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Balsalazide

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Contents

Abstract

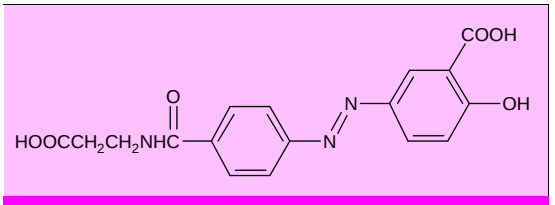
▲ Balsalazide is a prodrug of mesalazine which has an inert carrier molecule instead of the sulfapyridine moiety of sulfasalazine.

▲ Balsalazide 6.75 g/day was more effective than mesalazine 2.4 g/day in at least 1 trial and as effective as sulfasalazine 3 g/day for inducing remission in patients with acute ulcerative colitis in 8- and 12-week trials. Moreover, complete symptom relief occurred more promptly with balsalazide 6.75 g/day than with mesalazine 2.4 g/day.

▲ In long term studies, balsalazide 2 g/day was as effective as sulfasalazine 2 g/day and balsalazide 6 g/day was as effective as mesalazine 1.5 g/day, in maintaining remission in patients with ulcerative colitis.

▲ The tolerability profile of balsalazide is significantly better than that of sulfasalazine; 70% of sulfasalazine-intolerant patients were able to tolerate balsalazide.

Features and properties of balsalazide (BX 661A, balsalazine, balsalazide disodium)	
Indications	
Treatment of acute exacerbation and maintenance of remission in patients with ulcerative colitis	
Mechanism of action	
Prodrug releasing the anti-inflammatory mesalazine in the colonic lumen	
Dosage and administration	
Recommended dosage	6.75 g/day
Route of administration	Oral
Frequency of administration	3 times daily
Pharmacokinetic profile	
Colonic bacteria cleave the azo bond to release locally acting mesalazine from the inert carrier molecule, 4-aminobenzoyl-β-alanine (4-ABA). Small amounts of mesalazine and 4-ABA reach the systemic circulation (median peak plasma concentrations of 2.62 and <0.096 μmol/L, respectively), after a 2.25g dose	
Adverse events	
Most frequent	Abdominal pain (11%)



Balsalazide

Ulcerative colitis is a common inflammatory disease of the colon and rectum which has an estimated annual incidence of 0.002 to 0.006% (2 to 6 per 100 000 people) in the US.[1] Diffuse mucosal inflammation involves the rectum in 95% of cases and extends proximally and continuously to include parts or all of the large intestine. Occasionally, the terminal ileum is also involved.[2] The clinical symptoms of ulcerative colitis are bloody diarrhoea, stool urgency, tenesmus and abdominal discomfort; these events tend to wax and wane with time. Ulcerative colitis is classified as mild, moderate or severe on the basis of clinical and endoscopic findings. Salicylates, in either oral or topical formulation, are the drugs of first choice for obtaining remission or maintenance of remission in patients with mild to moderate disease. Topical, oral or intravenous glucocorticoids, mercaptopurine, azathioprine and surgical resection are reserved for patients affected with more severe forms of the disease.[1]

Balsalazide is an oral prodrug of mesalazine, in which the sulfapyridine moiety of sulfasalazine has been replaced with the inert carrier molecule, 4-aminobenzoyl-β-alanine (4-ABA).[3] The commonly used dose of balsalazide (6.75g) is equivalent to 2.3g of mesalazine.[4]

1. Pharmacodynamic Profile

• Like sulfasalazine, balsalazide is a prodrug which requires azo-reduction before it releases the active salicylate mesalazine (5-aminosalicylic acid; 5-ASA) in the lumen of the large intestine.[3]

• The possible mechanisms by which salicylates exert their therapeutic benefit in patients with ulcerative colitis include alteration of intestinal microflora; alteration of the mucosal prostaglandin profile and electrolyte transport; inhibition of the synthesis and release of proinflammatory mediators (e.g. nitric oxide, leukotrienes, thromboxanes and platelet activating factor); inhibition of the cellular functions of natural killer cells, mast cells, neutrophils, mucosal lymphocytes and macrophages; and scavenging of reactive oxygen metabolites.[5]

