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Drug Interference in Clinical Chemistry: Studies on Ascorbic Acid

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Summary: The expert group "Drug Interference in Clinical Chemistry" of the Bureau of Reference, Directorate General for Research, Science and Education of the Commission of the European Communities, consisting of one participant of each member of the European Communities, presents this first report on the final results of its activities.

Within the framework of a first stage basic program, the paper describes interferences of therapeutic and elevated doses of ascorbic acid on commonly used clinical chemical methods. This is the result of a bipartite study that was jointly planned, carried out and evaluated. Local and personal influences have been eliminated, as have variations due to methodology, measurement equipment and reagents, in order to be able to present distinct causal effects of ascorbic acid.

No definite influence of ascorbic acid on analytical values for urea, cholesterol, calcium, protein, bilirubin, aspartate aminotransferase and alkaline phosphatase could be detected.

At therapeutic concentrations, ascorbic acid distinctly interferes with the analysis of glucose, uric acid, creatinine and inorganic phosphate. The extent and direction of interferences vary, depending on the type of reaction, kit and apparatus. In some cases the influence of ascorbic acid results in severe disturbance of the analytical methods leading to useless values.

Arzneimittelstörungen in der Klinischen Chemie: Untersuchungen mit Ascorbinsäure

Zusammenfassung: Die Expertengruppe "Drug Interference in Clinical Chemistry" des "Büro für Standardisierung" im Generalsekretariat für Forschung, Wissenschaft und Erziehung der Europäischen Gemeinschaft, legt erste Abschlußergebnisse ihrer Tätigkeit vor. Im Rahmen eines vorab erarbeiteten Grundsatzprogrammes werden in einer gemeinsam geplanten, durchgeführten und ausgewerteten zweiteiligen Studie Störeinflüsse von therapeutischen und hohen Dosen von Ascorbinsäure auf gebräuchliche klinisch-chemische Untersuchungsmethoden beschrieben.

Nicht oder statistisch nicht sicherbar beeinflußt werden Bestimmungsmethoden für Harnstoff, Cholesterin, Calcium, Protein, Bilirubin, Aspartataminotransferase und alkalische Phosphatase.

Eindeutige Beeinflussungen bereits bei therapeutischen Ascorbinsäurekombinationen liegen vor bei Glucose, Harnsäure, Kreatinin und anorganischem Phosphat. Ausmaß und Richtung der Störung variieren in Abhängigkeit von Reaktionstyp, Reagenzienkombination und Gerät. In einigen Fällen führt der Einfluß der Ascorbinsäure zu schweren Störungen der analytischen Methode bis zur Unbrauchbarkeit der Werte.

Introduction

The development of a wide range of biological tests, mechanisation, and data processing have contributed to the discovery of many factors that cause variations in laboratory tests. Drugs are predominant among these factors, owing to their interference with analytical methods, as well as their pharmacological effects; there is an extensive literature on this problem (1–19).

Indeed, the interpretation of a laboratory result using colorimetric, spectrophotometric, fluorimetric or en-

[1]) Dr. *Lauer* died in August 1976. We are deeply grateful for his everlasting assistance.

zymatic methods may be difficult and even erroneous due to the following factors:

Analytical factors

Quality control is designed to detect most of these errors. The evolution towards more accurate and more specific techniques will make it possible to avoid, or at least control such errors.

Physiological or environmental factors

Variations due to age, sex, exercise, meal intake etc. are now well known, but the interference of environmental factors, such as climatic conditions, dietary habits, pesticides, and, of course, drugs, is also considerable and often more important.

With respect to environmental factors, it was considered necessary to initiate a systematic study of analytical interferences.

For this purpose a working sub-group "Drug Interference in Clinical Chemistry" (20) was founded by the Bureau of Reference, (Dr. *Lauer*) Directorate General for Research, Science and Education of the Commission of the European Communities. This group of experts consists of delegates of the national clinical chemical societies.

Within the framework of this group of experts in the European Communities the following goals shall be pursued:

1. Establish and keep an up-to-date list of drugs which are likely to effect reference and routine methods.
2. Prepare a protocol for the study of analytical interferences.
3. Seek out the methods least sensitive to analytical interference from drugs and their metabolites.
4. Prepare a control serum containing drugs and metabolites.
5. Establish the percentage interference due to drugs, to be used by clinical chemists and clinicians for correct interpretation of laboratory results.

