Interference by Analgesic and Antirheumatic Drugs in 25 Common Laboratory Assays

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Summary: Twenty five different analytical procedures, commonly used in clinical laboratories, were investigated for interference by eight analgesic and antirheumatic drugs. Ten of the investigated assays showed no statistically significant interference.

Acetylsalicylic acid interfered in six assays (for glucose, uric acid, protein and cholesterol). Aminophenazone significantly decreased glucose, bilirubin and protein values, whereas caffeine affected four methods (for glucose, protein and iron).

No definite influence of phenobarbital could be detected on any assay. Glucose, uric acid and iron values were altered in the presence of diclofenac. Indomethacin interfered in glucose, urea, uric acid and protein assays.

Samples containing ibuprofen had altered creatinine, bilirubin and iron values, whereas ketoprofen interfered in glucose and iron determination.

Introduction

In our previous investigation, effects of analgesic and antirheumatic drugs on the assay of serum enzymes (1) and SMA II procedures (2) were examined. Acetylsalicylic acid, aminophenazone, indomethacin, diclofenac, ibuprofen and ketoprofen are widely used in the treatment of various rheumatic diseases. Analgetic preparations containing acetylsalicylic acid, aminophenazone, phenobarbital or caffeine are also frequently used in self-medication. It is thus important to know whether these drugs alter clinical laboratory test results.
In the present work, we investigated the effects of these eight drugs (in vitro) on 25 of the most frequently used methods for the determination of glucose, urea, uric acid, creatinine, bilirubin, protein, cholesterol, triglycerides and iron.

Tab. 1. Concentrations of added drugs in reconstituted lyophilized human sera.

| Drug                                | Concentration (µmol/l) |
|-------------------------------------|------------------------|
| Acetylsalicylic acid [2-(acetyloxy)benzoic acid] | 8326                   |
| Aminophenazone (4-dimethylamino-2,3-dimethyl-l-phenyl-3 pyrazolin-5-one) | 540                    |
| Caffeine (1,3,7-trimethylxanthine)   | 772                    |
| Phenoarbital [5-ethyl,5-phenyl-2,4,6(1H,3H,5H)-pyrimidinetrione]       | 1076                   |
| Ibuprofen [α-methyl-4-(2-methylpropyl)-benzenacetic acid]               | 970                    |
| Diclofenac, 2-[2,6-dichlorophenyl]-amino-benzenacetic acid              | 71                     |
| Indomethacin [1-(p-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid] | 35                     |
| Ketoprofen [2-(3-benzoylphenyl)-propionic acid]                         | 236                    |

Materials and Methods

To examine the drug interferences in common laboratory assays, the general protocol by Sies et al. (3) was followed. Commercial lyophilized human sera were reconstituted with solutions of each drug tested. The drug concentrations (tab. 1) were approximately ten times the maximal therapeutic levels (4−7).

Aqueous solutions of acetylsalicylic acid, aminophenazone, caffeine, phenobarbital, diclofenac and indomethacin were made. For control sample preparation, the drug solutions were replaced by distilled water. To dissolve ibuprofen and ketoprofen, ethanol was added in a final concentration of 200 g/l, and additional control samples were prepared, containing the same concentration of ethanol.

Glucose, urea, uric acid, creatinine, bilirubin, protein, cholesterol, triglyceride and iron concentrations were determined by various methods commonly used in clinical laboratories. The principles and reference data of the methods are shown in Table 2.

For each method, six replicate tests were performed on control samples and samples containing the drug; the statistical parameters: mean value (x) and standard deviation (s) were determined. Using Student’s t-test, the significance of the differences between values obtained in sera with and without drugs was assessed. All tests for a specific group of samples (sera containing the drug and corresponding controls) were completed in a single run.

The interferences observed were studied further using lower drug concentrations down to the therapeutic levels. Concentrations of drugs in samples were gradually decreased and drug effects tested, until statistically insignificant differences were found.