• The *in vitro* production of reactive oxygen metabolites is greater in rectal mucosa from patients with versus without ulcerative colitis. Balsalazide (20 mmol/L) was as effective as mesalazine (20 mmol/L) in reducing reactive oxygen metabolite production in rectal mucosal specimens from 6 patients with ulcerative colitis (100 *vs* 93% reduction in chemiluminescence, $p < 0.05$ *vs* buffer control for both agents).[6]

2. Pharmacokinetic Profile

• After oral administration, balsalazide is split into mesalazine and 4-ABA via azo-reduction by the colonic microflora. Systemic absorption of balsalazide, mesalazine or 4-ABA is low.[7]

• The pharmacokinetic disposition of balsalazide and its metabolites was studied in 54 adult patients with ulcerative colitis in remission who had been receiving balsalazide 3 to 6 g/day (as 2 divided doses) for at least 1 year. The median values for balsalazide, after normalisation to a statim dose of 3.43 mmol, were as follows: peak plasma concentration (C_{max}) 0.324 μmol/L, trough plasma concentration (C_{min}) 0.035 μmol/L, area under the plasma concentration-time curve over 0 to 12 hours 1.34 μmol/L · h and clearance 4.5 L/h. 0.14% of the orally administered dose was recovered unchanged in the urine.[8]

• C_{max} of balsalazide was reached within 2 hours of the dose, and plasma concentrations had fallen to C_{min} values by 8 hours.[8] Median C_{max} of mesalazine and 4-ABA (2.62 and <0.096 μmol/L) were achieved 9 and 10 hours after a single dose of balsalazide 2.25g.[7]

• The concentrations of mesalazine and its metabolite *N*-acetyl-5-aminosalicylic acid in plasma were generally higher than those of balsalazide (C_{max} values of 3.95, 4.80, 0.324 μmol/L, respectively). In most instances, the plasma concentration of 4-ABA remained below the limit of quantification (20 μg/L) at all times.[8]

• Although the pharmacokinetic properties of balsalazide were unaffected by age >60 years, C_{max} and C_{min} were higher in female than in male patients.[8]

• In comparison with patients with normal renal function, patients with mild renal impairment (creatinine clearance <4.8 L/h) had higher C_{min} (0.06 *vs* 0.02 μmol/L) and lower clearance (4.03 *vs* 4.88 L/h) values. However, the areas under the plasma concentration-time curves were similar in both groups (1.17 *vs* 1.37 μmol/L · h).[8]

3. Therapeutic Trials

Acute Ulcerative Colitis

• The complete results of 1 trial have been published[9] and the results of other trials are available in abstract form.

• Balsalazide 6.75 g/day (n = 50) produced symptomatic remission in significantly more patients than did mesalazine 2.4 g/day (n = 49) in a 12-week randomised, double-blind trial[9] (fig. 1). In addition, a significantly higher number of patients achieved complete remission (no or mild symptoms, near-normal sigmoidoscopy findings, no rectal steroid use) with balsalazide than with mesalazine after 4 (38 *vs* 12%), 8 (54 *vs* 22%) and 12 (62 *vs* 37%) weeks.

• Balsalazide also had a more rapid action than mesalazine in this trial: patients treated with balsalazide experienced their first completely symptom-free day sooner than those treated with mesalazine (after a median of 10 *vs* 25 days, $p < 0.005$).[9]

• After 8 weeks, balsalazide 6.75 g/day was at least as effective as mesalazine 2.4 g/day and significantly more effective than balsalazide 2.25 g/day for improving symptoms of disease and quality of life in 154 patients with mild to moderate ulcerative colitis (number per group not stated) in a double-blind, multicentre trial.[4] The percentages of patients who showed improvement at 8 weeks with balsalazide 6.75 g/day, mesalazine 2.4 g/day or balsalazide 2.25 g/day according to the physicians' global assessment were 74, 62 and 51%. Sigmoidoscopic improvement occurred in 79, 61 and 53%, improvement in rectal bleeding occurred in 65, 53 and 32%, and reduction in stool frequency occurred in 59, 58 and 29% of patients. Although improvement in patients' functional assessment (71, 61 and 54%) and improvement in abdominal pain (41, 44 and 31%) were greater in patients receiving balsalazide 6.75 g/day or mesalazine 2.4 g/day as compared with those in patients receiving balsalazide 2.25 g/day, the difference in response rates did not attain statistical significance. Patient quality-of-life scores improved by 40.4, 39.1 and 22.1 points in each group.[4] Com-

