Original Articles

Steady-state plasma levels of salicylate in patients with rheumatoid arthritis: effects of dosing interval and tablet strength

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Forty patients who were admitted to hospital with rheumatoid arthritis received a total of 3.9 g/d of enteric-coated acetylsalicylic acid (ASA) (Entrophen) according to one of four dosing schedules: group 1 (n = 13), three 325-mg tablets four times daily; group 2 (n = 11), two 650-mg tablets three times daily; group 3 (n = 10), three 650-mg tablets twice daily; and group 4 (n = 6), two 975-mg tablets twice daily. Five to seven days after the start of therapy, when steady-state plasma salicylate levels had been achieved, 10 blood samples, 1 per hour, were collected. Three healthy volunteers who received plain ASA formed a control group. There was little fluctuation in the salicylate levels over the sampling period, regardless of the dosing interval, and no significant difference in the fluctuations between the five groups. Likewise, there was no significant difference in the mean salicylate levels at each sampling time, regardless of the dosing interval or tablet strength. These results suggest that different tablet strengths of enteric-coated ASA and different dosing intervals produce comparable plasma salicylate levels. Less frequent dosing may improve patient acceptance of salicylate therapy in the treatment of arthritis.

Quarante patients hospitalisés souffrant de polyarthrite rhumatoïde ont reçu 3.9 g par jour d'acide acétylsalicylique (ASA) à enrobage gastro-résistant (Entrophen) selon l'un des quatre régimes posologiques suivants: le groupe 1 (n = 13), trois comprimés à 325 mg quatre fois par jour; le groupe 2 (n = 11), deux comprimés à 650 mg trois fois par jour; le groupe 3 (n = 10), trois comprimés à 650 mg deux fois par jour; et le groupe 4 (n = 6), deux comprimés à 975 mg deux fois par jour. De 5 à 7 jours après le début du traitement, alors que les concentrations plasmatiques de salicylate étaient à l'état d'équilibre, 10 échantillons sanguins, 1 à chaque heure, ont été prélevés. Trois volontaires sains qui ont reçu de l'ASA ordinaire formaient le groupe témoin. Quel qu'eut été l'intervalle entre les doses, peu de variation a été observée dans les taux de salicylate au cours de la période de prélèvement, et aucune différence significative n'a été mesurée dans les variations entre les cinq groupes. De même, il n'y avait aucune différence significative dans les salicylémies à chaque temps de prélèvement, quel qu'eut été l'intervalle entre les doses ou la concentration par comprimé. Ces résultats indiquent que les différentes concentrations des comprimés d'ASA à enrobage gastro-résistant et les différents intervalles entre les doses produisent des concentrations plasmatiques comparables de salicylate. Des prises moins fréquentes sont susceptibles d'améliorer l'acceptation du patient de traitement au salicylate pour le polyarthrite.

Acetylsalicylic acid (ASA) continues to be the drug of choice in the management of many rheumatic diseases. The well recognized gastrointestinal distress experienced with the use of plain ASA has been substantially lessened by the use of enteric-coated tablets.[1,2] The reduced toxicity and reliable absorption of enteric-coated ASA make it the logical alternative to plain ASA.[3-5]

Traditionally ASA has been prescribed in a four-times-daily dosing schedule. However, both computer simulations[6] and clinical studies with choline magnesium trisalicylate[7] suggest that differences in the fractional dose and in the dosing interval have only minor effects on the steady-state plasma salicylate levels produced by a given dose of ASA. We have been unable to find any published studies that have recorded the steady-state salicylate levels achieved with enteric-coated ASA. Indeed, if the dosing interval were shown to have a negligible effect on these levels this drug could be taken

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less frequently and patient compliance could be improved.[8-11]

We therefore studied the effects of dosing interval and tablet strength on the steady-state plasma salicylate levels of patients with rheumatoid arthritis, and describe the results here.

