Aspirin

(**as**-pir-in)
ASA, Acetylsalicylic Acid
Analgesic, Antipyretic, Platelet Aggregation Reducer, Anti-Inflammatory (Systemic Drug)

Dosages Dosage Forms Drug Interactions Adverse Effects

Prescriber Highlights

- NSAID used for analgesic, anti-inflammatory, and antiplatelet effects in various species.
- Contraindicated in patients hypersensitive to aspirin or with active gastrointestinal bleeds; relatively contraindicated in patients with bleeding disorders, asthma, or renal insufficiency (but has been used to treat glomerular disease).
- Aspirin has a long half-life in cats (approximately 30 hours; dose carefully); dogs are relatively sensitive to gastrointestinal effects (bleeding).
- Low-grade teratogen and may delay labor; avoid use in pregnancy.
- Many drug and laboratory interactions.

Uses / Indications

Aspirin is used for its analgesic, antipyretic, and antiplatelet effects.

When treatment with cyclosporine is required, aspirin therapy may be advisable to offset cyclosporine-induced thromboxane synthesis.[1]

Pharmacology / Actions

Aspirin inhibits cyclooxygenase (COX-1, prostaglandin synthetase), thereby reducing prostaglandin and thromboxane (TXA2) synthesis. These effects are thought to be how aspirin produces analgesia, antipyrexia, reduces platelet aggregation, and reduces inflammation. Except platelets, most cells synthesize new cyclooxygenase. Therefore, aspirin causes irreversible platelet aggregation. A dog study investigating platelet function effects of various aspirin doses showed that doses <1 mg/kg/d or at 10 mg/kg/d did not have any statistically significant effect on platelet aggregation. Doses of 12 mg/kg/d inhibited platelet function and aggregation.[2]

Aspirin may decrease the clinical signs of experimentally induced anaphylaxis in calves and ponies.

While not directly inhibiting COX-2, aspirin, along with lipoxygenase (LOX), can modify COX-2 to produce a compound known as aspirin-triggered lipoxin (ATL). ATL may have gastric mucosal protective actions. This may explain why aspirin tends to have reduced gastric damaging effects when used over time.

Pharmacokinetics

Aspirin is rapidly absorbed from the stomach and proximal small intestine in monogastric animals. The rate of absorption is dependent upon stomach content, gastric emptying times, tablet disintegration rates, and gastric pH. In cattle, oral dosages of 50 mg/kg did not achieve therapeutic concentrations.[3]

During absorption, aspirin is partially hydrolyzed to salicylic acid, which is distributed widely throughout the body. The highest levels of salicylate are found in the liver, heart, lungs, renal cortex, and plasma. Aspirin's plasma protein binding is variable depending on species, serum salicylate, and albumin concentrations. Lower salicylate concentrations are 90% protein bound while higher salicylate concentrations are 70% protein bound. Salicylate is excreted into milk, but levels are very low. Salicylate crosses the placenta, and fetal levels may exceed those found in the mother.

Salicylate is metabolized in the liver primarily by conjugation with glycine and glucuronic acid via glucuronyl transferase. Cats are deficient in this enzymatic pathway resulting in prolonged half-lives of 27 to 45 hours, which may cause drug accumulation. Minor metabolites formed include gentisic acid, 2,3-dihydroxybenzoic acid and 2,3,5-trihydroxybenzoic acid. Gentisic acid appears as the only active metabolite, but low concentrations result in an insignificant role therapeutically. Metabolism is determined by first-order kinetics and dose-dependent kinetics, depending on the metabolic pathway. Serum half-life is approximately 8 hours in dogs, approximately 38 hours in cats, and averages 1.5 hours in humans. Generally, steady-state serum levels will increase to levels higher (proportionally) than expected with dosage increases. These effects have not been well studied in domestic animals, however.

Kidneys rapidly excrete salicylate and its metabolites by filtration and renal tubular secretion. Significant tubular reabsorption occurs, which is pH dependent. Raising urine pH to 5 to 8 can significantly increase salicylate excretion. Salicylate and metabolites may be removed using peritoneal dialysis or more rapidly using hemodialysis.

Contraindications / Precautions / Warnings

Aspirin is contraindicated in patients demonstrating previous hypersensitivity reactions to it or with bleeding ulcers. Relative contraindications include patients with hemorrhagic disorders, asthma, or renal insufficiency.

High protein binding to plasma albumin means patients with hypoalbuminemia may require lower aspirin dosages to prevent clinical signs of toxicity. Aspirin should be used cautiously with enhanced monitoring in patients with severe hepatic failure or diminished renal function.

If possible, halt aspirin therapy one week prior to surgical procedures due to its platelet effects. For animals at high risk for thrombotic complications, some authors have advocated discontinuing aspirin 48 hours prior to surgical procedures.[4] Additionally, the use of desmopressin acetate has been shown to reverse aspirin-induced platelet dysfunction in 3 dogs that required emergent surgery.[5]

Aspirin should be used cautiously in cats due to their inability to rapidly metabolize and excrete salicylates. Clinical signs of toxicity may occur if dosed recklessly or without stringent monitoring.

