

THE URIC ACID SOLVENT POWER OF URINE AFTER ADMINISTRATION OF PIPERAZIN, LYSIDIN, LITHIUM CARBONATE AND OTHER ALKALIES *

HOWARD D. HASKINS, M.D.
PORTLAND, ORE.

In a recent paper¹ I reported the results of an investigation of the uric acid dissolving power of hexamethylenamin. The mode of action of that drug is quite different from that of the rest of those substances which have been classed as "uric acid solvents." The latter, if they act at all as solvents, do so by virtue of being basic substances. The purpose of this paper is to report an investigation of the solvent power of the most important members of this class.

The organic compounds piperazin and lysidin are amine derivatives, and the nitrogen of their molecules imparts to these substances a basic character so that they combine with acids. They are supposed to form salts with uric acid which are very soluble. And it is true that in aqueous solution they dissolve a very large amount of uric acid (see Table 10).

Lithium carbonate and sodium bicarbonate are supposed to act as alkalies toward uric acid, forming lithium and sodium urates which are quite soluble. In aqueous solution they certainly do cause a considerable quantity of uric acid to go into solution (Table 10).

Furthermore, each of these four solvents when added to urine or phosphate mixture, causes the urine to take up much more uric acid than it could dissolve without the addition of the drug (Tables 8 and 9). It remains to be determined, therefore, whether after administration of these drugs the urine acquires a greater uric acid solvent power than normal urines of similar character (as regards concentration and acidity) would have; in other words, whether the drug is excreted in such form and concentration as to show demonstrable uric acid solvent action due to the drug itself. This is what we have tried to determine.

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* From the Department of Biochemistry, Medical School, University of Oregon.

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1. Haskins, H. D.: *THE ARCHIVES INT. MED.*, 1915, xvi, 1055.

TABLE 1.—URINES AFTER TAKING A DRUG—
LESS DILUTE URINES AFTER PIPERAZIN

Acidity	Dosage Gm.	Time Hours	Piper. Test	Uric Acid Content Mg.	Total Uric Acid Mg.	Uric Acid Dissolved Mg.
7.4*	2×2	0-2	+	71.36	612.48	541.12
7.3*	2	2-4	Trace	90.36	695.32	604.96
7.3*	2	0-2	..	43.63	484.94	441.31
7.2*	2	0-1¼	+	22.80	367.90	345.10
6.9	2	0-3½	+	62.24	664.92	602.68
6.9	2	2-3	+	16.64	309.24	292.60
6.9	2	0-2	+	75.92	288.72	212.80
6.9	2	0-3	+	80.24	203.60	123.36
6.85	2	3-4	+	12.08	214.24	202.16
6.75	2	3-4¼	..	18.87	221.53	202.66
6.2	2	0-2¼	+	79.72	500.00	420.28
....
6.0	2	0-5½	+	63.00	115.44	52.44
5.8	2	0-2	+	30.32	116.96	86.64

TABLE 2.—
DILUTE URINES AFTER PIPERAZIN

6.9	1	0 - ½	9.20	94.00	84.80
....
6.55	1	½-1¾	8.40	48.20	39.80
6.5	2	4 - 5½	23.20	82.00	58.80
6.5	1×2	1 - 1½	9.20	61.20	52.00
6.5	2	1½-2	10.00	60.40	50.40
6.45	1×4	0 - ½	7.60	19.60	12.00
6.4	1×4	¾-1¾	9.20	44.40	35.20
6.35	1	0 - 1	10.44	47.44	37.00
6.3	1×4	1½-2	9.20	43.60	34.40
....
6.25	1×3	¼-¾	8.40	18.00	9.60
6.1	2	3¼-4¼	10.00	52.80	42.80
6.1	2	½-1½	9.20	26.00	16.80
6.0	2	0 - 2½	7.52	55.40	47.88
6.0	2	2 - 2¾	8.40	25.20	16.80

TABLE 3.—
LESS DILUTE URINES AFTER LYSIDIN

7.1	2×2	½-2½	38.00	178.00	140.00
7.1	2×2	5 - 6	112.40	200.00	87.60
6.1	2	0 - 1	31.60	68.40	36.80
6.0	2×2	2½-4	22.00	51.60	29.60
5.85	2	0 - 3	56.92	130.64	73.72
5.85	2×2	0 - ½	52.00	71.60	19.60
5.8	2	0 - 4½	63.76	109.36	45.60
5.8	2	0 - 2¾	78.96	101.76	22.80