Materials and methods

We studied 40 patients with rheumatoid arthritis, 29 women and 11 men whose ages ranged from 28 to 82 (mean 53.6) years, who were admitted to the rheumatic disease unit of the Wellesley Hospital, Toronto. During the 5- to 7-day study period the doses of other anti-inflammatory agents and suppressant drugs were kept constant.

After giving written informed consent each patient was sequentially assigned to one of four treatment groups. No patient was in more than one group. All the patients had been receiving 3.9 g/d of enteric-coated ASA (Entrophen) in various forms and dosing schedules before their admission to hospital (Table I). Between 5 and 7 days after the start of supervised therapy, when steady-state plasma salicylate levels had been achieved, 10 blood samples were collected, 1 per hour, between 0800 and 1900 hours (except at 1200 and 1800 hours); these times were considered the most convenient for both patients and investigators.

Three healthy men (mean weight 74.0 ± 8.1 kg), who formed group 5 (control group), agreed to take six 325-mg tablets of plain ASA twice daily. After 7 days of therapy, when steady-state plasma salicylate levels had been achieved, blood samples were drawn hourly at the times used for the other groups.

The plasma salicylate levels were assayed by the Trinder method,[12] which in our laboratory has a coefficient of variation of 3%. The data were analysed by analysis of variance and by a test for the least significant difference, the difference being considered significant at $P < 0.05$. The data were adjusted to allow for variability in the mean salicylate levels between the patients in each group, thereby enabling an analysis of the levels over time. The time–concentration profile within each group was then analysed according to the following: If y_{ijk} is the observation on the k^{th} patient at time j with drug regimen i, the adjusted salicylate level is $y_{ijk} - (y_i - y_{i.k})$ where $y_{i.k}$ is the mean over time for the k^{th} patient with the i^{th} drug regimen and y_i is the

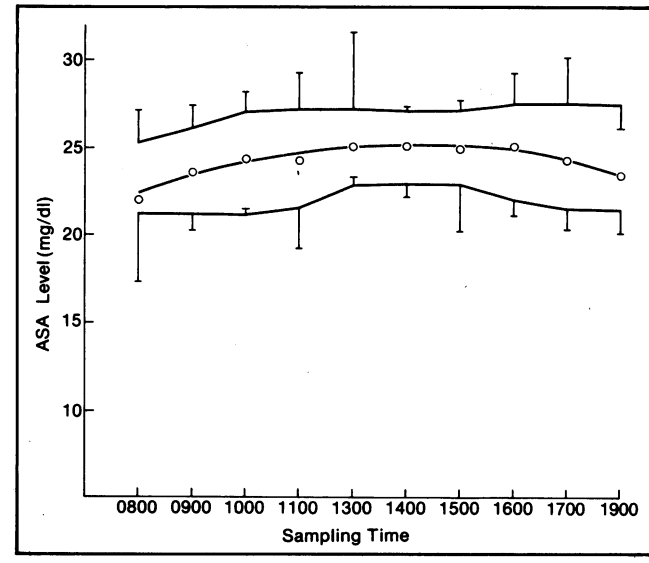

FIG. 1—Mean salicylate levels over time in 13 patients receiving three 325-mg tablets of enteric-coated acetylsalicylic acid (ASA) four times a day (group 1). Circles represent unadjusted means. Middle curve passes through smoothed adjusted means, whereas curves above and below pass through smoothed adjusted means ± standard deviation. Vertical bars represent maximum and minimum unadjusted salicylate levels.

