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Pharmacology and Pharmacokinetics of 5-Aminosalicylic Acid

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There is accumulating clinical evidence that 5-aminosalicylic acid (5-ASA), a primary metabolite of sulfasalazine (SAS), represents the therapeutic active moiety of the azo-compound SAS in the treatment of chronic inflammatory bowel disease (IBD). Since it is presumed that 5-ASA acts from the lumen of the intestine, it is important to know how much 5-ASA is released from its special galenic formulations. After liberation of 5-ASA in the terminal ileum (only slow release oral preparations of 5-ASA) and colon (5-ASA suppositories and enemas), 5-ASA is only partly absorbed. A major part of this 5-ASA is presystemically eliminated, eg, N-acetylated during its first passage through the intestinal mucosa and liver. Mean steady state plasma levels of unchanged 5-ASA are rather low (range 0.02 to 1.2 μg/ml) whereas those of Ac-5-ASA are always higher (range 0.1 to 2.9 μg/ml). This is due to the rapid elimination of 5-ASA ($t_{\frac{1}{2}}$ = 0.4 to 2.4h) and the slightly slower renal excretion of the Ac-5-ASA ($t_{\frac{1}{2}}$ = 6 to 9h, renal clearance = 200 to 300 ml/min). The knowledge of the pharmacokinetic properties of 5-ASA from different drug formulations might contribute to a better understanding of its mode of action in IBD.

KEY WORDS: pharmacokinetics; 5-aminosalicylic acid; chronic inflammatory bowel disease.

Sulfasalazine (SAS) has been used for treating inflammatory bowel disease (IBD) for 45 years. More recently, it became apparent that one of this azo drug's primary metabolites, 5-aminosalicylic acid (5-ASA), is mainly responsible for the therapeutic effect, and its other cleavage product, sulfapyridine (SP), causes most of its observed side effects (1). Consequently, novel approaches to the treatment of IBD have emerged (2): applying 5-ASA directly and azo-coupling it with other vehicles (Figure 1). However, it should be emphasized that such new therapeutic principles represent symptomatic treatment forms, since the etiology and pathophysiology of IBD are still unknown (see Figure 2).

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CLINICAL STUDIES WITH 5-ASA

From several controlled clinical trials, there is accumulating evidence that 5-ASA, whether administered rectally (Table 1) or orally (Table 2), is effective in the treatment of acute IBD. With doses between 0.4 and 4 g/day, remission rates of about 77% could be observed. Whether long-term prophylactic use of 5-ASA will keep IBD patients in remission cannot be finally stated yet; the published data are still too preliminary. From our own clinical trial (Table 3), an annual relapse rate of approximately 12% might be estimated.

To evaluate the therapeutic value of a novel compound, such as 5-ASA, its potential for toxicity in comparison to a standard treatment (in this case, SAS) should also be considered. Clinical experience with 5-ASA is still limited, but so far no serious side effects of its use have been observed.

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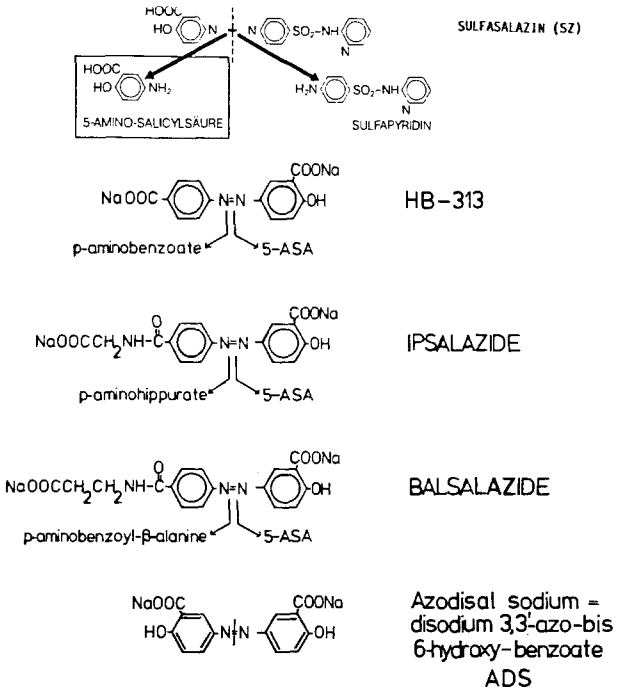

Fig. 1. Structures of sulfasalazine and its two major metabolites (top) as well as other prodrugs of 5-aminosalicylic acid.

