DETERMINATION OF CREATINE, CREATININE, ARGinine, GUANIDINOACETIC ACID, GUANIDINE, AND METHYL-GUANIDINE IN BIOLOGICAL FLUIDS*

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The non-specific analytical methods for the guanidinium compounds in biological fluids have been unsatisfactory for many years. The methods presented in this paper have a greatly improved specificity and are not too complex for use in the clinical laboratory.

A modified Sakaguchi color reaction for substituted guanidines is used in each procedure. Guanidinoacetic acid is measured by developing the color reaction with a \( \text{Ba(OH)}_2-\text{ZnSO}_4 \) protein-free filtrate. Arginine plus guanidinoacetic acid is measured by the color reaction with a tungstic acid protein-free filtrate. Creatinine is degraded to methylguanidine for measurement. Creatine is converted to creatinine by heat and acid and then degraded to methylguanidine. Methylguanidine and guanidine are determined by developing the color reaction on a \( \text{Ba(OH)}_2-\text{ZnSO}_4 \) protein-free filtrate (arginine-free) which has been treated with a strong anion exchange resin to remove guanidinoacetic acid. Any guanidine present must first be treated with dimethyl sulfate before the color reaction is applied.

Reagents—
Protein precipitation reagents.

1. \( \frac{3}{8} \text{ N H}_2\text{SO}_4 \) and 10 per cent sodium tungstate (1, 2).
2. 0.3 N Ba(OH)_2 (3).†

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† 30 gm. of reagent grade Ba(OH)_2 are dissolved in 1 liter of distilled water. The solution is allowed to stand tightly stoppered for 1 to 2 days to allow insoluble Ba(CO_3)_2 to precipitate. The clear supernatant solution is siphoned into another bottle. A portion of this supernatant solution is then titrated against the ZnSO_4 solution. The titration is performed by diluting 10 ml. of the ZnSO_4 solution to about 100 ml. and then running in the alkali dropwise with continual agitation un-
ANALYSIS OF GUANIDINIUM COMPOUNDS

3. 5 per cent ZnSO₄·7H₂O in 0.033 M biphthalate buffer, pH 5.0. Modified Sakaguchi color reagents.

1. (a) 10 per cent NaOH containing 10 mg. of thymine per ml. (for creatinine, creatine, guanidine, and methylguanidine); (b) 10 per cent NaOH containing 20 mg. of thymine per ml. (for arginine and guanidinoacetic acid).

2. 0.04 per cent α-naphthol in ethyl alcohol. This reagent is mixed with an equal volume of the alkaline thymine solution. The mixture is stable for 1 day.

3. (a) 0.50 per cent NaOCl (for creatine, creatinine, guanidine, and methylguanidine); 10 ml. of Clorox diluted to 100 ml. with H₂O; (b) 1.0 per cent NaOCl (for arginine, guanidinoacetic acid) made fresh daily.

4. 2 per cent sodium thiosulfate. 3 gm. of Na₂S₄O₈·5H₂O dissolved in 100 ml. of H₂O.

Reagents for conversion of creatinine to methylguanidine.

1. 7 per cent o-nitrobenzaldehyde (Eastman) in ethyl alcohol.
2. 1.25 N NaOH.
3. Phosphate buffer-sulfuric acid mixture. A 1.25 N H₂SO₄ solution is equilibrated against the 1.25 N NaOH. A 0.5 M phosphate buffer is prepared by mixing 30 ml. of 0.5 N NaOH with 50 ml. of 0.5 M monopotassium phosphate and diluting to 100 ml. The buffer should have a pH of 6.9 to 7.0. 1 volume of the 1.25 N H₂SO₄ is mixed with 1 volume of the phosphate buffer. The mixture is then diluted by mixing 4 volumes with 1 volume of water.

Creatine reagents.

1. 0.15 M potassium citrate buffer, pH 2.2, is prepared by mixing equal volumes of 0.15 M monopotassium citrate and 0.15 N H₂SO₄.
2. 1.66 N NaOH.

Guanidine and methylguanidine reagents.

1. Ion exchange resin IRA-400 (OH), 20 to 50 mesh in a column approximately 15 mm. in diameter and 150 mm. in length.
2. 4 N NaOH.
3. Dimethyl sulfate.