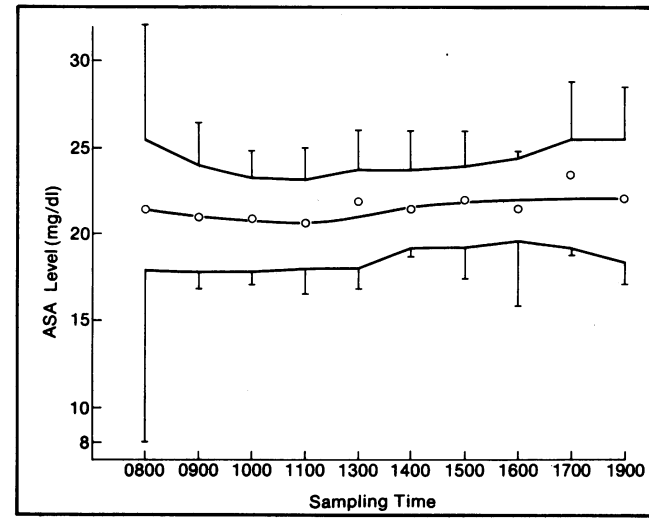

FIG. 2—Mean salicylate levels over time in 11 patients receiving two 650-mg tablets of enteric-coated ASA three times a day (group 2).

Table I—Characteristics of 40 patients with rheumatoid arthritis and dosing schedules of enteric-coated acetylsalicylic acid (ASA) used during the study period

Variable	Group 1 (n = 13)	Group 2 (n = 11)	Group 3 (n = 10)	Group 4 (n = 6)
Sex	8 F, 5 M	7 F, 4 M	6 F, 4 M	3 F, 3 M
Weight (mean ± standard deviation [SD]), kg	63.6 ± 9.3	61.0 ± 10.8	63.4 ± 14.3	68.1 ± 8.1
Dosing schedule	Three 325-mg tablets four times daily*	Two 650-mg tablets three times daily†	Three 650-mg tablets twice daily‡	Two 975-mg tablets twice daily‡

*At 0800 (with breakfast), 1130 (with lunch), 1630 and 2000 hours.
†At 0800 (with breakfast), 1130 (with lunch) and 1630 hours.
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overall mean over time with the regimen. Smoothed means and smoothed means ± standard deviation were used to reduce the amount of random variation from the essential features of the results.[13]

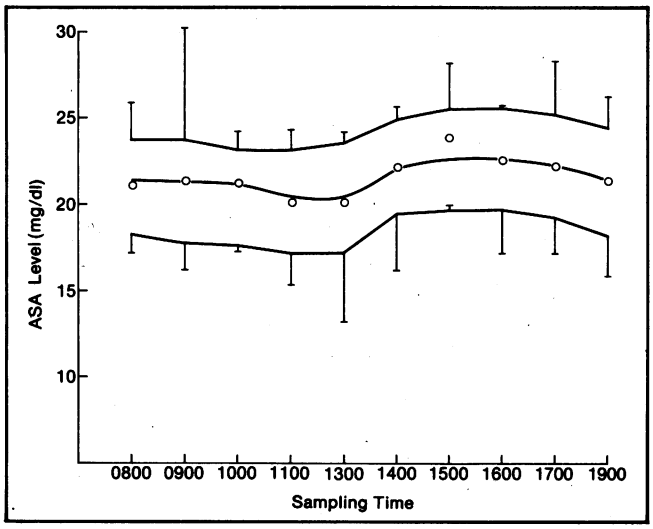

FIG. 3—Mean salicylate levels over time in 10 patients receiving three 650-mg tablets of enteric-coated ASA twice a day (group 3).