Moreover, in several crossover trials among patients who showed intolerance or allergic reactions to SAS and were switched to a treatment with 5-ASA, only about 10% showed similar reactions to 5-ASA (Table 4).

The "new" 5-ASA thus seems to be at least as effective as SAS in treating IBD, and it appears to be better tolerated than the "old" standard drug.

CLINICAL PHARMACOKINETICS OF 5-ASA

The therapeutically active moiety of 5-ASA is liberated in the colon by bacterial azo reduction of the "prodrug" SAS. About one third of the dose of 5-ASA is recovered in the urine, almost entirely as its acetylated metabolite Ac-5-ASA; about 50% is excreted with the feces, with more than twice as much being unchanged 5-ASA as Ac-5-ASA. Plasma concentrations of 5-ASA are very low (usually less than 0.5 μg/ml), but those of Ac-5-ASA are higher by a factor of two to four. After rectal administration of 5-ASA itself in the form of suppositories or enemas, only 10–35% of the 5-ASA is absorbed, and the ranges of the steady plasma levels of 5-ASA (0.1–0.3 μg/ml) and Ac-5-ASA (0.3–0.7 μg/ml) are similar to those during oral therapy with SZ (for review see reference 3).

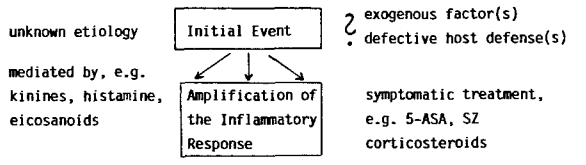

Fig. 2. Unknown etiology and symptomatic treatment of IBD.

TABLE 1. REMISSION RATES AFTER RECTAL 5-ASA IN CHRONIC INFLAMMATORY BOWEL DISEASE

Number of patients	*Dose (g/day)*	*Remission rate (%)*	*Reference*
21	0.7	71	Azad Khan et al, 1977 (5)
14	1.5	86	Klotz et al, 1980 (6)
15	0.4	60	van Hees et al, 1980 (7)
44	4.0	77–93	Campieri et al, 1981 (8)
14	1.5	86	Maier et al, 1982 (9)
13	0.75	77	Maier et al, 1983 (10)
12	1.5	83	Janssens et al, 1983 (11)
24	2 to 4	84	Campieri et al, 1984 (27)
14	1.0	50	Bondesen et al, 1984 (12)
6	3.0	100	Barber et al, 1985 (13)
29	4.0	69	Sutherland et al, 1986 (14)
9	4.0	78	Friedman et al, 1985 (15)
22	4.0	56	Hanauer et al, 1985 (16)

For the oral administration of 5-ASA, three slow-release preparations have been developed (Table 5 summarizes their galenic formulations, *in vitro* release patterns, and pharmacokinetic characteristics.) When Ba-labeled 5-ASA tablets were administered to six healthy male volunteers, radiographic monitoring showed that 5-ASA was released slowly in fine suspension in the ileocecal region about 2.5–4 hr after administration (Dr. Imschweiler, personal communication). This *in vivo* release is also

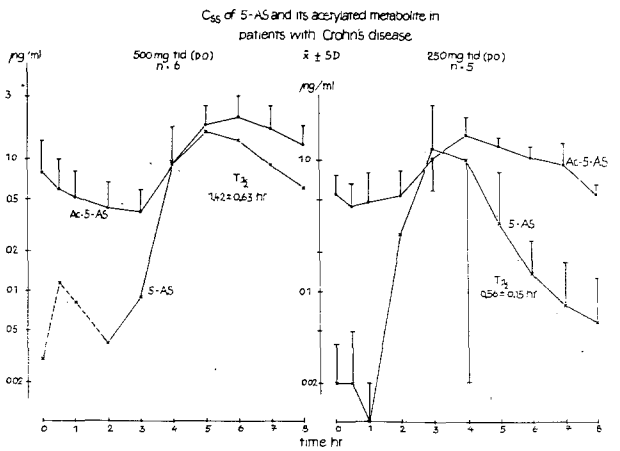

Fig. 3. Steady-state plasma concentrations of 5-ASA and Ac-5-ASA during a dosing interval in patients with IBD treated with 500 mg tid (left) or 250 mg tid (right).