—CONTROLS. URINES WITHOUT THE DRUG

LESS DILUTE CONTROL URINES

Uric Acid Dissolved Mg.	Total Uric Acid Mg.	Uric Acid Content Mg.	Acidity	Remarks
283.14	296.94	13.80	7.6*	* NaHCO ₃ administered.
350.00	446.55	96.55	7.3*	
255.75	360.75	105.00	7.3*	
223.50	279.00	55.50	7.2*	
198.40	247.60	49.20	7.0	
159.20	282.00	122.80	6.9	
158.84	230.20	71.36	6.9	
102.76	137.26	34.50	6.9	
154.40	216.40	62.00	6.8	
148.00	198.00	50.00	6.7	
31.20	75.60	44.40	6.4	
15.20	72.40	57.20	6.3	
8.80	34.00	25.20	6.1	
40.56	76.20	35.64	5.9†	† A very exceptional control.

—TABLE 2.—(Continued)

DILUTE NORMAL URINES

141.75	150.08	8.33	6.9	The drug seems to begin to be excreted very soon and to be present in the urine in appreciable amount for at least four hours. The urines in this table are too dilute to give tests for the drug.
111.75	120.00	8.25	6.9	
47.95	62.91	14.96	6.55	
63.92	76.16	12.24	6.5	
49.58	59.28	9.70	6.5	
50.80	66.00	15.20	6.5	
51.48	59.04	7.56	6.45	
31.20	38.80	7.60	6.4	
22.94	30.42	7.48	6.35	
33.75	41.25	7.50	6.3	
19.20	31.60	12.40	6.3	
19.50	27.06	7.56	6.25	
.....	
.....	
37.92	52.33	14.41	6.0	
12.00	22.00	10.00	6.0	

—TABLE 3.—(Continued)

LESS DILUTE CONTROL URINES

172.00	244.40	72.40	7.1	* A very exceptional control.
135.42	185.82	50.40	7.1	
8.80	34.00	25. 20	6.1	
.....	
40.56	76.20	35.64	5.9*	
.....	
.....	
.....	

The citrates and acetates of sodium and potassium are converted in the body into bicarbonate, so that their effect on the urine should be the same as that of sodium bicarbonate. It seemed advisable, however, to test sodium citrate experimentally so as to make sure of the effectiveness of this class of salts.

While conducting a research on atophan, its uric acid solvent power was determined incidentally, although there was no reason to suppose that it belonged to the class of uric acid solvents. I take this occasion to report the results. The urines from eight persons (twenty-four-hour samples) were of low enough acidity to lead to the expectation that they might dissolve extra uric acid. Their content of uric acid ranged from 80 to 132 mg. in 100 c.c. Only one of the urines took up any uric acid, however; this had an acidity of 6.8 and dissolved 46 mg., which was less than a normal urine of that acidity would be expected to dissolve. The indications are, therefore, that atophan may interfere with the solvent action of the urine.

The urines reported in the tables were all from normal individuals. They are not as numerous as we had hoped to secure, since few persons were willing to take these drugs.² Hospital urines were not obtainable.

The methods used in the present investigation were identical with those reported in the paper on hexamethylenamin. The results of our work are given in the tables where comparison is made of the uric acid dissolved by the drug urines with that dissolved by normal urines of similar acidity and concentration. In interpreting our results we take it for granted that the drug urine must show distinctly greater solvent power than the control normal urines, in order to permit us to argue that the drug plays any part in the solvent action.

The figures for uric acid are given as milligrams in 100 c.c. of urine. "Uric acid content" means the amount present in the urine as passed. "Total uric acid" means the amount present in the filtrate after shaking the urine with pure uric acid for twenty minutes at 37 C. The difference between these two is the "uric acid dissolved." This last is the index of the solvent power of the urine.

In the cases in which more than one dose of the drug was taken, the time interval for secretion of the urine was calculated from the time of taking the last dose.

In Table 9 the acidity figures are those of the phosphate mixture (NaH_2PO_4 and Na_2HPO_4 mixed as in urine) before any drug was added. The drugs rendered the solutions alkaline. In Table 10, on the other hand, the acidity figures are those of the solutions of the drugs.

2. The author wishes to express his gratitude to those, students and others, who did assist him so materially in this respect, foremost among whom were Dr. P. J. Hanzlik, Dr. R. J. Collins and C. J. Friedman. The assistance of Mr. Friedman in all the work of the research was invaluable.

In connection with Table 8, attention must be called to the fact that the urines of the same acidity are not different urines but portions of the same urine. The effect of the drugs in changing the reaction of the urine is of sufficient interest to report (Table 11).

