Aminosalicylates in inflammatory bowel disease

Aminosalicilati pri vnetni črevesni bolezni

Vojislav N. Perisic [1]

University Children's Hospital, Belgrade, Serbia

Korespondenca/ Correspondence:
Vojislav N. Perisic, MD, PhD, FRCPch (UK), University Children s Hospital, 10 Tirsova str, Belgrade, Serbia; Perisicvn@sezampro.rs

Ključne besede:
aminosalicilati, otroci, ulcerativni kolitis, Crohnova bolezen

Key words:
aminosalicylates, children, ulcerative colitis, Crohn's disease

Citirajte kot/Cite as:
Zdrav Vestn 2013; 82 supl 1: I-26–8

Prispelo: 21. maj 2013,
Sprejeto: 11. jun. 2013

Izvleček

Mnogi klinični preskusi so potrdili učinkovitost aminosalicilatov pri zdravljenju vnetne črevesne bolezni, posebej še ulcerativnega kolitisa. Študij, ki obravnavajo bodisi farmakokinetične lastnosti ali učinkovitost pri pediatričnih bolnikih, je malo. Obstajajo številna deljena mnenja o njihovi klinični uporabnosti, ki se nanašajo na optimalni odmerek in interval odmerjanja za dosego in vzdrževanje remisije, najprimernejši pripravek glede na klinično sliko, splošno učinkovitost pri Crohnovi bolezni, učinkovitost pri preprečevanju pooperativne ponovitve Crohnove bolezni itd. Novi pripravek mezalamina za peroralno uporabo MMX (večplastna tableta) omogoča, da mezalamin doseže še posebej oddaljene dele širokega črevesa tudi ob aplikaciji enkrat dnevno. Oblika tablet pa izključuje uporabo pri majhnih otrocih.

Abstract

Numerous clinical trials have supported the efficacy of aminosalicylates in the treatment of inflammatory bowel disease, particularly ulcerative colitis. There are few studies in paediatric patients addressing either pharmacokinetic properties or efficacy. There are a number of controversies in their clinical use, including: the optimum dose and dosing interval for induction and maintenance of remission, the most appropriate preparation given the clinical setting, the overall efficacy in Crohn's disease, the efficacy in preventing post-operative recurrence of Crohn's disease etc. A new oral mesalamine formulation, MMX (multi-matrix tablet), delivers mesalamine particularly to the distal colon even when given once daily. The tablet form still precludes use in small children.

Introduction

Aminosalicylates (5-aminosalicylates, 5-aminosalicylic acid, 5-ASA, mesalamine, mesalazine) are widelyused as first-line therapy in mild to moderate inflammatory bowel disease (IBD), particularly ulcerative colitis.[1] Their efficacy in the treatment of active Crohn's disease is questionable.[2] These drugs have a number of anti-inflammatory and immunomodulatory effects.

Pharmacokinetics

5-ASA, unless bound as prodrug or combined with another delivery system, is readily absorbed from the stomach and jejunum. Sulfasalazine delivered 5-ASA to the colon by combining it with sulfapyridine via an azo bond which is cleaved by colonic bacteria. The dose- limiting side effects of sulfapyridine were generating significant and frequent problems. Subsequent formulations have included pH-dependent and time--released preparations of 5-ASA. These drugs differ in the site of gastrointestinal tract in which the active drug is released.

Balsalazide and olsalazine (Dipentum) are prodrugs and have azo bonds that allow the release of 5-ASAin the colon. In olsalazine, the azo bonds connect two 5-ASA molecules. All the active medications of these prodrugs are released in the colon.

Delayed release of 5-ASA in the distal small bowel and colon are achieved by pH--dependent delivery system as well. Coating

5-ASA with acrylic-based resin, Eudragit, dissolves formulation at specific pH. Eudragit-S releases 5-ASA at a pH of 7 (Asacol, 5-ASA) initiating in the distal ileum and colon.

Preparations coated with Eudragit-L dissolve at pH 6 (Salofalk, Claversal) and release the drug starting from the mid-ileum, and continuing throughout the right colon.

Release of 5-ASA more proximally can provide active drug throughout the small bowel as well as the colon by time release mechanism (Pentasa). There is less active drug available in the distal colon.

Another new preparation utilizes a novel matrix system to deliver a high concentration of 5-ASA to the distal colon (multimatrix, MMX mesalamine). A dose of 1.2 g three times a day is effective as 5-ASA enemas (4gr/day) in inducing remission in patients with left-sided ulcerative colitis.[3] Administration of MMX mesalamine once daily was as effective as when given in split--dose regimen.

