ORIGINAL ARTICLE

# Urinary excretion of salicyluric and salicylic acids by non-vegetarians, vegetarians, and patients taking low dose aspirin

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**Aim:** To compare amounts of salicyluric acid (SU) and salicylic acid (SA) excreted daily in the urine of non-vegetarians and vegetarians not taking salicylate drugs, and patients taking 75 or 150 mg aspirin/day.

**Methods:** Urine excreted over 24 hours was collected from volunteers in the four groups. The volumes were recorded and the concentrations of SU and SA were determined electrochemically after separation by high performance liquid chromatography.

**Results:** Significantly more SU was excreted daily by vegetarians (median, 11.01; range, 4.98–26.60 μmol/24 hours) than by non-vegetarians (median, 3.91; range, 0.87–12.23 μmol/24 hours), although amounts were significantly lower than those excreted by patients taking aspirin. Median amounts of SU excreted by patients taking 75 and 150 mg/day of low dose aspirin were 170.69 (range, 13.15–377.18) μmol/24 hours and 165.17 (range, 5.61–429.12) μmol/24 hours, respectively. The amount of SU excreted by patients taking either 75 or 150 mg of aspirin/day was not significantly different. Significantly more SA was excreted by vegetarians (median, 1.19; range, 0.02–3.55 μmol/24 hours) than by non-vegetarians (median, 0.31; range, 0.01–2.01 μmol/24 hours). The median amounts of SA excreted by vegetarians and the patients taking aspirin were not significantly different.

**Conclusions:** More SU and SA is excreted in the urine of vegetarians than in non-vegetarians, consistent with the observation that fruits and vegetables are important sources of dietary salicylates. However, significantly less SU was excreted by vegetarians than patients taking aspirin, indicating that the daily intake of bioavailable salicylates by vegetarians is considerably lower than that supplied by a single 75 or 150 mg dose of aspirin.

We have reported previously that the concentrations of salicylic acid (SA) are significantly higher in the sera of vegetarians than those in the sera of non-vegetarians, and that they overlapped with the concentrations of SA in the sera of patients who took daily doses of 75 mg of aspirin.[1] However, the concentration of SA in serum provides only limited information concerning the intake of, or exposure to, salicylates, because SA is extensively metabolised and there is considerable interindividual variation in the amounts excreted in urine.[2 3] Aspirin is rapidly hydrolysed to SA in vivo, with SA undergoing further metabolism to various compounds, including salicyluric acid (SU), various acyl and phenolic glucuronides, and hydroxylated metabolites.[2 3] SU is the major metabolite of SA excreted in urine and it is present in the urine of people who have not taken salicylate drugs,[4] although it has no anti-inflammatory effects in humans or in animals.[5]

> "The concentration of salicylic acid (SA) in serum provides only limited information concerning the intake of, or exposure to, salicylates, because SA is extensively metabolised and there is considerable interindividual variation in the amounts excreted in urine"

Janssen *et al* reported an association between the nature of the diet and the amount of "total salicylate" excreted in urine, these authors having coined this term to describe the substance or substances converted into SA by heating acidified urine.[6] Their results revealed that "total salicylate" was positively correlated with the fibre content of the diet, and they suggested that vegetables were the source of salicylates. The variability of serum concentrations of SA makes its measurement less useful in the determination of the intake of salicylates. The measurement of salicylates in urine collected over a period of time is more likely to provide an integrated measurement of salicylate intake. To assess the extent of exposure of people to salicylates we have determined and compared the amounts of SU and SA excreted daily in the urine of vegetarians and non-vegetarians who did not take salicylate drugs, and patients who were taking aspirin, 75 or 150 mg/day.

