists from the participating hospitals (supplemental file A). Six case reports with a variety of interactions between laboratory tests and drugs from clinical practice were selected. The case reports contained a medical history, anamnesis, prescribed drugs and laboratory test results. In each case a DLTI alert was reported as shown in table 1. These alerts were extracted from a DLTI database developed and maintained by the Dutch Society of Clinical Chemistry and Laboratory Medicine (19).

The survey addressed the respondents' knowledge about DLTIs, the motivation to receive an alert and his or her opinion on the potential influence on medical decision making. Physicians from different departments (internal medicine, cardiology, intensive care, geriatrics and surgery) were requested to complete the survey. These departments had been selected, because data of automated DLTI messages in three of the participating hospitals showed the highest prevalence of possible interactions (unpublished data).

Laboratory specialists of all participating hospitals introduced the subject DLTIs in a clinical conference within their own hospital. In some hospitals time was reserved for physicians to complete the survey during the conference (100% response rate) and in other hospitals physicians were asked to complete the survey after the conference (33 to 66% estimated response rate).

We used descriptive statistics only, using the R statistical package (version 1.2.5033).

TABLE 1: DLTI alerts in the six cases of the survey

Case	Interaction	Alert
1	CgA – Proton pump inhibitor	The elevated concentration of chromogranin A (428 ug/L) could be the consequence of the use of OMEPRAZOLE 40 mg 1dd1. Advice: stop the use of proton pump inhibitor for at least 5 days before measuring chromogranin A.
2	Mg, Ca, K-Proton pump inhibitor	Low magnesium (0.25 mmol/L) can be a consequence of chronic use of OMEPRAZOL 40 mg 1dd1, due to decreased gastrointestinal absorption. Negative effects may be more likely with concomitant use of other magnesium-lowering medications, such as digoxin or diuretics. Low calcium (1.58 mmol/L) could be secondary to hypomagnesemia as a consequence of OMEPRAZOL 40 mg 1dd1. Low potassium (3.0 mmol/L) could be a consequence of the use of OMEPRAZOLE 40 mg 1dd1. This is a rare side effect secondary to hypomagnesaemia. Plasma electrolytes usually normalize after several weeks of discontinuation of proton pump inhibitors.
3	TSH / free T4-Amiodarone	Hyperthyroidism (TSH 0.18 mU/L, free T4 23 pmol/L) could be a consequence of the use of AMIODARONE 200 mg 1dd1 and can arise suddenly and worsen heart problems. It often arises from pre-existing thyroid disease in combination with detectable thyroid antibodies. On the other hand, there may also be a direct toxic effect of amiodarone on the thyroid gland. An amiodarone-induced thyrotoxicosis can last for weeks to months and can sometimes be very severe and resistant to therapy. Advice: Although TSH also normalizes in half of the cases when treatment is continued, the choice is usually made to stop treatment with amiodarone.
4	K-Thiazides	Low potassium (3.1 mmol/L) could be caused by HYDROCHLOROTHIAZIDE 12.5 mg 1dd1.
5	Creatinine-Trimethoprim	The elevated concentration of creatinine (178 µmol/L) could be a consequence of COTRIMOXAZOLE 480 mg 1dd1. The estimated Glomerular Filtration Rate could therefore be falsely decreased (20-25%). A week after discontinuation of the medication, creatinine will return to a reliable level. Cave: in rare cases, severe renal impairment may develop from sulfamethoxazole in cotrimoxazole.
6	Thrombocytes-Heparin	Decreased amount of thrombocytes (70 *10^9/L). Cave: heparin induced thrombocytopenia. Advice: determine clinical probability (based on 4T score) and if necessary initiate follow-up research.

CgA: Chromogranin A, Mg: Magnesium, Ca: Calcium, K: Potassium, TSH: Thyroid Stimulating Hormone, free T4: free Thyroxin

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RESULTS

A total of 210 surveys were included in our study. Table 2 shows the demographics of the respondents. Most respondents were working in the departments of internal medicine (37%) and cardiology (24%) and over 80% had more than 2 years of clinical experience.

TABLE 2: Demographics of respondents (n=210[a])

Sex (n=196)	
- Female	109(56%)
- Male	87 (44%)
Age: Mean (SD) (n=193)	36 (9)
Medical specialty (n=210)	
- Internal Medicine	77 (37%)
- Cardiology	51 (24%)
- Emergency Care	29 (14%)
- Geriatrics	14 (7%)
- Intensive Care	13 (6%)
- Gastroenterology	12 (6%)
- Paediatrics	7 (3%)
- Surgery	5 (2%)
- Clinical Pharmacy	2 (1%)
Medical job (n=195)	
- Intern	42 (22%)
- Resident	62 (32%)
- Specialist	91 (47%)
Clinical experience (n=196)	
- <2 years	40 (20%)
- 2-10 years	99 (51%)
- >10 years	57 (29%)

[a]note: not all respondents completed each question.

Of all respondents, 93% considered DLTI alerts in general to be useful. Between the case reports we observed a variation in the appreciated usefulness (Table 3). Only 11% of physicians were familiar with the interaction between chromogranin A and proton pump inhibitors (case 1) whereas the interaction between potassium and thiazides (case 5) was well known by almost all respondents (95%). In four out of six cases at least 33% of the respondents replied that they gained new knowledge from the DLTI message and in all cases at least 20% of the respondents expected that the DLTI alert saved time in interpreting test results. A minority of respondents (8-19%) indicated that a DLTI alert might result in ignoring another potential diagnosis: i.e. excessive focus on drugs as an explanation for an aberrant test result may result in ignoring a pathophysiological origin. For instance, in case 2, the DLTI alert about the use of proton pump inhibitors that may result in electrolyte disturbances might divert attention to kidney failure as a potential cause.

TABLE 3: Usefulness of DLTI alerts in six cases (n=210)

	Case 1	**Case 2**	**Case 3**	**Case 4**	**Case 5**	**Case 6**
Laboratory test(s) Drug	CgA Proton Pump Inhibitor	Mg, Ca, K Proton Pump Inhibitor	TSH, free T4 Amiodarone	K Thiazides	Creatinine Trimethoprim	Thrombocytes Heparin
Did you already consider this interaction without the DLTI alert?						
Number of respondents	210	204	199	207	195	193
Yes	11%	79%	77%	95%	56%	84%
No	89%	21%	23%	5%	44%	16%
Why was the DLTI alert useful for you?[a]						
New knowledge	80%	26%	27%	4%	39%	10%
Time saved	35%	28%	28%	21%	26%	41%
An alternative diagnosis	12%	10%	10%	1%	11%	8%
Risk of not considering alternative diagnosis	12%	19%	13%	8%	19%	12%
Not useful	4%	26%	24%	50%	19%	25%

CgA: Chromogranin A, Mg: Magnesium, Ca: Calcium, K: Potassium, TSH: Thyroid Stimulating Hormone, free T4: free Thyroxin, DLTI: drug- laboratory test interaction. [a]several answers were possible, % of 210 respondents

In all clinical cases, medical decision making was influenced by a DLTI alert ranging from 3% to 45% of respondents (Table 4). Respondents answered mostly to consult a colleague (0-18%), followed by a change in medication (0.5 – 9%) or ordering extra laboratory tests (0.5 – 9%). Medical decision making changed most frequently when the DLTI was not recognized in advance (45% in case 1).

TABLE 4: Change in medical decision making in six cases (n=210)

	Case 1	**Case 2**	**Case 3**	**Case 4**	**Case 5**	**Case 6**
Laboratory test(s) Drug	CgA Proton pump inhibitor	Mg, Ca, K Proton pump inhibitor	TSH / free T4 Amiodarone	K Thiazides	Creatinine Trimethoprim	Thrombocytes Heparin
Did the DLTI alert influence your medical decision making?						
Number of respondents	208	203	199	199	194	193
Yes	45%	18%	20%	3%	36%	14%
No	55%	82%	80%	97%	64%	86%
If yes; in what way did the DLTI alert influence your medical decision making?[a]						
Additional blood testing	9%	8%	4%	0%	9%	8%
Additional imaging	4%	0%	1%	0%	1%	0%
Consult a colleague	18%	5%	13%	0%	10%	8%
Wait-and-see	0%	1%	2%	1%	4%	2%
Start drugs	0%	7%	3%	2%	1%	0%
Change drugs	9%	12%	4%	7%	14%	5%
Multidisciplinary consultation	11%	0%	1%	0%	0%	2%
Referral to tertiary centre	3%	0%	0%	0%	0%	0%

CgA: Chromogranin A, Mg: Magnesium, Ca: Calcium, K: Potassium, TSH: Thyroid Stimulating Hormone, free T4: free Thyroxin, DLTI: drug-laboratory test interaction. [a]several answers were possible, % of 210 respondents

Respondents were also asked to reflect on the content and phrasing of the messages (supplemental table 1). In 4 out of 6 cases the content and phrasing of the DLTI messages was judged to be good or very good by 75 – 84% of respondents. The content of the DLTI message in case 2 and 3 scored moderate or bad in 32% and 38% respondents, respectively. Furthermore, the length of the text of these DLTI messages was too extensive according to 46 to 60%.

In supplemental table 2 an analysis is shown based on clinical experience of respondents. The majority of respondents with clinical experience less than 2 years failed to recognize the presented DLTIs without DLTI alert (in case 1 98%), whereas respondents with 5-10 years' experience most often recognized the DLTI without an alert (in case 1 24%). This group with 5-10 years' experience altered medical decision making least often based on a DLTI alert (0-24%), except in case 1 (51%).

Furthermore, responses of medical specialists from the two participating large tertiary care hospitals versus the four peripheral hospitals were analysed (supplemental table 3). The demographics of respondents from the tertiary care centres were different from those in the peripheral hospitals, such as medical specialty and clinical experience. Therefore, to make a good comparison, only internists were included in the final analysis. Internists from tertiary care centres already considered DLTIs more often without alert (23% in case 1 and 94 – 100% in case 2-6) compared to internists from peripheral hospitals (11% in case 1 and 84 – 97% in case 2-6). Peripheral hospital internists changed their medical decision making more often than tertiary care hospital internists in case 2,3,4 and 6 (11-23% versus 0-10%) and less often in case 1 (49 versus 61%).