Details concerning general rules, guide lines and first results up to 1975, have already been presented by *Siest*, *Lauer* et. al. (20) at Pont à Mousson and by *Appel*, *Lauer* et al. at Munich, 1976 (21).

In this paper results relevant to points 2–5 above are presented. Ascorbic acid was selected in preference to acetylsalicylic acid as the first substance to be investigated by the above mentioned expert group. It was necessary to test a simple drug molecule that was easy to find commercially in a pure state, and that was known to interfere with certain tests used in clinical chemistry. Ascorbic acid fulfills these criteria and was chosen as a model for the general protocol.

Materials and Methods

For this study, commercially available ascorbic acid (no special lot) and commercial, lyophilized human serum were chosen. An ascorbic acid overdose was simulated by mixing the control serum (redissolved in distilled water) and an "overloaded serum" (redissolved in an aqueous solution of ascorbic acid) (See Annexe "General protocol").

Data on the parameters studied, analytical methods, apparatus and technical equipment are given in table 1.

First study

The concentrations tested during the first study ranged from 0–2 g/l of ascorbic acid. Methods listed in table 1 were studied. Measurements were performed in duplicate on each overloaded solution.

The sera were prepared daily, and the analyses were carried out on 5 consecutive days by routine methods within routine work at 8 laboratories of different members of the expert group in different countries of the European Communities. The results are presented in μmol/l or in mmol/l depending upon the parameter, accompanied by specifications of the equipment used, techniques and variation coefficient in the zone of values measured.

Since the parameters showed a more or less clear interference, additional statistical studies were carried out (table).

- Test of significance between control (dose 0) and the first ascorbic acid overdose (0.71 mmol/l) for each laboratory, for all laboratories together, regrouping laboratories according to the techniques used.
- A 2-factor variance analysis was performed for each laboratory result. This made it possible to determine the significance of the difference between the control serum and the first serum (first concentration). Other analyses of variance were performed on the same parameters: one by regrouping all the laboratories, the other by regrouping laboratories using the same techniques (tab. 2).

Second study

This study was then extended in 4 laboratories, in order to identify the parameters that cause a distinct interference. Additional assays were performed at the following concentrations that are close to the therapeutic values: 0.14 mmol/l, 0.34 mmol/l, 0.71 mmol/l, 1.42 mmol/l. On the basis of this study with ascorbic acid, we have established a general protocol for the study of drug interference (cf. annexe).

The distribution of protocols and questionaires, samples of ascorbic acid and serum to each participant of the study, the collection and mathematical-statistical evaluation of experimental data and the preparation of results were performed under the supervision of the Chairman of the group, Dr. *Siest* (14). Discussion of results took place at the group's meetings at Geneva and Pont à Mousson.

Results

The evaluated "General protocol of analytical interference by ascorbic acid" is shown in the annexe.

First study

For certain parameters, no comment is called for, either because there is no interference, i.e.

Urea, *Cholesterol*, *Calcium* and *Protein*;

or because the dispersion is too great and the variations are not systematic, i.e.

Bilirubin, *Aspartate Aminotransferase*;

or because of the technical problems encountered, i.e.

Alkaline Phosphatase.

Tab. 1. Methods: Objectives, analytical methods, apparatus, and technical equipment.