Procedures

The reagents listed above are designed for a procedure in which the total volume in the colorimeter tube is 2.6 to 3.1 ml. If a colorimeter is used in which the total volume in the tube is at least 6 ml., all the reagents except the protein precipitation reagents and the guanidine and methylguanidine reagents are made up double strength.

til a pink color persists for at least 1 minute. The two solutions should be exactly equivalent. If they are not, the stronger one should be proportionately diluted to match the less concentrated one.
Modified Sakaguchi Color Reaction

The calorimeter tubes containing solutions to be measured are chilled in an ice bath. 0.5 ml. of the alkaline α-naphthol-thymine mixture is pipetted into the tubes. After mixing, 0.2 ml. of NaOCl solution is added with immediate mixing. Exactly 1 minute later, 0.2 ml. of Na₂S₂O₃ solution is added with immediate mixing. The tubes are read at 515 μ. The colors are stable in the cold for several hours.

Guanidinoacetic Acid—A 1:7 Ba(OH)₂-ZnSO₄ filtrate of whole blood or serum is made by adding to 1 volume of blood or serum 3 volumes of Ba(OH)₂ solution followed by 3 volumes of ZnSO₄ solution. To 1 volume of urine² (diluted 1:10) is added 1 volume of Ba(OH)₂ solution followed by 1 volume of ZnSO₄ solution. The mixtures are centrifuged and filtered. Color reactions on these filtrates represent guanidinoacetic acid.

Arginine—A 1:7 tungstic acid filtrate of blood or serum is prepared as follows: 1 volume of blood or serum is added to 4 volumes of H₂O; 1 volume of 10 per cent sodium tungstate is added, followed as soon as possible with the addition of 1 volume of $\frac{2}{3}$ N H₂SO₄.³ After standing for 15 minutes, the mixture is centrifuged and filtered. Urine is diluted 1:30. The color reaction on the filtrate or diluted urine represents arginine + guanidinoacetic acid. The difference between the value by this procedure and that for guanidinoacetic acid represents arginine.

Creatinine—1 ml. of the tungstic acid filtrate (1:7) or urine diluted 1:200 is pipetted into each of two calorimeter tubes. To Tube 1 are added 0.5 ml. of phosphate buffer-H₂SO₄ mixture and 0.2 ml. of 1.25 N NaOH. This is the blank tube and is ready for color development. To Tube 2 are added 1 drop of o-nitrobenzaldehyde and 0.2 ml. of 1.25 N NaOH. After mixing, the tube is left standing for 15 minutes (20 minutes for 6 ml. method). 0.5 ml. of the phosphate buffer H₂SO₄ mixture is added and the solution is mixed. The tube is then heated in a boiling water bath for 10 minutes. After cooling to room temperature, the Sakaguchi color is developed in both tubes. 1 drop of o-nitrobenzaldehyde is added to the blank tube just before the addition of the NaOCl solution. The difference in optical density of the two tubes represents the amount of creatinine present.

Creatine—1 ml. of the tungstic acid filtrate (1:7) or of diluted urine is pipetted into each of two color tubes. To Tube 1 are added 0.5 ml. of 0.15 M citrate buffer, pH 2.2, 0.2 ml. of 1.66 N NaOH, and 0.5 ml. of phosphate buffer-

² The urine sample should not have a specific gravity greater than 1.01 for any of the determinations and should be so diluted.

³ It is necessary that the sodium tungstate solution be added before the H₂SO₄ solution. The reversal of this procedure yields a protein-free filtrate that may turn black when the color reaction is applied. The protein-free filtrates of plasma or serum, but not of whole blood, are too acidic and must be neutralized with NaOH before analyses are made.
fer-H₂SO₄ mixture. This is the blank tube and is ready for color development. To Tube 2, 0.5 ml. of the citrate buffer is added; the tube is covered with a glass marble and then heated in a boiling water bath for 1½ to 2 hours. After cooling to room temperature, 0.2 ml. of 1.66 N NaOH is added and the creatinine procedure is followed. The difference in optical density represents the total creatine and creatinine present (as creatinine). This value less that for creatinine represents creatine (as creatinine).

Methylguanidine—For blood, a 1:7 Ba(OH)₂-ZnSO₄ filtrate is prepared with 10 ml. of the blood as under the guanidinoacetic acid procedure. The filtrate is run over an IRA-400 (OH) column, neutralized with dilute HCl to pH 4 to 6, and evaporated to dryness by placing in a warm water bath and allowing a stream of air to blow over the surface. The residue is dissolved in 2.5 ml. of H₂O and 2 ml. are withdrawn for the color reaction. For urine, to 1 ml. of urine are added 1 ml. of Ba(OH)₂ solution and 1 ml. of ZnSO₄ solution. The filtrate is run over the IRA-400 (OH) column and the color reaction is developed.