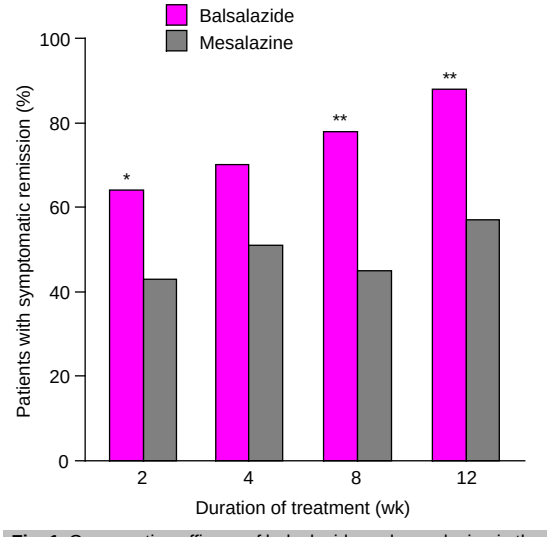


Fig. 1. Comparative efficacy of balsalazide and mesalazine in the management of acute ulcerative colitis. Balsalazide 2.25g three times daily (n = 50) or mesalazine 0.8g three times daily (n = 49) were administered in a randomised, double-blind manner to patients with acute ulcerative colitis.[9] * $p < 0.05$, ** $p < 0.001$ *vs* mesalazine.

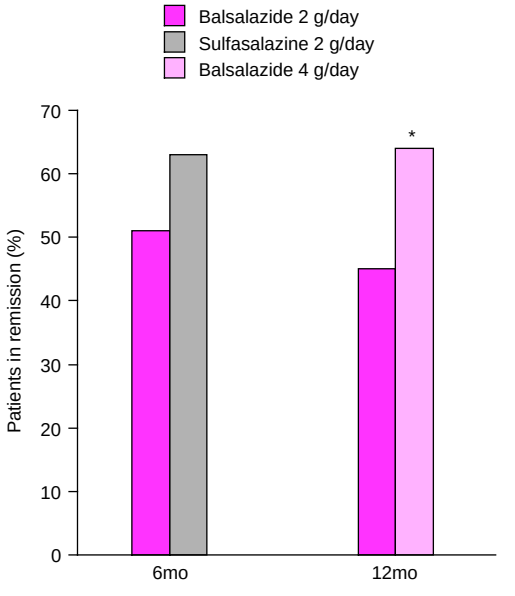


Fig. 2. Efficacy of balsalazide in maintaining of remission in patients with ulcerative colitis. Results of 2 randomised, double-blind trials. A 6-month trial compared the efficacy of balsalazide 2 g/day (n = 41) with that of sulfasalazine 2 g/day (n = 38),[13] whereas a 12-month trial compared the efficacy of balsalazide 2 g/day (n = 65) with that of balsalazide 4 g/day (n = 68) in patients with ulcerative colitis.[12] Remission was clinically and sigmoidoscopically assessed. ***** $p < 0.01$ *vs* balsalazide 2 g/day.

plete response rates (not defined) were low in all treatment groups (23, 19 and 20%).

• Sigmoidoscopic improvement occurred more rapidly in patients treated with balsalazide 6.75 g/day than in those treated with mesalazine 2.4 g/day (56 *vs* 32% of patients improved after 2 weeks, $p = 0.016$).[4]

• Remission (not defined) was induced in a similar proportion of patients with ulcerative colitis receiving either balsalazide 6.75 g/day (22 of 27 patients) or sulfasalazine 3 g/day (17 of 28 patients) in a 12-week, randomised, double-blind trial.[10]

• The efficacy of balsalazide 6.75 g/day was also similar to that of sulfasalazine 3 g/day over 8 weeks in a randomised, double-blind trial.[11] Treatment completers at end-point (17 of 20 patients in the balsalazide group and 6 of 17 patients in the sulfasalazine group) showed similar symptomatic improvement (values not provided).[11] Two balsalazide and 3 sulfasalazine recipients withdrew from treatment because of clinical deterioration; the remaining patients who stopped treatment did so because of poor tolerability.

