

Ancillary Therapies for Calf Diarrhea: Medical Use of Bismuth

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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 H₂S 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 <i>E. coli</i> . 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 <i>Helicobacter pylori</i> . Prevention and treatment of infective diarrhea (<i>E. coli</i>). | 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% <i>E. coli</i> 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 <i>E. coli</i> were the most common pathogens found in stool. | Figuroa-Quintanilla et al. 1993 |
| Synthetic bismuth compounds | In vitro | Synthetic and commercial bismuth compounds more effective in killing <i>Clostridium difficile</i> and <i>H. pylori</i> than <i>E. coli</i> , <i>P. aeruginosa</i> and <i>Proteus mirabilis</i> . Mechanism of action not understood; however, internalization of bismuth with activity against <i>C. difficile</i> 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 <i>E. coli</i> detected in 31% of subsample. | Chowdhury et al. 2001 |
| Bismuth subsalicylates | In vitro | BSS inhibits bacterial growth in dose and time dependent way; <i>E. coli</i> was least affected. | Alharbi et al. 2012 |

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|--|----------|--|--------------------------|
| Salicylates | Review | Decrease biofilm formation in <i>P. aeruginosa</i> , <i>E. coli</i> . Can affect bacterial motility. Protects mucosal surfaces from colonization. Antibiotic metabolism: *upregulates drug efflux pumps in some proteobacteria (e.g. <i>E coli</i> and <i>Salmonella</i>) involved in antibiotic clearance; hence increased resistance to fluoroquinolones, cephalosporin, ampicillin, chloramphenicol, tetracycline. *decrease membrane potential and facilitate drug entry e.g. treatment of <i>E. coli</i> and <i>K. pneumoniae</i> 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 <i>Clostridium difficile</i> , <i>Salmonella</i> , <i>Shigella</i> , shiga toxin-producing <i>E. coli</i> 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.

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