Eur J Clin Pharmacol (1982) 22: 309–314

European Journal of Clinical Pharmacology

Bioavailability of Acetylsalicylic Acid and Salicylic Acid from Rapid- and Slow-Release Formulations, and in Combination with Dipyridamol

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Summary. Acetylsalicylic acid (ASA) is a strong, irreversible inhibitor of platelet aggregation, but loses this activity following first-pass deacetylation to salicylic acid (SA). In order to compare the bioavailability of unchanged ASA from rapid- and slow-release formulations, the single-dose concentration profiles of ASA and SA were studied in healthy volunteers following intake of two different rapid-release (conventional and effervescent tablets) and three different slow-release (microencapsulated ASA in tablets and in capsules, and enteric-coated tablets) formulations of ASA, and of one slow-release formulation of sodium salicylate. Since anti-platelet therapy with ASA is often combined with dipyridamol, the influence of this drug was also examined. The concentrations of ASA and SA were measured by high-pressure liquid chromatography. While the bioavailability of SA from the 5 ASA formulations was essentially equal and similar to that of the salicylate formulation, the bioavailability and peak concentrations of ASA appeared to be the much greater after rapid-release than after slow-release formulations. Indeed, ASA was only rarely detected in systemic blood following intake of slow-release ASA. Co-administered dipyridamol did not significantly influence the kinetics of ASA or SA. It appears that rapid-release formulations of ASA should be prefered in anti-platelet therapy, either alone or in combination with dipyridamol.

Key words: acetylsalicylic acid, salicylic acid, dipyridamol; bioavailability, kinetics, rapid- and slow-release formulations

Acetylsalicylic acid (ASA, aspirin) is increasingly employed as an inhibitor of platelet aggregation [1–6]. ASA and its non-acetylated analogue salicylic acid (SA) are often considered jointly as "salicylate(s)", but it is must be realized that their effects are different. Thus, ASA causes strong and irreversible inhibition of cyclooxygenase due to acetylation of the enzyme protein, whereas SA produces only weak and reversible inhibition of it [7–9]. An important consequence of this difference is that even a low concentration of ASA can inhibit aggregation of platelets for their entire life-span, whilst even a high level of SA evokes little or no inhibition of platelet aggregation [6–9]. Indeed, SA may even abolish the anti-aggregatory effect of ASA [9, 10].

A complicating factor in the employment of ASA as an anti-aggregatory agent is the fact that ASA is extensively deacetylated to SA in the gastrointestinal tract [11]. Hence, the bioavailability of unchanged ASA may be highly dependent upon the formulation administered. The present study compared the bioavailability of ASA and SA from two different rapid-release and three different slow-release formulations. As anti-platelet therapy with ASA is often combined with dipyridamol [12], the possible influence of this drug on bioavailability was also assessed.

Material and Methods

Subjects and Drug Intake

Six, healthy, informed subjects, 4 females and 2 males, 26–36 years old, weight range 51–78 kg, participated in the study of the different ASA formulations. A further 8 volunteers, 4 females and 4 males, 28–41 years old, weight range 55–76 kg, were studied after intake of ASA 1 g[1] alone or in combination with dipyridamol 75 mg[6]. The protocols were approved by the Ethical Committee of the University of Lund. At least one week elapsed between tests. On different occasions, the first 6 subjects ingested ASA 1.0 g 1) as conventional, weakly buffered (MgO) ASA[1], 2) as so-