Mechanism of action

These medications have both anti-inflammatory and immunomodulatory properties.[4,5] One of the most important effects is the inhibition of cyclo-oxigenase and 5-lipoxygenase which blocks the production of the proinflammatory activity of prostaglandin E2 and leukotriens. Other effects are anti-oxidant and free radical scavenging, inhibition of antigen presentation, T--cell proliferation and antibody production of B-cells, inhibition of cellular function of NK cells, mast cells, neutrophils, mucosal lymphocytes, inhibition of expression of adhesion molecules and inhibition of IL-1 synthesis.[4,5]

Nuclear factor-kappa B activation is blocked as well.

Indications and efficacy

Ulcerative colitis

The efficacy of sulfasalazine and the newer 5-ASA preparations in inducing and maintaining remission is established and these medications remain the first-line therapy in treating mild-to-moderate ulcerative colitis.[6] Although there are theoretical benefits of one 5-ASA preparation over another, based on the site of release and location of disease in the colon, this has not been consistently demonstrated clinically. Preparations that are not released until they reach the colon may have advantage in treating more distal disease. The combination of an oral and rectal preparation was shown to be effective.

The doses currently used in children are variable but tend to fall within the range of 50–100 mg/kg/day.[3] In children who do no swallows pills, the preparations are limited to those in a form of microgranule formulations (Salofalk) and crushed tablets mixed with soft food (Pentasa).

Crohn's disease

The efficacy of mesalamine in the treatment of active Crohn's disease is questionable 7. The National Cooperative Crohn Disease Study from 1979 did show the benefit of sulfasalazine in ileocolonic and colonic disease.[8] More recently Pentasa has been used with success as first-line therapy in mild-to--moderate Crohn's disease.[9]

5-ASA preparations are used for the induction and maintenance of remission in paediatric patients with Crohn's disease.The lack of rigorous pharmacokinetic studies and clinical trials in children makes decision about the use of these drugs in paediatric patents with Crohn's disease difficult. Until more conclusive evidence is available in children, continued use in this setting of mild or mild-to-moderate.ileal, ileo-colonic and colonic Crohn's disease may be reasonable. Doses are similar to those for ulcerative colitis.

The adults studies demonstrated that there may be some efficacy of 5-ASA in maintaining surgically-induced remission in Crohn's disease. However, this effect appears to be modest at best. There have been no published trials in paediatric patients.

Adverse efefcts

Therapy with sulfasalazine is accompanied by frequent side effects. The majority of these effects are related to sulfapyridine: hypersensitivity reactions (fever, rash), agranulocytosis and haemolysis. The newer 5-ASA drugs are safe and well tolerated. The most common side effects are: headache, diarrhoea, abdominal pain, nausea and dyspepsia. Rare but severe side effects are: pancreatitis, alveolitis and nephritis.

There are infrequent report of exacerbation of colitis due to these drugs.

References

1. Bergaman R, Parkes M. Systematic review of use of mesalazine in IBD. Aliment Pharmacol Ther. 2006; 23: 841–55.
2. Griffits A, Koletzko S, Sylvester F, et al. Slow-release 5-aminosalicylic acid therapy in children with small intestinal Crohn s disase. J Pediatr Gastoenterol Nutr. 1993; 17: 186–92.
3. Moyer SM. 5-aminosalicylates therapy. Mamula P, Markowitz JE, Baldassano RN, eds. Pediatric inflammatory bowel disease, 1st ed. New York: Springer; 2008. p. 317–328.
4. MacDermott RP. Progress in understanding the mechanism of action of 5-aminosalicylic acid. Am J Gastroenterol . 2000; 95: 3343–3345.
5. Nikolaus S, Folsen U,Schriber S. Immunopharmacology of 5-aminosalicylic acid and of glucocorticoides in therapy of inflammantory bowel diseases. Hepatogastroenterology. 2000; 47: 71.82.
6. Kornbluth A, Sachar DB.Practice parametars committee of the American college of gastroenterology. Ulcerative colitis practice guidelines in adults (update). Am J Gasteroenterol. 2004; 99: 1371–85.
7. Rabizadeh S, Hyams JS, Dubinsky M. Crohn s disease.Wylie R, Hyams JS, Kay M, eds. Pediatric gastrointestinal and liver disease.2nd ed.Philadelphia: Elsevier; 2011. p. 472–489.
8. Summers RW, Switz DM, Sessions JT, et al. National cooperative study Crohn disease study: results of drug treatment. Gastroenterology. 1979; 77: 847–69
9. Hanauer SB, Sandborn W. Management of Crohn disease in adults. Am J Gastroenterol. 2001; 96: 635–43. Aminosalicylates