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# COMPARISON OF SERUM SALICYLATE LEVELS AND GASTRO-INTESTINAL BLOOD LOSS BETWEEN SALSALATE (DISALCID) AND OTHER FORMS OF SALICYLATES

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**ABSTRACT. In a first stage the effect of a single dose of 3 g of salsalate on serum salicylate level was compared with a single intake of 3 g of soluble or enteric-coated acetylsalicylates in 12 healthy subjects. Salsalate seems to resorb faster than the enteric-coated forms but more slowly than the soluble forms of acetylsalicylate. However, in comparison with these latter forms, salsalate activity is more protracted. In the second part of the study, 42 patients were admitted to a trial in which 3 to 5 g of salsalate was given daily and in which serum salicylate levels and blood loss in stools were measured using the method of labelling red blood cells with $Cr^{51}$. The ideal dosage to obtain a serum salicylate level of 20 mg/100 ml seems to lie between 3 and 4 g of salsalate a day. Salsalate caused abnormal gastro-intestinal blood loss in only 2 of the 42 patients studied, which is significantly fewer compared with the soluble, intravenous or enteric-coated forms of acetylsalicylates.**

Ingestion of acetylsalicylic acid results in gastric erosions and occult blood loss from the gastrointestinal tract in the majority of patients (3, 5). In previous studies (6, 10) we made a comparison between gastrointestinal blood loss associated with various forms of acetylsalicylates. Many of the side effects of acetylsalicylate, and especially the gastrointestinal ones, may be caused by the acetyl-group, which acetylates and inhibits prostaglandin synthetase (7, 8).

Salsalate (Disalcid) is an esterification product of two molecules of salicylic acid in which no acetyl-group constituent is present. After absorption, salsalate is slowly hydrolysed to 2 molecules of free salicylic acid. Absorption occurs in the small intestine. In view of these considerations we felt it to be of interest to carry out a study on salsalate-induced gastrointestinal blood loss.

## MATERIALS AND METHODS

In a first stage the effect on salicylate level of a single dose of 3 g salsalate was compared with a single intake of 3 g of soluble or enteric-coated acetylsalicylates in 12 healthy subjects. The second part of the study is concerned with measuring gstrointestinal blood loss in stool.

Forty-two patients, 24 men and 18 women, were admitted to the trial. All patients participating in the trial were hospitalized for later orthopeadic surgery and did not need anti-inflammatory therapy. They all gave informed consent to the trial, which was approved by the experimentation committee of the department. All patients remained in hospital during the trial.

The following individuals were excluded from the trial:

- all patients with a history of erosions, ulcer, or bleeding affecting the gastrointestinal tract
- all patients with a history of adverse reactions to salicylates
- all patients with a history of thrombo-embolic disease
- diabetic patients
- pregnant patients.

No anti-inflammatory, antidiabetic or anticoagulant drugs were administered during the trial. Other drugs were allowed, provided the dosage was not changed for 14 days prior to or during the trial itself. Salicylate concentration in blood was determined *ad modum* Brodie et al. (2). Blood loss in stool was measured by labelling red blood cells with $^{51}Cr$ (9). During the trial, tooth-brushing was prohibited. Blood loss in stool was determined by a "blind" third party (from the Department of Radiotherapy) who was not informed about salicylate forms or serum levels until the end of the entire study.

Most patients received 4 g of salsalate per day, but a few were given 3 g and 4 other patients 5 g. We tried to keep the salicylate level above 20 mg/100 ml, which is considered to be the anti-inflammatory level (1). The majority of patients could not tolerate 5 g a day because of tinnitus or impaired hearing.

Stools were collected from the instant of reaching constant serum salicylate levels (i.e. 4th day of treatment). Blood salicylate levels and blood loss in stools were thus determined before and during a 7-day treatment period with 4 g of salsalate (2 g in the morning, 1 g in the afternoon and 1 g in the evening). Salicylates were given approximately 2 hours after each meal. All patients were on a reasonably constant diet and water was allowed ad lib. $^{51}Cr$-labelling of red blood cells was performed on day 1. Salicylates were administered from day 5 to day 11 (Table