In this survey six cases with DLTIs were selected, but there are numerous other potential DLTIs that could be worthwhile for intervention and physicians were asked which ones they would add to a DLTI decision support tool. Responses varied widely. A small group of physicians suggested adding specific DLTIs, whereas other responses ranged from the wish to receive alerts for all possible DLTIs to no DLTI alerts at all.

DISCUSSION

In this survey a large group of physicians from six Dutch hospitals evaluated different clinical laboratory cases with a DLTI alert. The vast majority of respondents appreciated the DLTI alerts and medical decision making altered in all cases of the survey, although with a variability between cases. We showed that some, but definitely not all DLTIs are well known by the respondents. Also, the knowledge and clinical experience of the physician seemed related to the appreciation of a DLTI alert. The educative effect of DLTI messages was highest for physicians with limited clinical experience. On the other hand, medical specialists with extensive clinical experience (>10 years) seemed to be less familiar with some DLTIs than residents with shorter clinical experience. Our results also suggest that physicians from university hospitals are more familiar with DLTIs and less frequently change their medical decision making based on DLTIs alerts than physicians from peripheral hospitals.

Studies have shown the added value of automated decision support applications to alert health care professionals on possible DLTIs. The effectiveness of such a system increases when a refined set of clinical rules is determined in cooperation with health care professionals using the system (15, 18). Our study results confirm a positive attitude of physicians towards DLTI warning messages and underline the need for input of physicians to improve the use of the messages.

Since physicians are able to take DLTIs into account in the interpretation of test results, it is expected to lead to an improvement of patient outcomes. Also, unnecessary extra diagnostics can be avoided when DLTIs are immediately recognized (2). Besides these intended benefits, there is also a risk of DLTI alerts, in that alternative diagnoses might not be considered. Therefore, medical decision making should never be solely based on a DLTI warning message. Physicians should be aware that DLTI warning messages only support and do not replace their medical judgment in each individual patient. This potential risk was emphasized by cardiologists in the third case of our survey (fT4 and amiodarone). Cardiologists expressed their concern about physicians changing medication based on a DLTI alert, i.e. stop amiodarone in case of hyperthyroidism. The consequence of such a medication change was thought not to be sufficiently assessed by medical specialists who are not prescribing this anti-arrhythmic drug.

In this survey, a combination of relevant DLTIs was selected with frequently requested laboratory tests and drugs as well as an infrequently requested laboratory test. It gives an impression of physicians' attitude towards DLTI alerts, but does not cover all DLTIs and does not directly reflect the effects of the alerts in clinical practice. Therefore, an evaluation with physicians of real-time DLTI messages reported with the laboratory test results of patients is highly recommended.

Although we did not perform an analysis for separate medical specialties, there are some indications that the appreciation and effect on medical decision making of DLTI alerts differs among medical specialties. Surgeons, for example, replied that DLTIs are not relevant for them, since in case of (serious) deviant test results a colleague of internal medicine is always consulted. Surgical medical decision making would therefore never be influenced by DLTI alerts. Another example is the response of cardiologists

that a specific DLTI alert about amiodarone and hyperthyroidism will not influence their medical decision making, since they are already aware of this interaction.

The results of the survey underline the need to customize DLTI alerts in a clinical decision support system according to knowledge and preferences of the receiving medical specialty.

Besides the characteristics of the receiving medical specialist, patient characteristics and medical information about the patient also influence the potential relevance of a DLTI alert. Evaluation of individual alerts would be a valuable addition to a DLTI decision support tool to continuously improve it.(20, 21).

Not only should the medical content of each message be discussed with the receiving physicians. The way DLTI alerts are presented should also be considered carefully. The alerts could be shown during test ordering or at the time results are reported. In this survey the last option was chosen, because alerts can be reduced to test results outside reference ranges, which increases clinical relevance and decreases alert fatigue. However, there are examples that an alert at test ordering is also relevant: when Chromogranin A is ordered, a DLTI alert about proton pump inhibitors could make physicians consider temporary discontinuation of the drug. To avoid suboptimal diagnostic interpretation of this usually only once requested test to exclude a neuro-endocrine tumour, proton pump inhibitors can sometimes be safely temporarily discontinued. DLTI alerts can be added to the individual test result or report. The alert could be shown as a pop-up or as a text below the results. Alerts could also be presented to a laboratory specialist for review prior to release. Laboratory specialists could also decide to contact the requesting physician. All these options should be evaluated before and during implementation of DLTI decision support.

A refined set of clinical rules must prevent excessive numbers of DLTI alerts and consequently so-called 'alert fatigue' of physicians or laboratory specialists (22-24). DLTI case reports are widely described in literature, but their impact in clinical practice is often unknown. DLTIs could potentially disturb the diagnostic process in a large group of patients, since many patients receive multiple drugs and laboratory testing is performed regularly.

We believe clinical decision support for DLTIs could reduce diagnostic errors and improve patient safety. The appreciation of DLTI alerts by clinicians is an important prerequisite for its introduction in clinical care. Further research with real time DLTI alerts is needed to assess whether they provide added value for patient care.

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CHAPTER 5

ADDED VALUE OF DRUG-LABORATORY TEST INTERACTION ALERTS IN TEST RESULT AUTHORISATION

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The use of diagnostics such as laboratory testing is expanding and test panels are becoming increasingly complex. Therefore, test interpretation has become more complicated and prone to diagnostic errors (1). One cause of diagnostic errors is the unrecognized presence of drug-laboratory test interactions (DLTIs). Failure to identify these interactions may lead to misinterpretation, a delayed or erroneous diagnosis, or unnecessary extra diagnostic tests or therapy (1).

DLTIs are categorized as physiological or analytical interactions or both. Physiological interactions are in vivo processes. For example, an elevated level of chromogranin A as a side effect of proton pump inhibitor use (2). Analytical interactions are in vitro processes. In these cases, the interactions between drugs and laboratory tests disturb the analytical process and consequently the laboratory test results do not reflect the patient's clinical condition. An example of such an analytical interaction is a monoclonal protein band in electrophoresis due to treatment with daratumumab (3). Numerous interactions have been reported (4) making it virtually impossible to recognize and consider all these possible interactions when interpreting laboratory results. Electronic clinical decision support systems (CDSS) could offer a solution to this problem.

CDSS for DLTI alerts have only scarcely been described in the literature (5). In two studies, DLTI alerts from CDSS were reported and evaluated with questionnaires among clinicians and judged as useful. A recent survey including clinical cases with a potential DLTI also shows a positive attitude from clinicians towards DLTI alerts (6). However, the usefulness of DLTI alerts for specialists in laboratory medicine applied in test authorisation and interpretation has not yet been examined. Therefore, the aim of the current survey was to examine the appreciation and usefulness of DLTI alerts according to specialists in laboratory medicine and their willingness to implement a CDSS.

A web-based survey was designed with six clinical cases with a variety of interactions between laboratory tests and drugs from clinical practice (table 1). These cases contained a short clinical summary (patient's symptoms at hospital arrival and clinical diagnosis), prescribed drugs and laboratory test results. The survey was brought to the attention of 408 registered specialists in laboratory medicine and specialists in training of the Dutch Society of Clinical Chemistry and Laboratory Medicine in February 2020. The survey addressed the knowledge about DLTIs, motivation to receive an alert for test authorisation and to forward an alert to clinicians of the departments of internal medicine, surgery and emergency or intensive care. Furthermore, the respondents were asked if they would consider implementation of a CDSS for DLTI alerts and if so, whether they expected any barriers for implementation.

We used descriptive statistics, using the R statistical package (version 1.2.5033).

TABLE 1: DLTI alerts in the six clinical cases of the survey

Case	Interaction	Alert
1	CgA – Proton pump inhibitor	The elevated concentration of chromogranin A (428 ug/L) could be the consequence of the use of OMEPRAZOLE 40 mg 1dd1. Advice: stop the use of proton pump inhibitor for at least 5 days before measuring chromogranin A.
2	Mg, Ca, K-Proton pump inhibitor	Low magnesium (0.25 mmol/L) can be a consequence of chronic use of OMEPRAZOL 40 mg 1dd1, due to decreased gastrointestinal absorption. Negative effects may be more likely with concomitant use of other magnesium-lowering medications, such as digoxin or diuretics. Low calcium (1.58 mmol/L) could be secondary to hypomagnesemia as a consequence of OMEPRAZOL 40 mg 1dd1. Low potassium (3.0 mmol/L) could be a consequence of the use of OMEPRAZOLE 40 mg 1dd1. This is a rare side effect secondary to hypomagnesaemia. Plasma electrolytes usually normalize after several weeks of discontinuation of proton pump inhibitors.
3	TSH / free T4-Amiodarone	Hyperthyroidism (TSH 0.18 mU/L, free T4 23 pmol/L) could be a consequence of the use of AMIODARONE 200 mg 1dd1 and can arise suddenly and worsen heart problems. It often arises from pre-existing thyroid disease in combination with detectable thyroid antibodies. On the other hand, there may also be a direct toxic effect of amiodarone on the thyroid gland. An amiodarone-induced thyrotoxicosis can last for weeks to months and can sometimes be very severe and resistant to therapy. Advice: Although TSH also normalizes in half of the cases when treatment is continued, the choice is usually made to stop treatment with amiodarone.
4	K-Thiazides	Low potassium (3.1 mmol/L) could be caused by HYDROCHLOROTHIAZIDE 12.5 mg 1dd1.
5	Creatinine-Trimethoprim	The elevated concentration of creatinine (178 µmol/L) could be a consequence of COTRIMOXAZOLE 480 mg 1dd1. The estimated Glomerular Filtration Rate could therefore be falsely decreased (20-25%). A week after discontinuation of the medication, creatinine will return to a reliable level. Cave: in rare cases, severe renal impairment may develop from sulfamethoxazole in cotrimoxazole.
6	Thrombocytes-Heparin	Decreased number of thrombocytes (70 *10^9/L). Cave: heparin induced thrombocytopenia. Advice: determine clinical probability (based on 4T score) and if necessary initiate follow-up research.

