Reminders of Drug Effects on Laboratory Test Results

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Drug effects on laboratory test results are difficult to take into account without an online decision support system. In this study, drug effects on hormone test results were coded using a drug-laboratory effect (DLE) code. The criteria that trigger the reminders were defined. To issue reminders, it was necessary to write a computer program linking the DLE knowledge base with databases containing individual patient medication and laboratory test results. During the first 10 months, 11% of the results from hormone samples were accompanied by one or more DLE reminders. The most common drugs to trigger reminders were glucocorticoids, furosemide, and metoclopramide. Physicians facing the reminders completed a questionnaire on the usefulness of the reminders. All respondents considered them useful. In addition, DLE reminders had caused 74% of respondents to refrain from additional, usually performed examinations. In conclusion, drug effects on laboratory tests should always be considered when interpreting laboratory results. An online reminder system is useful in displaying potential drug effects alongside test results.

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Drugs often alter laboratory test results; the literature reports >40 000 drug effects on laboratory tests (1). These effects may cause misinterpretation of laboratory data and lead to unnecessary further tests, missed diagnoses, and additional costs, as pointed out in the case report below. The vast amount of medical information, with its varying quality and ready availability, has to date made it laborious to take drug-laboratory effects (DLEs) into account in everyday patient care. The prevalence of DLEs is not negligible: as many as 12% of patients have had laboratory results potentially affected by drugs in a general medical ward (2). The effects of drugs on laboratory tests have been published in extensive catalogs (1, 3–6), from which data have to be sought manually with active effort. A modern solution for bringing this knowledge to clinical routine is computerization and automatic reminders. Because physicians are already flooded with information, it is important to remind them only of the effects relevant for the patient in question. This requires storing individual medications in a structured way and coding the data on DLEs in a logical way as well as building a reminder system that can be integrated into the laboratory information system (LIS) and hospital information system (7). Until now, there have been very few computer applications offering automatic monitoring of DLEs (2, 8).

In Turku University Central Hospital, coding of drug effects in clinical chemistry was started in 1995 when a DLE code was developed (9). In November 1998, an online reminder system built on the DLE knowledge base became operational. The system produces reminders in cases where patient medication may affect the results of hormonal laboratory tests. This report describes the DLE reminder system in detail and presents the reminders issued during the first 10 months as well as clinicians’ attitudes toward the reminders.

Case

In April 1998, a 66-year-old man was admitted to our hospital because of vertigo and impaired swallowing and speech. He had a history of obstructive bronchitis, diabetes, and left hemiparesis following cerebral infarction. His medication comprised dipyridamole, glibenclamide, and

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inhalations of salbutamol and beclomethasone. A computed tomographic scan with and without contrast medium enhancement did not visualize cerebral infarction. However, as the symptoms progressed, intravenous heparin was started on the day after admission.

Three days after hospitalization, the patient was tachycardic (pulse rate, 110/min) and mildly exophthalmic. Previously, he had had no signs suggesting hyperthyroidism. The patient’s serum thyroid-stimulating hormone (TSH) was 5.4 mIU/L (reference interval, 0.4–4.5 mIU/L), his free thyroxine (FT₄) was >83 pmol/L (reference interval, 9.6–17.1 pmol/L), and his free triiodothyronine was 19.0 pmol/L (reference interval, 4.3–7.5 pmol/L). A TSH stimulation test did not confirm thyroidal hyperthyroidism (TSH, 6.5 mIU/L at 0 min, 22.0 mIU/L at 20 min, and 18 mIU/L at 60 min), but rather the laboratory results seemed to suggest either thyroid hormone resistance or pituitary hyperthyroidism. Magnetic resonance imaging of the brain was partly unsuccessful because the patient was claustrophobic. The patient was discharged 15 days after admission with almost regained speech and swallowing.

After discharge, the patient’s serum TSH was 5.5 mIU/L, similar to the earlier concentration, but his FT₄ was now within the reference interval, i.e., 17 pmol/L. His medication at the time of the first sampling was now checked. It was concluded that intravenous heparin had most probably caused the increase in FT₄ during hospitalization. The reminder system described below had not been implemented at that time. The drug-affected result had thus caused expensive additional examinations (magnetic resonance imaging, repeated laboratory tests, consultations).

