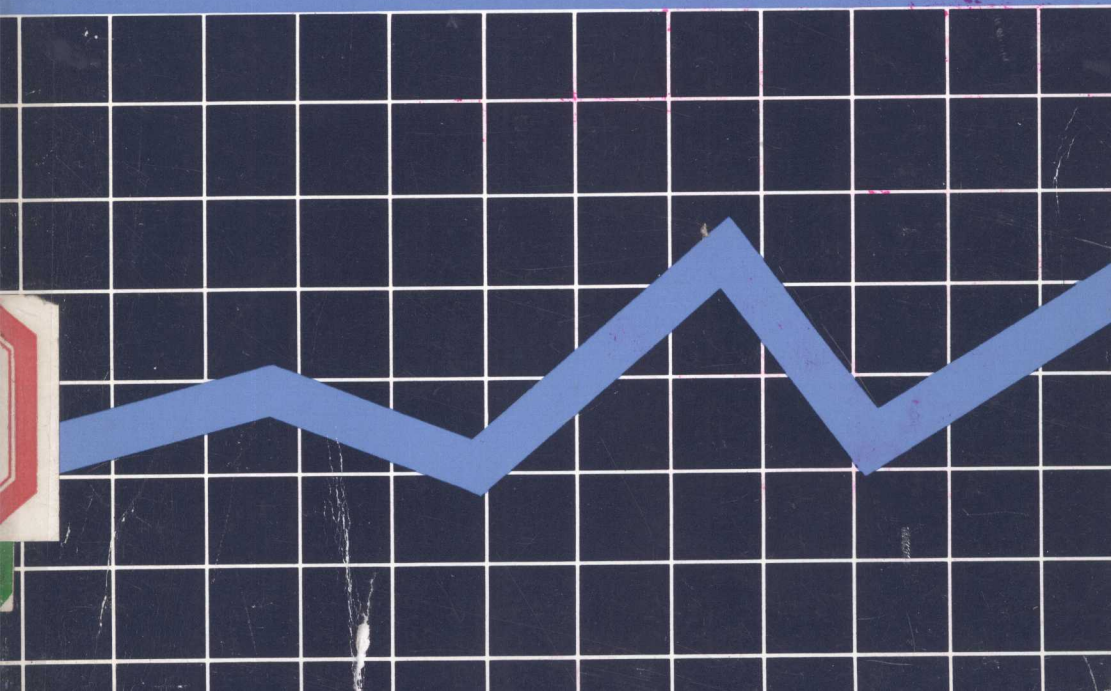
DRUG EFFECTS ON LABORATORY TEST RESULTS

Analytical Interferences and Pharmacological Effects

Gérard Siest / Marie-Madeleine Galteau



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DRUG EFFECTS ON LABORATORY TEST RESULTS.
ANALYTICAL INTERFERENCES AND PHARMACOLOGICAL EFFECTS

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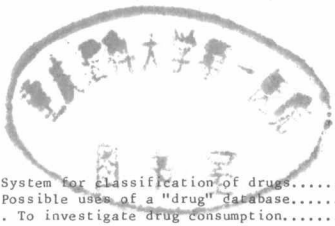
Contents



FOREWORD

J. Frei

The directors and staff of clinical chemistry laboratories, as well as physicians, are confronted daily with a problem of whose consequences they are largely unaware: the interference of drugs with many constituents of blood and urine. In recognition of the importance of the problem, the International Federation of Clinical Chemistry created the Expert Panel on Drug Effects in Clinical Chemistry, of which Professor Gérard Siest is appointed chairman. The first major work in this field was D.S. Young's computerized list (Clin. Chem., 1972, 18, 1041-1303), and other publications have followed. However the topic is so important and our knowledge has progressed so steadily, that the present contribution, by Professor Siest and his co-workers at the Center for Preventive Medicine in Vandoeuvre-les-Nancy, France, is particularly welcome. The authors wish to heighten the awareness of clinical chemists and at the same time to offer them a reference work. Their approach is novel, including much of their own work. They have sought to help the reader to understand a difficult and often confused field, by means of a scientific, didactic, and pragmatic approach. They have taken into consideration the latest publications, and have drawn on their wide experience gained over many years at the Center for Preventive Medicine and in a specialist working group of the European Economic Community. The original version was published in French but considering the importance of the matter the authors estimated necessary to publish an English version which was reviewed by Dr D.S. Young, a specialist in the field of drug interferences. The group at Vandoeuvre has created a data bank concerning drug interferences, which is descri-

bed in the last chapter: the data bank is also accessible through the "Minitel" system of the "Société Française de Biologie Clinique".