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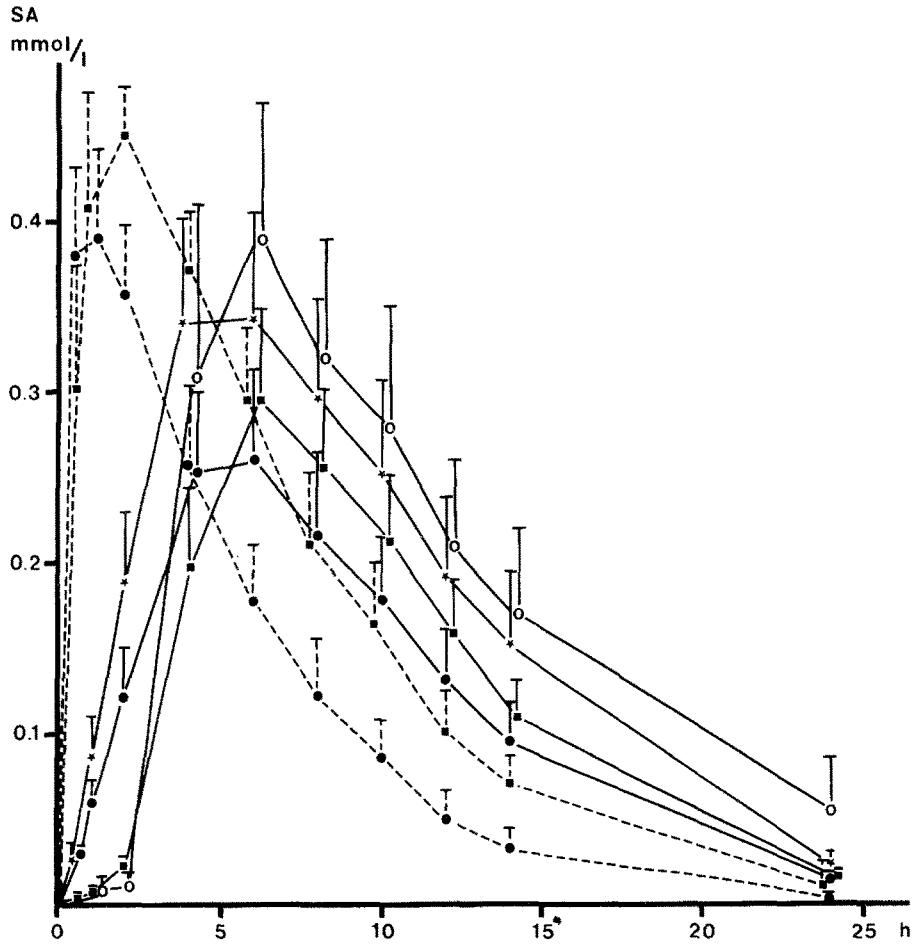

Fig. 1. Concentrations (mean ± SEM) of salicylic acid (SA) in 6 healthy volunteers following ingestion of acetylsalicylic acid 1.0 g (ASA) in conventional, weakly buffered (MgO) tablets (■-----■), in sodium bicarbonate – citrate buffered effervescent tablets (●-----●), microencapsulated ASA 1.0 g in compressed tablets (●——●), and in capsules (■——■), enteric-coated ASA 1.0 g (○——○) and sodium salicylate 1.0 g in a controlled-release preparation, based on porous membrane diffusion (★-----★)

dium bicarbonate-citrate buffered effervescent ASA[2], 3) as micro-encapsulated ASA in compressed tablets[3], 4) as micro-encapsulated ASA in capsules[4], and 5) in an enteric-coated preparation[5]. On a sixth occasion, controlled-release SA 1.0 g as sodium salicylate was taken as depot tablets[7] based on porous membrane diffusion. Five subjects always took the drugs in the fasting state with water 100 ml, and one always took them with 100 ml water at least 1 h after a light breakfast. No other liquid or food was allowed for at least 2 h after drug ingestion. Subsequently, 5 of the 6 subjects were re-examined after a second dose of conventional ASA 1.0 g, with particular reference to ASA and SA levels during the first 75 min (see below). The second group of subjects, who took ASA with and without dipyridamol, always ingested the drugs in the fasting state.

[1] Magnecyl®, ACO, Stockholm, Sweden
[2] Albyl®-Selters, Leo, Helsingborg, Sweden
[3] Acetard®, Benzon, Copenhagen, Denmark
[4] Reumyl®, Hässle, Mölndal, Sweden
[5] Premaspin®, Lääke/Farmos, Turku, Finland
[6] Persantin®, Boehringer Ingelheim, Ingelheim/Rhein, Federal Republic of Germany
[7] Bidocyl®, Ferrosan, Malmö, Sweden

Blood Sampling and Chemical Analyses

Blood 10 ml was obtained by venepuncture before (0 h) and ½, 1, 2, 4, 6, 8, 10, 12, 14 and 24 h after drug intake. After the second dose of conventional ASA (see above), samples were also obtained at 7.5, 15, 30, 45, 60 and 75 min. The blood was either collected in Vacutainer® tubes prepared with heparin and fluoride, or in heparinized tubes with subsequent addition of physostigmine (10^{-4}M) to plasma after centrifugation; fluoride and physostigmine prevent ASA deacetylation to SA for at least 1 week [13]. The plasma concentrations of ASA and SA were measured by high-pressure liquid chromatography, as recently described [13], and the assays were always carried out on the day after collection of the samples.

