The Effects of Oral Salicylate on Serum Uric Acid Levels

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ABSTRACT

Thirteen males and six females were given 40 grains of oral salicylate daily for six days. The serum uric acid of 16 of the 19 subjects fell, the mean post-treatment level being 1.1 mg. % less than the control mean. In five males and five females, administration of 20 grains of oral salicylate daily for six days resulted in a uniform rise of serum uric acid, the post-treatment mean being 1.4 mg. % above the pretreatment mean. Salicylate therapy in common dosage may therefore falsely elevate or depress serum uric acid levels. An accurate evaluation of a serum uric acid level can be made only if the patient is not under the influence of salicylates.

THE paradoxical effects of low and high doses of salicylates on serum uric acid levels have been described since 1883.[1, 2] Klemperer and Bauer,[3] in a brief report in 1944, concluded that small amounts of acetylsalicylic acid had a "slight and possibly insignificant effect in raising serum uric acid in normals". In 1957, Yu and Gutman[4] studied 23 patients with gout and reported the effects of varied doses of oral salicylate on serum uric acid levels and the renal mechanisms for urate excretion. They found that less than 2 g. per day caused urate retention while 3 g. or more daily generally caused a uricosuric effect with lowering of serum urate. At the time the present study was initiated, there had been no detailed studies on the effects of salicylate in commonly used doses on serum uric acid levels in individuals without gout or hyperuricemia.

Recently, however, Grayzel, Liddle and Seegmiller[5] reported on the effects of low doses of salicylate on serum uric acid levels in normal individuals and patients with gout. They found that, in general, oral salicylate in a dosage of 1.2 g. per day produced a rise in serum uric acid while 2.4 g. per day tended to produce a fall in serum uric acid.

METHODS

Twenty-three subjects were studied. Of these, 10 were in hospital but did not have gout or arthritis (eight of the 10 were recovering from fractures and two were convalescing from unrelated illness); thirteen were healthy clerical and laboratory personnel. All but one were under the age of 45 years.

The subjects were studied in two groups. The first group consisted of 13 men and six women who were given 40 grains (2.7 g.) of salicylate daily. The second group, consisting of five men and five women, received 20 grains daily. In both groups serum uric acids were measured on two control days and again on two consecutive days following six to seven days of oral salicylate.

Six of the individuals were included in both groups, making a grand total of 29.

None of the subjects was receiving anticoagulants, adrenal corticosteroids or therapy for heart failure, and blood urea nitrogen levels were normal in the hospital patients. Diets were uncontrolled throughout the study.

All serum uric acid levels were determined by the uricase method using a Beckman DB ultraviolet spectrophotometer. Repeated determinations on both standard sera and standard uric acid solutions, as well as recovery studies using standard serum with added uric acid, have shown reproducibility by our method to be within ± 0.3 mg. %. Therefore changes in serum uric acid of less than 0.6 mg. %, after salicylate administration, were not considered significant.

TABLE I.—MEAN SERUM URIC ACID LEVELS IN NORMAL SUBJECTS

	Males		*Females*	
	Number of subjects	*Serum uric acid ± S.D. mg./100 ml.*	*Number of subjects*	*Serum uric acid ± S.D. mg./100 ml.*
Present series.....	52	4.7 ± 0.84	28	3.4 ± 0.93
Grayzel *et al.*[5-7]....	969	5.07 ± 0.98	168	4.04 ± 0.93
Popert and Hewitt[8]	436	4.46	475	3.70

RESULTS

Table I shows the mean serum uric acid levels, with the standard deviation, derived by us from a study of 80 normal subjects who were predominantly laboratory personnel and medical students. The other data shown in Table I for comparison are mean values computed by Grayzel, Liddle and Seegmiller[5] from their findings and others,[6, 7] and the mean values of Popert and Hewitt[8] in a recent population survey. The mean values vary appreciably, although in each of these studies the ultraviolet spectrophotometric method incorporating uricase was employed. Nevertheless it can be seen that our values conformed to those of the other investigators and demonstrate once again the significantly higher serum uric acid levels in men than in women.

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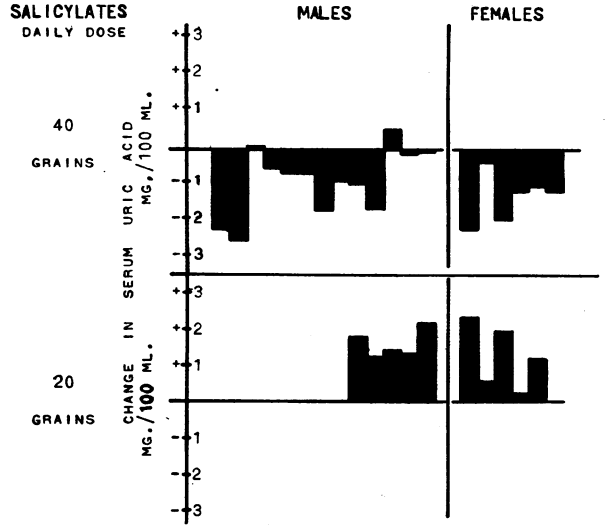

Fig. 1.—Changes in serum uric acid levels after oral acetylsalicylic acid (each black bar represents one subject).