**Materials and Methods**

We first collected data on drug effects on hormone tests from catalogs and individual publications. Because some older publications classify effects that have since been found to be analytical as biological, all information was carefully evaluated. A doctor working in the field of clinical chemistry then brought together the results of different studies and coded the effects using the DLE code. Another doctor then checked the coding. Collaboration with Nils Tryding, who has studied and evaluated the literature concerning drug effects for nearly 30 years; 7000 references, substantially enhanced the coding and brought about some changes to the code that further focused the reminders.

The DLE code consists of nine features that describe the following aspects of the DLEs:

- Nature of effect (analytical effect, biological effect, or unknown mechanism)
- Route of administration (effect is probably valid with all “systemic”, parenteral, or oral administration, or with drugs absorbed from the mouth, and so forth)
- Direction and strength of effect (decreasing, slightly decreasing, transient decreasing, no effect, transient increasing, slightly increasing, increasing effect, or contradictory data on the effect)
- Level of documentation (effect has been studied with healthy volunteers and sometimes with patient populations as well, or with patient populations, or effect is assumed or widely known, or effect has not yet been well documented)
- Sex of patient (effect is probably valid in males and females, only males, or only females)
- Age of patient (effect is probably valid in adults and children, only in adults, or only in children)
- Onset of effect after starting the medication (unknown, in 1 day, in 1 week, or in 1 month)
- Duration of effect after stopping the medication (unknown, at maximum 1 week, at maximum 1 month, or >1 month)
- Clinical significance of effect (major clinical significance, moderate clinical significance, no clinical significance, clinical significance with high doses, or clinical significance in rare cases)

In addition, there is a field for a free additional text comment for the reminder, if needed. Each code is accompanied by a list of most relevant references of the effect.

During a pilot study, during which reminders were not forwarded to the wards, it was noted that some reminders were unnecessary, bringing no new information for clinicians. These included reminders of the desired therapeutic effects of drugs, e.g., the decreasing effect of bromocriptine on serum prolactin (12). Therefore, in Turku University Central Hospital, an option to disregard reminders of such DLEs was included in the system. In addition to this “Link to LIS on/off switch”, another restriction was added: If a patient is taking a medication with a desired effect on the laboratory test in question (e.g., thyroxine or carbimazole, which affect TSH decreasing, transient decreasing, no effect, transient increasing, slightly increasing, increasing effect, or contradictory data on the effect)

![Fig. 1. Model of a laboratory result report.](https://academic.oup.com/clinchem/article-abstract/46/9/1395/5641178)
or \( \text{FT}_4 \)), all reminders of drug effects for that analyte are disregarded automatically. The therapeutic drugs are defined for each laboratory test in a laboratory database.

The function of the DLE reminder system is to issue individual reminders, i.e., the system reminds when the patient actually is taking a medication potentially affecting the tests requested. To achieve this, the reminder system links the DLE knowledge base with the databases of laboratory test results and individual medications (7). Nurses routinely store individual medications using trade names listed in a separate database, making available clear printouts with precise data of medication. The medication database includes the Anatomical, Therapeutic, Chemical (ATC) codes (WHO Collaborating Centre for Drug Statistics Methodology, Oslo, Norway), which describe the generic names of drugs. The ATC codes are also used in the DLE knowledge base. Laboratory tests are coded using national codes [laboratory test identification codes (IDs)] in both the test result database and the DLE knowledge base. In all databases, patients are identified by their social security numbers (patient IDs). Consequently, with the patient ID, the computer program is able to retrieve relevant patient medication from the medication database. Using the laboratory test IDs and ATC codes of the patient’s drugs, it then runs a query in the DLE knowledge base to find the DLE codes for drug effects. If all conditions for a DLE reminder are fulfilled as described below, the system generates a brief structured description of the possible DLE, e.g., “Haloperidol may have increased prolactin value”. The reminder appears alongside the laboratory test result in both the LIS, which is used by wards, and in paper printouts (Fig. 1). To date, a laboratory physician has checked the reminders before forwarding them with results to clinicians. Clinicians can obtain additional information on the reminders by opening the DLE knowledge base, which is accessible on the hospital Intranet (Fig. 2).