## METHODS AND MATERIALS

The non-vegetarians (n = 27; median age, 36 years; range, 16–56; 10 men) were from Dumfries, Scotland, UK. The vegetarians (n = 21; median age, 43.5 years; range, 25–71; 15 men) were Buddhist monks, of mixed European origin, who were in retreat at the Samye Ling Monastery, Eskdalemuir, Dumfries and Galloway, Scotland, UK. The patients who took 75 mg of aspirin/day (n = 15; median age, 61 years; range, 31–79; five men) were from a general medical practice in Dumfries. Those patients taking 150 mg aspirin/day (n = 25; median age, 66 years; range, 51–79; 22 men) were recruited from the diabetes clinic at Dumfries and Galloway Royal Infirmary. It has been suggested that patients with diabetes might need a higher dose than 75 mg of aspirin to help prevent

**Abbreviations:** SA, salicylic acid; SU, salicyluric acid



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**Table 1** Amounts (μmol/24 hours) of salicyluric (SU) and salicylic (SA) acid excreted in the urine of non-vegetarians (n=27), vegetarians (n=21), and patients taking aspirin (75 mg/day (n=15) and 150 mg/day (n=24))

| | | | Patients taking aspirin | |
|---|---|---|---|---|
| | Non-vegetarians | Vegetarians | 75 mg | 150 mg |
| SU (24 h) | 3.91 (0.87–12.23) | 11.01 (4.98–26.60) | 170.69 (13.15–377.18) | 165.17 (5.62–429.12) |
| SA (24 h) | 0.31 (0.01–2.01) | 1.19 (0.02–3.55) | 0.41 (0.00–3.88) | 0.36 (0.04–7.10) |

The values shown are median (range). SU: vegetarians *v* non-vegetarians, p<0.001; difference between the medians, 6.07 μmol/24 hours; 95% confidence intervals (CI), 3.92 to 9.31. SA: vegetarians *v* non-vegetarians, p=0.0166; difference between the medians 0.63 μmol/24 hours; 95% CI, 0.06 to 1.38. SU: aspirin 75 mg *v* 150 mg, difference between the medians not significant (p=0.743). SA: vegetarians *v* aspirin 75 mg; difference between the medians not significant (p=0.157). SA: vegetarians *v* aspirin 150 mg; difference between the medians not significant (p=0.369).

cardiovascular disease.[7] The diets of the non-vegetarians and patients taking aspirin were not recorded, although the patients taking aspirin had probably been given dietary advice to increase their consumption of fruit and vegetables. A drug history was obtained for all of the vegetarians and non-vegetarians to ensure that they were not taking salicylate drugs. These investigations were approved by the local research ethics committee and informed consent was obtained.

Urine excreted over a period of 24 hours was collected and its volume was recorded. It was divided into portions and stored at –70°C until examination. The concentrations of SU and SA were determined electrochemically after separation by high performance liquid chromatography, essentially as described previously.[4] However, in our present work, the concentration of the internal standard (4-methylsalicylic acid) was increased to 20 μmol/litre. The concentrations reported for the non-vegetarians include 10 values that were published previously in our description of the analytical method.[4] Because the amounts of SU and SA excreted daily did not appear to be distributed normally, median amounts and the ranges of amounts observed are reported. Tests of significance were performed by means of the Mann-Whitney U test.

## RESULTS

Table 1 shows the amounts of SU and SA excreted daily in the urine of the individuals in the four groups. The amounts of SU excreted by vegetarians were significantly higher than those excreted by non-vegetarians. However, they were substantially lower than the amounts excreted by patients taking aspirin. The results of one patient who took 150 mg of aspirin were excluded from the analyses because SU was not detected in the patient's urine. This patient excreted a much greater amount of SA (101.74 μmol in 24 hours) than that excreted by the other patients, and it was thought that he might lack the capacity to conjugate SA with glycine. One other patient who took 150 mg aspirin/day excreted 5.62 μmol of SU and 0.42 μmol of SA in 24 hours. It is possible that this patient was not compliant in taking aspirin; however, these values are included in our analyses. The amounts of SU excreted by patients taking either 75 or 150 mg of aspirin daily were not significantly different. The amounts of SA excreted by all four groups of people were much smaller than those of the conjugated metabolite. The amount of SA excreted daily by vegetarians was greater than that excreted by non-vegetarians (table 1). The differences in the median amounts of SA excreted daily by the vegetarians and the patients who took 75 or 150 mg of aspirin/day were not significant.