Maintenance of Remission in Ulcerative Colitis

• Balsalazide 4 g/day (n = 68) was significantly more effective than balsalazide 2 g/day (n = 65) for preventing relapse over a period of 1 year in a double-blind, multicentre trial (relapse occurred in 36 *vs* 55% of patients, $p < 0.01$)[12] (fig. 2).

• In 108 patients, remission was maintained in a similar percentage of those receiving balsalazide 3 g/day (n = 54) and those receiving 6 g/day (n = 54) over a period of 1 year in a randomised, double-blind trial (77 *vs* 68%),[14] indicating that 3 g/day may be the optimal dose of balsalazide for maintaining remission in patients with ulcerative colitis.

• As reported in a series of abstracts,[15-17] patients in remission at the end of the above trial[14] were continued on balsalazide and follow-up was extended over the next 3 years. 67 patients who were in remission after the first 12 months were crossed over to the alternative dosage of balsalazide and monitored for a further 12 months; blinding was maintained for the full 2 years. Remission rates were again similar with each dosage (69% with balsalazide 3 g/day and 77% with balsalazide 6 g/day).[15]

• 45 patients in remission after the second year of the above trial were treated for a further 12 months with balsalazide 3 g/day (increased to 6 g/day if symptoms recurred) in a nonblind fashion. Remission was maintained in 80% of patients.[16]

• Patients in remission at the conclusion of the third year of the above trial received balsalazide 1.5 to 6 g/day in a nonblind fashion over a further 12 months (patient number not specified). Over the entire 4-year treatment period, 38% of patients remained in remission.[17]

• There was no significant difference in the percentage of patients treated with 2 g/day of either balsalazide (n = 41) or sulfasalazine (n = 38) who remained in remission over a period of 6 months (51 *vs* 63%) in a randomised, double-blind trial[13] (fig. 2). However, mean haemoglobin levels after the 6-month trial period had increased by 2 g/L in balsalazide recipients and decreased by 5 g/L in sulfasalazine recipients ($p < 0.0002$).[13]

• Maintenance of remission over 6 months in patients with ulcerative colitis with balsalazide 6 g/day (79%) was similar to that with mesalazine 1.5 g/day (60%) and significantly ($p = 0.002$) better than that with balsalazide 3 g/day (45%) in a randomised, double-blind, multicentre trial in 133 patients.[18]

• In a randomised, double-blind, multicentre trial in patients with inactive ulcerative colitis, balsalazide 3 g/day (n = 49) was associated with significantly more asymptomatic nights (90 *vs* 77%, $p = 0.0011$) and significantly less relapse (10 *vs* 28%, $p = 0.0354$) than mesalazine 1.2 g/day (n = 46) after 3 months. However, similar numbers of patients (58%) were in remission in both groups after 12 months.[19]

4. Tolerability

• Apart from abdominal pain (11 *vs* 0%), the incidence of adverse events with balsalazide maintenance treatment (dose range not stated, n = 1092) in patients with ulcerative colitis was similar to that with placebo (n = 15): headache (12 *vs* 13%), nausea (9 *vs* 7%), diarrhoea (8 *vs* 7%), flatulence (7 *vs* 7%) and fatigue (6 *vs* 7%).[20]

• In patients with acute ulcerative colitis, the incidence and range of adverse events encountered with sulfasalazine were greater than those with either balsalazide or mesalazine.[21] The comparative incidence of adverse events occurring in >5% of patients with balsalazide 6.75 g/day, mesalazine 2.4 g/day or sulfasalazine 3.0 g/day in 5 double-blind trials[21] is shown in figure 3.