CgA: Chromogranin A, Mg: Magnesium, Ca: Calcium, K: Potassium, TSH: Thyroid Stimulating Hormone, free T4: free Thyroxin
NB Table published before (19). These alerts were extracted from a DLTI database developed and maintained by the Dutch Society of Clinical Chemistry and Laboratory Medicine (only accessible to members).

A total of 98 surveys were completed by specialists in laboratory medicine. Half of the respondents were female, 15% was a specialist in training and 63% had more than 5 year's clinical experience. Respondents were working in laboratories serving primary care (11%), teaching hospitals (72%) and university medical centres (16%).

Of all respondents, 92% considered DLTI alerts in general to be useful. Variation in the appreciated usefulness was observed between cases (Table 2). All DLTI alerts were considered as relevant information in the decision to authorise test results by at least

50% of respondents. Of all respondents, 47-62% answered that DLTI alerts could reduce time to interpret test results. However, 15-40% of respondents feared for the possibility of not considering another diagnosis: i.e. excessive focus on drugs as an explanation for an aberrant test result and therefore ignoring other pathophysiological origins.

The specialists in laboratory medicine were willing to forward DLTI alerts to clinicians; most frequently in case 1 with the interaction between chromogranin A and proton pump inhibitors (81-94%). Clinicians of internal medicine would most often receive a DLTI alert from specialists in laboratory medicine, ranging from 47-94% of respondents depending on the case. Clinicians of the departments of surgery and emergency care would also be eligible to receive a DLTI alert (ranging from 39-81%).

The majority of specialists in laboratory medicine would like to implement CDSS for real-time DLTI monitoring (84%), but barriers were frequently reported, such as lack of time (63%), technical issues (54%), insufficient budget (49%) and lack of support from colleagues (29%).

In this survey among specialists in laboratory medicine, the majority appreciated DLTI alerts in different clinical cases for laboratory test authorisation and would like to implement a Clinical Decision Support System (CDSS) for this purpose.

Recently we showed a positive attitude of clinicians towards receiving DLTI alerts (6) and the current study shows that specialists in laboratory medicine would also like to receive DLTI alerts in their practice of authorisation and interpretation of laboratory test results. This survey does not cover all DLTIs and does not directly reflect the effects of the alerts in clinical practice. Therefore, an evaluation of real-time DLTI alerts for specialists in laboratory medicine is needed to assess their value for patient care.

DLTI case reports are widely described in literature, but their impact in clinical practice is often unknown. With CDSS, DLTIs that otherwise remain unrecognized can be systematically detected and consequently, the prevalence and impact can be further explored.

Refinement of clinical rules with patient characteristics other than drugs could increase the effectiveness of CDSS and prevent an overload of DLTI alerts. Considerations for refinement are part of a continuous clinical evaluation of individual alerts, which is highly recommended in CDSS (8). A refined set of clinical rules must prevent an excessive amount of DLTI alerts and consequently so-called 'alert fatigue' (24- 26). Alert fatigue could also be avoided with tailor made DLTI alerts per medical specialty based on their knowledge and preferences (7).

TABLE 2: Usefulness of DLTI messages in 6 clinical cases according to specialists in laboratory medicine (n=98)

Laboratory test(s) Drug	**Case 1** CgA Proton pump inhibitor	**Case 2** Mg, Ca, K Proton pump inhibitor	**Case 3** TSH/free T4 Amiodarone	**Case 4** K Thiazides	**Case 5** Creatinine Trimethoprim	**Case 6** Thrombocytes Heparin
Why was the DLTI alert useful for you?[a]						
Relevant information for authorisation test results	75%	59%	53%	50%	61%	59%
Time saved	62%	48%	47%	57%	50%	56%
Risk of not considering other diagnosis	15%	27%	20%	18%	32%	17%
Not useful	1%	9%	18%	19%	14%	9%
Why do you think a requesting physician will find the DLTI alert useful?[a]						
New knowledge	60%	52%	40%	22%	60%	27%
Time saved	74%	53%	47%	65%	61%	66%
An alternative diagnosis	14%	17%	19%	8%	18%	28%
Risk of not considering other diagnosis	16%	34%	17%	21%	40%	19%
Yes, I would send this DLTI message to a requesting MD of the following department						
Internal medicine	94%	63%	47%	52%	65%	75%
Surgery	83%	53%	40%	59%	56%	69%
Emergency Care /Intensive Care	81%	60%	39%	57%	59%	70%

[a]Multiple answers were possible, CgA: Chromogranin A, Mg: Magnesium, Ca: Calcium, K: Potassium, TSH: Thyroid Stimulating Hormone, free T4: free Thyroxin, DLTI: drug- laboratory test interaction.

We believe specialists in laboratory medicine should take the lead in implementation of CDSS for DLTI monitoring, since interpretation of test results is their core expertise (9). They can understand the value and limitations of DLTI alerts from CDSS and are an essential participant in a multidisciplinary team with clinicians, pharmacists and information technology consultants. Once the system is implemented, specialists in laboratory medicine should authorise DLTI alerts before they are being reported to clinicians.

We have shown that specialists in laboratory medicine support and value the application of DLTI alerts in clinical practice. DLTI alerts are a potential new dimension to add clinical utility to laboratory test reports. It expands the toolbox of the specialist in laboratory medicine for interpretative commenting. If applied correctly, diagnostic errors could be reduced and patient safety enhanced.

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CHAPTER 6

AWARENESS OF DRUG LABORATORY TEST INTERACTIONS IS IMPORTANT FOR PREVENTION OF UNNECESSARY ADDITIONAL DIAGNOSTICS: AN EXAMPLE

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ABSTRACT

Background
Elevated levels of Chromogranin A (CgA) may be indicative of a neuroendocrine tumour (NET), but increased levels are also observed after intake of proton pump inhibitors (PPIs). The incidence of diagnostic confusion because of this drug-laboratory test interaction (DLTI) was examined.

Methods
Medical records of 238 patients with elevated CgA concentrations were obtained from three hospitals. The following data were extracted: PPI prescription at the time of CgA measurement, medical decision making based on elevated CgA concentrations, final diagnosis, comorbidity and other prescribed drugs.

Results
From 238 patients with elevated CgA concentrations, 132 used PPIs. Of these patients, 57 patients did not have a NET. In 9 of these 57 patients (16%), diagnostic work up revealed no medical cause of an elevated CgA concentration. Somatostatin receptor imaging was ordered in 4 out of 9 cases, with no abnormalities observed. In 6 out of 9 cases, CgA measurement was repeated after PPI discontinuation resulting in normalisation of CgA concentrations.

Conclusion
In this retrospective patient record study we observed that part of the elevated CgA concentrations in patients could be caused by the usage of PPIs causing unnecessary diagnostic work-up for the exclusion of a NET. These observations illustrate the need for better DLTI awareness.

INTRODUCTION

Diagnostic tests, such as laboratory analysis of body fluids, represent an important part of today's healthcare. The quality of diagnostic testing depends on careful performance of the complete analytical work-up including the so-called 'post-analysis', which includes reporting and interpretation of test results (1). Deviating laboratory test results are indicative of illness, but may also be a consequence of possible drug-laboratory test interactions (DLTIs). Ignorance of possible interactions between drugs and laboratory tests may lead to incorrect diagnosis and treatment, as well as unnecessary follow-up (2). An example of such an interaction is an elevated concentration of chromogranin A (CgA) caused by frequently prescribed proton pump inhibitors (PPIs) (3). PPIs stimulate gastric enterochromaffin-like cells which causes elevated concentrations of CgA. The serum concentration of CgA is used as a marker for neuroendocrine tumours (NETs) (4). NETs are rare neoplasms which may arise from several anatomical sites, such as the small intestine, pancreas and lungs. NETs are characterized by the ability to synthesize, store and secrete different peptides and neuroamines, such as CgA (5). Case-reports have described elevated CgA concentrations in patients, who underwent expensive imaging with no abnormalities and a normalized CgA level after discontinuation of the PPI (3). These cases illustrate that this DLTI is not always immediately recognized in clinical practice with consequent unnecessary discomfort for patients and healthcare expenditure.

Since this unrecognized DLTI has serious consequences for an individual patient and healthcare expenditures in general, it is imperative to better estimate its incidence.

Therefore, the aim of this retrospective medical record study was to investigate the incidence and possible impact of diagnostic misinterpretation of an elevated CgA concentration caused by PPIs.

6

MATERIAL AND METHODS

All patients with an elevated CgA concentration in two large non-academic hospitals between 2014 and 2018 were included. In addition, in one University Medical Centre, a random selection from a larger cohort of patients was made with elevated CgA concentration. To avoid selection bias, randomization was performed with the function 'sample' in the statistical program 'R'. Patients that were referred from the non-academic hospitals to the University Medical Centre were excluded from the latter study group.

From the patients' medical records, the following data were extracted: sex, age, known NET, CgA concentration, specialism of requesting physician, prescribed PPIs (including

type and dosage), indication for CgA measurement, medical decision following the elevated CgA concentration measurement, referral to a tertiary care centre and final diagnosis. Renal, hepatic and gastro-intestinal diseases were also extracted, because it is known that these conditions also cause elevated CgA concentrations (6-8). Besides PPIs, other prescribed drugs were also registered. All CgA measurements in serum were performed in the university medical center with a generation II assay (BRAHMS Kryptor) (9) as part of the usual care. No extra CgA measurements were performed for this study.

Descriptive statistics were performed (frequency, mean, SD, median, quantiles) and the Mann Whitney U test to compare differences, using the R statistical package (version 1.2.5033). P value below 0.05 was considered as statistically significant.

The study was performed under the tenets of the Helsinki declaration, local laws and regulations and was approved by all participating institutions. The Dutch Medical Research involving Human Subjects Act (WMO) did not apply to this study, which was confirmed with a waiver from the Medical Ethical Committee.

RESULTS

Figure 1 shows a flowchart of the study design. In total, 327 patients with a measured CgA concentration were included, of which 141 were diagnosed with a NET.