Objectives	Method	Instrument
Aspartate aminotransferase	UV-test, kinetic, opt.	Eppendorf 5020
		LKB 8600
	UV-test, kinet. non opt.	ABA 100
		Greiner GSA II
	UV-test, end point	SMA 12/60
	Colorimetric test	Autochemist
		ACA DuPont
Phosphatase, alkaline	Kinetic-test, *p*-nitrophenyl phosphate, buffer: diethanolamine	Eppendorf 5020
	Kinetic-test, *p*-nitrophenyl phosphate, buffer: glycine	LKB 8600
	End-point-test, *p*-nitrophenyl phosphate, buffer: 2-amino-2-methyl-1-propanol	SMA 12/60
	End-point-test, *p*-nitrophenyl phosphate	ACA DuPont
		Greiner GSA II
		Beckman DSA
	End-point-test, phenyl disodium phosphate	SMA 12/60
		Autochemist
Bilirubin	Sulfanilic acid-caffein	SMAC
		SMA 12/60
		Eppendorf 1101
		Beckman DSA
		Autochemist
		Bilirubinometer
	Dichloraniline-nitrite	Greiner GSA II
Calcium	*o*-Cresolphthalein-complexon	SMA 12/60
		ACA DuPont
		SMAC
	Flame photometry	Zeiss PF 5
		Autochemist
	Thymolphthalein-complexon	Greiner GSA II
	Calcein	Oxford Titrator
Cholesterol	Acetic anhydride-acetic acid *Liebermann-Burchard, Huang, Watson*	SMA 12/60
		Eppendorf 1101
		Autochemist
		LKB 7400
	Esterase/oxidase-catalase	ABA 100
	Esterase-hydrogen peroxidase	Greiner GSA II
Creatinine	Alkaline picrate (*Jaffé*) without deproteinisation	Autochemist
	Alkaline picrate (*Jaffé*) with dialysis	SMA 12/60
	Picric acid, kinetic test	LKB 8600
		Eppendorf 5020
Glucose	Glucose oxidase-Perid	SMA 12/60
		Vitatron UC 200 S
	Glucose oxidase-peroxidase	LKB 7400
	Glucose oxidase-*Trinder* method	Gilford
	Neocuproin	SMA 12/60
Phosphate, inorganic	Molybdate-hydroquinone-ascorbate	Autochemist
	Molybdate-*p*-methylaminophenolsulfate	Eppendorf 1101
	Molybdate-vanadate	LKB 7400
	Molybdic acid-stannous chloride-hydrazine	SMA 12/60
Protein, total	Biuret-reaction	SMAC
		SMA 12/60
		Greiner GSA II
		ACA DuPont
		LKB 2071/7400
		Beckman DSA
		C 4 Perkin Elmer
		Vitatron UC 200
Urea	Diacetylmonoxime	SMA 12/60
	Urease-diacetylmonoxime	SMA 12/60
	Urease-*Berthelot*	Greiner GSA II
		Eppendorf 5020
	Urease-*Fawzett-Scott*	LKB 2071/7400
	Urease-glutamate dehydrogenase	ACA DuPont
	Urease-nitroprusside-phenol	Autochemist
Uric acid	Phosphotungstic acid-hydroxylamine	SMA 12/60
	Uricase	Eppendorf 1101
		LKB 2071/8600
	Uricase-Ca^{++}-neocuproin	Autochemist

Tab. 2. Variation coefficients (CV), level of significance between dose 0 and dose 1 (0.71) mmol/l)
GOD = glucose oxidase $F = \frac{s_x^2}{s_y^2}$ = critical values in 2-factor variance analysis testing the null hypothesis at 0.05 (= 5%) significance levels.

Glucose			Uric acid			Inorganic phosphorus			Creatinine		
Lab. No.	CV [%]	level of significance	lab. No.	CV [%]	level of significance	lab. No.	CV [%]	level of significance	lab. No.	CV [%]	level of significance
1	↓ 10	0.001	1	↓ 1.7	n.s	1	↓ 1.5	n.s.	1	↑ 4.9	0.01
3	↓ 19	0.001	3	↓ 1.1	n.s.	2	↓ 0.9	n.s.	2	↑ 0.1	n.s.
6	↓ 1	n.s.	7	↓ 1.6	n.s.	5	↓ 1	n.s.	3	↑ 9	0.01
7	↓ 15.4	0.001	2	↑ 6.2	0.001	7	↓ 2.4	n.s.	4	↑ 2.2	0.05
8	↓ 7.8	0.01	4	↑ 5.3	0.001	3	0		5	↑ 2.4	n.s.
2	↑ 4	0.001	5	↑ 5.4	0.001	6	0		6	↑ 2.3	n.s.
4	↑ 2.1	0.01	6	↑ 6.8	0.001	8	↑ 4.8	0.05	7	↑ 3.1	n.s.
5	↑ 2	0.001	8	↑ 55.3	0.001				8	↑ 6.7	0.01
		F			F			F			F
All lab.		4.44 0.05	all lab.		11.4 0.001	all lab.		0.013 n.s.	all lab.		1.80 n.s.
Lab. 1, 3, 7, 8 (GOD Perid)		15.64 0.001	lab. 2–6		5.14 0.01	lab. 2, 3, 5, 6		0.065 n.s.	lab. 2–6		0.97 n.s.
Lab. 2, 4–6 (neocuproin)		0.41 n.s.									