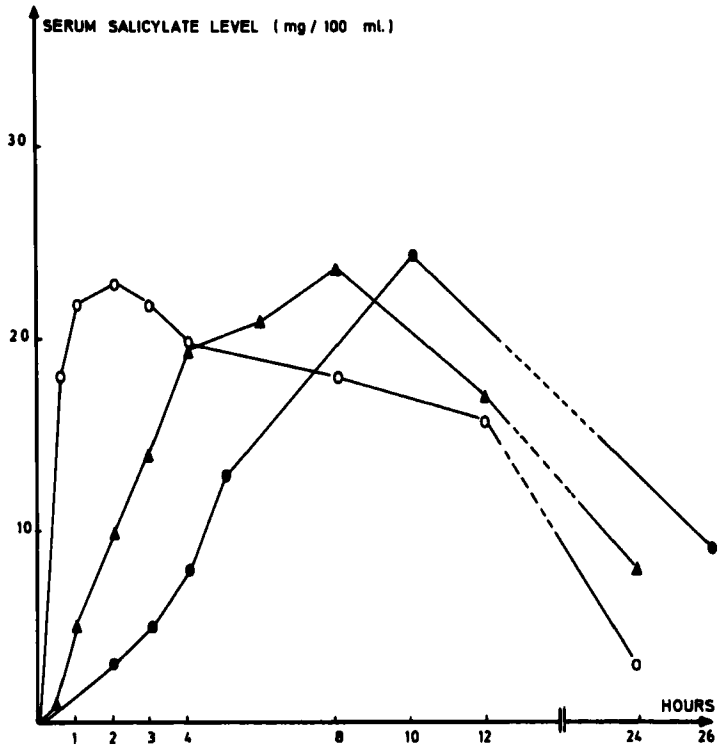


*Fig. 1.* Serum salicylate levels after a single dose of 3 g of soluble acetylsalicylate (O), 3 g of enteric-coated acetylsalicylate (●) and 3 g of salsalate (▲).

I). Fasting blood salicylate levels were measured on day 2, before treatment, and on days 6, 9 and 11 (2nd, 5th and 7th day of treatment). Determination of blood salicylate levels was carried out on day 2 before administration of salicylates in order to exclude patients taking salicylates without our knowledge.

Stools for the whole day were collected on days 3 and 4 before treatment and on days 8–11 during treatment. Subjects with values of blood loss in stool exceeding the upper limit of physiological blood loss (1.83 ml/day) (6) were exluded from the trial. It was felt that other factors resulting in blood loss in stool must be present in such patients which could interfere with the results after administration of salicylates.

Table I. *Protocol of the study*

| Day | Treatment | Stool collection (24 h) | Blood collection, fasting |
|---|---|---|---|
| 1 | $^{51}$Cr-labelling | | |
| 2 | | | × |
| 3 | | × | |
| 4 | | × | |
| 5 | | | |
| 6 | Daily administration of salsalate | | × |
| 7 | | | |
| 8 | | × | |
| 9 | | × | × |
| 10 | | × | |
| 11 | | × | × |

## RESULTS

In Fig. 1, serum salicylate levels are compared after a single dose of 3 g salsalate and a single dose of 3 g of enteric-coated and 3 g of soluble acetylsalicylate. Serum salicylate levels and blood loss in stool before and after treatment are grouped in Tables II and III. Salicylate concentrations in blood showed a normal frequency distribution.

Since we know from our previous study that the upper limit of physiological blood loss is 1.83 ml a day, 2 patients were withdrawn from the study because of higher values before treatment. Two other patients left the trial for other reasons.

## DISCUSSION

In a first stage the serum salicylate level reached after a single dose of 3 g of salsalate was compared with the level after a single dose of 3 g of enteric-coated or soluble form of acetylsalicylates (Fig. 1). It is obvious that the curve of the salsalate serum

Table II. *Serum salicylate levels on pre-treatment day, 2nd, 5th and 7th day of treatment, and blood loss in stool before and after administration of 3 or 5 g of salsalate*

| | Salicylate level (mg/100 ml) | | | | Blood loss, stool (ml/d) | |
|---|---|---|---|---|---|---|
| Patient | Pre | 2nd d | 5th d | 7th d | Before | After |
| *Salsalate 3 g per day* | | | | | | |
| 1 | 3.1 | 11.8 | 15.0 | 14.1 | 0.53 | 0.51 |
| 2 | 3.1 | 8.5 | 7.2 | 8.4 | 1.80 | 0.25 |
| 3 | 1.5 | 8.3 | 16.3 | 21.1 | 0.20 | 0.72 |
| 4 | 7.3 | 12.9 | 14.4 | 14.1 | 0.34 | 0.39 |
| 5 | 3.7 | 16.4 | 19.0 | 20.9 | 0.08 | 0.33 |
| 6 | 4.3 | 13.1 | 14.1 | 12.4 | 1.25 | 0.57 |
| 7 | 3.4 | 8.8 | 7.7 | 8.5 | 1.50 | 0.77 |
| 8 | 4.3 | 8.8 | 11.8 | 9.4 | 0.33 | 0.22 |
| Mean | 3.8 | 11.1 | 13.2 | 13.6 | | |
| *Salsalate 5 g per day* | | | | | | |
| 1 | 4.4 | 16.7 | 40.2 | 43.8 | 0.43 | 1.28 |
| 2 | 3.5 | 25.5 | 44.2 | 49.7 | 1.24 | 0.31 |
| 3 | 4.2 | 16.7 | 29.4 | 30.0 | 0.27 | 0.27 |
| 4 | 4.1 | 22.7 | 27.2 | 23.4 | 0.70 | 0.85 |
| Mean | 4.0 | 20.4 | 35.2 | 36.7 | | |