TABLE 2. REMISSION RATES AFTER ORAL 5-ASA IN CHRONIC INFLAMMATORY BOWEL DISEASE

Number of patients	*Dose (g/day)*	*Remission rate (%)**	*Reference*
34	1.2	26 relapse within 16 weeks (UC)	Dew et al, 1982 (17)
32	2.7	22 relapse within 6 months (UC)	Dew et al, 1983 (18)
18	1.5	72 (CD)	Rasmussen et al, 1983 (30)
6	1.5	clinical improvement (CD)	Saverymuttu et al, 1984 (20)
15	?	clinical improvement 73 (UC)	Austin et al, 1984 (21)
15	1.5	60–86 (UC)	Maier et al, 1985 (22)
15	1.5	87 (CD)	Maier et al, 1985 (22)
19	1.6–2.4	89 (UC)	Habal and Greenberg, 1985 (23)
6	0.4–4.8	83 (UC)	Schröder and Tremaine, 1985 (24)

*UC = ulcerative colitis; CD = Crohn's disease.

TABLE 3. LONG-TERM PROPHYLACTIC TREATMENT WITH 5-ASA (OWN RESULTS)

Diagnosis	*N*	*Duration of treatment with 5-ASA*	*Relapse (N)*
Crohn's disease	11	18.5 ± 6.4 months with	2
Ulcerative colitis	6	0.75–1.5 g/day per os	1
Ulcerative colitis	17	30.2 ± 11.6 months with 0.75 g/day suppositories	2 (>32 months)
Ulcerative colitis	29	12 months with 4 g/day enemas (G. d'Albasio et al, 1986 (25))	5

TABLE 4. DRUG REACTIONS TO SULFASALAZINE (SAS) AND 5-AMINOSALICYLIC ACID (5-ASA)

Intolerance or allergic reaction		
To SAS	*To 5-ASA*	*References*
35 patients	3 of those patients	Dew et al, 1983 (26)
24 patients	4 of those patients	Campieri et al, 1984 (27)
15 patients	2 of those patients	Austin et al, 1984 (21)
7 patients	no	Hanauer et al, 1985 (16)
5 patients	no	Schröder and Tremaine, 1985 (24)
1 patient with pure-red-cell aplasia	no	Anttila et al, 1985 (28)
37 patients	4 of those patients	Donald and Wilkinson, 1985 (29)

TABLE 5. 5-ASA SLOW-RELEASE ORAL PREPARATIONS

	Salofalk, Claversal	*Pentasa*	*Asacol*
Galenic formulation	250 mg 5-ASA + Na_2CO_3 coating with cellulose ether and Eudragit L	250 mg 5-ASA coated with ethyl cellulose	400 mg 5-ASA coated with Eudragit S (80–120 μ)
In vitro release pattern	stable at pH <5.5 dissolution in 0.5–2.0 hr at pH > 7.5	slow dissolution at pH 2–6; at pH 7.5 in 4–8 hr	
Plasma levels			
t_{lag} (hr)	3–4		variable (0.5–10)
t_{max} (hr)	5–6	3	variable (4–6)
C_{max} (μg/ml)	0.5–1.5	1.1–2.9 (Ac-5-ASA)	0.1–9.7
Urinary recovery (% of dose)	44 (15–67)	53	20
Fecal recovery (% of dose)	35 (24–47)	40	
Reference	Klotz et al, 1985 (4)	Rasmussen et al, 1982 (19)	Dew et al, 1983 (18)

reflected in the plasma concentration–time profiles (Figure 3). The steady-state levels of 5-ASA and Ac-5-ASA begin to rise in patients with IBD about 2 hr after ingestion (4).