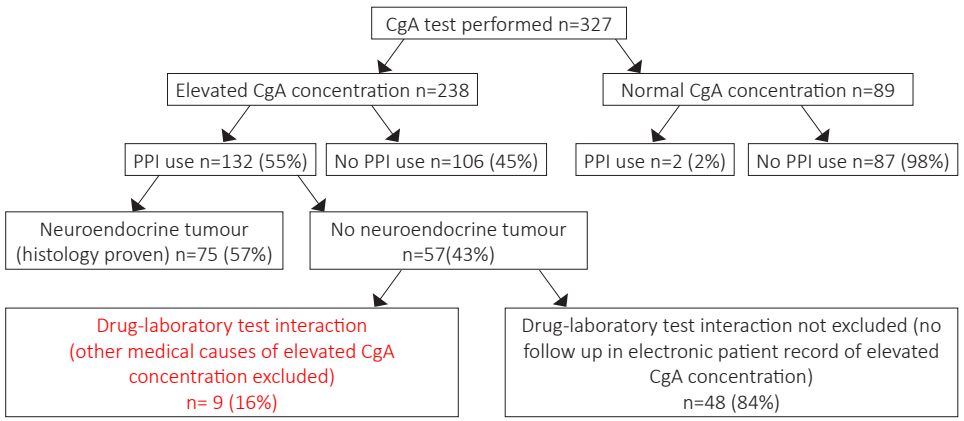

FIGURE 1: Flowchart of study design

In the study population, 238 patients had an elevated CgA concentration and 132 of them had a prescribed PPI (55%). Of these patients, 57 received another diagnosis than NET (43%). In this group, CgA test results of 9 patients were probably influenced by PPIs (16%), because no other medical cause of the elevated CgA concentration was identified. Of the 89 patients with a normal CgA concentration, only 2 patients used a PPI (2%)).

Table 1 summarizes the demographics of the study populations with an elevated CgA concentration of the three hospitals. From the university medical centre (hospital 1), 101 patients were included and from the non-academic hospitals (hospital 2 and 3) a total of 137 patients were included. Age and sex were comparable in the populations.

CgA measurement was most frequently requested by the department of internal medicine in hospital 1, whereas surgery and oncology were the main requesting departments in hospital 2 and 3 respectively. In hospital 1, the median CgA concentration was the highest, as well as the number of diagnosed NETs.

TABLE 1: Demographics of patients with elevated CgA concentration (n=238)

	Hospital 1 (n=101) University medical centre	**Non-academic Hospital 2 (n=86)**	**Non-academic Hospital 3 (n=51)**
Age			
- Mean (SD)	71(13)	69 (10)	68 (10)
Sex			
- Female: N(%)	51 (51%)	46 (54%)	28(55%)
Medical speciality requesting physician			
- Gastroenterology	1	0	13
- Internal medicine*	59	30	10
- Surgery	11	36	7
- Oncology	29	15	14
- Other	1	5	7
CgA concentration median(25-75 quantile) [µg/L]	428 (200- 892)	294 (139-605)	283 (159- 812)
Diagnosis			
- Neuroendocrine tumour	87 (86%)	22 (26%)	33 (65%)
- Gastro-intestinal, pancreas and bile duct carcinoma	9 (9%)	44 (51%)	2(4%)
- Other malignancy	3 (3%)	3 (3%)	0 (0%)
- benign**	2 (2%)	15 (17%)	6 (12%)
- Unknown	0 (0%)	2 (2%)	10 (20%)

* Including endocrinology **such as gastritis, pancreatitis, and irritable bowel disease
From the 142 patients diagnosed with a NET, 75 used a PPI

Table 2 shows details of nine patients with an elevated CgA concentration, probably as a consequence of an interaction with PPIs. The CgA concentration ranged from 129 up to 4993 µg/L (reference value < 100 ug/L). All patients were from non-academic hospitals. From the 9 patients, 8 were female with an age between 47 and 75 years. In 6 out of 9 patients, CgA measurement was repeated between 3 weeks and 2 months after discontinuation of the PPI. The CgA concentration decreased in the repeated measurement, but not always below the upper reference limit. In 4 out of 9 patients somatostatin receptor PET imaging was performed without discovering any abnormalities. In 6 out of 9 patients no diagnosis was made, other than a description of the symptoms.

Figure 2 shows boxplots of the CgA concentration in patients with and without prescribed PPIs. These groups were divided in patients with and without NET. In the patients without a NET, CgA concentrations were significantly higher compared to those without prescribed PPIs (median 324 versus 162 µg/L, p<0.05). This difference was not seen in patients with a NET.

Supplemental table 1 shows the association between diseases that are known to possibly increase the CgA concentration (5). We found no statistically significant difference in CgA concentration between patients with and without renal failure, hypertension, pancreas carcinoma, obstructive lung disease and/or gastrointestinal or liver disease, but subgroups were small. In the study population, 62 patients had renal failure, defined as an estimated glomerular filtration rate below 60 ml/min. All these patients had elevated CgA concentrations with an average of 2875 µg/L (range 103-87430 µg/L). Of these patients, 46 were diagnosed with a NET and their main CgA concentration was 3495 µg/L (range 103-87340 µg/L). In the other 16 patients without a NET, the main CgA concentration was 1096 µg/L (range 112 – 2329 µg/L).

Supplemental table 2 shows the association between prescribed drugs and the CgA concentration. Except for PPIs, we did not find a statistically significant difference in CgA concentration in patients with a specific drug.

H2 receptor antagonists and serotonin reuptake inhibitors have been described to cause elevated CgA concentrations (7). In our population these drugs were prescribed in twelve patients. Of these patients, all measured CgA concentrations were elevated, ranging from 181 to 4629 µg/L. Among them, eight were diagnosed with a NET. In the non-NET group, 2 patients had CgA concentration > 1000 µg/L.

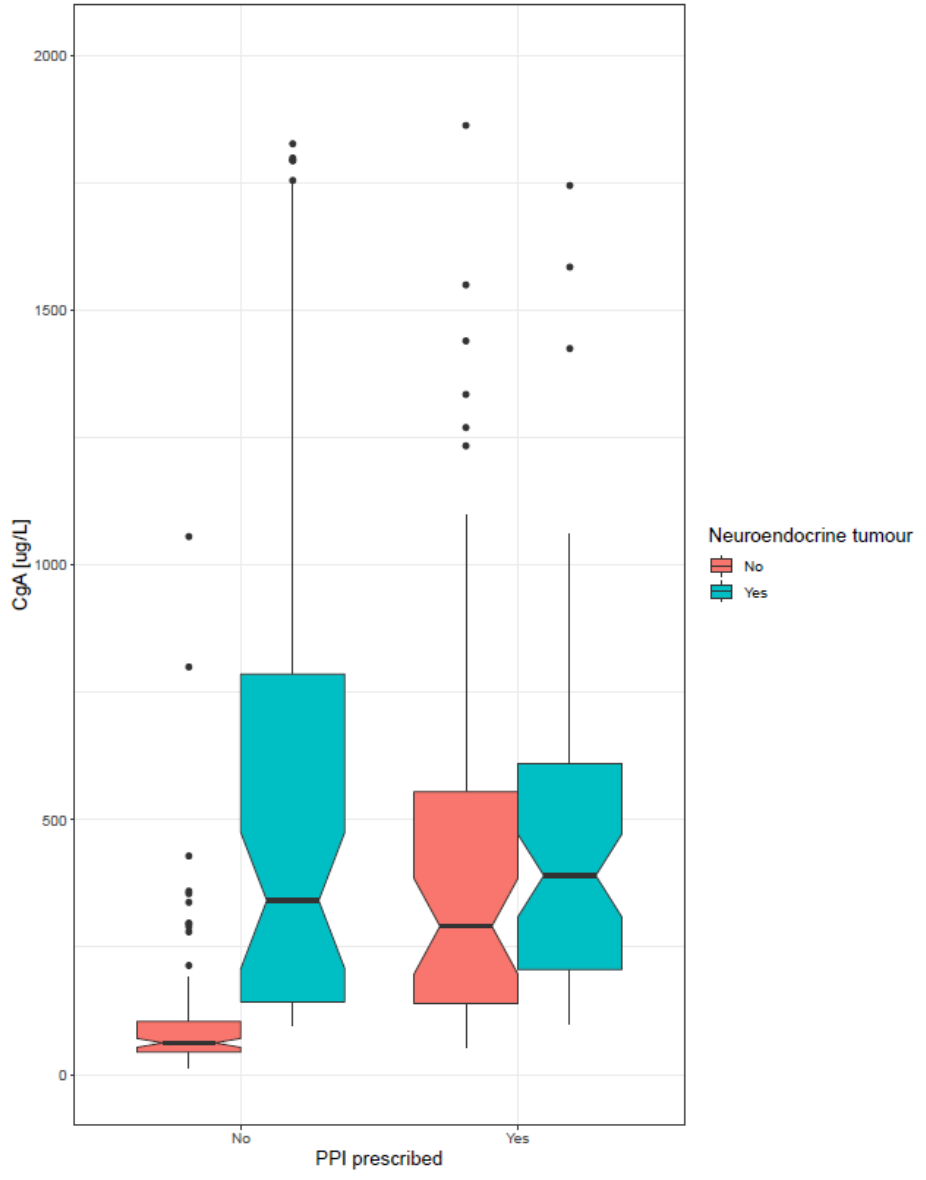

FIGURE 2: Boxplot of CgA concentration in patients with and without prescribed PPI and with and without a neuroendocrine tumour
Patients with a performed CgA test (n=327): neuroendocrine tumour (n=142), no neuroendocrine tumour (n=168), Patients without known diagnosis were excluded (n=17)
Limit of Y-axis = 2000
Boxplot represent interquartile range (25-75th percentile), bold line in the middle represents median

TABLE 2: Details of cases with an elevated CgA concentration and a diagnostic error as a consequence of missed Drug Laboratory Test Interaction