Table III. *Serum salicylate levels on pre-treatment day, 2nd 5th and 7th day of treatment, and blood loss in stool before and after administration of 4 g of salsalate*

| | Salicylate level (mg/100 ml) | | | | Blood loss, stool (ml/d) | |
|---|---|---|---|---|---|---|
| Patient | Pre | 2nd d | 5th d | 7th d | Before | After |
| *Salsalate 4 g per day* | | | | | | |
| 1 | 4.5 | 9.2 | 17.4 | 18.5 | 0.19 | 0.18 |
| 2 | 3.7 | 18.5 | 25.8 | 22.1 | 0.58 | 0.52 |
| 3 | 2.7 | 14.2 | 21.0 | 21.0 | 0.28 | 0.47 |
| 4 | 3.7 | 20.5 | 25.7 | 30.1 | 0.46 | 0.38 |
| 5 | 4.1 | 18.6 | 28.5 | 28.5 | 1.66 | 0.50 |
| 6 | 1.6 | 27.0 | 26.1 | 32.5 | 1.13 | 1.62 |
| 7 | 2.3 | 20.2 | 29.4 | 27.9 | 0.36 | 0.79 |
| 8 | 2.0 | 21.6 | 22.7 | 32.6 | 0.45 | 0.22 |
| 9 | 2.3 | 22.5 | 43.7 | 36.5 | 0 | 0.31 |
| 10 | 5 | 18.3 | 33.7 | 36.7 | 0.52 | 0.97 |
| 11 | 8.2 | 17.3 | 29.6 | 37.7 | 0.59 | 0.54 |
| 12 | 2.2 | 25.8 | 20.1 | 25.8 | 0.57 | 0.69 |
| 13 | 5.8 | 6.1 | 32.1 | 37.2 | 0.68 | 0.97 |
| 14 | 4.8 | 6.7 | 20.5 | 22.7 | 0.25 | 0.49 |
| 15 | 2.5 | 2.0 | 30.7 | 38.0 | 0.57 | 0.61 |
| 16 | 4.3 | 6.0 | 27.6 | 24.6 | 0.50 | 0.51 |
| 17 | 2.8 | 3.6 | 38.0 | 42.7 | 0.65 | 0.60 |
| 18 | 1.5 | 5.0 | 26.2 | 30.7 | 0.20 | 0.26 |
| 19 | 4.0 | 9.9 | 26.4 | 34.7 | 0.50 | 0.72 |
| 20 | 4.0 | 2.7 | 43.6 | 45.8 | 1.42 | 2.55 |
| 21 | 5.2 | 7.4 | 22.4 | 24.3 | 0.32 | 0.36 |
| 22 | 5.1 | 8.4 | 24.5 | 27.2 | 0.10 | 0.45 |
| 23 | 3.1 | 9.9 | 44.7 | 42.9 | 0.50 | 0.62 |
| 24 | 4.1 | 2.3 | 38.9 | 27.0 | 0.90 | 1.92 |
| 25 | 2.2 | 1.7 | 41.5 | 33.5 | 1.25 | 1.50 |
| 26 | 5.2 | 2.1 | 15.0 | 17.2 | 0.40 | 0.27 |
| Mean | 3.72 | 11.82 | 29.06 | 30.89 | | |