Guanidine—For blood, the procedure is the same as the methylguanidine method except that, instead of dissolving the residue in 2.5 ml. of H₂O, it is dissolved in 2 ml. of 4 N NaOH, 0.5 ml. of dimethyl sulfate is added, and the mixture is shaken at 35-40° for 1 hour or until the dimethyl sulfate has disappeared. The color reaction is run on 2 ml. of this mixture. For urine, the procedure is the same as the urine-methylguanidine method except that the filtrate from the column is evaporated to dryness as under blood methylguanidine. The guanidine is treated with dimethyl sulfate as under the blood guanidine procedure.4

Results

The analytical range for blood may be increased or decreased by preparing a more dilute or a more concentrated protein-free filtrate. The procedures as described have the following ranges in mg. per 100 ml. of blood: creatinine, creatine, arginine, and guanidinoacetic acid all from 0.5 to 10.0, methylguanidine 0.02 to 0.4, and guanidine 0.05 to 1.0. Amounts of creatine less than 150 mg. per 24 hour urine sample may not be measured because of the large amounts of creatinine present. 20 to 500 mg. of arginine or guanidinoacetic acid, 1 mg. of methylguanidine, and 2 mg. of guanidine may be measured in a 24 hour urine sample. The sensitivity for arginine, guanidinoacetic acid, guanidine, and methylguanidine in urine may not be increased to any great extent by working with a more concentrated urine because urea then begins to interfere in the color reaction.

4 The color reaction in the guanidine and methylguanidine procedures for blood and urine sometimes produces a slight yellow color which is not the result of any methylguanidine or guanidine present. The color may be distinguished from that of methylguanidine by the fact that it has a maximal absorption at 350 μμ.
Table I shows the recoveries of the compounds added to blood and urine. In Table II are shown the average values determined on thirty-five normal blood and urine samples and a list of the reported values obtained by other methods.

DISCUSSION

Creatinine has been determined by non-specific chromogenic reactions (4–14) with picric acid (1, 15) or 3,5-dinitrobenzoic acid (16–18) in the presence of alkali. The modification of these procedures by adsorption of creatinine on fuller’s earth (Lloyd’s reagent) (19–22), by oxidation of interfering reducing substances (12, 23), or by incubation with a creatinine-destroying enzyme (24, 25) has increased the specificity. Recently Stelgens has reported a method based on its reaction with potassium-mercury thiocyanate (26).

### Table I

Recoveries of Guanidinium Compounds

<table>
<thead>
<tr>
<th>Mg. added to 100 ml.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole blood</td>
</tr>
<tr>
<td>Creatinine</td>
</tr>
<tr>
<td>Creatine</td>
</tr>
<tr>
<td>Arginine</td>
</tr>
<tr>
<td>Guanidinoacetic acid</td>
</tr>
<tr>
<td>Guanidine</td>
</tr>
<tr>
<td>Methylguanidine</td>
</tr>
</tbody>
</table>

Analysis performed as under “Procedures.” A 95 to 100 per cent recovery was obtained with each compound.

The conversion of creatine to creatinine and its subsequent measurement have never been satisfactory. Non-creatinine, Jaffe-positive chromogens are formed when acidified biological fluids are heated. Some of the non-creatinine chromogens produced in the heating process can be removed by ether extraction (27). Creatine has been measured directly with the diacetyl color reaction (28) for guanidinium compounds. Ennor and Stocken (29), using this color reaction and a specific creatine-destroying bacterial enzyme preparation, have developed a specific method for creatine.

Arginine and guanidinoacetic acid have been separated from each other for colorimeter measurement by means of ion exchange (30, 31) or by incubation with the enzyme arginase (32). Guanidine and methylguanidine supposedly have been measured by the non-specific alkaline nitroprusside-ferricyanide reagent (33–39) which will not distinguish between the two compounds.