Case	CgA [µg/L]	Sex (M/F)	Age [years]	Medical specialty requesting physician	PPI (total daily dose)	Use of other drugs known to cause CgA elevation	Presence of comorbidity known to cause CgA elevation	Medical decision on CgA result	Repeated CgA [µg/L][a]	Diagnosis
1	129	M	51	Internal Medicine	Omeprazole 40 mg	-	-	^{68}Ga-DOTATATE PET/CT scan	-	Cyclic vomiting syndrome
2	137	F	65	Internal Medicine	Pantoprazole 40 mg	-	-	No further diagnostics because of spontaneous improvement of symptoms	-	Chronic diarrhoea without known cause
3	154	F	56	Gastroenterology	Omeprazole 40 mg	-	Chronic pancreatitis, IBD or IBS	^{68}Ga-DOTATATE PET/CT scan	-	Chronic pancreatitis
4	314	F	56	Gastroenterology	Omeprazole 80 mg	-	IBD and asthmatic bronchitis	^{68}Ga-DOTATATE scan and repeated CgA measurement after discontinuation PPI	271	Chronic diarrhoea without known cause
5	440	F	47	Oncology	Pantoprazole 40 mg	-	-	Repeated CgA measurement after discontinuation PPI	29	Cured from radically removed NET
6	830	F	72	Oncology	Omeprazole 80 mg	-	Pancreatic adenocarcinoma	Repeated CgA measurement after discontinuation PPI	311	Pancreatic adenocarcinoma
7	1270	F	61	Internal Medicine	Omeprazole 20 mg	H2 receptor antagonist	Hypertension	Repeated CgA measurement after discontinuation PPI	56	Diarrhoea and flushes without known cause
8	3912	F	66	Internal Medicine	Omeprazole 40 mg	Selective serotonin reuptake inhibitor	Hypertension and heart failure	^{111}In-DTPA-Octreotide PET/CT scan and repeated CgA measurement after discontinuation PPI	132	Chronic diarrhoea without known cause
9	4993	F	75	Gastroenterology	Pantoprazole 80 mg	-	Hypertension and COPD	Repeated CgA measurement after discontinuation PPI	247	Reflux without known cause

CgA: Chromogranin A, IBD: Irritable bowel disease, IBS: Irritable bowel syndrome, COPD: Chronic obstructive pulmonary disease
[a]upper reference limit 100 µg/L

DISCUSSION

This multicentre retrospective medical record study demonstrates the importance of awareness of DLTIs, specifically when CgA is measured in patient with prescribed PPIs. We studied the incidence of the interaction between CgA and PPIs and the possible impact of this DLTI. We found that in patients without a NET, an elevated CgA concentrations as a consequence of PPIs may lead to extra diagnostic testing (16%) for the exclusion of a NET, i.e. repeated CgA measurements and even somatostatin receptor PET imaging and referral to a tertiary care centre. In the other 84% of patients with an elevated CgA concentration and prescribed PPIs, no follow-up was described in the electronic patient record. In these cases, clinicians might have attributed the elevated CgA concentration to prescribed PPIs.

In patients without a NET we also showed a significantly higher CgA concentration in patients with versus those without a prescribed PPI (fig 2). However, in patients with a NET, PPIs do not significantly change CgA concentrations (fig 2). Therefore, these data suggest that PPIs do not have to be discontinued in case of a CgA measurement in patients with a histologically proven NET.

CgA concentrations in patients with prescribed PPIs and no other causes for CgA elevations were both mildly and severely elevated, suggesting that the degree of elevation does not reflect possible PPI interaction.

In patients with an estimated eGFR<60 ml/min, all CgA concentrations were elevated, even in the absence of a NET. Therefore, our data confirm that the CgA concentration as a marker for a NET is inadequate in patients with renal failure.

When determining the diagnosis and treatment of a NET, histopathology of the tumour mass is leading (10). CgA is mainly recommended as a marker for follow-up according to the European Neuroendocrine Tumour Society guideline (2). The specificity of CgA assays as a diagnostic marker is limited in a population with other diseases, such as inflammatory bowel disease and renal failure (11, 12). In our population, CgA concentrations >1000 µg/L were found in patients without a histopathology proven NET. These data confirm the low specificity of CgA as a diagnostic marker, even when CgA concentrations are high (> 3 times the upper reference limit). However, it is clear that CgA is still used in clinical practice to exclude or judge the probability of a NET.

The NET prevalence in patients with prescribed PPIs and an elevated CgA concentration is high (57%). These data underline the fact that it is not possible to exclude a NET in a patient with an elevated CgA concentration and prescribed PPIs. To prevent extra

diagnostics for the exclusion of a NET, we would suggest to alert at the time of CgA test ordering. In case a CgA test is already performed under prescribed PPIs, we would recommend to first retest CgA after one week discontinuation of a PPI since this is less invasive and expensive than immediate radioactive labeled imaging.

Diagnostic uncertainty caused by DLTIs is undesirable. This study shows that the interaction between CgA and PPIs causes extra diagnostic work-up in a substantial number of patients with extra healthcare expenditure and may harm patients. An electronic clinical decision support system that alerts for possible DLTIs is a promising solution and clinicians are positive about the concept (13). It may increase the awareness of DLTI and thereby prevent diagnostic confusion and improve patient safety.

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SUPPLEMENTARY

SUPPLEMENTAL TABLE 1: Association between CgA concentration and disease in patients with elevated CgA concentrations (n=238)

Disease	Yes		No		
	N	Median CgA (µg/L)	N	Median CgA (µg/L)	P-value[a]
Neuroendocrine tumour	142	441	96	267	<0.001
Renal failure (eGFR<60 ml/min)	62	434	176	334	0.16
Hypertension	85	382	153	322	0.50
Pancreas carcinoma (non-NET)	45	310	193	347	0.82
Obstructive lung disease	20	323	218	338	0.71
Gastro-intestinal/liver	23	210	215	357	0.23

[a] Difference was tested with a Mann Whitney U test
Only for neuroendocrine tumours a statistical significant difference in CgA concentration was found

SUPPLEMENTAL TABLE 2: Association between CgA concentration and prescribed drugs in patients with elevated CgA concentration (n=238)

Drug prescribed	Yes		No		
	N	Median CgA (µg/L)	N	Median CgA (µg/L)	P-value
ACE inhibitor	36	432	202	280	0.30
Acenocoumarin	10	319	228	335	0.70
Acetaminophen	20	382	218	319	0.82
Acetylsalicylic acid	35	340	203	335	0.99
ARBS	25	538	213	335	0.72
Beta-blocker	72	444	166	303	0.08
H2-receptor antagonists	6	320	232	338	0.44
Laxatives	17	344	221	336	0.70
Loop diuretics	8	387	230	336	0.72
Metformin	34	387	204	322	0.36
NSAIDs	12	283	226	338	0.63
Opiates	43	382	195	322	0.26
PPIs	132	432	106	280	0.02
SSRIs	6	1143	232	328	0.17
Statins	28	422	210	315	0.14
Thiazides	22	346	216	336	0.59
ACE inhibitor	36	447	202	303	0.30

[a]Difference was tested with a Mann-Whitney U test
Only for proton pump inhibitors a statistical significant difference in CgA concentration was found

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CHAPTER 7

GENERAL DISCUSSION

DIAGNOSTIC ERROR

In healthcare, good medical decision making starts with a correct diagnosis. A diverse range of publications have suggested that the diagnosis is incorrect in approximately 10 to 15% of cases (1,2). Moreover, the best estimates indicate that every human-being will likely experience a meaningful diagnostic error during his life (3). An erroneous diagnosis may lead to unnecessary extra diagnostic tests, therapy or hospital revisits.

Better identification, analysis, and implementation of approaches to improve diagnosis and reduce diagnostic error are needed throughout all settings of care. Without a dedicated focus on improving diagnosis, these errors will likely worsen as the delivery of healthcare and the diagnostic process continue to increase in complexity.

THE AIM AND SCOPE OF THIS THESIS

The complexity in clinical chemical diagnostics is increasing with the expanding number of laboratory tests, especially for non-laboratory professionals (4). A common source of diagnostic error is the lack of knowledge of the presence of drug-laboratory test interactions (DLTIs) (5–7). Approximately 50,000 DLTIs have been described in the literature (8), making it seemingly impossible for healthcare professionals to have knowledge of all these interactions with misinterpretation of test results as a consequence.

The use health information technology is recommended to improve the diagnostic process (3). In this thesis, health IT was used to support diagnostic laboratory test interpretation by identifying potential DLTIs. It was hypothesized that real-time monitoring using a clinical decision support system (CDSS) could prevent diagnostic error as a consequence of missed DLTIs and thereby improve patient safety.

In chapter 2, scientific articles describing CDSS to detect DLTIs were reviewed. The literature about this subject was limited and over the last 20 years no publications have been found (9–12). Apparently, the concept of CDSS to detect DLTIs has not been used and has not been further developed during the last decades. However, the results of these studies reported a high prevalence of DLTIs in hospitalized patients, a high appreciation of the interviewed medical staff to receive DLTI alerts and even changes in medical policy as a consequence of DLTI alerts. Each study was performed in only one single centre with a limited number of laboratory tests and the effectiveness of the CDSS for DLTI monitoring was not always evaluated with clinicians. Thus, the use of CDSS for DLTI monitoring was promising according to these previous studies, but the full impact has not yet been elucidated.

The aim of this thesis was twofold: [1] to examine the incidence and impact of a subset of DLTIs and [2] to study a proof of concept of real-time monitoring of DLTIs in daily practice using CDSS. The experienced usefulness of DLTI alerts to clinicians and specialists in laboratory medicine was also evaluated.

CHALLENGES AND OPPORTUNITIES IN CDSS

In chapter 3, the implementation of DLTI decision support in three hospitals was described. As was already known from the literature (13,14), the implementation of CDSS was challenging and time consuming.

Algorithms, or so-called ‘clinical rules’(15) were designed in the CDSS. The content of these clinical rules was based on the Dutch DLTI database containing a structured report of a DLTI with a list of scientific literature and an alert text that could be used to inform healthcare professionals about the interaction in their individual patients (16). With these clinical rules, the CDSS could identify potential DLTIs using data from the electronic health record (EHR), the laboratory information system and in some hospitals data from the pharmacy information system.