Calculations

The peak concentration (C_{max}) was defined as the highest concentration recorded, and the time to reach peak concentrations (t_{max}) was determined accordingly. Elimination half-lives ($t_{½}$) were calculated by regression analyses. The areas under plasma concentration curves (AUC) were estimated by the trapezoidal

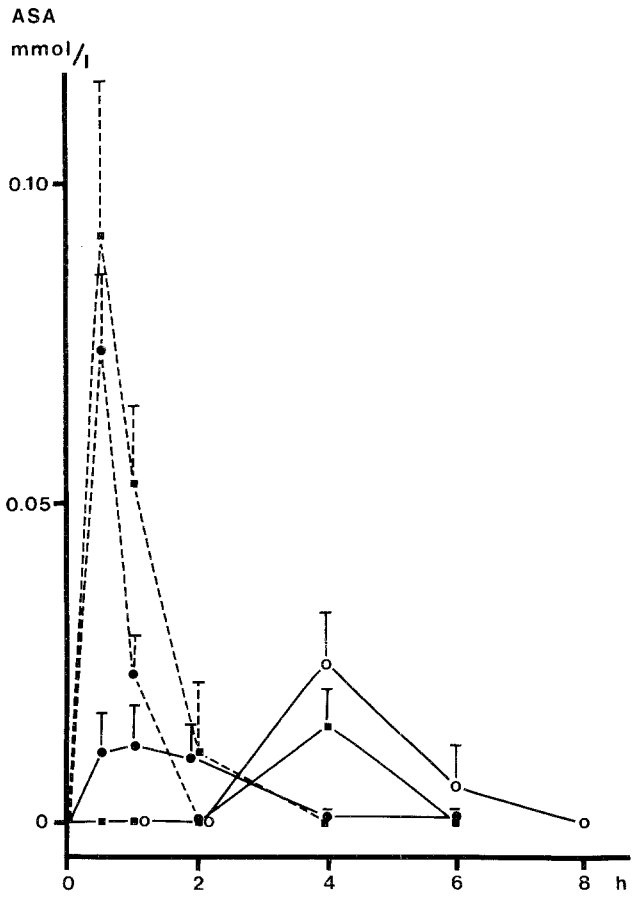

Fig. 2. Concentrations (mean ± SEM) of acetylsalicylic acid (ASA) following ingestion of ASA as described in Fig. 1

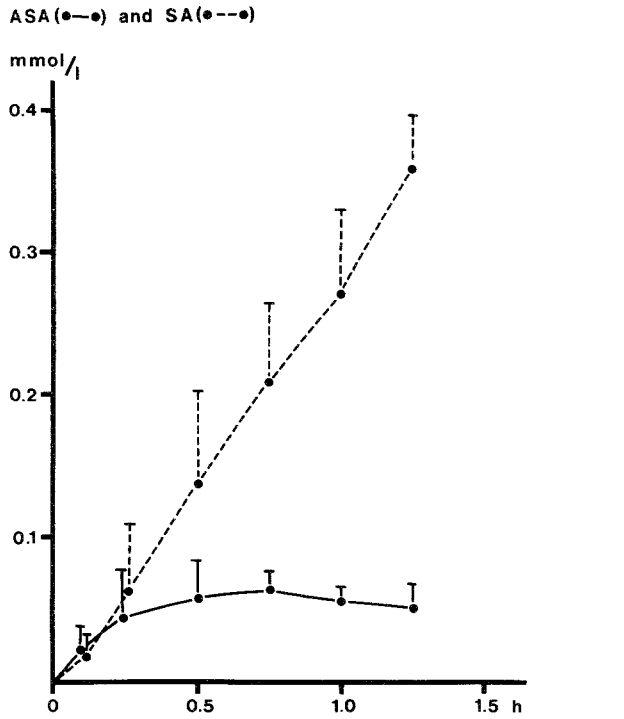

Fig. 3. Concentrations (mean ± SEM) of acetylsalicylic acid (ASA) and salicylic acid (SA) during the first 75 min after ingestion of ASA 1.0 g conventional, weakly buffered (MgO) tablets

rule. The statistical significance of intraindividual differences was calculated by the Wilcoxon signed-rank test for paired observations.