The procedures presented in this paper differ from previous methods in
### TABLE II

**Guanidinium Compounds in Adult Male**

<table>
<thead>
<tr>
<th></th>
<th>Blood Amount (mg. per 100 ml.)</th>
<th>Methods* and literature references</th>
<th>Urine Amount</th>
<th>Methods* and literature references</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Creatinine</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.6</td>
<td></td>
<td></td>
<td>95-100% of picric acid value</td>
<td>2b (22)</td>
</tr>
<tr>
<td>1.3</td>
<td>2 (65)</td>
<td>90-100%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.6</td>
<td>2b (18)</td>
<td>95-97%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.5</td>
<td>3 (18)</td>
<td>Same as picric acid value</td>
<td>6 (26)</td>
<td></td>
</tr>
<tr>
<td>0.5</td>
<td>2g† (12)</td>
<td></td>
<td>2a (24)</td>
<td></td>
</tr>
<tr>
<td>0.7</td>
<td>6 (26)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.7</td>
<td>2a‡ (25)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.86</td>
<td>2a‡ (24)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Creatine</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.7</td>
<td>2e (65)</td>
<td>&lt;150 mg. per day</td>
<td>2f (66)</td>
<td></td>
</tr>
<tr>
<td>3.0 –7.0</td>
<td>2e (65)</td>
<td>0-200</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.13</td>
<td>6e (26)</td>
<td>180-352 mg. per day</td>
<td>2f (67)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>5-40 γ per ml.</td>
<td>1a (29)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>None detected</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Arginine</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.6</td>
<td>5e§ (69)</td>
<td>32 mg. per day</td>
<td>d (70)</td>
<td></td>
</tr>
<tr>
<td>1.5</td>
<td>d (71)</td>
<td>24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.99</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Guanidinoacetic acid</strong></td>
<td></td>
<td>45 mg. per day</td>
<td>4c (73)</td>
<td></td>
</tr>
<tr>
<td>&lt;0.3</td>
<td>4c (72)</td>
<td>40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.33</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Guanidine</strong></td>
<td></td>
<td>&lt;2 mg. per day</td>
<td>7 (33)</td>
<td></td>
</tr>
<tr>
<td>&lt;0.04</td>
<td>7 (74, 34)</td>
<td>3-10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.2 –0.3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Methylguanidine</strong></td>
<td></td>
<td>&lt;1 mg. per day</td>
<td>7 (33)</td>
<td></td>
</tr>
<tr>
<td>&lt;0.02</td>
<td>7 (74, 34)</td>
<td>3-10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.2 –0.3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Color reactions, (1) diacetyl, (2) picric acid, (3) dinitrobenzoic acid, (4) α-naphthol-NaOCl, (5) ninhydrin, (6) K-Hg thioxyanate, (7) nitroprusside-ferrieyanide. (a) Enzyme incubation, (b) fullers' earth, (c) ion exchange, (d) microbiological, (e) heat in the presence of mineral acid, (f) heat in the presence of picric acid, (g) oxidation of interfering reducing compounds.

† Serum. ‡ Calculated from separate analysis of plasma and erythrocytes.

§ Plasma.

230
that a modified Sakaguchi color reaction (40) is used for every compound. Although studies on the specificity of this color reaction have been made by Poller (41) and Mold et al. (42), the reaction has been further checked for specificity. Of the Sakaguchi-positive compounds, only arginine, guanidinoacetic acid, and methylguanidine have been thought to occur in normal blood and urine (43). The data in the paper show that methylguanidine is not a normal constituent. The apparent isolation of this compound from blood and urine by other investigators (44-47) was explained by Ewins in 1916 (48), Greenwald in 1919 (49), and Baumann and Ingvaldsen in 1918 (50), when they showed that mercury and silver salts used in the various isolation procedures converted creatinine to methylguanidine. Investigators who have attempted to isolate the compound without employing the metal salts have failed to find methylguanidine (51). The detection of the compound in normal blood by previous workers can probably be attributed to the non-specificity of the colorimetric methods (37).

Modifications of the Sakaguchi color reaction have been many (30, 31, 43, 52-57). In our investigation it was found that a solution of sodium thiosulfate could be used instead of urea (58) and that the addition of thymine (5-methyluracil) to the reaction mixture further increased the stability and intensified the color 6-fold (Fig. 1). It is thought that thymine produces a more favorable oxidation potential for the colored complex, since either excess thymine or sodium hypochlorite decreased the color. Fig. 2 shows standard curves for the guanidinium compounds plotted on a molar basis. The fact that the curve for guanidine is much lower than that for methylguanidine is probably the result of very incomplete (only 25 per cent) methylation to methylguanidine or perhaps the formation of some other compound.