Application specialists and administrators of each database were crucial for the correct linking of data, as well as network security officers. Furthermore, laboratory specialists gave their input on the functional design of the connected systems. They were also responsible for the validation of the clinical rules. Trouble-shooting was frequently needed during the validation phase due to unexpected problems, such as incorrect clinical rules, linking of data, and coding errors.

In our study, three out of six initially participating hospitals failed to implement the CDSS due to a lack of resources, such as time and resources. Cooperation on a higher (national) level was experienced as favourable to overcome implementation issues.

Thus, many technical challenges had to be overcome to implement the CDSS for DLTI monitoring and the refinement and extension of the system will be challenging. Refinement and extension of the system will also bring new opportunities.

In this thesis, DLTI monitoring was only examined in the hospital care setting, but involving general practitioners would be an opportunity, since they probably are unfamiliar with DLTIs. Moreover, general practitioners highly appreciate the input from

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specialists in laboratory medicine in test interpretation which improves adequacy of clinical management (17).

For the implementation of DLTI monitoring in the overall healthcare system, the free flow of information is critical. Improved interoperability across healthcare organizations and across information systems is needed to achieve this information flow (18). Ideally, cooperation and consensus should be reached on an (inter)national level, concerning standards for interoperability, security, and privacy as well as ethical and legal concerns. A few standards are already available and 'Connectathons' are organized for vendors to test interoperability and conformance to standards and technical frameworks (19).

CDSS offers many more opportunities besides supporting test interpretation. For example, CDSS might support the selection of the most appropriate test panel (13). Much attention has already been paid to the inappropriate underuse of tests and treatments but until recently, little attention has focused on the overuse that does not add value to patients and may even cause harm and represent a significant contributor to healthcare costs. A well designed CDSS might be able to reduce such overuse. 'Choosing Wisely' is an international campaign to engage clinicians and patients in conversations about unnecessary tests, treatments and procedures (20). The IFCC Task Force on the Impact of Laboratory Medicine on Clinical Management and Outcomes committed to the same issue (21). Thus, CDSS could be part of the solution of this problem.

CDSS DRIVEN BY ARTIFICIAL INTELLIGENCE

There are many types of CDSS, ranging from simple logical judgments, like the DLTI algorithms used in this thesis, to complex AI algorithms based on for example machine learning, deep learning or data mining (22,23). Simple logical CDSS requires input from human experts to construct a series of algorithms in a particular knowledge domain. These algorithms work well up to a point and are easy to understand. However, a disadvantage is that if the knowledge domain changes, changing the rules can be difficult and time-consuming. Approaches based on data and machine learning algorithms could be an alternative. Machine learning algorithms are able to support human intelligence with machine intelligence to discover novel, previously unknown insights from data mining approaches. Data mining, also known as knowledge discovery in data, is the process of uncovering patterns and other valuable information from large data sets (24). Data mining could be a valuable technique for the discovery of yet unknown DLTIs.

The main drawback of these new Artificial Intelligence (AI) technologies concerns the potential loss of control in the Human-AI relationship (25). In many cases it will be necessary to understand how a machine decision was made and to assess the quality of the outcome.

Furthermore, the integration of the complete diagnostic information from patients, e.g., from anamnesis, physical examination, imaging, laboratory diagnostics, and its comprehensive analysis by artificial intelligence (AI)-based tools is expected to improve diagnostic precision (26). Attempts to integrate medical knowledge into complex algorithms, with the goal to support diagnosing are well known (27). However, to integrate all diagnostic information, data from multiple medical databases need to be connected. This will be even more challenging than the implementation of CDSS for DLTI monitoring, since only laboratory test results and prescribed drugs were needed. Strong project management and cooperation between all stakeholders were the key in this thesis.

CDSS or AI technologies are not intended to replace the judgment of healthcare professionals, nor should it be viewed as any kind of authoritative decision-making tool. Instead, these technologies may advance patient care by improving the accuracy of clinicians' diagnoses, shorten confirmed diagnosis times and hospitalization days, which was already shown in a retrospective real-world studies (28). In chapter 4 and 5 of this thesis, an expected reduced time in interpreting test results was reported thanks to DLTI alerts.

RECOMMENDATIONS FOR FURTHER RESEARCH

The major recommendation for further research is to investigate the clinical utility of DLTI alerts, because alerts with low clinical utility cause alert fatigue of clinicians. In chapter 3, high frequencies of DLTI alerts were shown. The clinical utility of these alerts in real-time was only briefly evaluated with clinicians (unpublished data). The clinical utility of a DLTI alert depends on patient characteristics, such as comorbidity. For example, a DLTI alert as an explanation for elevated Creatin Kinase concentrations is probably less useful in patients presenting in the first aid with a major trauma, because an elevated Creatin Kinase also reflects muscle damage.

The clinical utility of a DLTI alert also depends on the actual test results and the degree of test result deviation, because larger deviations in test results often reflect more serious illness. A change in cut-off values could be considered for DLTI alerts from reference values to for example critical care values.

Another recommendation is to search for more evidence about the nature of DLTIs, because strong scientific evidence about DLTIs is conditional before use in test

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interpretation. New evidence is needed to expand existing information about DLTIs, which is often fragmentarily described and sometimes even contradictory (12). So far, interactions were mainly reported in the literature in the form of case reports, such as the interaction between chromogranin A and proton pump inhibitors, described in chapter 6. With CDSS, systematic research and signalling of possible DLTIs is possible in a large cohort.

The most challenging part for further research will be to assess whether health outcomes are improved as a consequence of DLTI monitoring (24,29). Evaluations of supportive diagnostic tools like these are complex, especially because these in general do not affect health outcomes directly, but instead have an indirect impact by affecting patient management decisions. In a recent review about the effects of CDSS on laboratory test ordering and test interpretation, patient-related outcomes (e.g. length of stay and mortality rate) were not well investigated in the included studies (30). However, healthcare processes are likely to be affected by DLTI monitoring. The correct diagnosis could be obtained more quickly, risk assessment refined and the diagnostic process simplified.

Furthermore, benefits, harms and costs must be weighed for all aspects of care, including laboratory medicine, to ensure that resources are used as effectively as possible to improve health (31). Therefore, a health economic assessment of CDSS for DLTI monitoring would complete the scientific loop.

IMPLICATIONS FOR PRACTICE

The logical next step with an implemented CDSS for DLTIs is to start reporting the alerts in real-time and evaluate the usefulness with clinicians on a regular basis.

The software used in this study contains the opportunity to personalize alert settings per medical specialty. Our survey study in chapter 4 shows that this is a valuable quality of the system, because clinicians from various departments reported different needs on receiving DLTI alerts. For example, cardiologists were well aware of the interaction between the anti-arrhythmic drug amiodarone and thyroid function and therefore, the appreciated usefulness of such a DLTI alert was lower than from other medical specialists. The appreciated usefulness of DLTI alerts also varied among specialists in laboratory medicine, as was described in chapter 5. It seems ideal if clinicians or specialists in laboratory medicine could change their own settings in preferences of reported alerts. Unexperienced healthcare professionals would probably appreciate receiving more DLTI alerts, since they might lack knowledge on common DLTIs. In case of a learning curve, the professional could decide to opt out some frequently reported DLTI alerts to avoid alert fatigue.

Flexibility in alert settings per end-user is just one way to improve appreciated usefulness and efficacy of the system. As was already shown in other applications of CDSS, continuous evaluation is needed to refine clinical rules (35).

TAKING THE LEAD IN A MULTIDISCIPLINARY TEAM

Contemplating a diagnosis is a collaborative effort (3). The diagnostic process often involves intra- and interprofessional teamwork, with a special role for diagnostic disciplines, such as radiologists, pathologists and specialists in laboratory medicine. Support and consultation of clinicians for the interpretation of laboratory test results has become a more prominent task of specialists in laboratory medicine (33,34). Therefore, they should take responsibility to address the problem of unrecognized DLTIs in test interpretation. They may authorise DLTI alerts before they are reported to clinicians as part of their quality control routine. DLTI alerts are also a potential new dimension to add clinical utility to laboratory test reports. It expands the toolbox of the specialist in laboratory medicine for interpretative comments.

Time spent by diagnostic disciplines, such as specialists in laboratory medicine, to give advice to clinicians who order a test is not covered by current procedural terminology codes. The Society to Improve Diagnosis recommends to create such codes and provide coverage for additional evaluation and management activities, including the selection, use, and interpretation of diagnostic testing for specific patients.

The implementation of IT innovations in healthcare is also a collaborative effort. Information specialists are crucial for technical linking of electronic data, whereas clinicians and specialists in laboratory medicine must evaluate the clinical utility of the alerts. Pharmacists are also an essential partner in the evaluation of the clinical utility of DLTI alerts. Pharmacists also use CDSS for drug monitoring (35,36). To avoid duplications and consequently alert fatigue, specialists in laboratory medicine, pharmacists and clinicians have to agree where, when, why and in which way interactions are reported.

GENERAL CONCLUSION

From this thesis it can be concluded that laboratory test interpretation will enhance when DLTI awareness increases (chapter 2, 4 and 5). As a consequence of unrecognized DLTIS, both diagnostic errors and subsequent unnecessary diagnostic testing might be reduced (chapter 6). A high prevalence of DLTI alerts was shown from CDSS in three large teaching hospitals with a diversity of drug and laboratory test combinations (chapter 3).

Furthermore, specialists in laboratory medicine and clinicians were positive to receive DLTI alerts (chapter 4 and 5).

More research needs to be performed in clinical practice to evaluate CDSS for DLTI monitoring in close cooperation with specialists in laboratory medicine, pharmacists and clinicians to refine clinical rules and DLTI alerts in order to optimize their clinical utility. Additionally, the set of DLTI algorithms in the CDSS needs to be expanded with other relevant DLTIs. Besides the new insights that were received from this thesis, a new and ready-to-use CDSS for DLTI detection was designed, which may be implemented in other laboratories. The CDSS for DLTI detection will be further evaluated and developed by the users in clinical practice.

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APPENDICES

SUMMARY

One of the main tasks of a physician is to find the cause of symptoms of a patient. The physician provides a diagnosis, which is the start of medical decision making.

