

Uric acid metabolism in starvation

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Hyperuricaemia has long been known to be one of the biochemical changes accompanying starvation (Lennox, 1924). In order to investigate the development of this hyperuricaemia, quantitative measurements have been made in blood and urine over a 14-day starvation period. The effect of inhibition of uric acid formation by means of allopurinol during the starvation period has also been studied.

Methods

SUBJECTS' REGIMEN

All subjects were obese and were admitted to hospital for therapeutic starvation. The majority were female, insufficient males being included to allow a between-sex comparison. After 1 to 2 days on a normal ward diet when base-line values were obtained, subjects underwent 14 days of total starvation (Gilliland, 1968). One group of nine subjects was given allopurinol in a dose of 200 mg. twice daily. The other group of nineteen subjects was not given any drugs during the course of the starvation period. These are referred to as the allopurinol and control groups respectively. Daily morning specimens of serum were collected for measurement of uric acid concentration, and urines were collected for measurement of 24-hour uric acid excretion.

CHEMICAL METHOD

Quantitative measurements of uric acid in serum and urine were made on the Technicon Autoanalyser, using the method of Brown and Freier (1967), which is based on the carbonate-phosphate method of Caraway (1963). It has an advantage over the recommended Autoanalyser method (N-13 B) in that the use of the toxic cyanide-urea reagent is avoided.

A comparison of its accuracy with the uricase method of Liddle, Seegmiller, and Laster (1959) gave correlation coefficients (r) of 0.986 with sera over 7 mg./100 ml., and of 0.988 with sera under 7.1 mg./100 ml. (Brown and Freier, 1967). The reproducibility of the method was assessed by calculating the between-batch rather than the within-batch precision, since this was considered to be a more valid estimate in this study. The "95 per cent. limits" of a pooled sera with a mean value of 5.21 mg./100 ml. were found to be ± 0.29 mg./100 ml.

Results

The mean and standard error of the daily serum uric acid concentrations are shown in Fig. 1. In the control group of subjects the mean serum uric acid concentration rose from 5.4 mg./100 ml. on Day 0 (before starvation), reaching a maximum of 12.2 mg./100 ml. on Day 11. Five subjects attained concentrations of 15 mg./100 ml. or more, the highest recorded figure being 17.1 mg./100 ml., and the lowest peak 8.6 mg./100 ml. In the allopurinol group of subjects (undergoing starvation) the mean level fluctuated only slightly from an initial value of 5.7 mg./100 ml. to a maximum of 8.2 mg./100 ml. on Day 9, and to a final value of 6.4 mg./100 ml.

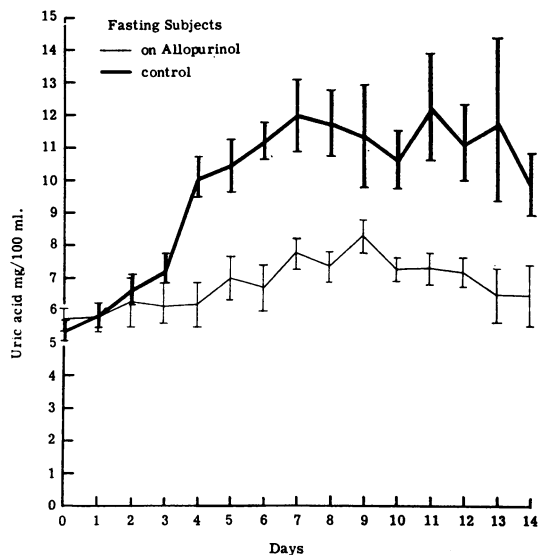


FIG. 1 Daily serum uric acid levels in subjects fasting for 14 days.

The pattern of 24-hour uric acid excretion in the two groups of subjects is shown in Fig. 2. The 24-hour urinary excretion in the control group decreased from a mean of approximately 500 mg. on Day 0 to approximately 300 mg. on Day 4, and remained

at this level throughout the starvation period. In the allopurinol group the mean 24-hour uric acid excretion was 542 mg. for the first 2 days of starvation. It then fell to a mean value of 200 mg. on Day 5 and remained approximately at this level for the rest of the fasting period. Hence uric acid excretion fell to a lower level in the allopurinol group (Fig. 2).

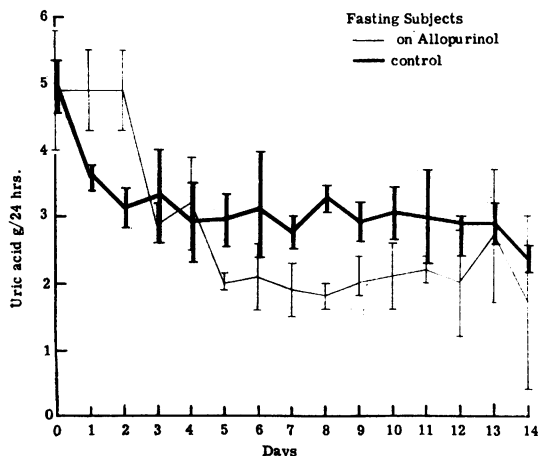


FIG. 2 Urinary uric acid excretion per 24 hrs in subjects fasting for 14 days.