The assays were performed with a Pye Unicam spectrophotometer SP 8-100.
Results and Discussion

The effects of analgesic and antirheumatic drugs on 25 common laboratory assays are shown in tables 3—5. The concentrations of analytes and their variations obtained using different methods in samples with and without the drugs are given, as well as the corresponding p values. Ten assays showed no statistically significant interference, i.e. the determination of glucose (hexokinase method), urea (with glutamate dehydrogenase and phenol-hypochlorite method), uric acid (direct UV test and phosphotungstate method), creatinine (continuous and Slot's method), bilirubin (Jendrassik-Grof), cholesterol and triglycerides (enzymatic assays). No definite influence of phenobarbital could be detected on any method (tab. 4).

Acetylsalicylic acid interfered in six assays (for glucose, uric acid, protein and cholesterol determination) (tab. 3). Out of five glucose assays tested, two were affected by the drug: the glucose dehydrogenase method and the glucose oxidase-peroxidase procedure using ABTS as chromogen. Acetylsalicylic acid has been reported to have no in vitro effect on the alkaline ferricyanide, p-HBAH and o-toluidine methods (33). In sera containing the drug, apparent concentrations of uric acid (with uricase and catalase) and protein (direct spectrophotometric assay) were very significantly increased (p < 0.01 and p < 0.005, respectively). Wirth & Thompson (34) reported interference by acetylsalicylic acid in the Polin-Ciocalteu protein assay in body fluids. Lower cholesterol values were obtained using the Liebermann-Burchard method (p < 0.01), which is in agreement with findings reported by Caraway & Kammeyer (35).

Aminophenazone significantly decreased the results for glucose (with ABTS, p < 0.001), bilirubin (with dimethylsulphoxide, p < 0.05), and protein (biuret method, p < 0.05). The drug is also known to increase the results of the cholesterol determination based on reaction with ferric ions in acetic acid-sulphuric acid (33, 35).

Tab. 3. Effects of acetylsalicylic acid, aminophenazone and caffeine on some common laboratory tests (N = 6, number of the degrees of freedom $\phi = 2N - 2 = 10$).

| Analyte, method | Control without drug | Acetylsalicylic acid | Aminophenazone | Caffeine |
|-----------------|----------------------|----------------------|----------------|---------|
| Glucose (mmol/l) |                      |                      |                |         |
| hexokinase      | 4.75 0.156           | 4.68 0.148           | >0.4           |         |
| glucose dehydrogenase | 4.24 0.099 | 4.32 0.339 | >0.6           |         |
| 2,4-dichlorphenol | 3.69 0.245           | 4.10 0.155           | <0.02          |         |
| ABTS            | 3.93 0.078           | 4.03 0.037           | <0.05          |         |
| o-toluidine     | 5.09 0.061           | 5.16 0.066           | >0.01          |         |
| Urea (mmol/l)   |                      |                      |                |         |
| glutamate dehydrogenase | 6.00 0.241 | 5.79 0.273 | >0.2           |         |
| phenol-hypochlorite | 6.66 0.543 | 6.18 0.188 | <0.05          |         |
| diacetylmonoxime | 6.60 0.155           | 6.83 0.560           | >0.4           |         |
| Uric acid (μmol/l) |                  |                      |                |         |
| uricase-catalase | 167 5.34            | 177 4.45             | <0.01          |         |
| aldehyde dehydrogenase | 170 2.58 | 170 11.92 | >0.9           |         |
| direct UV-test   | 178 16.18           | 171 13.61            | >0.4           |         |
| phosphotungstate | 214 10.41           | 218 4.59             | >0.4           |         |
| Creatinine (μmol/l) |                  |                      |                |         |
| continuous with deproteinization | 90.8 1.94 | 89.6 1.09 | >0.25         |         |
| 85.6 1.602            | 83.3 2.077 | >0.05               | 84.4 1.788 | >0.25 |
| 95.7 9.18            | 98.2 8.57 | >0.6                | 98.9 2.94 | >0.4  |
| Bilirubin (μmol/l)  |                      |                      |                |         |
| Jendrassik-Grof    | 29.2 1.699          | 28.9 0.389           | >0.6           |         |
| dimethylsulphoxide | 20.1 1.542          | 20.6 0.446           | >0.5           |         |
| spectrophotometric | 20.2 1.470          | 19.8 1.664           | >0.6           |         |
| Protein (g/l)      |                      |                      |                |         |
| biuret            | 59.5 0.969          | 55.6 3.313           | <0.025         |         |
| spectrophotometric | 51.1 1.282          | 55.8 1.970           | <0.005         |         |
| Cholesterol (mmol/l) |                |                      |                |         |
| enzymatic         | 2.63 0.140          | 2.59 0.130           | >0.6           |         |
| Liebermann-Burchard | 3.31 0.103         | 3.08 0.109           | <0.01          |         |
| Triglycerides (mmol/l) |               |                      |                |         |
| enzymatic         | 0.78 0.041          | 0.79 0.045           | >0.8           |         |
| Iron (μmol/l)      |                      |                      |                |         |
| bathophenanthroline | 16.9 0.956        | 16.0 0.821           | >0.1           |         |
| Ramsay            | 28.4 1.607          | 19.5 0.687           | >0.2           |         |

