WASHINGTON STATE UNIVERSITY
VETERINARY MEDICINE EXTENSION

ag animal health *spotlight*
VETERINARY MEDICINE EXTENSION

WASHINGTON STATE UNIVERSITY EXTENSION & WSU COLLEGE OF VETERINARY MEDICINE

Ancillary Therapies for Calf Diarrhea: Medical Use of Bismuth

Josephine Afema, Dale A. Moore, William M. Sischo

History

Bismuth compounds have been used to treat gastrointestinal and other disorders for centuries, however, their mechanism of action is not well understood.

Pharmacokinetics

In humans, bismuth subsalicylate is hydrolyzed in the stomach to salicylic acid and bismuth salts. Over 90% of the salicylic acid is absorbed in the small intestines and excreted in urine. Most bismuth salts are insoluble and excreted in feces. The salts react with H_2S produced by anaerobic bacteria in the large intestine to form bismuth sulfide creating dark stools.

KEY POINT

Bismuth subsalicylate has substantial evidence behind it for treatment of simple diarrhea and is considered the symptomatic treatment of choice for acute diarrhea.

Medical use and potential mechanism of action

A number of potential mechanisms of action have been suggested. Cyto-protection may work within the lumen of the gastrointestinal tract. Insoluble bismuth salts increase in gastric and duodenal mucosa following oral administration, protecting the mucosa from entero-pathogens. In addition, the salicylic acid portion works as an anti-inflammatory, inhibiting local intestinal prostaglandin activity (Ericsson et al. 1990).

Bismuth may also have antimicrobial activity. In vitro studies suggest bismuth binds and kills bacteria by inhibiting ATP synthesis and disrupting membrane integrity. Salicylic acid prevents/down-regulates formation of biofilms in some bacteria (including *E. coli, Salmonella*) and prevents them from colonizing.

Bismuth compounds may also affect antibiotic metabolism (examples in table) by upregulating drug efflux pumps in some bacteria leading to resistance. Conversely, it can decrease membrane potential and facilitate drug entry.

These compounds may also have anticancer properties and anti-leishmanial activity.

Evidence, knowledge gaps and future research

The benefits of bismuth compounds in reducing severity and duration of acute diarrhea, reducing hospital stay, and improving weight gain in humans are well documented (see table). Currently, bismuth alone or in combination with other therapies (antibiotics, analgesics, fluids) is widely used to manage calf diarrhea,

however, studies documenting its efficacy in calves are lacking. The dose used in animals is derived from human studies (Riviere and Papich 2017). Veterinary medical researchers reported a need to evaluate the efficacy of bismuth in treating calf diarrhea in randomized clinical trials (Roussel and Brumbaugh 1991).

Drug	Study type	Main findings and/or mechanism of action	Reference
Bismuth subsalicylates (BSS)	In vitro	Binds and kills different bacterial species including *E. coli.* Suggested mechanism of action: cessation of ATP synthesis (decreased intracellular ATP) and loss of membrane integrity.	Sox and Olson 1989
Bismuth subsalicylates	Review	Insoluble bismuth salts are closely associated with gastric mucosa; act as cyto-protectants.	Bierer 1990
Bismuth subsalicylate and other bismuth salts	Review	Protects gastric mucosa; Antibacterial property; BSS and amoxicillin resulted in 95% reduction of *Helicobacter pylori.* Prevention and treatment of infective diarrhea *(E. coli).*	Lambert 1991
Bismuth subsalicylate	Randomized controlled clinical trial in 4 - 28 m old children with acute diarrhea	BSS combined with fluid therapy resulted in short duration of illness and hospitalization compared to fluid therapy alone. Eradicated 100% *E. coli* from stool suggesting BSS has antimicrobial properties.	Soriano-Brucher 1991
Bismuth subsalicylate	Randomized controlled clinical trial in children with acute diarrhea	Decreased duration of diarrhea and hospital stay in treated group compared to placebo group. Rotavirus and Entero-pathogenic *E. coli* were the most common pathogens found in stool.	Figueroa-Quintanilla et al. 1993
Synthetic bismuth compounds	In vitro	Synthetic and commercial bismuth compounds more effective in killing *Clostridium difficile* and *H. pylori* than *E. coli*, *P. aeruginosa* and *Proteus mirabilis*. Mechanism of action not understood; however, internalization of bismuth with activity against *C. difficile* suggests uptake required for antimicrobial activity.	Mahoney et al. 1999
Bismuth compounds	Review	Used to treat several gastrointestinal disorders including general, infectious, inflammatory and digestive conditions.	Briand and Burford 1999
Bismuth subsalicylates	Randomized clinical trial in 4-36 m old children in Bangladesh	BSS treated children had less severe illness, shorter duration of illness and more weight gain compared to placebo group. However, there was no difference between groups in development of persistent diarrhea. Rotavirus detected in 56% of all children and enterotoxigenic *E. coli* detected in 31% of subsample.	Chowdhury et al. 2001
Bismuth subsalicylates	In vitro	BSS inhibits bacterial growth in dose and time dependent way; *E. coli* was least affected.	Alharbi et al. 2012