The effects of salicylate on serum uric acid levels in normal individuals are shown in Table II and Fig. 1.

Forty grains (2.7 g.) per day caused a decrease in serum urate of more than 0.7 mg. % in 13 of 19 subjects (five of six women, eight of 13 men), with a mean decline of 1.1 mg. % (27%) over premedication control levels. The mean decline in men was 0.8 mg. % (20%), while in women the decline was considerably greater at 1.3 mg. % (32%).

At a dose of 20 grains (1.3 g.) daily, the effect was one of urate retention, seven of nine patients (three of five women, four of four men) showing an increase in serum urate of more than 1.0 mg. %, with a mean increase of 1.4 mg. % (33%) over control values. The male and female responses appeared to be similar at this dosage, the men retaining 1.5 mg. % (31%) over control levels, the women demonstrating 1.2 mg. % retention (39%) over control values.

The considerable individual variation in the response to the salicylate is readily seen in Fig. 1, as well as the definite trend to a depression of serum uric acid by 40 grains per day and a urate-retaining effect by 20 grains per day.

Discussion

The results, as outlined in Table II and Fig. 1, showed that oral salicylate in the lower dose generally produced an elevation in serum uric acid, while the larger dose tended to cause a fall.

Grayzel, Liddle and Seegmiller[5] in their study on normal individuals found similar results and suggested that the response of serum uric acid to salicylates differed in men and women. They used 2.4 g. of salicylate daily and found a fall in serum uric acid in only three of seven men but in eight of eight women; the other four men showed, in fact, a rise in serum urate. Our studies supported

TABLE II.—EFFECTS OF ORAL SALICYLATE ON SERUM URIC ACID LEVELS IN NORMAL SUBJECTS

Subject	Acetylsalicylic acid (grains/day)	Serum uric acid mg./100 ml. Before salicylate Average of two readings	Serum uric acid mg./100 ml. After salicylate Average of two readings	Change (mg./100 ml.)	Change Percentage of control	Mean changes
Males						
1	40	5.5	5.5	0	0	
2	40	5.6	5.5	−0.1	− 2	
3	40	4.5	5.1	+0.6	+13	
4	40	4.9	3.3	−1.6	−33	
5	40	3.8*	2.9	−0.9	−24	Males
6	40	5.5	4.7	−0.8	−15	
7	40	4.1	2.4	−1.7	−41	−0.8 mg.%
8	40	3.6	2.9	−0.7	−19	
9	40	6.1	5.4	−0.7	−11	−20%
10	40	4.8	4.3	−0.5	−10	
11	40	5.2	5.3	+0.1	+ 2	
12	40	4.0	1.6	−2.4	−60	
13	40	3.7	1.6*	−2.1	−57	Combined −1.1 mg.% −26%
Females						
14	40	4.1	1.9	−2.2	−54	
15	40	4.3	4.0	−0.3	− 7	Females
16	40	4.6	2.7	−1.9	−41	
17	40	4.3	3.2	−1.1	−26	−1.3 mg.%
18	40	3.6	2.6	−1.0	−28	
19	40	3.0	1.9	−1.1	−37	−32%
Males						
9	20	5.9	8.0	+2.1	+36	
10	20	4.2	5.5	+1.3	+31	Males
20	20	5.6	7.0*	+1.4	+25	+1.5 mg.%
21	20	3.7	4.9	+1.2	+32	
22	20	4.8	6.5	+1.7	+35	+32% Combined +1.4 mg.% +36%
Females						
16	20	4.1	6.4	+2.3	+56	Females
17	20	3.9	4.5	+0.6	+16	
18	20	2.8	4.7	+1.9	+68	+1.2 mg.%
19	20	2.5	2.7*	+0.2	+ 8	
23	20	2.3	3.4	+1.1	+48	+39%

*One determination only.

this observation, for, after taking 2.7 g. of aspirin per day, only eight of 13 men but five of six women showed a significantly decreased serum uric acid, with a mean fall of 0.8 mg. % in men and 1.3 mg. % in women.

With 20 grains of salicylate daily both studies showed an increase in serum urate in both men and women, the mean rise being slightly greater in men. There were no significant uricosuric effects at that dose.

The present study was in general agreement with the data of Grayzel, Liddle and Seegmiller[5] and contrary to the earlier findings of Klemperer and Bauer.[3]

In Yu and Gutman's studies on patients with gout, 45 grains (3 g.) of salicylates daily produced a fall in serum uric acid of more than 0.5 mg. % in only four of seven patients, with a mean decline of only 8% over control values. Grayzel, Liddle and Seegmiller[5] gave 2.4 g. of salicylate daily to 11 male gouty patients and only one of 11 showed a fall of serum uric acid of 0.5 mg. %, while in eight of the remainder the serum urate actually rose more than 0.5 mg. %. In the same study, three of seven normal men and, in the present series, eight of 13 showed a significantly decreased serum uric acid on even less salicylate. Therefore, it would seem that greater doses of salicylate are required to produce a fall in serum uric acid in patients with gout than in normal men.