COMMENT ON THE TABLES

In the case of the dilute urines (Tables 2 and 4) after taking piperazin and lysidin, the results are not significant, possibly because dilution of the drug reduces its effect so that no conclusion as to solvent action can be drawn.

In Table 1 are found some very striking results. The first, second, third and fifth urines dissolved an excessive amount of uric acid, much beyond our expectations of what could be dissolved by any substance excreted into the urine. The sixth urine shows a high result for a urine of an acidity 6.9. Even though the solvent action be due in part to the bicarbonate taken also, yet there can be no doubt whatever that the piperazin has been excreted in sufficient quantity to exert a very decided solvent action.

It is true that the 2 gm. doses are extratherapeutic, but we see no reason why the maximum therapeutic dose should not have a distinct effect, at least when the urine is not dilute and is not acid in reaction.

In the case of lysidin, the two alkaline urines, the first two of Table 3, do not show sufficient solvent action to be able to attribute any of it to the drug. The dosage being equal to the maximum therapeutic dose, we expected to secure evidence of some solvent action if there was enough action to be worth considering.

We knew of no way of determining whether lysidin is excreted either unchanged or as a derivative which could be effective as a uric acid solvent.

The results in Table 8 indicate that lysidin ought to be an effective solvent provided it is excreted unchanged and rapidly enough to give a proper concentration in the urine. We may also add the qualifying statements as in the case of piperazin, that the urine should not be dilute nor acid in reaction.

We would not expect that the basic compounds, piperazin and lysidin, could show any solvent action in acid urines, yet several surprising results are to be found in Tables 1 and 3. The eleventh urine in Table 1, of 6.2 acidity, took up 420 mg. of uric acid, a result which is quite remarkable. Several more acid urines showed distinct solvent power beyond what we have ever secured with normal urines of those acidities. These are the last urine of Table 1 (5.8 acidity, 86 mg. dissolved), and the fifth (5.85 acidity, 73 mg. dissolved) and seventh (5.8 acidity, 45 mg. dissolved) urines of Table 3. Our experience with normal urines has led us to expect no solvent action whatever if the

TABLE 4.—

DILUTE URINES AFTER LYSIDIN

Acidity	Dosage Gm.	Time Hours	Uric Acid Content Mg.	Total Uric Acid Mg.	Uric Acid Dissolved Mg.
6.75	2×2	0 - $\frac{3}{4}$	14.00	121.20	107.20
6.35	1×4	$\frac{3}{4}$ -1 $\frac{1}{2}$	8.40	52.40	44.00
6.35	1×4	0 - $\frac{3}{4}$	7.60	43.60	36.00
6.3	2×2	3 $\frac{3}{4}$ -5	10.80	42.80	32.00
6.2	1×4	1 $\frac{1}{2}$ -2 $\frac{1}{2}$	8.40	62.00	53.60
6.1	1×2	0 - $\frac{1}{4}$	7.60	58.00	50.40
6.0	1	0 - $\frac{3}{4}$	10.80	59.60	48.80
6.0	1×4	2 $\frac{1}{2}$ -4	9.20	43.60	34.40
6.0	2	2 -3	9.20	26.00	16.80

TABLE 5.—URINES AFTER ADMINISTRATION OF ALKALIES—
LESS DILUTE URINES AFTER LITHIUM CARBONATE

Acidity	Dosage Gm.	Drug	Uric Acid Content Mg.	Total Uric Acid Mg.	Uric Acid Dissolved Mg.
7.0	†	Li ₂ CO ₃	50.80	176.40	125.60
6.85	†	Li ₂ CO ₃	29.20	142.00	112.80

TABLE 6.—

DILUTE URINES AFTER LITHIUM CARBONATE

7.6	1.0	Li ₂ CO ₃	15.40	244.34	228.94
7.2	1.0	Li ₂ CO ₃	19.33	421.52	402.19
....
....
7.15	0.5×2	Li ₂ CO ₃	12.40	114.80	102.40
7.0	0.5×2	Li ₂ CO ₃	18.40	136.50	118.10
6.95	†	Li ₂ CO ₃	12.40	214.80	202.40
6.95	†	Li ₂ CO ₃	13.20	159.60	146.40
6.95	†	Li ₂ CO ₃	11.60	145.20	133.60
6.9	0.5×2	Li ₂ CO ₃	9.20	142.00	132.80