More than twenty chapters of this book are devoted to the analytical (in vitro) and pharmacological (biological; in vivo) effects of drugs on the concentrations of the most commonly estimated biochemical constituents (metabolites, electrolytes, enzymes, etc.) and on some hematological parameters. The authors also review physiological and pathological aspects of each constituent, the reference intervals for each, and the preanalytical factors that can affect the results.

The drug effects discussed in the book are part of the vast background of factors that can interfere with clinical laboratory investigation of patients. Unforeseen and often serious consequences may follow if these factors are poorly understood, or ignored. Thus this book is recommended to those who provide and those who use clinical laboratory results, as well as to teachers of clinical chemistry and medicine.

LABORATORY TESTS AND DRUGS

G. Siest

The administration of drug(s) to humans (or to animals) can alter laboratory tests, which are widely used to monitor the effects of taking these very drug(s) (300). We have developed different approaches to study the undesirable effects and the optimal use of laboratory tests:

(i) drugs or their metabolites can affect laboratory tests by either analytical or pharmacological means. This problem must be placed in its proper perspective. And conversely,

(ii) laboratory tests are widely used to assess toxicity of drugs in animals, and then during clinical trials in humans; and they are also used to monitor therapy.

The interpretation of laboratory test values in the presence of drugs will be different in these two situations. Drugs must be included among the variables affecting laboratory tests. They are factors which must be understood so that their effects may be eliminated or controlled.

1. EFFECTS OF DRUGS ON LABORATORY TESTS

A drug taken before the collection of a blood specimen can induce an increase or a decrease in the concentration of a plasma constituent. This effect can arise in two ways (750). One is purely analytical: the drug and/or its metabolites may at any stage affect the measurement of a constituent. In laboratory medicine this is called "analytical interference".

The second means is biological: the drug induces a change in a biological parameter by a physiological, pharmacological, or toxicological mechanism. This constitutes what is customarily called the

effects of a drug on laboratory tests (744). This very general (too general) term therefore encompasses the unexpected secondary effects, desirable or undesirable, of drugs. It also sometimes includes the results of drug interactions, a term which has been proposed but which should be restricted to pharmacology.
These effects may remain unnoticed, since laboratory tests are often ordered without knowledge of the drugs being taken by a person. Yet laboratory procedures may be used to investigate the liver, the kidney, or the phosphorus/calcium metabolism of a patient who is undergoing unrelated treatment with tranquillizing, hypnotic, or contraceptive drugs. This is one more reason to make a great effort to educate clinicians and clinical chemists. Of the factors that cause variation in laboratory test values, drugs are thought to be as important as age or excess weight (754, 755, 758).

For more than 10 years three organizations have considered this problem:
First of all, in 1974 the European Economic Community set up a working group on "Drug Interference in Clinical Chemistry", which produced a report (738) and general recommendations. (The members were: G. Siest, W. Appel, G.B. Blijenberg, B. Capolaghi, M.M. Galteau, C. Heughem, M. Hjelm, K.L. Lauer, B. Le Perron, V. Loppinet, C. Love, R.J. Royer, G. Tognoni, and P. Wilding.).
On the boarder topic of the effects of drugs, including both analytical interference and pharmacological variations as undesirable effects, and on the other hand as a means of following and monitoring drugs, International Federation of Clinical Chemistry (IFCC) set up a group of experts (Expert Panel on "Drug Effects in Clinical Chemistry": G. Siest (Chairman), P.A.G. Malya, J.G. Salway, F.W. Sunderman, G. Tognoni, and N. Tryding), and the Société Française de Biologie Clinique (SFBC) (French Society of Clinical Chemistry) established a French-speaking commission (on "Effets des médicaments sur les examens de laboratoire") (Drug Effects on Laboratory Tests), comprising: G. Siest (Chairman), M. Azria, A. Cloarec, J. Delattre, A. Galli, M.M. Galteau, D. Gouy, J.F. Guelfi, P. Jouanel,