The conditions that trigger reminders were defined as
follows: the clinical significance of the effect must be at least moderate; the effect must be well documented in the literature; the route of administration and administration dates must match the route, onset of the effect and duration of the effect fields in the code; and the patient’s sex and age must match those in the code. In addition, as described above, the “Link to LIS switch” must be “on”, and the patient must not have therapeutic medication that affects the test in question in the desired manner.

The DLE reminders were given, when appropriate, with the laboratory analytes listed in Table 1. They were issued to all wards (inpatient settings) and outpatient clinics that store patient medications in the medication database (nine internal medicine wards, three neurology wards, three oncology wards, three obstetrics and gynecology wards, three pulmonary disease wards, one pediatric neurology ward, two ophthalmologic diseases wards, and one rehabilitation ward as well as nephrology and pediatric neurology outpatient clinics). The tests usually are requested and interpreted by trainee resident physicians in the wards and by experienced specialist physicians at the outpatient clinics.

To evaluate the system, the physicians facing DLE reminders in the department of internal medicine were asked to fill out a questionnaire about their views on the reminders. The physicians were asked whether they had agreed with the reminders on a scale from 1 (never) to 5 (always), whether they considered the reminders useful (1 not useful, 2 slightly useful, 3 useful, 4 very useful, 5 extremely useful), and whether the reminders sometimes made further examinations unnecessary, e.g., radiological examinations otherwise performed because of similar laboratory test results (1 never, 5 all reminders).

The DLE reminders issued between December 1, 1998, and September 30, 1999, and the results of the questionnaire are presented below.

### Results

The DLE reminders issued during the study period and the number of each hormone test taken in the participating wards and outpatient clinics are presented in Table 1. Overall, DLE reminders were issued for 10.7% of the hormone tests taken. Most DLE reminders, 55%, concerned drug effects on serum TSH, 26% on parathyroid hormone, and 12% on FT4. In relative amounts, DLE reminders were most often attached to serum renin (54% of the renin results had one or more DLE reminders), parathyroid hormone (30%), and testosterone (18%). The five most common drugs that caused DLE reminders were glucocorticoids (121 reminders), furosemide (94), diltiazem (23), isoniazid (20), and metoclopramide (16). We looked further into the reminders accompanying serum TSH and FT4 results. There were 26 cases (9% of TSH and FT4 reminders) in which the reminder clearly aided in the interpretation of the hormonal results;
changes around lower or upper reference limits in particular were clarified by reminding of a drug effect. For example, there were cases where FT₄ was within the reference interval but a glucocorticoid had decreased the TSH result to below the reference range although the patients were euthyroid. In addition, some clinically or subclinically hypothyroid patients with increased TSH results had low-normal FT₄ that probably had been increased by a drug, e.g., valproic acid.

The questionnaire was returned by 23 physicians, 15 who were specialists in internal medicine and 8 who were trainee resident physicians. The answers between the groups were similar. Fifteen of the physicians (65%) always or often agreed with the reminders, 6 (26%) sometimes agreed, and 2 (9%) seldom agreed. No one always disagreed with the reminders. All respondents considered the reminders useful to at least some extent (at least 3 on the scale); two respondents (9%) considered the reminders extremely useful. According to eight respondents (35%), half or more of the reminders made further examinations unnecessary. Nine respondents (39%) had rarely and three (13%) had never refrained from other examinations because of DLE reminders.

Discussion

The online DLE reminder system is a novel decision support system for clinicians. It brings knowledge of DLEs from difficult-to-reach catalogs and publications to everyday practice and thus saves time. It is also probable that automatic reminders decrease the need for further examinations and thus save money. This effect is, however, difficult to study, and therefore, exact figures cannot be given.