For other parameters, *a more or less clear interference* is noted.

Glucose

Glucose oxidase methods yield results that are low (22–25), neocuproin methods yield results that are high with both methods (24, 26, 27); the variations are statistically significant.

Uric acid

Methods using uricase are not affected by ascorbic acid (28, 29) except when the second stage is based on copper reduction. Phosphotungstate techniques are affected significantly even at the lowest concentration of ascorbic acid (5, 23, 25, 30–32).

Creatinine

Three laboratories use methods without deproteinization. The interference is greater if measurement is preceded by dialysis. This might be due to a change in physical properties of the serum upon the addition of ascorbic acid (33–35).

Inorganic Phosphate

The dispersion of results is great, the observed variations do not appear to be significant.

Second study

The results of this second study are demonstrated by four graphs.

Glucose (fig. 1)

Neocuproine methods show increasing, *glucose oxidase-Perid* methods decreasing values with increasing concentrations of ascorbic acid; the effect is already apparent at therapeutical levels of ascorbic acid.

Methods using *glucose oxidase without indicator reaction*, *hexokinase/glucose-6-phosphate dehydrogenase* or *glucose dehydrogenase respectively*, are not influenced by ascorbic acid.

Uric acid (fig. 2)

Phosphotungstate methods show increasing values with increasing concentrations of ascorbic acid.

Uricase methods do not behave in a uniform manner depending on the nature of the secondary reaction:

Uricase-hydrazone methods yield greatly decreased values, *uricase neocuproin* methods greatly increased values, being useless with higher concentrations of ascorbic acid.

The uricase/catalase/formaldehyde reaction (*Kageyama*) is not affected (36).

Creatinine (fig. 3)

Jaffe's reaction, used in mechanized analysis systems without deproteinization, is influenced by ascorbic acid in different ways. Methods with dialysis show a primary decrease followed by an elevation up to normal values.

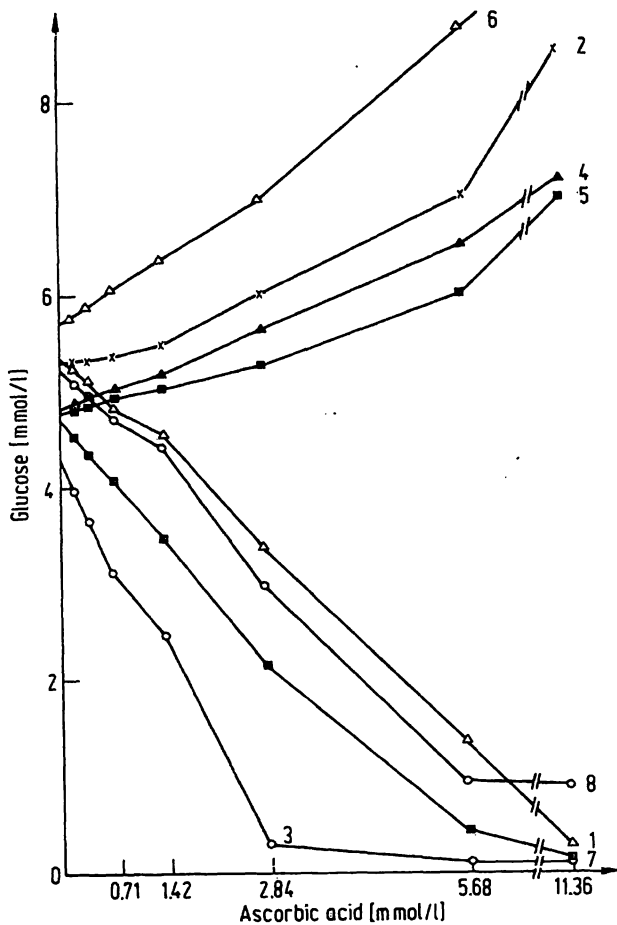

Fig. 1. Interference by ascorbic acid in glucose tests.