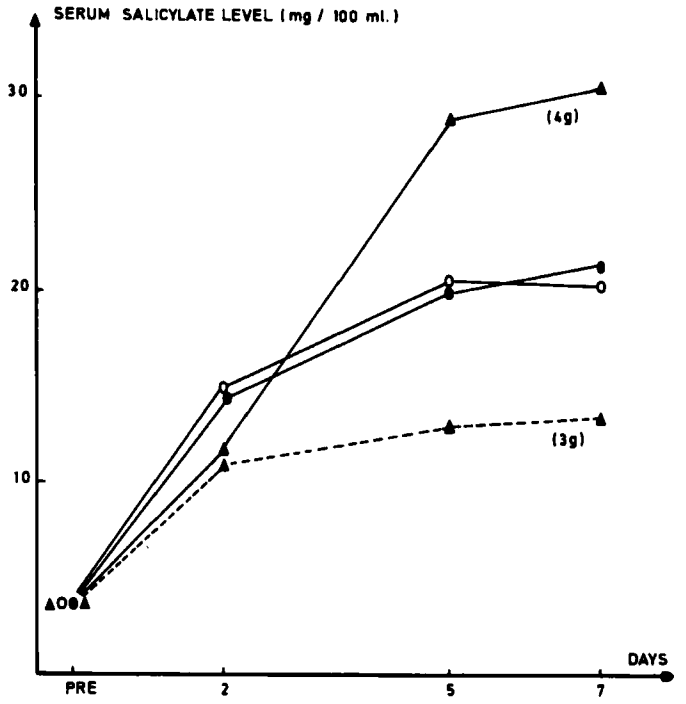


*Fig. 2.* Serum salicylate levels during treatment with 5 g of soluble acetylsalicylate (○), 3 g of enteric-coated and intravenous acetylsalicylate (●), 3 g of salsalate (△) and 4 g of salsalate (▲).

salicylate levels lies between the curves of the soluble and the enteric-coated forms. Salsalate seems to resorb faster than the enteric-coated forms more slowly—this agrees very well with the fact that salsalate is absorbed in the intestine—than the soluble forms of acetylsalicylate. On the other hand the serum salicylate level is maintained longer than with the soluble forms but falls to lower values than the serum levels of enteric-coated forms after 24 hours. Peak levels of serum salicylate are reached after 8 hours.

In a previous study, we found no difference between serum salicylate levels when comparing 3 g of enteric-coated with 5 g of soluble acetylsalicylate (6).

Comparison of salsalate serum salicylate levels on the 7th day of treatment with 3 g of enteric-coated or intravenous acetylsalicylate administration or with 5 g of soluble acetylsalicylate, shows statistically significantly lower values ($p<0.01$) with 3 g of salsalate and statistically significantly higher values ($p<0.01$) with 4 g of salsalate (Fig. 2). From this it can be concluded that the ideal salsalate dosage required, to obtain a serum salicylate level of 20 mg/100 ml, is about 3.5 g a day.

As in previous studies (6, 10), we found that the frequency distribution of blood loss in stool was neither normal nor log-normal. Therefore the determination of mean blood loss and standard deviation for an entire population is of no practical value. The Rankit-test demonstrates that the non-bleeders are a Gaussian population ($r=0.92$ $2\alpha<0.001$) and that this population is statistically different from the bleeders' population. This confirms the division between "bleeders" and "non-bleeders" after ingestion of salicylates (6).

Table IV. *Number of bleeders after intake of different forms of salicylates*

| | Dosage | Total no. of pats. | *Blood loss* <1.83 ml/d | *Blood loss* >1.83 ml/d |
|---|---|---|---|---|
| Soluble buffered forms of acetylsalicylates | 5 g/d | 60 | 28 | 32 |
| Enteric-coated and intravenous forms of acetylsalicylates | 3 g/ | 35 | 24 | 11 |
| Salsalate | 3 g/d | 8 | 8 | 0 |
| | 4 g/d | 26 | 24 | 2 |
| | 5 g/d | 4 | 4 | 0 |
| | Total | 38 | 36 | 2 |

In the entire population of 39 patients who could be evaluated after treatment with salsalate, only 2 patients had a blood loss in stool exceeding 1.83 ml per day. From this it may be concluded that gastrointestinal bleeding with salsalate is very rare and that gastric erosions occur only exceptionally. Considering the $\chi^2$-test, blood loss in stool was statistically significantly lower with salsalate than with soluble forms of acetylsalicylate ($\chi^2=13.9\ p<0.001$) or with enteric-coated or intravenous forms of acetylsalicylate ($\chi^2=3.7\ p<0.05$) (Table IV).

The extremely low incidence of gastro-intestinal bleeding with salsalate in comparison with acetylsalicylate can on the one hand be explained by the fact that salsalate is absorbed only in the small intestine and has thus no direct contact with gastric mucosa and, on the other hand, by the absence of an acetyl group which causes inhibition of prostaglandin synthetase (8), altering the mucous layer of the gastric mucosa (4). However, it should be stressed that, in this study, we did not measure the anti-inflammatory activity of salsalate. Since it is generally accepted that the anti-inflammatory activity of salicylate is achieved by inhibition of prostaglandin synthetase, the anti-inflammatory effect of salsalate is questionable. However, it may be concluded from this study that salsalate causes practically no gastrointestinal bleeding, and can be considered a safe analgetic drug in the salicylate group.

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