## DISCUSSION

Our results (table 1) show that more SU is excreted in the urine of vegetarians than in the urine of non-vegetarians, and this finding is entirely consistent with the observation that fruits and vegetables are the major dietary sources of salicylates.[6] These results independently support and strengthen our earlier finding,[1] obtained from serum measurements, that foodstuffs derived from plants contribute greatly to our intake of salicylates.

Janssen and colleagues[6] determined that a median amount of 10 μmol/24 hours (range, 3–34) of total salicylate was excreted in the urine of 17 volunteers who had not taken salicylate drugs and who had consumed a variety of diets. All but one of the subjects studied were described as eating a diet that contained plant based foodstuffs, and many of them excluded fish and meat from their diets. In their analytical method, Janssen *et al* had added HCl to the urine (to a concentration of 5 mol/litre) and then they heated the mixture for two hours at 120°C.[6] As a result, they were unable to speciate the salicylates that had been present. Nevertheless, the median amounts quoted by Janssen and colleagues[6] and those reported here for the vegetarian group (table 1) are similar.

> "These results independently support and strengthen our earlier finding, obtained from serum measurements, that foodstuffs derived from plants contribute greatly to our intake of salicylates"

Although it is interesting to note the hypothesis[8] that our intake of synthetic salicylates (compounds added to processed food, toiletries, and cosmetics) is continually increasing, and might contribute to the decreasing incidence of cardiovascular disease, our results shed very little new light on this possibility. In our earlier work,[1] a considerable overlap in the concentrations of SA in the sera of vegetarians and people taking 75 mg of aspirin/day was noted. There is some degree of overlap in the amounts of SU and SA excreted daily by vegetarians and patients taking low dose aspirin, although it is much less pronounced than that observed with serum SA concentrations. It is not known whether the dietary intake of salicylates or the serum concentrations of SA found in vivo, especially in vegetarians, have beneficial effects on health. Paterson and Lawrence[9] have suggested that SA, and its precursors, may be important components of a diet rich in plant based foodstuffs, which helps prevent disease, especially colorectal cancer. SA is an anti-inflammatory compound common to both aspirin and a diet rich in plant based foodstuffs, both of which reduce the risk of colorectal cancer. We are currently investigating the potential health benefits of dietary SA in both animal and human studies.

Interestingly, there was almost no difference in the amounts of SU excreted daily by the two groups of patients taking either 75 or 150 mg of aspirin/day. It is unlikely that there is a major difference in the pharmacokinetics of aspirin



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**Take home messages**

- Vegetarians excrete more salicyluric acid (SU) and salicylic acid in their urine than do non-vegetarians, probably because fruits and vegetables are important sources of dietary salicylates
- However, much less SU was excreted by vegetarians than by patients taking aspirin, indicating that the daily intake of bioavailable salicylates by vegetarians is considerably lower than that supplied by a single 75 or 150 mg dose of aspirin

between diabetic and non-diabetic subjects. However, it has been reported that the metabolic conjugation (formation of SU) and renal clearance of SA are "saturable".[10] Saturation of these processes appears to occur when doses of aspirin greater than 100 mg/day are taken, and this observation might explain why the amounts of SU excreted daily by the two groups of patients taking aspirin (75 and 150 mg/day) were very similar. It is suggested that when daily doses of aspirin greater than 100 mg are taken, the amounts of SU and SA that appear in the urine may not provide a reliable assessment of exposure to salicylates. The amounts of SA, relative to SU, excreted in all four groups were relatively low, which probably reflects the number of metabolic routes that SA can take. Thus, when the rate of metabolism of SA to SU is maximal, SA will probably be metabolised by these other routes.

At lower doses of aspirin or SA, the time course of excretion of SU and SA in urine appears to be useful in estimating the exposure to salicylates, as shown in our study by the significant differences observed between non-vegetarians, vegetarians, and patients who took 75 mg of aspirin/day.

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