Unfortunately, diagnoses are incorrect in approximately 10 to 15% of cases. Moreover, the best estimates indicate that each human-being will likely experience a meaningful diagnostic error during his life. An erroneous diagnosis may lead to unnecessary extra diagnostic tests, therapy or (hospital) revisits and may harm patients.

The expanding range and complexity of laboratory diagnostics make it increasingly difficult for clinicians to correctly interpret test results. The specialist in laboratory medicine is therefore more often consulted for the interpretation of test results than 20 years ago. This trend is recognized and embraced by the Dutch Society of Clinical Chemistry and Laboratory Medicine. Initiatives are being developed to provide laboratory results with interpretive commentary and it is even one of the most important spearheads of the profession for the coming years.

Abnormal laboratory test results can indicate illness, but can also be a direct result of drug use. These drug laboratory test interactions (DLTIs) often concern a physiological effect of the drug in vivo and sometimes an analytical reaction in vitro. The analytic interaction is misleading, because the measured analyte concentration in a sample does not reflect the actual concentration in blood or urine in the patient. Physiological interactions are in vivo processes, in which drugs affect patients' laboratory test results and may also cause diagnostic confusion. A clear example is an elevated level of chromogranin A, which is indicative of the activity of a neuroendocrine tumour, but may also be the result of the frequently prescribed proton pump inhibitors. Both the physiological and the analytical interactions are not all known by specialists in laboratory medicine and clinicians. Unrecognized DLTIs can cause diagnostic error.

Electronic signalling systems or so-called clinical decision support systems (CDSS) may offer a solution to the problem of unrecognized DLTIs. CDSS send automatic alerts about DLTIs based on algorithms, which use data from pharmacy and laboratory data systems. A prerequisite for CDSS for DLTI monitoring is structured information about DLTIs.

A working group of Dutch laboratory specialists developed a database in which scientific evidence on specific DLTIs was gathered and summarized. The database facilitates specialists in laboratory medicine in test interpretation with up-to-date and structured information about DLTIs and can also be used for decision support.

In chapter 1, the general introduction, the aims of this thesis were described.

The aim of this thesis was twofold: [1] examine the incidence and impact of a subset of DLTIs and [2] study a proof of concept of real-time monitoring of DLTIs in daily practice using CDSS.

It was hypothesized that such a CDSS would be of great value to clinicians and specialists in laboratory medicine, since these DLTI alerts are immediately applicable in test interpretation of individual patients.

In chapter 2, a literature search was described on the use of CDSS to alert clinicians for potential DLTIs. A total of only four reports was found. One study found a prevalence of up to 43% of DLTI alerts in hospitalized patients, depending on the specific ward. Another study reported a prevalence of up to 11% of all endocrinological test results. The clinical benefit was determined from surveys with clinicians. One study only briefly mentioned positive feedback from specialists about DLTI information. In the other two studies, clinicians reported that 30 to 100% of DLTI messages were useful. These differences in reported usefulness could be explained by differences in study design. The study in which all DLTI alerts were considered useful, 48 DLTIs were included and DLTI alerts were automatically selected based on predefined usefulness criteria and judged by the laboratory specialist before reporting to the responsible physician. In the other study with 30% appreciated usefulness of DLTI alerts, 20,000 different DLTIs were included, no selection prior to reporting was performed and the usefulness of alerts was studied with a retrospective patient record study.

Thus, there was a limited number of studies about CDSS for DLTI monitoring, but the studies that were found showed many interaction alerts and a high appreciation from clinicians and even changes in medical decision making based on DLTI alerts.

In Chapter 3, a proof of concept of a CDSS which can automatically identify potential DLTIs in clinical practice was described. The implementation of the system succeeded in three large teaching hospitals.

A random selection of interactions from the DLTI database of the Dutch Society of Clinical Chemistry and Laboratory Medicine was integrated in 43 clinical rules, including 24 tests and 25 drugs. Well-established interactions between frequently prescribed drugs or frequently requested laboratory tests were used. Some interactions were applicable to a group of drugs (e.g. Angiotensin Converting Enzyme-inhibitors) and others only to a specific drug (e.g. trimethoprim). Per day, approximately 65 potential DLTIs were detected in each hospital. Frequencies of DLTI alerts were comparable in the

three hospitals. Most DLTI alerts were generated for patients from the Department of Internal Medicine (42%), followed by the Intensive Care Unit (23%) and the Department of Cardiology (18%).

We demonstrated that our CDSS is applicable in three different hospitals with different electronic patient records, pharmacy and laboratory information systems.

In chapter 4 the appreciated usefulness of DLTI alerts for specialists in laboratory medicine was described. In this chapter the usefulness of DLTI alerts has been investigated using a survey with six clinical cases. A total of 98 Dutch specialists in laboratory medicine completed the survey and the majority was positive about receiving DLTI alerts (92%). The respondents were willing to forward DLTI alerts to clinicians; most frequently in a case describing the interaction between chromogranin A and proton pump inhibitors (81-94%). Clinicians of internal medicine would most often receive a DLTI alert from specialists in laboratory medicine, ranging from 47 to 94% of respondents depending on the case. Clinicians of the departments of surgery and emergency care would in the opinion of respondents also be eligible to receive a DLTI alert (ranging from 39 to 81% of respondents).

A majority of respondents was willing to implement CDSS for DLTI monitoring (84%), but barriers for implementation were frequently reported, such as a lack of time (63%), technical issues (54%), insufficient budget (49%) and a lack of support from colleagues (29%).

In Chapter 5, the results of a survey among 210 clinicians from six different hospitals were described about DLTI alerts in six clinical cases. The clinicians were positive about receiving DLTI alerts. Although an analysis for separate medical specialties was not performed, there are some indications that the appreciation and effect on medical decision making of DLTI alerts differed among medical specialties. Cardiologists, for example, replied that a specific DLTI alert about amiodarone and hyperthyroidism will not influence their medical decision making, since they are already aware of this interaction. The results of the survey underline the need to customize DLTI alerts in a clinical decision support system according to knowledge and preferences of the medical specialists.

In chapter 6 a retrospective medical record study was performed about the clinical impact of the interaction between chromogranin A, a marker for neuro endocrine tumours (NET), and proton pump inhibitors (PPI), a frequently prescribed drug.

In the study population, 238 patients had an elevated CgA concentration and 132 of them used a PPI (55%). CgA test results of 9 patients were probably influenced by PPIs (16%), because no other medical cause of the elevated CgA concentration was identified. Of these 9 patients, CgA measurement was repeated in six patients between 3 weeks and 2 months after discontinuation of the PPI. The CgA concentration decreased. In 4 of the 9 patients somatostatin receptor PET imaging was performed without discovering any abnormalities. These results suggest that CgA should be preferably measured after discontinuation of PPIs to prevent unnecessary expensive and invasive diagnostics. A systematic alert of an interaction between CgA and prescribed PPIs can be useful in the test ordering phase.

In chapter 7 the study results of the previous chapters were reviewed. The research was put in the context of current healthcare and developments in laboratory diagnostics in particular.

The work described in this thesis reflects a first initiative to create more awareness of Drug Laboratory Test Interactions (DLTIs) in laboratory test interpretation. DLTI algorithms were designed in a clinical decision support system and implemented in three hospitals for real-time monitoring of DLTIs. DLTI alert frequencies were substantial. Specialists in laboratory medicine and clinicians were positive about receiving the alerts. A retrospective medical record study showed unnecessary diagnostics when a possible DLTI was not immediately recognized. Further research must reveal the value and impact of DLTI monitoring in patient care.

A

SAMENVATTING

Een van de belangrijkste taken van een arts is om de oorzaak van medische klachten van een patiënt te achterhalen. Als de diagnose gesteld is, kan de arts besluiten of en welke behandeling nodig is. Volgens diverse publicaties, zijn de diagnoses in 10-15% van de gevallen helaas onjuist. Bovendien blijkt dat ieder mens ooit in het leven te maken zal krijgen met een relevante diagnostische fout. Een verkeerde diagnose kan leiden tot onnodig extra diagnostische testen, behandeling en follow-up en zelfs schade aan patiënten.

De toename en complexiteit van laboratoriumtesten maken het steeds moeilijker voor artsen om testresultaten van hun patiënten correct te interpreteren. Daarom wordt de specialist laboratoriumgeneeskunde steeds vaker in consult gevraagd voor de interpretatie van testresultaten. Deze trend wordt herkend door de Nederlandse Vereniging voor Klinische Chemie en Laboratoriumgeneeskunde (NVKC). Er worden initiatieven ontwikkeld om laboratoriumtestrapporten te voorzien van interpretatief commentaar en dit is bovendien een van de belangrijkste speerpunten van de beroepsgroep voor de komende jaren.

Afwijkende laboratoriumtestresultaten kunnen wijzen op ziekte, maar kunnen ook het directe gevolg zijn van medicijn gebruik. Deze geneesmiddel-test interacties (GTIs) zijn vaak (gewenste of ongewenste) fysiologische effecten van het medicijn in vivo en soms een analytische interactie in vitro. Deze effecten zijn misleidend, omdat de gerapporteerde concentratie van een bepaling in de patiënt niet correspondeert met de werkelijke concentratie. Zowel de fysiologische als de analytische interacties zijn niet allemaal bekend bij specialisten laboratoriumgeneeskunde en clinici. GTIs die niet herkend worden kunnen zorgen voor diagnostische fouten.

Elektronische signaleringssystemen, ook wel klinische beslisondersteuningssystemen genoemd, kunnen een oplossing zijn voor het probleem van niet herkende GTIs.

Beslisondersteuning is al geïmplementeerd bij andere toepassingen binnen de klinische chemie, bijvoorbeeld als ondersteuning bij het kiezen van een test panel en het alarmeren op levensgevaarlijke testafwijkingen. Bij andere medische specialismen wordt beslisondersteuning ook gebruikt. Een voorbeeld is de apotheek bij het monitoren van interacties tussen geneesmiddelen. Beslisondersteuningssystemen kunnen automatische berichten sturen over GTIs op basis van algoritmes die gebruik maken van data uit het apotheker informatiesysteem (voorgeschreven geneesmiddelen) en het laboratorium informatiesysteem (laboratoriumtest resultaten).

