

Mini Review

Jasmijn A. van Balveren*, Wilhelmine P.H.G. Verboeket-van de Venne, Lale Erdem-Eraslan, Albert J. de Graaf, Annemarieke E. Loot, Ruben E.A. Musson, Wytze P. Oosterhuis, Martin P. Schuijt, Heleen van der Sijs, Rolf J. Verheul, Holger K. de Wolf, Ron Kusters and Rein M.J. Hoedemakers, on behalf of the Dutch Society for Clinical Chemistry and Laboratory Medicine, task group ‘SMILE’: Signalling Medication Interactions and Laboratory test Expert system

Diagnostic error as a result of drug-laboratory test interactions

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Abstract

Background: Knowledge of possible drug-laboratory test interactions (DLTIs) is important for the interpretation of laboratory test results. Test results may be affected by physiological or analytical drug effects. Failure to recognize these interactions may lead to misinterpretation of test results, a delayed or erroneous diagnosis or unnecessary extra tests or therapy, which may harm patients.

Content: Thousands of interactions have been reported in the literature, but are often fragmentarily described and some papers even reported contradictory findings. How can

healthcare professionals become aware of all these possible interactions in their individual patients? DLTi decision support applications could be a good solution. In a literature search, only four relevant studies have been found on DLTi decision support applications in clinical practice. These studies show a potential benefit of automated DLTi messages to physicians for the interpretation of laboratory test results. All physicians reported that part of the DLTi messages were useful. In one study, 74% of physicians even sometimes refrained from further additional examination.

Summary and outlook: Unrecognized DLTIs potentially cause diagnostic errors in a large number of patients. Therefore, efforts to avoid these errors, for example with a DLTi decision support application, could tremendously improve patient outcome.

*Corresponding author: **Jasmijn A. van Balveren**, MSc, Laboratory for Clinical Chemistry and Haematology, Jeroen Bosch Hospital, Henri Dunantstraat 1, PO Box 90153, 's-Hertogenbosch, The Netherlands; and Department of Health Technology and Services Research, Technical Medical Centre, University of Twente, Enschede, The Netherlands, Phone: +31 (0)73-553 27 64, Fax: +31 (0)73-5532958, E-mail: j.v.balveren@jzbz.nl

Wilhelmine P.H.G. Verboeket-van de Venne and Wytze P. Oosterhuis: Department of Clinical Chemistry, Zuyderland Medical Centre, Heerlen, The Netherlands, E-mail: w.vandevenne@zuyderland.nl (W.P.H.G. Verboeket-van de Venne); w.oosterhuis@zuyderland.nl (W.P. Oosterhuis)

Lale Erdem-Eraslan: Department of Clinical Chemistry, Erasmus University Medical Centre, Rotterdam, The Netherlands, E-mail: l.erdem@erasmusmc.nl

Albert J. de Graaf: Department of Clinical Chemistry, Medical Spectrum Twente, Enschede, The Netherlands, E-mail: a.degraaf@medlon.nl <https://orcid.org/0000-0001-5451-3010>

Annemarieke E. Loot: Department of Clinical Chemistry, Certe, Groningen, The Netherlands, E-mail: a.loot@certe.nl

Ruben E.A. Musson: Laboratory for Clinical Chemistry and Haematology, University Medical Centre Utrecht, Utrecht, The Netherlands, E-mail: r.e.a.musson@umcutrecht.nl

Martin P. Schuijt: Department of Clinical Chemistry, Slingeland Hospital, Doetinchem, The Netherlands, E-mail: m.schuijt@slingeland.nl

Heleen van der Sijs: Department of Hospital Pharmacy, Erasmus Medical Centre, University Medical Centre Rotterdam, Rotterdam, The Netherlands, E-mail: i.vandersijs@erasmusmc.nl

Rolf J. Verheul: Department of Clinical Chemistry, LabWest/HMC Westeinde, The Hague, The Netherlands, E-mail: r.verheul@labwest.nl

Holger K. de Wolf: Department of Clinical Chemistry, Rivierenland Hospital, Tiel, The Netherlands, E-mail: holger.dewolf@zrt.nl

Ron Kusters: Laboratory for Clinical Chemistry and Haematology, Jeroen Bosch Hospital, 's-Hertogenbosch, The Netherlands; and Department of Health Technology and Services Research, Technical Medical Centre, University of Twente, Enschede, The Netherlands, E-mail: r.kusters@jzbz.nl

Rein M.J. Hoedemakers: Laboratory for Clinical Chemistry and Haematology, Jeroen Bosch Hospital, 's-Hertogenbosch, The Netherlands, E-mail: r.hoedemakers@jzbz.nl

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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, especially for non-laboratory professionals [1].