TABLE 7.—

LESS DILUTE URINES AFTER SODIUM SALTS

7.6	4	NaHCO ₃	13.80	296.94	283.14
7.3	4	NaHCO ₃	96.55	446.55	350.00
7.3	4	NaHCO ₃	105.00	360.75	255.75
7.3	3	Sod. citrate	70.50	283.87	213.37
7.3	3	Sod. citrate	129.24	313.85	184.61
7.25	3	Sod. citrate	56.00	227.20	171.20
7.25	3	Sod. citrate	72.00	222.26	150.26
7.2	2	NaHCO ₃	55.50	279.00	223.50
7.2	3	Sod. citrate	52.02	218.94	166.92
7.15	3	Sod. citrate	27.00	210.41	183.41
7.1	2	Sod. citrate	30.57	197.88	167.31

—TABLE 4.—(Continued)

DILUTE NORMAL URINES

Uric Acid Dissolved Mg.	Total Uric Acid Mg.	Uric Acid Content Mg.	Acidity	Remarks
83.00	91.25	8.25	6.75	These drug urines are too dilute doubtless to show solvent action due to the drug.
48.75	68.40	19.65	6.4	
22.94	30.42	7.48	6.35	
33.75	41.25	7.50	6.3	
7.20	22.80	15.60	6.2	
.....	
37.92	52.33	14.41	6.0	
12.00	22.00	10.00	6.0	
14.82	25.50	10.68	5.95	

—CONTROL URINES

LESS DILUTE CONTROL URINES

Uric Acid Dissolved Mg.	Total Uric Acid Mg.	Uric Acid Content Mg.	Acidity	Remarks
187.60	240.00	52.40	7.0	† 1.5 gm. in 1 L. water taken in one day.
131.20	174.00	42.80	6.8	

—TABLE 6.—(Continued)

DILUTE CONTROL URINES

144.75	154.50	9.75	7.3	* Urines containing bicarbonate.
157.29	172.25	14.96	7.1	
283.14	296.94	13.80	7.6*	
350.00	446.55	96.55	7.3*	
255.75	360.75	105.00	7.3*	
.....	† (As above.)
118.40	138.80	20.40	7.0	
105.66	122.16	16.50	6.95	
141.75	150.08	8.33	6.9	
130.07	139.06	8.99	6.9	
111.75	120.00	8.25	6.9	

—TABLE 7.—(Continued)

LESS DILUTE CONTROL URINES

.....	All of these urines showed presence of bicarbonate.
.....	
.....	
.....	
.....	
188.50	234.34	45.84	7.2	
188.16	250.08	61.92	7.2	
.....	
182.04	238.36	56.32	7.2	
172.00	244.40	72.40	7.1	
162.40	207.60	45.20	7.0	

acidity was as great as 5.8 or 5.9 and the urine was not dilute. The control urine given in Tables 1 and 3, 5.9 acidity 40 mg. dissolved, stands out as the sole (and unexplained) exception.

We have no explanation to offer as to how it is possible for piperazin and lysidin to show uric acid solvent power in these acid urines, but we can not avoid the conclusion that these results are very striking evidence that such solvent power exists.

Although we admit that lysidin may impart to the urine solvent properties due to the drug, we do not consider it practical to use it, because of the enormous dosage that would be necessary in order to secure pronounced effects comparable to the effect of piperazin.

Piperazin, however, would seem to be especially suitable for securing an intense uric acid solvent action, provided very large doses are given for a short time, together with sodium citrate or bicarbonate (so that the urine is alkaline).

The acid urines which we obtained after administration of alkalis are not reported in Tables 5, 6 and 7 for the following reason: The fact that the urine remains acid shows that the alkali has been neutralized in the body and is being excreted in the form of a salt. The only chance for the alkali increasing the solvent power of the urine in such a case would be by causing an increase in the amount of monohydrogen phosphate, and such increase would have but a moderate effect, resulting in no greater uric acid solvent power than could be duplicated by normal urines.

A massive uric acid solvent action, however, is shown by some alkaline urines, probably because they bring about colloidal solution of the uric acid. Schade and Boden³ secured colloidal solutions of uric acid by using aqueous solutions of alkalis. Such an action is shown apparently by the second urine of Table 6 (7.2 acidity, 402 mg. dissolved). This is the only significant result with lithium carbonate. The solvent action is greater than we have secured with urines rendered alkaline by giving sodium bicarbonate or citrate. Having secured toxic symptoms in two persons taking lithium, we did not attempt to use very large doses nor to give it to many individuals. We are certain that lithium carbonate is not effective in smaller doses than those used by us. There is no real reason for giving it, since it is much safer to use the sodium salts.