6 100 naturally occurring biological compounds were screened for interference. The following compounds when added to blood at levels of at least 200 mg. per 100 ml. produced no interference either by failing to produce any color which could likely be mistaken with that given in the Sakaguchi color reaction with the compounds measured or by preventing proper color development: the commercially available purines, pyrimidines, nucleotides, nucleosides and nucleic acids, the amino acids including ornithine and glutamine, the water-soluble and fat-soluble vitamins (including vitamin P), the mono-, di-, and polysaccharides, the citric acid cycle compounds, ketone bodies, common steroids and bile acids, bile pigments, fatty acids, di- and tripeptides, and the miscellaneous compounds sarcosine, histamine, furfural, phenylacetic acid. 50 commonly used drugs were also checked for interference. These included the most important antibiotics, analgesics, antispasmodics, cardiovascular agents, sedatives, antihistaminics, parasympathomimetics, antimalarials, alkaloids, the xanthines, and curare. Penicillin above concentrations of 500 units per ml. and streptomycin above concentrations of 200 mg. per 100 ml. of fluid interfered by preventing the color reaction. Hemin interferes by forming a black color. Urea in amounts greater than 3.0 mg. per color tube prevented proper color development. Only arginine, guanidinoacetic acid, and methylguanidine gave a positive reaction.
Arginine is separated from guanidinoacetic acid by a Ba(OH)$_2$-ZnSO$_4$ protein precipitation (58). The amount of arginine that can be removed by this process is limited, in that amounts greater than 15 mg. per 100 ml. of blood or urine (diluted 1:10) are incompletely removed. Since methylguanidine could not be detected in normal blood or urine filtrates, it is assumed that only these two Sakaguchi-positive compounds are present.

In 1939 Riegert reported the use of the Sakaguchi color reaction in the measurement of creatinine. He converted creatinine to methylguanidine by heating for 5 minutes in the presence of HgO and alkali (59). It was found in our laboratory that 20 per cent of the creatinine (or methylguanidine) was destroyed under these conditions. Furthermore, as much as 50 per cent of the creatine present was converted to methylguanidine. All attempts to convert creatinine to methylguanidine selectively by heating with various inorganic oxidizing agents (Cu$^{++}$, Hg$^{++}$, Ce$^{+++}$) were unsuccessful.

An investigation of the alkaline picrate reaction revealed a possible procedure for converting creatinine, but not creatine, to methylguanidine. The reaction product of creatinine and picric acid in the presence of alkali was found to be methylguanidine. This suggested that the chromogen formed in the alkaline picrate reaction was a reduction product of picric acid, rather than a tautomer of creatinine picrate as previously suggested.
This would explain why many reducing compounds interfere in the alkaline picrate method.

![Graph showing standard curves of the guanidinium compounds.](image)

**Fig. 2.** Standard curves of the guanidinium compounds. All colors developed as under "Procedures." All solutions were made up to an equal volume of 3.1 ml. with water before reading at 515 μm.

Several nitrobenzene compounds were tested for their ability to oxidize creatinine to methylguanidine. o-Nitrobenzaldehyde was found to be very effective in this conversion and the mechanism in Fig. 3 is proposed.

![Mechanism diagram](image)
The oxidation reaction proceeds rapidly in the presence of alkali without application of heat; therefore, the conversion of creatine to creatinine and the destruction of methylguanidine are negligible. The hydrolysis reaction proceeds rapidly at a neutral pH with the application of heat. Methylguanidine is not destroyed and the o-nitrobenzaldehyde exerts no oxidizing action under these conditions; therefore, any creatinine formed from creatine in the heating process is not converted to methylguanidine. o-Nitrobenzaldehyde has an additional advantage in that the reaction mixture is colorless and does not interfere in the Sakaguchi color reaction. The yield of methylguanidine from creatinine was 95 per cent.

Oxalymethylguanidine was isolated from a reaction mixture and identified by melting point and mixture melting point with the compound synthesized by the method of Traube and Gorniak (64).

**SUMMARY**

New analytical methods for the guanidinium compounds are presented. The average values in whole blood were found to be as follows: creatinine 0.6, creatine 2.7, arginine 1.6, guanidinoacetic acid less than 0.3, guanidine less than 0.04, and methylguanidine less than 0.02 mg. per 100 ml. The average amounts excreted in the urine were found to be as follows: creatine less than 150, arginine 32, guanidinoacetic acid 45, guanidine less than 2, and methylguanidine less than 1 mg. per day. The urinary creatinine values were for all practical purposes identical with those obtained with the alkaline picrate procedure.

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