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Caffeine affected four tests (tab. 3). Glucose values were very significantly increased (ABTS method, \( p < 0.005 \)), as well as protein (spectrophotometric assay, \( p < 0.001 \)). Interference by caffeine in the uric acid assay using phosphotungstate has been reported (35), but the effect was found to be significant only in the determination of uric acid in urine.

Effects of diclofenac and indomethacin are shown in table 4. In samples containing these drugs, the values for glucose (with ABTS) and uric acid values (with uricase and catalase and with aldehyde dehydrogenase) were elevated. Indomethacin affected very significantly the results of the glucose determination (with glucose dehydrogenase, \( p < 0.005 \)), and the protein determination (biuret method, \( p < 0.005 \)).

Creatinin (with deproteinization) and iron (Ramsay) values were increased in sera containing ibuprofen (tab. 5). Ketoprofen interfered in glucose (with ABTS, \( p < 0.02 \)) and iron assays (with bathophenanthrolene, \( p < 0.05 \) and Ramsay method, \( p < 0.005 \)). No data have been previously reported on analytical interferences by diclofenac, indomethacin and ketoprofen.

The effects found were studied further using lower concentrations of drugs, down to the therapeutic levels. Interference by aminophenazone in the glucose determination (with ABTS) was still evident at 216 μmol of drug per liter (\( p < 0.025 \)). Lower concentration of diclofenac (28 μmol/l) significantly increased the results of the same test (\( p < 0.05 \)). Figure 1 shows the dose dependence of these two interferences. In lower concentrations, other drugs did not interfere with any assay, so the effects found are significant only in cases of drug overdosage or poisoning.