Results

Salicylic Acid (SA)

SA concentrations following intake of the different preparations are shown in Fig. 1, and the individual kinetic estimates are given in Table 1. It may be seen that every formulation produced considerable amounts of SA in the systemic circulation, and that the appearance of SA was delayed after administration of the four slow-release preparations. In one subject, no SA was detected until 24 h after intake of enteric-coated ASA (Premaspin®).

Acetylsalicylic Acid (ASA)

ASA concentrations following intake of the different formulations are shown in Fig. 2, and the individual kinetic estimates are given in Table 2. It appears that considerable amounts of ASA rapidly entered the systemic circulation after ingestion of the two rapid-release formulations, the mean C_{max} being 0.10 (conventional tablets) and 0.074 (effervescent tablets) mmol/l, respectively, and the mean AUC (± SEM) being 6.2 and 3.3 mmol × min 1^{-1}, respectively.

The three slow-release formulations of ASA gave a very low ASA concentration in the systemic circulation. Indeed, ASA could only be detected in occasional samples, and in five individual tests (2 with Acetard®, 1 with Premaspin®, and 2 with Reumyl®) no ASA was detected in any sample. Hence, no AUC calculations could be made, and the C_{max} definitions became uncertain. No ASA was detected after intake of sodium salicylate.

In order to assess the earliest phase after ASA intake, 5 of the 6 subjects were re-examined after taking a conventional ASA preparation. As shown in Fig. 3, both ASA and SA appeared within 7.5 min, and the ASA concentrations were equal to or higher than the SA concentrations during the first 15 min.

Influence of Dipyridamol

Co-administration of dipyridamol did not significantly influence the kinetics of ASA or SA (Fig. 4; Table 3).

Table 1. Kinetic parameters of salicylic acid (SA) in 6 healthy volunteers after oral intake of acetyl salicylic acid 1 g (ASA) in 2 rapid-release (1 and 2) and 3 slow-release (3, 4 and 5) formulations: (1) sodium bicarbonate-citrate buffered effervescent ASA, (2) conventional, weakly buffered ASA, (3) micro-encapsulated ASA in compressed tablets, (4) micro-encapsulated ASA in capsules, and (5) conventionally enteric-coated ASA. Sodium salicylate 1 g in an enteric-coated formulation with porous membrane diffusion (6) was also taken

Subject	C_{max} [mmol/l]						t_{max} [h]					
	(1)	(2)	(3)	(4)	(5)	(6)	(1)	(2)	(3)	(4)	(5)	(6)
1	0.27	0.48	0.15	0.27	0.41	0.38	2.0	2.0	10.0	6.0	6.0	6.0
2	0.30	0.44	0.44	0.17	0.53	0.55	1.0	4.0	6.0	7.0	4.0	6.0
3	0.51	0.50	0.20	0.24	0.57	0.46	1.0	1.5	10.0	8.0	6.0	4.0
4	0.35	0.58	0.41	0.53	0.49	0.54	1.0	0.5	4.0	6.0	6.0	4.0
5	0.50	0.41	0.15	0.26	0.19[a]	0.12	0.5	1.0	4.0	6.0	24.0	6.0
6	0.51	0.51	0.31	0.34	0.49	0.25	1.0	2.0	6.0	6.0	4.0	4.0
No significant difference in intraindividual Wilcoxon tests except between (2) and (4).							[b]	[b]				
$\bar{X} \pm SEM$	0.41 ± 0.05	0.49 ± 0.02	0.28 ± 0.05	0.30 ± 0.05	0.45 ± 0.06	0.38 ± 0.07	1.1 ± 0.2	1.8 ± 0.5	6.7 ± 1.1	6.5 ± 0.3	8.3 ± 3.2	5.0 ± 0.5

[a] only value obtained

[b] $p < 0.05$ vs. (3), (4), (5) and (6) in intraindividual Wilcoxon tests. Other differences not significant

Discussion

As far as SA is concerned, it was seen that, irrespective of the brand, the slow-release formulations of ASA all caused a significantly delayed appearance of SA in the systemic circulation as compared to the rapid-release formulations. The concentration curves and AUC values of SA were very similar for the three slow-release forms of SA, and were also similar to those following the slow-release preparation of sodium salicylate. Furthermore, the AUC values of SA did not significantly differ from those seen after administration of the rapid-release formulations of ASA. In addition, co-administration of dipyridamol did not significantly alter SA kinetics after ASA administration. Thus, the bioavailability of SA was essentially the same, irrespective of whether ASA or sodium salicylate was given, whether a slow- or rapid-release formulation was used, whether the slow release was achieved by microencapsulation in tablets