2, 4, 5, 6	Neocuproin	SMA 12/60
1	Glucose oxidase Perid method Boehringer ref. 15754	Vitatron UC 200 S + Digilog DRP 200
3	Glucose oxidase-perid	Technicon
7	Glucose oxidase-peroxidase	LKB 7400
8	*Trinder* method, glucose oxidase	Gilford

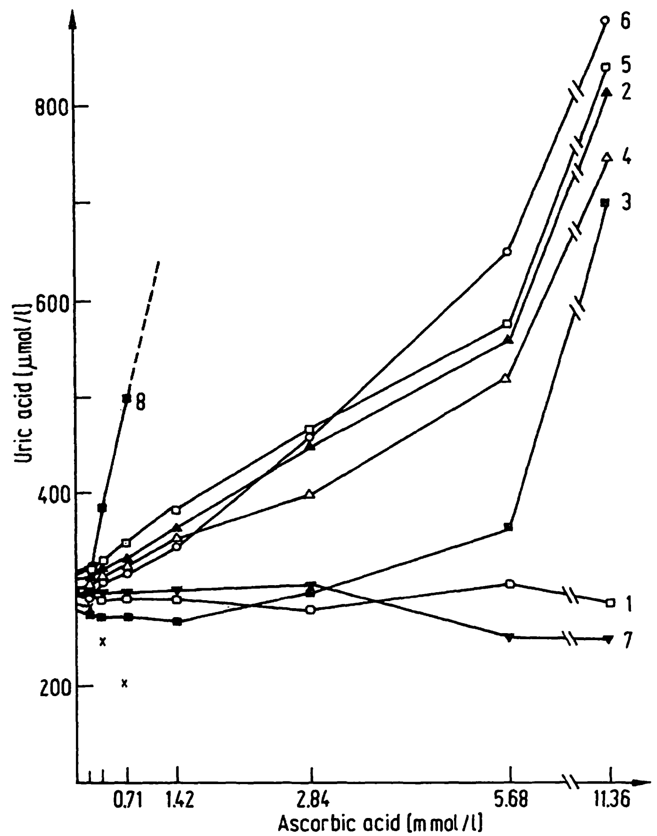

Fig. 2. Interference by ascorbic acid in uric acid tests.

2, 3, 4, 5, 6	Phosphotungstic acid-hydroxylamine	SMA 12/60
1	Enzymatic color test Uricase, Boehringer ref. 15865	Eppendorf 1101
7	UV test Uricase-Boehringer ref. 15986	LKB 2071–LKB 8600
8	Uricase-Ca^{++}-neocuproin	Autochemist
9	Uricase-hydrazone	–

Kinetic methods tend to elevated values with increasing amounts of ascorbic acid. All effects are more or less pronounced depending on the type of reagent or kit.

Inorganic phosphate (fig. 4)

$SnCl_2$-hydrazine methods tend to lowered values with higher concentrations of ascorbic acid, but the difference is not significant.

Methods using *hydroquinone-ascorbate*, *vanadate* and *p-methylaminophenol* are not influenced by ascorbic acid.

Discussion

The spread of results obtained by the 8 laboratories was considerable. As in all surveys, there is primarily a problem of accuracy. Each laboratory was not expected to change its calibration. In a special trial, a serum having an "assigned" value was integrated into the series and the results adjusted using this value. The addition of the drug in vitro did not appear to increase the dispersion. Therefore, depending on the analytical systems, principles of the methods, combinations of reaction steps, reagents, kits, and instruments, it is not possible to discuss in a simple way the factors concerned in the interference by ascorbic acid.

Methods that are not influenced by ascorbic acid are listed in table 3. These results agree with the existing literature. Table 4 shows those analytical methods for glucose, uric acid, and creatinine that are regarded as less recommendable. Concerning the risk of false interpretation of results, the concentrations and pharmacokinetic data for ascorbic acid *in vivo* cannot be neglected. The concentrations used in this study cover the zone of therapeutic values (0–0.125 g/l ≙ 0–0.71 mmol/l) and likewise values which may be attained due to therapeutic accidents (21). To achieve more information it is necessary to perform studies in vitro as