| Analyte, method | Control without drug | Phenobarbital | Diclofenac | Indomethacin |
|-----------------|----------------------|---------------|------------|--------------|
|                 | \( \bar{x} \)       | \( s \)       | \( \bar{x} \) | \( s \)       | \( p \)       | \( \bar{x} \) | \( s \)       | \( p \)       |
| Glucose (mmol/l) | hexokinase           | 4.75          | 0.156      | 4.88        | 0.215        | >0.3        | 4.84        | 0.276        | >0.5         | 4.76          | 0.108        | >0.9 |
|                 | glucose dehydrogenase| 4.24          | 0.099      | 4.26        | 0.067        | >0.6        | 4.16        | 0.139        | >0.3         | 4.44          | 0.071        | <0.005 |
|                 | 2,4-dichlorphenol    | 3.69          | 0.245      | 3.84        | 0.167        | >0.3        | 3.87        | 0.079        | >0.1         | 3.71          | 0.232        | >0.3 |
|                 | ABTS                 | 3.93          | 0.078      | 4.00        | 0.084        | >0.1        | 4.11        | 0.059        | <0.005       | 4.05          | 0.073        | <0.05 |
|                 | \( \alpha \)-toluidine| 5.09          | 0.061      | 5.00        | 0.086        | >0.05       | 5.15        | 0.057        | >0.1         | 5.18          | 0.047        | <0.05 |
| Urea (mmol/l)   | glutamate dehydrogenase| 6.00         | 0.241      | 6.10        | 0.192        | >0.4        | 6.24        | 0.128        | >0.05        | 6.23          | 0.352        | >0.2 |
|                 | phenol-hypochlorite   | 6.66          | 0.543      | 6.60        | 0.310        | >0.08       | 6.32        | 0.450        | >0.3         | 6.49          | 0.328        | >0.5 |
|                 | diacetylmonoxime      | 6.60          | 0.155      | 6.39        | 0.199        | >0.3        | 6.77        | 0.563        | >0.5         | 6.29          | 0.169        | >0.02 |
| Uric acid (μmol/l) | uricase-catalase   | 167           | 5.34       | 171         | 8.31         | >0.3        | 180         | 8.19         | <0.02        | 179           | 9.18         | <0.05 |
|                 | aldehyde dehydrogenase| 170          | 2.58       | 165         | 6.37         | >0.1        | 195         | 9.02         | <0.001       | 183           | 9.70         | <0.02 |
|                 | direct UV-test       | 178           | 16.18      | 182         | 9.31         | >0.6        | 176         | 3.30         | >0.7         | 184           | 17.20        | >0.5 |
|                 | phosphotungstate     | 214           | 10.41      | 217         | 12.10        | >0.6        | 212         | 7.81         | >0.8         | 222           | 17.87        | >0.3 |
| Creatinin (μmol/l) | continuous            | 90.8          | 1.94       | 90.7        | 0.75         | >0.8        | 89.5        | 2.38         | >0.3         | 88.7          | 1.47         | >0.05 |
|                 | with deproteinization| 85.6          | 1.602      | 85.4        | 0.767        | >0.8        | 84.1        | 1.376        | >0.1         | 84.7          | 1.591        | >0.3 |
|                 | \( Slot \)           | 95.7          | 9.16       | 95.4        | 8.96         | >0.9        | 100.1       | 9.87         | >0.4         | 101.2         | 9.08         | >0.3 |
| Bilirubin (μmol/l) | \( Jendrassik-Gröf \) | 29.2          | 1.699      | 29.9        | 0.609        | >0.8        | 28.4        | 0.841        | >0.3         | 29.4          | 0.982        | >0.8 |
|                 | dimethylsulphoxide   | 20.1          | 1.542      | 20.7        | 1.232        | >0.5        | 18.6        | 1.774        | >0.1         | 18.8          | 1.554        | >0.2 |
|                 | spectrophotometric   | 20.2          | 1.470      | 19.0        | 1.471        | >0.2        | 20.8        | 0.914        | >0.4         | 21.5          | 1.255        | >0.1 |
| Protein (g/l)   | biuret               | 59.5          | 0.969      | 57.9        | 2.607        | >0.1        | 60.9        | 2.738        | >0.25        | 57.8          | 0.568        | <0.005 |
|                 | spectrophotometric   | 51.1          | 1.282      | 49.9        | 2.282        | >0.3        | 51.4        | 2.083        | >0.8         | 52.0          | 3.144        | >0.05 |
|                 | Cholesterol (mmol/l)  | 2.63          | 0.140      | 2.58        | 0.164        | >0.6        | 2.62        | 0.125        | >0.8         | 2.63          | 0.211        | >0.9 |
|                 | enzymatic            | 3.31          | 0.103      | 3.18        | 0.102        | >0.25       | 3.32        | 0.175        | >0.9         | 3.25          | -0.151       | >0.4 |
|                 | \( Liebermann-Burchard \) | 0.78          | 0.041      | 0.80        | 0.055        | >0.5        | 0.79        | 0.039        | >0.8         | 0.78          | 0.035        | >0.9 |
|                 | Triglycerides (mmol/l) | enzymatic     | 16.9        | 0.956      | 16.4        | 1.029        | >0.5        | 16.4        | 0.835        | >0.4         | 16.5          | 0.964        | >0.5 |
|                 | Iron (μmol/l)        | 20.4          | 1.607      | 19.2        | 0.964        | >0.1        | 18.4        | 0.377        | <0.02        | 21.0          | 1.009        | >0.4 |

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Tab. 5. Effects of ibuprofen and ketoprofen on some common laboratory tests (N = 6, number of the degrees of freedom $\phi = 10$).