J. Migne, J. Nachbaur, M. Sergant, F. Trivin, M. Cortes, P. Delwaide, and R. Galimany; with, as corresponding members, C. Bachmann, J. Breuer, M. Dobrescu, J.G. Salway, T. Spiro, F.W. Sunderman, G. Tognoni, and N. Tryding.

The SFBC has published, or will publish, the following documents:

- Document A, Notions générales concernant l'effet des médicaments sur les examens de laboratoire **(General concepts concerning the effects of drugs on laboratory tests)**, Ann. Biol. Clin., 1981, 39, 91-98
- Document B, Lignes directrices pour l'étude et la définition d'une interférence analytique. Proposition d'un protocole **(Guidelines for the study and definition of analytical interference: Proposed protocol)**, Ann. Biol. Clin., 1984, 42, 137-144
- Document C, Lignes directrices pour la mise en évidence des effets biologiques des médicaments sur les examens de laboratoire **(Guidelines for the demonstration of biological effects of drugs on laboratory tests)**, Inform. Scient. Biol., 1984, 10, 160-163
- Document D, Les examens de laboratoire au cours des études de toxicologie sur animaux de laboratoire **(Laboratory tests during toxicity studies on laboratory animals)**, Inform. Scient. Biol., 1984, 10, 403-406
- Document E, Les examens de laboratoire au cours des essais cliniques chez l'homme **(Laboratory tests during clinical trials in humans)**, Inform. Scient. Biol., 1985, 11, 52-55
- Document F, Utilisation des examens de laboratoire pour la surveillance thérapeutique **(Use of laboratory tests to monitor therapy)**, Inform. Scient. Biol., 1985, 11, 99-106
- Document G, Banques de données **(Data banks)**, Ann. Biol. Clin., sous presse.

The International Federation of Clinical Chemistry has published or will publish the following documents:

- Part 1, The basic concepts, J. Clin. Chem. Clin. Biochem., 1984, 22, 271- 274 and Clin. Chim. Acta, 1984, 139, 215F-221F

. Part 2, Guidelines for evaluation of analytical interference, J. Clin. Chem. Clin. Biochem., 1984, 22, 275-279 and Clin. Chim. Acta, 1984, 139, 223F-230F
. Part 3, Evaluation of biological effects of drugs, submitted in J. Clin. Chem. Clin. Biochem.
. Part 4, Clinical laboratory tests on laboratory animals during toxicity studies, submitted in J. Clin. Chem. Clin. Biochem.
. Part 5, Laboratory tests during clinical trials, submitted in J. Clin. Chem. Clin. Biochem.
. Part 6, Laboratory tests in monitoring drug administration, submitted in J. Clin. Chem. Clin. Biochem.
. Part 7, Data banks, submitted in J. Clin. Chem. Clin. Biochem.

1.1. Analytical interference

Analytical interference constitutes part of the total effects, but represents only about 20 % of the cases in the list drawn up by Young et al. (929). It may be due either to the drug itself or to its metabolites. The effect may be because the interfering substance has a structure similar to that of the compound being estimated; thus, methyldopa is included in the measurement of total catecholamines. Alternatively the interfering substance may affect spectrophotometric reactions: (a) it may yield a similar color as with salicylates which react the same way with Folin's reagent as do urates (or may produce a different color); or (b) it may have its own fluorescence or, more often, may inhibit another compound's fluorescence (quenching); or (c) it may cause turbidity or a precipitate. This latter type of interference is common when the reactions take place in very acid or very alkaline media.

Interference may also be due to the chemical properties of the drugs present, but this type appears in general only at high concentrations. The reducing power of the drugs and/or of their metabolites is often the main factor; thus, ascorbic acid interferes with many determinations because of its pronounced reducing properties.