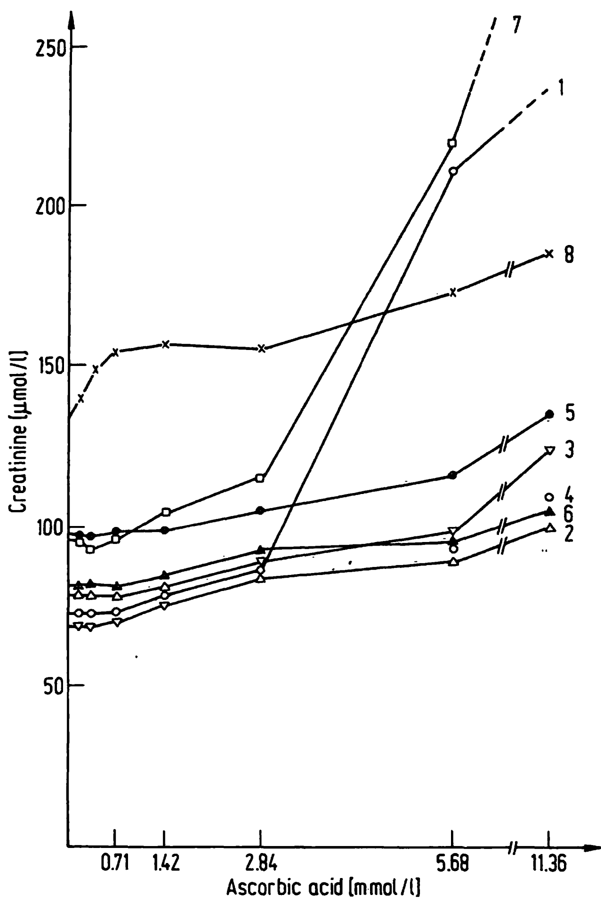

Fig. 3. Interference by ascorbic acid in creatinine tests.

2, 3, 4, 5, 6	Alkaline picrate + dialysis (*Jaffé*)	SMA 12/60
1	Kinetic test-picric acid Merckotest ref. 3385 (without deproteinisation)	Eppendorf 5020/II
7	Kinetic test-picric acid Merckotest ref. 3384 (without deproteinisation)	LKB 8600
8	Alkaline picrate (*Jaffé*)	Autochemist

well as in vivo to link plasma concentrations of ascorbic acid to quantitative data of interferences in the analytical method. This aim overlaps with the field of "drug interactions" and is regarded as part of clinical pharmacology.

Restricting our attention to the basic program, we have been able to reduce errors and misleading conclusions to a minimum by exclusion of interlaboratory, interdisciplinary, economic and political-specific and unspecific interests and influences.

The coupling of a method to one instrument by a manufacturer may force the responsible clinical chemist to use methods with a higher risk of drug interference: in such a case, method, kit or machine should be changed. Considering the consumption of ascorbic acid as vitamin tablets, juices, vegetables and fruits (including canned food with ascorbic acid as preservative), especially when there is a risk of infection the clinical chemist and

Tab. 3. Analytical methods *not influenced* by ascorbic acid.

Objectives	Methods
Aspartate aminotransferase	UV-test, kinetic, opt. 25 °C[1]) UV-test, kinetic, non opt. 37 °C[1]) UV-test, end point[1]) Colorimetric test[1])
Phosphatase, alkaline	Kinetic-test, *p*-nitrophenyl phosphate[1])[2]) Kinetic-test, phenyl disodium phosphate[2]) Kinetic-test, 4-aminoantipyrin-disodium-hydrogencarbonat[2])
Bilirubin	Sulfanilic acid-caffein[1]) Dichloraniline-nitrite[1])
Calcium	*o*-Cresolphthalein-complexon Thymolphthalein-complexon Flamephotometry Calcein-titration
Cholesterol, total	Acetic anhydride-acetic acid *Huang*, *Liebermann-Burchard*, *Watson* Esterase/oxidase-catalase Esterase-hydrogen peroxidase
Creatinine	(Alkaline picrate (*Jaffé*) without deproteinisation or with dialysis)
Glucose	Hexokinase/glucose-6-phosphate dehydrogenase Glucose dehydrogenase
Phosphate, inorganic	Molybdate-hydroquinone-ascorbate Molybdate-*p*-methylaminophenolsulfate Molybdate-vanadate
Protein, total	Biuret-reaction
Urea	Diacetyl-monoxime methods Urease-*Berthelot* Urease-glutamate dehydrogenase Urease-nitroprusside-phenol
Uric acid	Uricase, *Kageyama*'s reaction

( ) = Interference at higher concentrations of ascorbic acid.
[1]) No clear conclusion by reason of non systematic variations.
[2]) No clear conclusion by reason of technical problems.