Summary and Conclusions

Oral salicylates in doses of 20 or 40 grains per day were administered to 23 normal young men and

women and the effects on serum uric acid levels were measured. In general, 20 grains (four tablets) of oral salicylate daily produced an elevation of serum uric acid with a mean rise of 1.4 mg. %, while 40 grains (eight tablets) of salicylate daily usually caused a fall in serum uric acid with a mean decline of 1.1 mg. %. The women tended to show a greater uricosuric effect at the higher dose and a lesser urate-retaining effect at the lower dose than the men. The results were compared with previous and similar studies on normal patients and individuals with gout.

Thus, on casual or prescribed oral salicylate therapy, individuals with no disorder of uric acid metabolism may have falsely elevated or depressed serum uric acid levels. The serum uric acid levels may be elevated to such a degree as to mislead the clinician to an erroneous diagnosis of gout or hyperuricemia.

The dose of oral salicylate required to produce a fall in serum uric acid appears to be higher in men than in women and higher in individuals with gout than in normal subjects.

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REFERENCES

1. SALOME, E. G.: Quoted by Grayzel, A. I., Liddle, L. and Seegmiller, J. E.: *New Engl. J. Med.*, 265: 763, 1962.
2. SEE, G.: Quoted by Grayzel, A. I., Liddle, L. and Seegmiller, J. E.: *Ibid.*, 265: 763, 1962.
3. KLEMPERER, F. AND BAUER, W.: *J. Clin. Invest.*, 23: 950, 1944 (abstract).
4. YU, T. F. AND GUTMAN, A. B.: *Ibid.*, 38: 1298, 1959.
5. GRAYZEL, A. I., LIDDLE, L. AND SEEGMILLER, J. E.: *New Engl. J. Med.*, 265: 763, 1962.
6. HAUGE, M. AND HARVALD, B.: *Acta Med. Scand.*, 152: 247, 1955.
7. STETTEN, D., JR. AND HEARON, J. Z.: *Science*, 129: 1737, 1959.
8. POPERT, A. J. AND HEWITT, J. V.: *Ann. Rheum. Dis.*, 21: 154, 1962.

CASE REPORT

Atheromatous Embolism:

An Entity with a Polymorphous Symptomatology

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CONSIDERING the frequency of atheromatosis as an autopsy finding, it seems rather paradoxical that the entity termed "atheromatous embolism" has been known for a relatively short time

To the authors' knowledge, to date only 93 cases have been reported[3] and no cases were found during a search of the Canadian medical literature. Although this pathological entity was first described in 1862,[1] it was not generally recognized until Flory[2] reported nine cases in 1945. He amplified his description by carrying out experimental work. By the injection of atheromatous pap into an artery of a rabbit's ear, he reproduced in the animal the lesions observed in man. These experiments were verified recently by Snyder and Shapiro.[2] Since then, many authors have emphasized the variable symptomatology of this condition which depends upon the organs affected, the spread of the lesions and the importance of the obliterated vessels.

In the following case presentation, which was discussed by one of us at a clinicopathological conference, the authors wish to emphasize the polymorphous characteristic of the related pathology of atheromatous embolism. At times it is only comparable to the variety presented by some of the collagen diseases.

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Mrs. C.L. was in excellent health until her 67th year. At that time, she developed symptoms of infectious hepatitis. In July 1960, at 72, she was again admitted to hospital, presenting the classical clinical picture of gastric ulcer. The presence of this lesion was confirmed radiologically; it was a juxtapyloric ulcer measuring 1 cm. in diameter. During the previous three years she also complained of constrictive retrosternal pain when walking, progressive dyspnea on exertion, and orthopnea. She had had two or three episodes of paroxysmal nocturnal dyspnea, and also intermittent claudication. Three weeks before admission she felt numbness of the face and almost choked when swallowing.

Physical examination revealed an obese woman, obviously in pain; the mouth was deviated to the left and the speech was dysarthric. Muscular strength was slightly diminished on the left side. Diffuse abdominal pain was provoked on palpation, especially at the epigastrium. The deep plantar and posterior tibial arteries were palpated with difficulty. The blood pressure, which was reported to have been 140/80 mm. Hg five years previously, was 210/110. In addition to the radiographic study of the stomach mentioned above, an electrocardiogram was performed and revealed an old infarction of the posterior wall and evidence of ischemia of the left lateral wall.

In July 1961, at the age of 73, she asked for medical advice at the outpatient department because of nausea and vomiting. After violent efforts to vomit, the patient became very weak and was aware of a choking