| Analyte, method | Control without drug | Ibuprofen $\bar{x}$ | Ibuprofen $s$ | p | Ketoprofen $\bar{x}$ | Ketoprofen $s$ | p |
|-----------------|----------------------|---------------------|---------------|---|---------------------|---------------|---|
| Glucose (mmol/l) |                      |                     |               |   |                     |               |   |
| hexokinase      | 4.83 0.229           | 4.95 0.233          | > 0.4         |   | 5.02 0.081          | > 0.1         |   |
| glucose dehydrogenase | 4.36 0.112 | 4.21 0.150          | > 0.1         |   | 4.30 0.163          | > 0.5         |   |
| 2,4-dichlorphenol | 4.00 0.061           | 4.03 0.108          | > 0.6         |   | 4.10 0.184          | > 0.25        |   |
| ABTS            | 4.10 0.081           | 4.11 0.044          | > 0.8         |   | 4.26 0.082          | < 0.02        |   |
| o-toluidine     | 5.04 0.090           | 5.01 0.136          | > 0.7         |   | 5.06 0.078          | > 0.7         |   |
| Urea (mmol/l)   |                      |                     |               |   |                     |               |   |
| glutamate dehydrogenase | 6.13 0.278 | 6.05 0.324          | > 0.6         |   | 6.16 0.107          | > 0.7         |   |
| phenol-hypochlorite | 6.65 0.353 | 6.55 0.582          | > 0.7         |   | 6.79 0.556          | > 0.6         |   |
| diacetylmonoxime | 6.19 0.225           | 6.23 0.264          | > 0.7         |   | 6.16 0.118          | > 0.7         |   |
| Uric acid (μmol/l) |                    |                     |               |   |                     |               |   |
| uricase-catalase | 178 8.75            | 181 8.60            | > 0.6         |   | 174 11.96           | > 0.5         |   |
| aldehyde dehydrogenase | 172 9.50 | 183 6.02            | > 0.05        |   | 178 14.66           | > 0.3         |   |
| direct UV-test   | 155 6.53            | 160 9.83            | > 0.3         |   | 159 10.29           | > 0.7         |   |
| phosphotungstate | 331 11.28           | 333 13.96           | > 0.7         |   | 346 12.92           | > 0.05        |   |
| Creatinine (μmol/l) |                    |                     |               |   |                     |               |   |
| continuous with deproteinization | 92.3 1.94 | 92.8 2.31           | > 0.7         |   | 92.9 0.57           | > 0.5         |   |
| Spectrophotometric | 88.3 1.357 | 91.0 1.010          | > 0.005       |   | 86.9 1.668          | > 0.1         |   |
| Protein (g/l)   |                      |                     |               |   |                     |               |   |
| biuret           | 58.2 2.469           | 59.2 2.256          | > 0.25        |   | 60.8 1.457          | > 0.05        |   |
| spectrophotometric | 50.2 2.313 | 50.6 1.562          | > 0.7         |   | 52.3 2.023          | > 0.1         |   |
| Cholesterol (mmol/l) |                    |                     |               |   |                     |               |   |
| enzymatic       | 2.88 0.080           | 2.90 0.103          | > 0.6         |   | 2.92 0.124          | > 0.4         |   |
| Liebermann-Burchard | 3.33 0.125 | 3.29 0.150          | > 0.8         |   | 3.35 0.114          | > 0.8         |   |
| Triglycerides (mmol/l) |                |                     |               |   |                     |               |   |
| enzymatic       | 0.86 0.017           | 0.87 0.009          | > 0.5         |   | 0.87 0.028          | > 0.4         |   |
| Iron (μmol/l)   |                      |                     |               |   |                     |               |   |
| bathophenanthroline | 22.3 1.332 | 20.0 1.170          | < 0.02        |   | 20.3 1.210          | < 0.05        |   |
| Ramsay          | 16.6 0.838           | 19.6 0.361          | < 0.001       |   | 19.49 1.372         | < 0.005       |   |

Fig. 1. Dose dependence of aminophenazone (a) and diclofenac (b) interference in the glucose assay with glucose oxidase and peroxidase using ABTS as chromogen.
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