A common source of diagnostic error is the lack of knowledge of the presence of drug-laboratory test interactions (DLTIs). Misinterpretation of test results may lead to an erroneous diagnosis, unnecessary extra diagnostic tests, therapy or follow-up.

There are two main categories of DLTIs: physiological and analytical interactions. 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 levothyroxine treatment. However, 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 by the frequently prescribed proton pump inhibitors (PPIs). An elevated level of chromogranin A can be indicative of the activity of a neuroendocrine tumor. Case reports describe expensive imaging with no abnormalities and a normalized chromogranin A level after the discontinuation of the PPI [2]. This example illustrates that unnecessary discomfort and expenditure could have been avoided if this unintended physiological interaction had been recognized promptly.

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, as 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 interpretations 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 or maltose) that can be present in CAPD fluid [3]. The

improper administration of insulin has resulted in fatal consequences in a number of these cases [4].

Impact of DLTI in clinical practice

The number of DLTIs described in the literature is substantial, approximately 50,000 [5].

Therefore, the application of a knowledge-based electronic expert system with DLTI information seems necessary. An expert system may send automatic messages about interactions based on algorithms, which use data from pharmacy and laboratory data systems.

To build DLTI algorithms, relevant information about interactions is conditional. Information about DLTI can be found in the literature, but is often fragmentarily described and sometimes even contradictory effects are reported, i.e. the effect of a drug on a laboratory test may result in either an increase or decrease of measured values [6]. Therefore, several DLTI databases have been introduced to provide an overview of interactions and the corresponding available literature [7–10].

In a literature review [11], only four studies were found about automated DLTI decision support in clinical practice [12–15]. The added value of the system was evaluated with extensive surveys among physicians receiving DLTI messages in two studies [12, 13] and a retrospective evaluation of patient reports by an expert panel in one study [13].

The studies have shown a high prevalence of DLTIs in hospitalized patients (up to 43% of all patients, depending on the ward [12] and up to 11% of endocrinological test results [13]).

Apart from the prevalence of DLTIs, another important issue that was examined in the studies was the clinical usefulness of the interaction messages. In one study, the medical staff reported 30% of the messages to be useful and in 4% of cases their medical policy changed because of the DLTI message [12]. In another study, all the physicians considered the DLTI messages to be useful and 74% of the physicians reported to sometimes refrain from additional further examinations as a consequence of DLTI 'reminders' [13].

Discussion

The existing literature shows a high prevalence of DLTIs in a variable range of laboratory tests and drugs. However, it is likely that the prevalence of DLTIs is even higher, as the interactions are not systematically examined or reported.

Studies have shown the added value of automated decision support applications to alert healthcare professionals on possible DLTIs. The effectiveness of such a system increases when a refined set of clinical rules is determined in cooperation with healthcare professionals who use the system [12, 13]. These refined clinical rules are needed to prevent excessive numbers of DLTI messages and consequently the so-called ‘alert fatigue’ of physicians [16].

Although the benefit of DLTI decision support was already shown in the past, it is not widely implemented today. To implement a DLTI decision support tool, interoperability of a laboratory information system, an electronic patient record and a decision support application are crucial. The interoperability of information technology (IT)-systems is not yet realized in many laboratories and hospitals. To implement such an IT-system, an intensive cooperation between medical IT-specialists, laboratory specialists, pharmacists and physicians is needed.

DLTIs could potentially disturb the diagnostic process in a large number of patients, as many patients receive drugs and thousands of laboratory test results are produced in each hospital every day. Further research is needed to better estimate the prevalence and impact of DLTIs in daily practice. Decision support applications probably improve DLTI recognition by healthcare professionals. These DLTI decision support tools could prevent diagnostic errors and consequently improve diagnosis and treatment of patients.

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