Discussion

Lennox (1924) studied the serum uric acid levels in nineteen subjects on total starvation for periods of 3 to 21 days. Two of these were normal controls and the remainder were epileptics. He showed that the serum uric acid concentration rose to a maximum after one week of starvation and that thereafter an uneven elevation was maintained until the end of the fast. He postulated a number of mechanisms to explain this phenomenon, amongst which was the suggestion that 'other factors could temporarily interfere with the uric acid excretory power of the kidney'. He showed that in some cases there was a decreased uric acid excretion in the urine, but was unable to show evidence of disturbance of renal function.

Numerous workers have subsequently shown that hyperuricaemia during starvation is due to reduced uric acid clearance. Under normal physiological conditions the uric acid in glomerular filtrate is re-absorbed and that appearing in the urine is mainly derived from tubular secretion: a reduction in uric acid clearance is probably due to inhibition of tubular secretion (Gutman, Yü, and Berger, 1959). There is good evidence that a raised level of beta-hydroxybutyric acid in the blood can cause such inhibition and that this may be the mechanism operative in starvation and other ketotic states (Scott, McCallum, and Holloway, 1964; Goldfinger,

Klinenberg, and Seegmiller, 1965). Hyperuricaemia is a feature of lactic acidosis of diabetic ketosis (Padova and Bendersky, 1962) and also of ketosis resulting from a high fat diet (Harding, Allin, Eagles, and Van Wyck, 1925; Scott and others, 1964).

During the second half of the starvation period in our control group (Figs 1 and 2), a near steady state was obtained, in which there was little change either in the raised serum concentrations or in the reduced urinary output of uric acid. If there is no increase in the total uric acid pool during this second period, the low urine excretion could reflect one or more of the following:

- (a) Absence of dietary nucleoproteins;
- (b) Increased intestinal loss;
- (c) Reduced endogenous production.

About 200 to 300 mg. uric acid are obtained from a normal daily diet (Gutman, 1967). Absence of dietary nucleoproteins alone could account for the reduction in urinary excretion of uric acid, which amounted to about 200 mg. per 24 hours in our patients.

About one-third of uric acid loss is intestinal, mainly by bacterial degradation of uric acid in intestinal secretions (Sorensen, 1959). This would be expected to decrease during starvation, and hence to increase the amount of uric acid handled by the kidneys.

A further possibility is that higher uric acid concentrations suppress endogenous uric acid production, probably by the inhibition of enzymatic reactions by feed-back mechanisms.

Side-effects

Allergic rashes occurred in three subjects on allopurinol during the first few days of the fast, and it was necessary to discontinue the drug. These three subjects are not included in the results. The rashes were not serious, and rapidly cleared when the drug was stopped. Diarrhoea, vomiting, colic, headache, fever, and chills have been recorded in subjects receiving allopurinol (Klinenberg, Goldfinger, and Seegmiller, 1965). Minor examples of these other toxic reactions were seen in a few of our subjects on allopurinol. Boyd (1959) showed that the toxicity of drugs is much increased in the fasting animal. Starvation has also been shown to depress the activity of liver microsomal enzymes (Dixon, Shultice, and Fouts, 1960). It seems likely, therefore, that starvation could account for the increased incidence in side-effects shown by our patients on allopurinol.

Gout

No acute attacks of gout were precipitated in any of our fasting subjects (94 in all), including three

who were known to suffer from gout. Occasional attacks have been recorded but only after prolonged fasting. Drenick, Swendseid, Blahd, and Tuttle (1964) described two cases of gout. One subject had starved for 3 months and developed an acute arthritis of an ankle; this settled spontaneously but recurred 2 weeks later, after which the fast was terminated. The other subject, after starving for 40 days, developed an acute arthritis which responded to colchicine. Neither subject had previously suffered from gout. During a fast of only 2 weeks there seems little necessity to use allopurinol or other uricosuric agents. The asymptomatic hyperuricaemia seen in these patients again serves to emphasize

the importance of other poorly-understood factors in the pathogenesis of gout.

Summary

Serum and urinary uric acid levels were studied in nineteen subjects undergoing 14 days' total starvation for obesity. A rise in mean serum uric acid levels over this period was accompanied by a corresponding fall in urinary uric acid. A group of nine comparable subjects given allopurinol showed only a minimal rise in serum uric acid and an even greater fall in urinary uric acid as compared with the control group. No attack of gout was seen in either group.

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