• Treatment withdrawal due to drug intolerance occurred in significantly greater numbers of patients receiving sulfasalazine 3 g/day than among

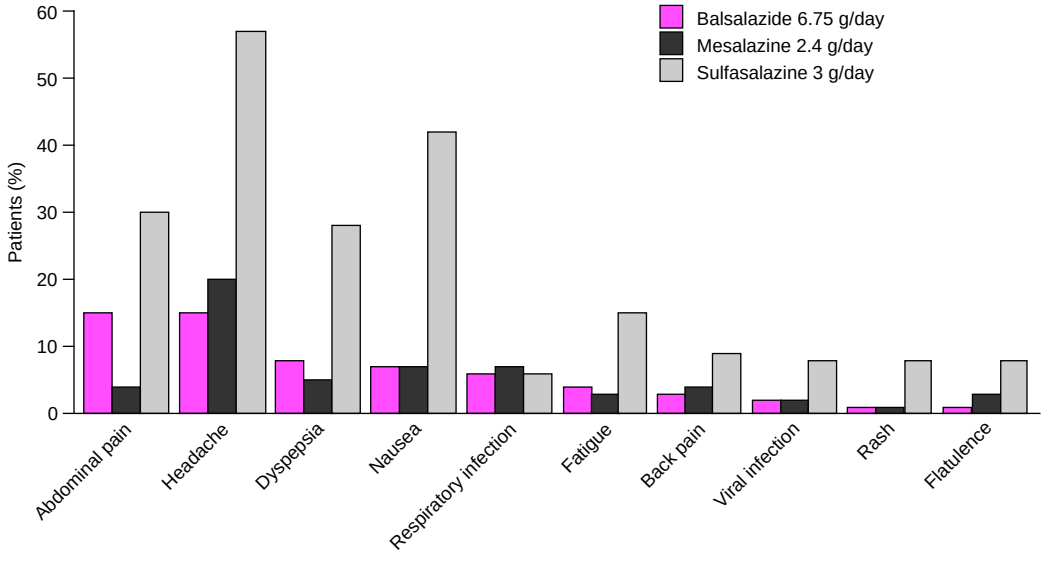


Fig. 3. Comparative tolerability of balsalazide, mesalazine and sulfasalazine. The cumulative incidence of the most common adverse events reported in >5% of patients with acute ulcerative colitis treated with balsalazide (n = 229), mesalazine (n = 100) or sulfasalazine (n = 53) in 5 double-blind trials.[21]

those receiving balsalazide 6 or 6.75 g/day in 3 double-blind trials in patients with acute ulcerative colitis (number of dropouts 5 *vs* 0, p = 0.021;[22] 9 *vs* 2, p = 0.041;[23] and 8 *vs* 1, p = 0.02[11]).

• Significantly fewer patients (5 *vs* 26%, p = 0.017) reported troublesome adverse events with balsalazide 2 g/day (n = 41) than with sulfasalazine 2 g/day (n = 38) in a double-blind maintenance trial over 6 months.[13]

• Although one patient in each group withdrew from the trial because of poor tolerability, significantly fewer patients (48 *vs* 71%, p < 0.05) reported adverse events with balsalazide 6.75 g/day (n = 50) than with mesalazine 2.4 g/day (n = 49) in a randomised, double-blind trial conducted in patients with acute ulcerative colitis.[9]

• The tolerability of randomly assigned balsalazide 2 g/day, mesalazine 1.2 g/day and olsalazine 1 g/day was evaluated over 90 days (30 days with each drug) in 43 sulfasalazine-intolerant patients with ulcerative colitis or Crohn's disease. Four patients were intolerant to all 3 drugs; however, 30 (70%) could tolerate balsalazide, 27 (63%) could tolerate mesalazine and 30 (70%) could tolerate olsalazine.[24]

• In 2 patients who had presented with infertility after 9 to 60 months of treatment with sulfasalazine 2 to 3 g/day, substitution of balsalazide 2 g/day for 4 months led to normalisation of sperm count and motility. Remission of ulcerative colitis was also maintained by balsalazide in these patients.[25]

• Administration of balsalazide 2 or 4 g/day for 1 year did not affect any of the measured laboratory parameters (haematology, blood or urine chemistry) in 133 patients with ulcerative colitis.[12]

5. Balsalazide: Current Status

Balsalazide is a prodrug of mesalazine that has shown clinical efficacy in the management of acute exacerbations, and in maintenance of remission of ulcerative colitis and has a significantly superior tolerability profile than that of sulfasalazine.

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