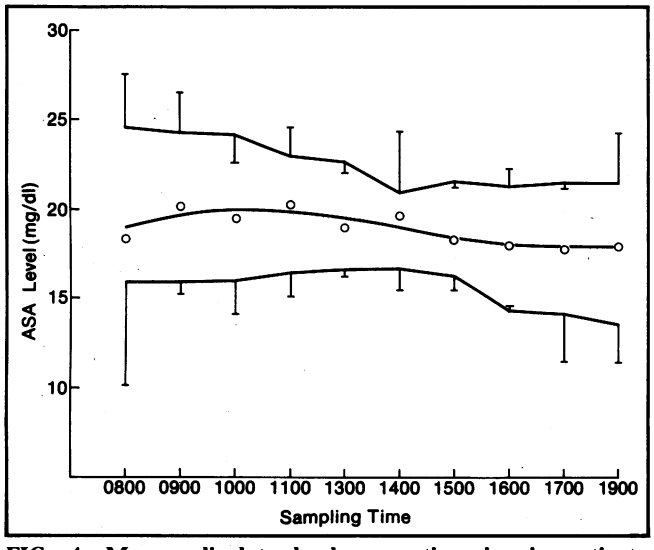

FIG. 4—Mean salicylate levels over time in six patients receiving two 975-mg tablets of enteric-coated ASA twice a day (group 4).

Results

As expected, the steady-state plasma salicylate levels varied considerably, from 8 to 32 mg/dl, among the patients. However, the individual time–concentration profiles showed little fluctuation in the mean levels during the sampling period, regardless of the dosing interval (Figs. 1 to 5).

We found no significant differences in the mean unadjusted salicylate levels overall between the five drug regimens. There was no significant fluctuation in the mean levels during the sampling period, regardless of the dosing interval or the tablet strength (Table II). The overall mean for all the sampling times and dosing intervals was 21.9 mg/dl.

With our study design there was an 84% chance of detecting a mean difference of 10 mg/dl or larger between the drug regimens and an 85% chance of detecting a mean difference of 2 mg/dl or greater between the sampling times.

Discussion

The results of our study suggest that different tablet

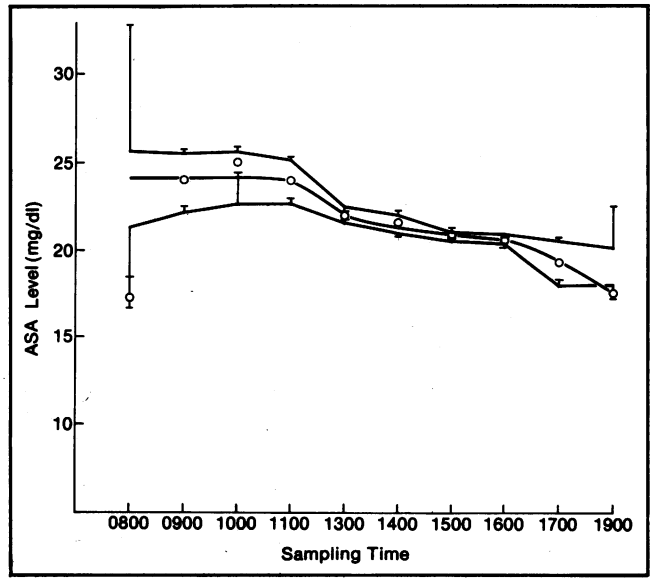

FIG. 5—Mean salicylate levels over time in three control subjects receiving six 325-mg tablets of plain ASA twice a day (group 5).

Table II—Effect of dosing interval and tablet strength on mean unadjusted ASA levels

Variable	ASA level (mg/dl), mean ± SD			
	Group 1	Group 2	Group 3	Group 4
Sampling time (h)				
0800	22.0 ± 6.0	21.5 ± 7.3	21.1 ± 7.4	18.3 ± 8.1
0900	23.6 ± 6.6	21.0 ± 7.8	21.4 ± 6.3	20.2 ± 5.8
1000	24.4 ± 6.5	21.0 ± 7.1	20.3 ± 5.7	19.5 ± 5.0
1100	24.3 ± 5.9	19.7 ± 6.6	20.2 ± 6.9	20.3 ± 5.4
1300	25.1 ± 5.9	20.9 ± 6.0	20.3 ± 6.7	19.0 ± 3.6
1400	25.1 ± 5.4	21.5 ± 5.9	22.3 ± 6.1	19.6 ± 1.9
1500	24.9 ± 5.4	22.1 ± 5.0	23.9 ± 4.7	18.3 ± 2.2
1600	25.1 ± 6.3	21.6 ± 5.6	22.7 ± 5.3	18.0 ± 2.6
1700	24.4 ± 6.5	23.5 ± 5.4	22.2 ± 5.3	17.8 ± 3.5
1900	23.5 ± 5.5	22.1 ± 5.8	21.4 ± 4.9	18.0 ± 3.5
Overall	24.2 ± 5.3	21.5 ± 6.1	21.6 ± 6.1	18.9 ± 6.0