Table 2. Peak concentrations of ASA [mmol/l] in 6 healthy volunteers after oral intake of 2 rapid-release and 3 slow-release formulations of ASA, as described in Table 1

Subject	(1)	(2)	(3)	(4)	(5)
1	0.060	0.165	0.034	0.018	0.030
2	0.065	0.065	0.030	0.005	0.017
3	0.080	0.050	0.010	0.035	0.060
4	0.130	0.140	0	0.030	0.040
5	0.060	0.055	0	0	0
6	0.050	0.125	0.025	0	0.020

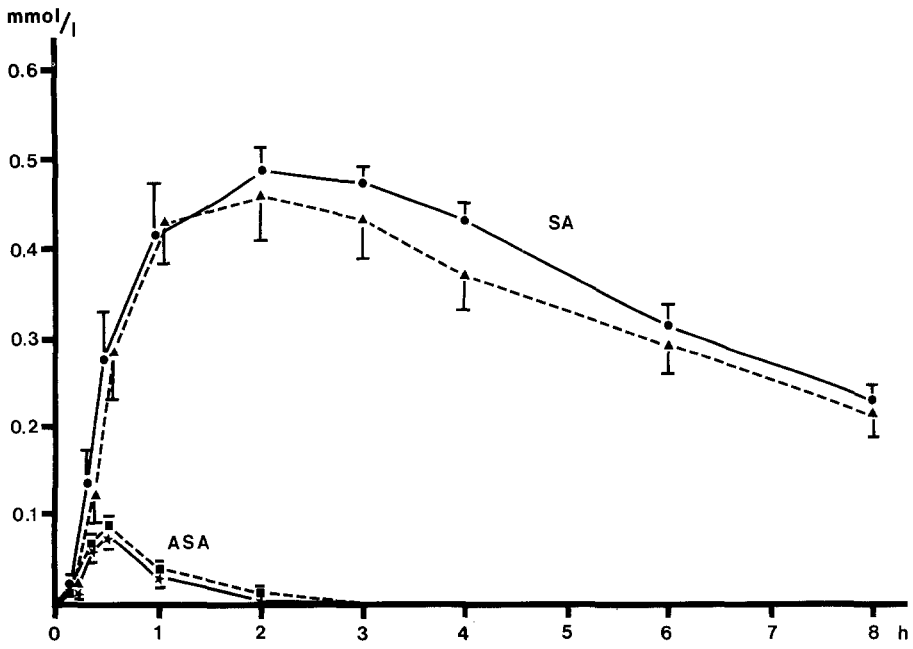

Fig. 4. Concentrations (mean ± SEM) of acetylsalicylic acid (ASA) and salicylic acid (SA) after ingestion of ASA 1.0 g alone (——) and in combination with dipyridamol 75 mg (-----). The dipyridamol had no significant effect (see Table 3)

Table 1. C_{max} = Maximum concentration recorded
t_{max} = Time of C_{max}
$t_{½}$ = Terminal elimination half-life
AUC = Area under the plasma concentration curve

$t_{½}$ [h]							AUC 0 → ∞ [mmol × min × 1^{-1}]					
(1)	(2)	(3)	(4)	(5)	(6)		(1)	(2)	(3)	(4)	(5)	(6)
2.7	4.0	3.8	2.3	3.5	3.9		100	278	90[c]	179	298	335
3.9	2.5	4.0	2.3	3.2	3.7		118	250	280	107	337	312
3.8	4.0	3.9	4.8	4.9	5.0		279	310	175	187	417	408
3.1	5.8	2.8	3.8	4.2	3.0		144	243	288	332	307	310
2.1	5.4	2.0	2.7	–[d]	4.3		117	117	66	111	–[d]	91
2.3	3.2	2.5	2.7	3.2	3.0		184	184	157	200	194	115
						N.S.						
3.0 ± 0.3	4.2 ± 0.5	3.2 ± 0.4	3.1 ± 0.4	3.8 ± 0.3	3.8 ± 0.3		157 ± 27	236 ± 27	176 ± 38	186 ± 33	311 ± 36	262 ± 52