Table 6 shows the averaged steady-state plasma concentrations and urinary excretion during treatment with three dosages. After the highest dosage (1 g tid) plasma levels seem to increase more than

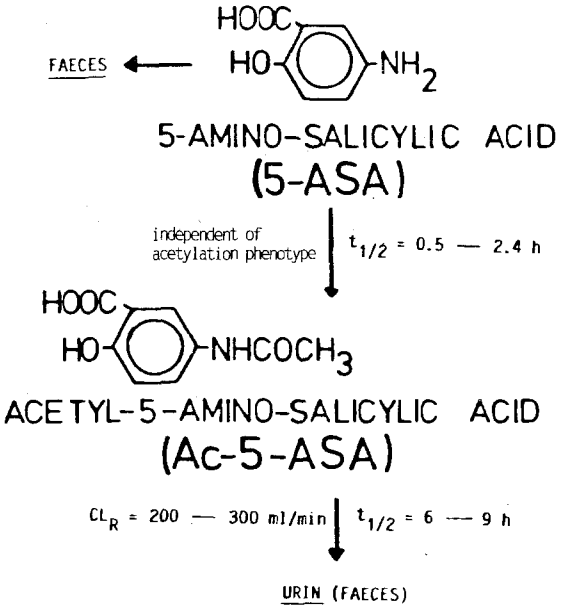

Fig. 4 Metabolic scheme and elimination pattern of 5-ASA.

proportionately, indicating some nonlinearity in the disposition of 5-ASA. Also, total 5-ASA recovered in the urine decreases as the dose increases, suggesting a dose-dependent absorption process. The standard dosage of 5-ASA (500 mg tid) has been more thoroughly investigated in terms of different routes of elimination and/or excretion (Table 7). The low protein binding and the minor excretion with breast milk can be neglected. The rapid elimination of 5-ASA ($t1/2$ = 0.7–2.4 hr) is also very effective during hemodialysis (dialysance 60–100 ml/min in the form of Ac-5-ASA). The recovery of the drug in urine (44%) and feces (35%) suggests that enough 5-ASA is available to cause its anticipated local action (stool concentrations range between 1.3 and 7.8 mM) and hypothetical systemic effects.

In summary, as outlined in Figure 4, after rectal or oral administration of 5-ASA, a considerable amount of the drug is excreted unabsorbed with the feces. The absorbed fraction of 5-ASA is rapidly acetylated (independent of the phenotype, cf SAS) in the liver as well as in the gastrointestinal wall and excreted in this form in urine. Whether Ac-5-ASA contributes to the therapeutic action of the parent drug is still controversial.

TABLE 6. STEADY-STATE DISPOSITION OF 5-ASA IN PATIENTS WITH IBD*

Mean ± SD (range)	*250 mg tid* (*N* = 5)	*500 mg tid* (*N* = 6)	*1 g tid* (*N* = 7)
mean C^{ss} (μg/ml)			
5-ASA	0.4 ± 0.2 (0.2–0.6)	0.7 ± 0.4 (0.2–1.2)	1.9 ± 1.3 (0.3–4.4)
Ac-5-ASA	1.0 ± 0.2 (0.8–1.3)	1.2 ± 0.3 (0.8–1.5)	3.5 ± 1.6 (0.8–5.3)
urinary excretion (mg/day)			
5-ASA	116 ± 128	1.62 ± 143	469 ± 236
Ac-5-ASA	379 ± 150	498 ± 182	552 ± 261
urinary recovery (% of oral dose)	66 ± 67 (23–100)	44 ± 21 (15–67)	34 ± 12 (7–45)

C^{ss} = steady state concentration.
*Klotz et al, 1985 (4).

TABLE 7. PHARMACOKINETIC PROPERTIES OF ORAL 5-ASA (500 MG TID)

	Mean	*Range*
$t_{1/2}$ (hr)	1.4	0.7–2.4 (Ac-5-ASA = 6–9 hr)
C^{ss} (μg/ml)		
5-ASA	0.7	0.2–1.2
Ac-5-ASA	1.2	0.8–1.5
f_u (%)		
5-ASA	57	50–63
Ac-5-ASA	22	20–24
Urinary recovery (%)	44	15–67
Fecal recovery (%)	35	28–47
Total recovery (%)	79	55–110
Extraction ratio at hemodialysis	of Ac-5-ASA	0.3–0.5
Dialysance (ml/min)	of Ac-5-ASA	60–100
Excretion in breast milk	of Ac-5-ASA	0.1% of the dose
Renal clearance (ml/min)	of Ac-5-ASA	200–300

C^{ss} = steady state concentration. f_u = fraction unbound in plasma.

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