In our experience, clinicians are not well aware of all potential drug effects related to hormones. Therefore, we have reason to believe that reminders have some impact on clinical decision making. It would be useful to study this impact, although evaluation in medical informatics is complex because of the intersection of medicine and healthcare delivery, evaluation methodology, and computer-based information systems, as described by Friedman and Wyatt (13). In the present study, some of the physicians facing DLE reminders completed a questionnaire on the usefulness of the reminders. The feedback was positive. All respondents considered the reminders useful to at least some extent. Seventy-four percent of the respondents had sometimes refrained from further examinations because of a DLE reminder. Because the two participating outpatient clinics were small, trainee resident physicians working on wards received most of the DLE reminders. In our teaching hospital, the DLE reminders contribute to the education of residents in different disciplines.

For greater benefit, some modifications to the system have been suggested. For example, reminders should be accompanied by a mention of the magnitude of the possible effect. This has been considered but, for the moment, not implemented because the magnitude often is affected by the dose of the drug, which at present is not in a standard format. Another suggestion was to send a reminder of the effects when tests are requested. This would be most useful when a physician enters requests, which is not, however, customary in our hospital at present. It must also be emphasized that many drugs that cause DLE reminders are commonly prescribed, e.g., antihypertensives and antiepileptics, and thus often are capable of disturbing interpretation of laboratory test results.

Until now, it has been very difficult to recognize DLEs in everyday practice without an automatic reminder system. In 1987, the IFCC tackled this problem and put forward recommendations made by an expert panel (14). The panel concluded that databases are needed to obtain reliable information of drug effects on laboratory tests in a practical form. According to the recommendations, the information should be available interactively via data terminals, and it should be possible to integrate information from databases into local computers and into routine hospital work. In addition, such databases should be able to exchange information with other systems and have the potential to expand. It also should be possible to modify the databases without altering existing programs. The DLE reminder system meets these recommendations. The data included in the DLE knowledge base have been critically examined, which is also required by the IFCC recommendations. In addition, each DLE code is accompanied by relevant references for further information.

The present study suggests that as many as 10% of hormone test results may be affected by medication. With the reminder system, the drug effects cannot be disregarded. Most of the reminders concerned thyroid laboratory tests (54% concerned serum TSH and 10% FT₄), which reflects the common use of thyroid tests. In this study, serum TSH and serum FT₄ seemed to be affected by drugs in 12% and 6% of the tests taken, respectively. In our pilot study (11), there were relatively more reminders for these hormones. The reason for the reduction seen in the present study was that acetylsalicylic acid administered in small doses was noted not to affect these thyroid determinations. Thus, the reminders of its effects on serum TSH and FT₄ were switched off. This example demonstrates the importance of testing applications in a real clinical environment.

The DLE codes have now been completed for the most important hormones and proteins. Coding of the DLEs was started with hormones because many common drugs have a considerable effect on hormonal laboratory results. Furthermore, serum hormone tests often refer to a specific diagnosis instead of a symptom and are not consistently included in the safety tests required before new drugs are introduced. DLE coding and the reminder system will next be extended to cover, e.g., serum glycosylated hemoglobin and lipids. The DLE knowledge base is updated and/or extended two to four times a year. Experts in
clinical chemistry are invited to present new codes or modifications to the existing ones. Familiarity with the structure of the code is not needed because the effects are described in plain language both in the reminder system and in the DLE knowledge base. The structure of the code enables rapid translation of the effects from English into other languages.

To build an online reminder system, some programming is needed inside the LIS. If introduction of new programs is likely to cause technical problems, it is possible to consult the DLE knowledge base independently outside the LIS. In the future, it will be possible to query the DLE knowledge base for DLEs over the Internet from any hospital or laboratory. A query can be sent using standard TCP/IP and HL-7. The DLE server will answer the query in just seconds. An Internet query requires less programming inside the LIS. In addition, it allows the use of the latest version of the DLE knowledge base. There are no confidentiality problems because queries show no patient identification.

In conclusion, drug effects on laboratory test results should always be considered when interpreting laboratory results. This can be facilitated by automatic decision support systems such as our online reminder system.

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