Een voorwaarde voor het gebruik van elektronische beslisondersteuning is gestructureerde informatie over GTIs. Een werkgroep van Nederlandse specialisten laboratoriumgeneeskunde hebben een database ontwikkeld met wetenschappelijke onderbouwing en een samenvatting over specifieke GTIs. Deze database faciliteert specialisten laboratoriumgeneeskunde bij testinterpretatie met up-to-date en gestructureerde informatie over GTIs, die ook gebruikt kan worden als basis voor algoritmes in een beslisondersteuningssysteem.

In hoofdstuk 1 staat het doel en de deelonderwerpen van dit promotieonderzoek beschreven. Het doel van dit onderzoek was het onderzoeken van de waarde van een beslisondersteuningssysteem voor het real-time monitoren van GTIs in de klinische praktijk. De verwachting was dat dergelijke beslisondersteuning van belangrijke waarde kan zijn voor specialisten laboratoriumgeneeskunde en clinici, omdat de GTI-berichten direct van toepassing zijn bij test interpretatie van de individuele patiënt. Verder is de incidentie van een selectie van potentiële GTIs onderzocht.

In hoofdstuk 2 is de beschikbare literatuur beschreven over de inzet van beslis-ondersteuning voor GTI-monitoring. In totaal werden er vier relevante publicaties gevonden. Één studie liet een prevalentie zien tot 43% van GTI-berichten bij ziekenhuis patiënten, afhankelijk van de klinische afdeling. Een andere studie liet een prevalentie zien van 11% GTI-berichten bij endocrinologische test resultaten. De klinische waarde werd onderzocht met enquêtes onder artsen. Eén studie benoemt alleen kort positieve feedback van specialisten over GTI-berichten. In de andere twee studies werden 30 tot 100% van GTI-berichten als bruikbaar beoordeeld. De verschillen in gerapporteerde bruikbaarheid kan worden verklaard door verschillen in studieopzet. De studie waarbij alle GTI-berichten als bruikbaar werden beoordeeld, bevatte 48 verschillende GTIs en GTI-berichten werden automatisch geselecteerd op basis van voorgedefinieerde bruikbaarheidscriteria en beoordeeld door een specialist laboratoriumgeneeskunde voordat het werd gerapporteerd aan de arts. In de andere studie waarbij maar 30% van GTI-berichten als bruikbaar werd beoordeeld waren 20,000 verschillende GTIs geïncludeerd en er vond geen selectie plaats voor rapportage aan de arts. Tevens werd bij de laatste studie de bruikbaarheid vastgesteld met retrospectief patiëntendossieronderzoek.

Er was dus een klein aantal studies beschikbaar over beslisondersteuning voor het monitoren van geneesmiddel-test interacties. De studies lieten een hoge waardering van artsen zien wat betreft GTI-berichten en zelfs veranderingen in medisch beleid op basis van GTI-berichten.

In hoofdstuk 3 werd een proof of concept studie beschreven waarbij een elektronisch beslisondersteuningssysteem werd ingezet voor GTI-monitoring. Het systeem werd in

drie grote perifere ziekenhuizen geïmplementeerd.

Een willekeurige selectie van interacties vanuit de GTI-database van de NVKC werd geïntegreerd in 43 algoritmes met hierin 24 verschillende laboratoriumtesten en 24 medicijnen. Alleen interacties tussen frequent aangevraagde testen of veel voorgeschreven medicijnen werden geïncludeerd. Sommige interacties waren van toepassing op een groep medicijnen (bijv. ACE-remmers) en anderen op een specifiek medicijn (bijv. trimethoprim). Iedere dag werden ongeveer 65 potentiële GTIs gedetecteerd in de ziekenhuizen. De frequenties van de verschillende GTI-berichten kwamen ongeveer overeen in de drie ziekenhuizen. De meeste GTI-berichten werden gegenereerd bij patiënten van de interne geneeskunde (42%), gevolgd door de intensive care (23%) en cardiologie (18%).

Onze studieresultaten hebben laten zien dat de beslisondersteuning toepasbaar was in drie ziekenhuizen met verschillende elektronische patiëntendossiers en apotheker informatiesystemen en laboratorium informatiesystemen.

In hoofdstuk 4 is de bruikbaarheid van GTI-berichten voor specialisten laboratorium-geneeskunde onderzocht met een enquête als onderdeel van een E-learning over GTIs bij zes verschillende casussen. GTI-berichten kunnen aan specialisten laboratoriumgeneeskunde worden gerapporteerd voor de analytische validatie van testresultaten. De specialisten kunnen de GTI-berichten ook gebruiken als een nieuwe dimensie om laboratoriumtest resultaten te voorzien van interpretatief commentaar.

In totaal hebben 98 Nederlandse specialisten laboratoriumgeneeskunde de enquête ingevuld en de meerderheid was positief over het ontvangen van GTI-berichten (92%). De respondenten waren ook bereid om de berichten door te sturen naar artsen; het vaakst in de eerste casus met een interactie tussen Chromogranine A en protonpompremmers (81-94%). Internisten zouden het vaakst een GTI-bericht ontvangen van de respondenten, variërend van 47—94%, afhankelijk van de casus. Chirurgen en SEH-artsen zouden naar de mening van de respondenten ook GTI-berichten mogen ontvangen (variërend van 39-81% van de respondenten).

De meerderheid van de respondenten zou beslisondersteuning willen implementeren voor het monitoren van GTIs (84%), maar er werden wel drempels voor implementatie gerapporteerd, zoals een gebrek aan tijd (63%), geld (49%), draagvlak (29%) of technische problemen (54%).

In hoofdstuk 5 is een enquête studie beschreven met 210 artsen van zes verschillende ziekenhuizen over de bruikbaarheid van GTI-berichten bij klinische casuïstiek. De artsen waren positief over het ontvangen van GTI-berichten. Uit de enquête kwamen ook aanwijzingen naar voren dat de bruikbaarheid van GTI-berichten en het effect op medisch beleid verschilt per specialisme. Een voorbeeld zijn cardiologen, die de interactie tussen amiodaron en schildklier parameters niet gerapporteerd wilden krijgen, omdat de invloed van amiodaron op de schildklier basiskennis is van een cardioloog. De resultaten van de enquête onderstrepen dat GTI-opmerkingen aangepast moeten worden aan de kennis en voorkeuren van het ontvangende medisch specialisme.

In hoofdstuk 6 is een retrospectief statusonderzoek beschreven over de klinische impact van de interactie tussen Chromogranine A (CgA), een marker voor neuro endocriene tumoren (NET) en protonpompremmers (PPIs), een frequent voorgeschreven medicijn. In de studiepopulatie waren 238 patiënten met een verhoogde CgA concentratie, waarvan 132 een PPI gebruikte (55%). In deze groep werden CgA testresultaten bij 9 patiënten naar alle waarschijnlijk beïnvloed door PPI gebruik, omdat andere oorzaken werden uitgesloten. Bij 6 patiënten werd de CgA concentratie nogmaals gemeten na 3 weken tot 2 maanden na staken van een PPI. De CgA concentratie bleek bij de tweede meting lager. Bij 4 patiënten werd een radioactief gelabelde PET-scan uitgevoerd, waarbij geen afwijkingen werden gezien. Deze resultaten suggereren dat CgA het beste direct gemeten kan worden na het stoppen van PPIs om onnodige dure en invasieve diagnostiek te voorkomen. In dit geval kan een systematisch melding van een potentiële interactie tussen CgA en voorgeschreven PPIs in de fase van het aanvragen van de CgA test zinnig zijn.

In hoofdstuk 7 is gereflecteerd op de uitkomsten van de voorgaande hoofdstukken en is het onderzoek in de context geplaatst van de huidige gezondheidszorg en ontwikkelingen in de laboratoriumdiagnostiek in het bijzonder.

Dit proefschrift is een begin om meer bewustzijn te creëren over geneesmiddel-test interacties (GTIs) bij laboratoriumtest interpretatie. GTI-algoritmes werden ontworpen in een beslisondersteunend systeem en geïmplementeerd in drie ziekenhuizen ten behoeve van real-time monitoring van GTIs in de dagelijkse patiëntenzorg. Het aantal gerapporteerde GTI-berichten bleek substantieel. Specialisten laboratoriumgeneeskunde en artsen waren positief over het ontvangen van GTI berichten. Uit retrospectief statusonderzoek bleek dat er onnodige dure en invasieve diagnostiek is uitgevoerd, omdat er niet direct aan een GTI werd gedacht. Verder onderzoek moet aantonen wat de waarde en impact is van het monitoren van GTIs in de dagelijkse patiëntenzorg.

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CURRICULUM VITAE AND PUBLICATIONS

Curriculum vitae

Jasmijn Anna van Balveren-Schasfoort was born on May 24, 1988 in Winterswijk. She attended secondary school at the Driemark in Winterswijk and graduated in 2006. She studied medicine at the Radboud University of Nijmegen and obtained her master's degree in 2014. During her studies she followed international internships in France (2010) and Indonesia (2013). After her graduation, Jasmijn worked at the internal ward as a physician for 9 months in 2014. Thereafter she started her postgraduate education in clinical chemistry at the Jeroen Bosch hospital in 's-Hertogenbosch. In 2017 her residency in clinical chemistry was combined with a PhD project at the Jeroen Bosch Hospital and at the department of Health Technology and Services Research (HTSR) at the University of Twente. Her PhD project concerned drug laboratory test interactions in the interpretation of laboratory test results. The results of this PhD project are described in this dissertation. As part of the PhD project, Jasmijn is chairwoman of the task group 'SMILE': Signalling Medication Interactions and Laboratory test Expert system of the Dutch Society of Clinical Chemistry and Laboratory Medicine.

In 2020 Jasmijn finished her residency and was registered as a clinical chemist. Currently she works at the laboratory of clinical chemistry and haematology in the St Jansdal hospital in Harderwijk.

Jasmijn is married and has a daughter.

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