Salicylates	Review	Decrease biofilm formation in *P. aeruginosa, E. coli*. Can affect bacterial motility. Protects mucosal surfaces from colonization. Antibiotic metabolism: *upregulates drug efflux pumps in some proteobacteria (e.g. *E coli* and *Salmonella*) involved in antibiotic clearance; hence increased resistance to fluoroquinolones, cephalosporin, ampicillin, chloramphenicol, tetracycline. *decrease membrane potential and facilitate drug entry e.g. treatment of *E. coli* and *K. pneumoniae* with aminoglycosides.	Damman 2013
Bismuth containing drugs	Review	Gastro-protection; Antimicrobial properties; Current interest in bismuth compounds as anti-leishmania, anti-cancer drugs. Some mechanisms of action related to bismuth targeting protein biomolecules especially cysteine-rich domains.	Keogan and Griffith 2014
Bismuth subsalicylates and bismuth oxychloride	In vitro	3-9 log reduction in growth of *Clostridium difficile*, *Salmonella*, *Shigella*, shiga toxin-producing *E. coli* strains and norovirus indicating antimicrobial activity against diverse diarrhea causing pathogens. Bismuth bound to bacterial membrane and accumulated in cell for bacterial inhibition to occur.	Pitz et al. 2015

Conclusions

Bismuth subsalicylate has substantial evidence for treatment of simple diarrhea and is considered the symptomatic treatment of choice for acute diarrhea (Dowling, 2016). However, most veterinary products recommend that a veterinarian be consulted if the diarrhea persists for more than two days.

References

Alharbi SA, Mashat BH, Al-Harbi NA, et al. 2012. Bismuth-inhibitory effects on bacteria and stimulation of fungal growth in vitro. Saudi J Biol Sci. 19:147-150.

Bierer DW. 1990. Bismuth subsalicylate: history, chemistry, and safety. Rev Infect Dis. 12 Suppl 1:S3-S8.

Briand GG, Burford N. 1999. Bismuth compounds and preparations with biological or medicinal relevance. Chem Rev. 99:2601-2658.

Chowdhury HR, Yunus M, Zaman K, et al. 2001. The efficacy of bismuth subsalicylate in the treatment of acute diarrhoea and the prevention of persistent diarrhoea. Acta Paediatr. 90:605-610.

Damman CJ. 2013. Salicylates and the microbiota: A new mechanistic understanding of an ancient drug's role in dermatological and gastrointestinal disease. Drug Development Research. 74:344-352.

Dowling, PM. 2016. Drugs used in treatment of diarrhea. Merck Veterinary Manual Online https://www.merckvetmanual.com/pharmacology/systemic-pharmacotherapeutics-of-the-digestive-system/drugs-used-in-treatment-of-diarrhea-monogastric

Ericsson CD, Tannenbaum C, Charles TT. 1990. Antisecretory and antiinflammatory properties of bismuth subsalicylate. Rev Infect Dis. 12 (Suppl 1):S16-20.

Figueroa-Quintanilla D, Salazar-Lindo E, Sack RB, et al. 1993. A controlled trial of bismuth subsalicylate in infants with acute watery diarrheal disease. N Engl J Med. 328:1653-1658.

Keogan DM, Griffith DM. 2014. Current and potential applications of bismuth-based drugs. Molecules. 19: 15258-15297.

Lambert JR. 1991. Pharmacology of bismuth-containing compounds. Rev Infect Dis. 13 Suppl 8:S691-S695.

Mahoney DE, Lim-Morrison S, Bryden L, et al. 1999. Antimicrobial activities of synthetic bismuth compounds against Clostridium difficile. Antimicrob Agents Chemother. 43:582-588.

Pitz AM, Park GW, Lee D, et al. 2015. Antimicrobial activity of bismuth subsalicylate on Clostridium difficile, Escherichia coli O157:H7, norovirus, and other common enteric pathogens. Gut Microbes. 6:93-100.

Riviere J, Papich M. 2017. Veterinary pharmacology and therapeutics. 10th Ed. John Wiley & Sons:Hoboken, NJ. P. 1263.

Roussel AJ, Jr., Brumbaugh GW. 1991. Treatment of diarrhea of neonatal calves. Vet Clin North Am Food Anim Pract. 7:713-728.

Soriano-Brucher H, Avendano P, O'Ryan M, et al. 1991. Bismuth subsalicylate in the treatment of acute diarrhea in children: a clinical study. Pediatrics. 87:18-27.

Sox TE, Olson CA. 1989. Binding and killing of bacteria by bismuth subsalicylate. Antimicrob Agents Chemother. 33:2075-2082.

Veterinary Medicine Extension - Washington State University
P.O. Box 646610
Pullman, WA 99164-6610
(509) 335-8221 VetExtension@vetmed.wsu.edu