[c] The residual area in this case (from 14 h → ∞) was 27% and so not included. In all other cases the residual area was less than 20%
[d] No SA was detected until 24 h after drug intake

Table 3. Kinetic parameters of acetylsalicylic acid (ASA) and salicylic acid (SA) after oral intake of rapid-release ASA 1 g alone (A) and in combination with dipyridamol 75 mg (B)

ASA

Subject no.	C_{max} [µmol/l]		t_{max} [h]		$t_{½}$ [min]		AUC 0 → 8 h [µmol · h · 1^{-1}]	
	A	B	A	B	A	B	A	B
7	113	123	0.3	0.5	15	24	63	101
8	40	85	0.5	0.5	–	–	23	43
9	110	128	6.5	0.3	–	19	57	69
10	90	92	0.5	0.5	–	20	48	70
11	140	85	6.5	0.3	–	17	79	53
12	38	80	0.5	0.5	74	22	50	58
13	63	97	0.5	0.5	–	–	40	56
14	35	30	0.5	1.0	–	–	22	40
	(NS)		(NS)		(NS)		(NS)	
X̄ ± SEM	79 ± 14	90 ± 11					48 ± 7	61 ± 7

SA

Subject no.	C_{max} [µmol/l]		t_{max} [h]		$t_{½}$ [min]		AUC 0 → 8 h [µmol · h · l^{-1}]	
	A	B	A	B	A	B	A	B
7	615	663	1.0	2.0	4.2	4.6	3341	3442
8	458	450	2.0	1.0	4.7	2.7	2417	1800
9	523	518	2.0	2.0	4.9	4.8	3066	2827
10	460	447	3.0	3.0	5.5	7.7	2911	2760
11	598	608	1.0	2.0	4.6	3.6	3627	3597
12	520	495	3.0	3.0	3.0	4.2	2868	2863
13	480	504	1.0	2.0	4.4	3.6	2556	2542
14	440	225	3.0	2.0	4.9	–	2448	1567
	(NS)		(NS)		(NS)		(NS)	
X̄ ± SEM	512 ± 23	489 ± 46	2.0 ± 0.3	2.0 ± 0.2	4.5 ± 0.3	4.5 ± 0.6	2904 ± 153	2675 ± 251

C_{max} = Maximum concentration recorded
t_{max} = Time of C_{max}
$t_{½}$ = Terminal elimination half-life
AUC = Area under the plasma concentration curve

or in capsules, or by enteric coating[7], and whether or not dipyridamol was given concurrently.

The kinetics of unchanged ASA, on the other hand, differed pronouncedly between rapid-release and slow-release formulations. Indeed, ASA was only occasionally detectable following ingestion of the latter, and the peak concentrations, if measurable at all, were much lower than those following the rapid-release formulations. Probably, the delayed and prolonged release allows more extensive first-pass deacetylation of ASA than does rapid absorption limited to a short segment of the gastrointestinal tract.

It might be argued that the recorded differences were relevant only for the formulations examined. This appears unlikely, however, as essentially similar ASA curves were seen with the two rapid-release formulations, even though one was a low-buffered conventional preparation and the other was a high-buffered effervescent formulation, and little or no ASA was found after any of the three slow-release preparations, despite the fact that one was enteric-coated, one was microencapsulated in tablets and one in capsules. Similar results have also been obtained with one rapid- and one slow-release formulation available on the American market [15].

The findings are important in view of the pronounced difference between ASA and SA with respect to inhibition of platelet aggregation. It follows that rapid-release formulations of ASA would be more appropriate than slow-release ones in the prevention of platelet aggregation. In addition, it seems likely that dipyridamol may be co-administered without affecting the bioavailability of ASA.

Acknowledgements. The study was supported by grants from the Swedish Medical Research Council (Project no. 3880), the Swedish Board of Health and Welfare (the Dalby project), the Leo Research Foundation, Helsingborg, AB Ferrosan, Malmö, Sweden, and Boehringer-Ingelheim GmbH, Ingelheim, Federal Republic of Germany.

[7] It should be noted, however, that in one instance the enteric-coated preparation (Premaspin®) gave no detectable SA during the entire 24 h period. Similar observations have been made in patients (Hanson & Wollheim, personal communication), and in another study the variability of SA kinetics was greater after Premaspin® than after Reumyl® [14]

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Received: August 10, 1981
accepted in revised form: December 1, 1981

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