Table 7 shows that the sodium salts give a sufficiently marked and a very reliable uric acid solvent action, whenever they have rendered the urine at least faintly alkaline. We can not see why any other drugs should ever be chosen in preference to them.

3. Schade and Boden: *Ztschr. f. physiol. Chem.*, 1913, lxxxiii, 347.

TABLE 8.—EFFECT OF DRUGS ADDED TO URINE

Acidity	Drug Added	Per Cent. of Drug	Control Uric Acid Dissolved (No Drug) Mg.	Uric Acid Dissolved (After Drug Was Added) Mg.	Excess of Uric Acid Dissolved Due to the Added Drug Mg.
5.0	Piperazin	0.680	0.00	233.32	233.32
6.24	Piperazin	0.125	19.50	99.84	80.34
6.0	Piperazin	0.132	27.30	103.74	76.44
5.8	Piperazin	0.085	19.00	47.12	28.12
5.8	Piperazin	0.142	19.00	78.28	59.28
5.8	Piperazin	0.170	19.00	85.12	66.12
5.8	Piperazin	0.200	19.00	103.36	84.36
5.8	Piperazin	0.230	19.00	120.08	101.08
5.8	Piperazin	0.260	19.00	152.76	133.76
6.0	Lysidin	0.050	27.30	60.84	33.54
6.0	Lysidin	0.100	27.30	99.06	71.76
6.0	Lysidin	0.200	27.30	186.42	159.12
5.0	Lysidin	1.000	0.00	129.96	129.96
5.0	Li ₂ CO ₃	0.157	0.00	245.48	245.48
5.0	NaHCO ₃	1.000	0.00	288.80	288.80

TABLE 9.—EFFECT OF DRUGS ADDED TO PHOSPHATE SOLUTION

6.8	Piperazin	0.500	120.00	274.00	154.00
6.8	Piperazin	1.000	120.00	511.40	391.40
6.8	Li ₂ CO ₃	0.168	138.24	340.40	202.16

TABLE 10.—EFFECT OF DRUGS ADDED TO WATER

....	Piperazin	0.50	8.4	250.80	242.40
7.25	Piperazin	0.65	8.4	541.80	533.40
....	Piperazin	1.00	8.4	527.60	519.20
7.4	Lysidin	1.00	8.4	455.92	447.52
7.4	Li ₂ CO ₃	0.16	8.4	503.80	495.40
7.25	NaHCO ₃	1.00	8.4	484.80	476.40

TABLE 11.—ACIDITY OF THE URINE AS AFFECTED BY DRUGS

Before the Drug	After the Drug	Drug Used	Per Cent.
5.0	7.4	Piperazin	0.68
5.0	7.1	Lysidin	1.0
5.0	7.1	Li ₂ CO ₃	0.157
5.0	6.8	NaHCO ₃	1.0
5.8	6.0	Piperazin	0.085
5.8	6.25	Piperazin	0.142
5.8	6.55	Piperazin	0.17
5.8	6.85	Piperazin	0.20
5.8	6.95	Piperazin	0.23
5.8	7.2	Piperazin	0.26

We called attention in the previous paper to the favorable effect of dilution of the urine. Probably the greatest total solvent action would be secured by combining diuresis from heavy drinking of water with the alkalization of the urine by sodium bicarbonate or citrate.

Whenever normal urine becomes alkaline and it contains a considerable concentration of metal ions as a result of the diet, it will show marked uric acid solvent action, exactly as it would if sodium bicarbonate had been taken and for the same reason. Blatherwick⁴ has also observed this fact. We have found that normal alkaline urines always contain bicarbonate as well as the alkaline urines passed after taking sodium citrate or bicarbonate.

CONCLUSIONS

1. Piperazin can cause the urine to dissolve more uric acid than it would without the drug, and this effect is most marked if sodium citrate or bicarbonate be also given and if diuresis be avoided.
2. Lysidin can act as a uric acid solvent but is not a practical therapeutic agent because of the large doses required.
3. Lithium carbonate is a uric acid solvent if large enough doses are used, but is unsafe and possesses no advantage over sodium citrate or bicarbonate.
4. Sodium citrate and bicarbonate are reliable and satisfactory uric acid dissolving agents when given in such dosage as to keep the urine alkaline.

761 Lovejoy Street.

4. Blatherwick, N. R.: THE ARCHIVES INT. MED., 1914, xiv, 409.