Tab. 4. Analytical methods regarded as being less recommendable.

Objective	Method
Glucose	Glucose oxidase methods with indicator reaction Neocuproin methods
Uric acid	All phosphotungstic methods Uricase methods with copper reduction Uricase-hydrazone methods
Creatinine	Picrate methods without deproteinisation preceded by dialysis (Picric acid, kinetic tests, depending on different type of reagents or kits)

( ) = Interference at higher concentrations of ascorbic acid.

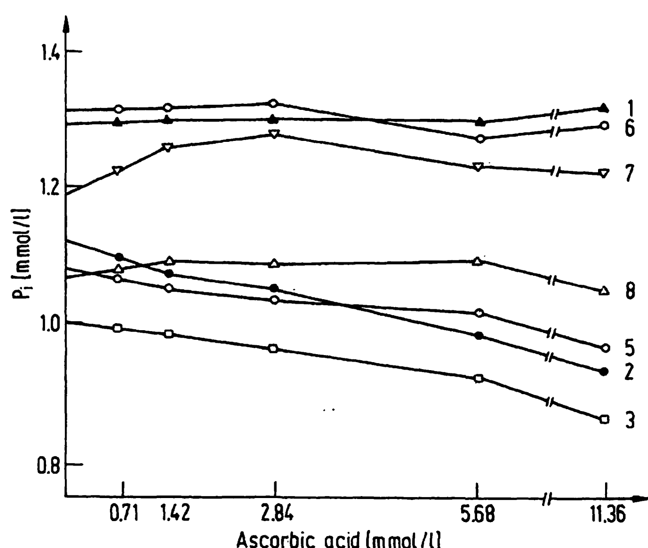

Fig. 4. Interference by ascorbic acid in phosphate tests.

2, 3, 5, 6	Molybdic acid-stannous chloride-hydrazine	SMA 12/60
1	Molybdate-*p*-methyl-aminophenol Sulfate, Merckotest ref. 3331	Eppendorf 1101
7	Molybdate-vanadate, Boehringer ref. 15920	LKB 7400
8	Molybdate-hydro-quinone	Autochemist

physician may indeed expect ascorbic acid interference in some of his analyses. Part of the aim of this European-Communities-study was to assist his decision in using more reliable methods.

The study will be concluded by pilot investigations on the influence of ascorbic acid on the qualitative and semiquantitative determination of urinary glucose, by glucose oxidase-paper strip combinations.

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Annexe

General protocol of analytical interference by ascorbic acid

6 specimens were analysed in duplicate on each of three days.

Materials provided

- Ascorbic acid
- Bottles lyophilised serum (to make 10 ml after reconstitution)

Procedure

1. Prepare a 11.36 mmol/l (2 g/l) ascorbic acid solution in redistilled water
2. Preparation of overloaded serum
   a) Using this solution daily reconstitute two bottles of lyophilised serum (using 10 ml)
   b) Mix the contents of the two bottles
3. Preparation of control serum
   a) Dissolve four bottles of lyophilised serum daily in redistilled water (using 10 ml)
   b) Mix the contents of the four bottles
4. Preparation of specimens for analyses
   Prepare the following dilutions:

Specimen No.	Concentrations of ascorbic acid obtained		Overloaded serum	Control serum
	mmol/l	g/l		
1	0	0	0 ml	8 ml
2	0.14	0.025	0.1 ml	7.9 ml
3	0.43	0.075	0.3 ml	7.7 ml
4	0.71	0.125	0.5 ml	7.5 ml
5	1.42	0.25	1 ml	7 ml
6	2.84	0.5	2 ml	6 ml

N.B.: Prepare all serum and the ascorbic acid solution fresh daily

5. Assesment of interferences
   On each of the above dilutions perform the analyses, in duplicate and in order of increasing concentrations
6. Results
   a) Specify the methods and instruments used
   b) Indicate the analytic variation coefficient of your technique in the zone of values we are concerned with.

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