strengths of enteric-coated ASA are interchangeable and produce comparable plasma salicylate levels. The issue of tablet strength as a variable in dosing schedules for salicylates has been virtually ignored, except in one study that demonstrated comparable plasma levels of salicylate with 975-mg and 650-mg tablets of enteric-coated ASA.[14]

Our study demonstrated minimal fluctuation in the mean plasma salicylate levels from hour to hour independent of dosing interval or tablet strength. Because we were able to detect with 85% confidence a difference of at least 2 mg/dl in the salicylate level at each sampling time, we can conclude that our finding of no significant difference in the salicylate levels at each sampling time was indeed real. However, our interpretation of the results of this study is limited by the small size of some of the groups; we could detect a mean difference in salicylate level of only 10 mg/dl or greater with confidence. Although, ideally, one would want to detect a mean difference of 5 mg/dl, we had only a 27% chance of doing so because of our study design.

We found that the dosing frequency of enteric-coated ASA can be reduced without significantly compromising the therapeutic plasma levels of salicylate. With all of the dosing schedules we studied, the mean steady-state plasma salicylate level was well within the therapeutic range (15 to 30 mg/dl).[15] This finding confirms those of Cassell and colleagues,[7] who used choline magnesium trisalicylate, and Bensen and associates,[16] who used enteric-coated ASA; they demonstrated that twice-daily administration of ASA is effective and reproducible. These results can be explained on the basis of the well documented kinetics of ASA[17] and further confirm the impression that differences in the dose and in the dosing interval have only minor effects on the steady-state salicylate levels produced by a given daily dose of ASA. Thus, the maintenance of therapeutic plasma salicylate levels when ASA is given twice daily can be attributed solely to the fact that increasing doses prolong the salicylate half-life.

The importance of the slow absorption pattern seen when a single enteric-coated tablet is given is minimized with multiple dosing. Although absorption is slow, at steady-state levels the rate-limiting step, which determines the overall pattern of elimination of the drug, is not the rate of absorption but the overall clearance of salicylate. This was confirmed by our study, in which the time–concentration profiles in the control group, volunteers who received plain ASA, were similar to those in the patients receiving enteric-coated ASA.

In our study we did not address the question of efficacy or adverse effects of the various drug regimens. Most of the patients had severe rheumatoid arthritis that did not respond to salicylates alone. Therefore, additional agents were given when the kinetic study ended, which made it difficult to evaluate the efficacy of salicylate alone. Other investigators noted an increase in the frequency of tinnitus in patients given a 12-hour regimen;[7,18] we found no increases in the frequency of any side effect, but the short duration of our study limits the value of our observations.

The dosing regimens we studied provided therapeutic plasma concentrations in most patients regardless of the dosing frequency. In the few exceptions it is possible that inadequate doses of salicylates were being taken before the patients' entry to the study. We did find that when enteric-coated ASA was given twice a day the therapeutic levels were comparable to those when it was given four times a day. Less frequent dosing may improve patient acceptance of salicylate therapy in the treatment of arthritis.

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"An age of pills"

I will lift up mine eyes unto the pills. Almost everyone takes them, from the humble aspirin to the multi-coloured, king-sized three deckers, which put you to sleep, wake you up, stimulate and soothe you all in one. It is an age of pills.

—Malcolm Muggeridge (1903–)