Aspirin should be used cautiously in neonatal animals, as adult doses may lead to toxicity.

Hypoglycemic agents' effects may be potentiated with concurrent aspirin use. Monitor blood glucose accordingly.

High-dose aspirin therapy used concurrently with the carbonic anhydrase inhibitor dichlorphenamide should be considered contraindicated; metabolic acidosis may result. Use caution with other carbonic anhydrase inhibitors.

Adverse Effects

The most common adverse effect of aspirin at therapeutic doses is gastric (eg, nausea, anorexia, vomiting) or intestinal irritation. Varying degrees of occult gastrointestinal blood loss may occur. The resultant irritation may cause vomiting and/or anorexia. Severe blood loss consequences could include secondary anemia or hypoproteinemia. In dogs, plain uncoated aspirin may irritate the gastric mucosa more than either buffered aspirin or enteric-coated tablets. Misoprostol has been shown to reduce gastrointestinal bleeding and vomiting in dogs receiving aspirin. Hypersensitivity reactions in dogs are rarely reported. Cats may develop acidosis from aspirin therapy.

Reproductive / Nursing Safety

Salicylates are possible teratogens and have been shown to delay parturition; their use should be avoided during pregnancy, particularly during the later stages. In humans, the FDA categorizes this drug as category ***D*** for use during pregnancy (*There is evidence of human fetal risk, but the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks*). In a separate system evaluating the safety of drugs in canine and feline pregnancy,[6] this drug is categorized as class: ***C*** (*These drugs may have potential risks. Studies in people or laboratory animals have uncovered risks, and these drugs should be used cautiously as a last resort when the benefit of therapy clearly outweighs the risks*).

Overdose / Acute Toxicity

Clinical signs of acute overdose in dogs and cats include depression, vomiting (may be blood tinged), anorexia, hyperthermia, and increased respiratory rate. Initially, a respiratory alkalosis occurs with a compensatory hyperventilation response. A profound metabolic acidosis follows. Without treatment, muscular weakness, pulmonary and cerebral edema, hypernatremia, hypokalemia, ataxia, and seizures may develop with eventual coma and death.

There were 1939 single-agent exposures to aspirin reported to the ASPCA Animal Poison Control Center (APCC) during 2009 to 2013. There were 1749 dogs exposed, 712 of which were symptomatic. The most common signs included: vomiting (75%), lethargy (21%), panting (9%), hyperthermia (8%), and bloody vomiting (7%). Of the 177 cats, 54 were symptomatic with vomiting (56%), anorexia (22%), lethargy (13%), and bloody vomiting (6%).

Acute overdose treatment initially consists of gut emptying if ingestion occurred within 12 hours, activated charcoal, oral cathartic, placing an IV line, beginning fluids, and lab work (eg, blood gases). Some clinicians suggest performing gastric lavage with a 3% to 5% solution of sodium bicarbonate to delay aspirin absorption. Dextrose 5% in water is a reasonable IV solution to correct dehydration. Acidosis treatment and forced alkaline diuresis with sodium bicarbonate should be performed for

serious ingestions, but only if acid-base status can be monitored. Diuresis may be enhanced by the administration of mannitol (1 – 2 grams/kg/h). Gastrointestinal protectant medications should be administered. Seizures may be controlled with IV diazepam. Treatment of hypoprothrombinemia may be attempted by using phytonadione (2.5 mg/kg divided every 8 – 12 hours) and ascorbic acid (25 mg parenterally). Ascorbic acid may negate some urinary alkalinization of bicarbonate. Consider peritoneal dialysis or exchange transfusions in very severe ingestions when heroic measures are desired.

Drug Interactions

The following drug interactions with aspirin have either been reported or are theoretical in humans or animals and may be of significance in veterinary patients. Unless otherwise noted, use together is not necessarily contraindicated, but weigh the potential risks and perform additional monitoring when appropriate.

- **ACE INHIBITORS**: The effect of ACE inhibitors may be decreased with concomitant aspirin use. The nephrotoxic effects of ACE inhibitors may be increased with concomitant aspirin use.
- **ALENDRONATE**: Increased risk of upper gastrointestinal adverse effects when used concurrently with aspirin.
- **AMINOGLYCOSIDES** (eg, **gentamicin**, **amikacin**): Some clinicians feel aspirin should not be given concomitantly with aminoglycoside antibiotics because of an increased likelihood of nephrotoxicity developing. The actual clinical significance of this interaction is unclear. Weigh the risks versus benefits when contemplating therapy.
- **ANTIDEPRESSANTS, SSRI** (eg, **sertraline**, **fluoxetine**, **paroxetine**): The antiplatelet effects of aspirin may be increased with concurrent use increasing bleeding risk.
- **BLOOD GLUCOSE LOWERING AGENTS**: Hypoglycemic effects may be potentiated by aspirin.
- **CALCIUM CHANNEL BLOCKERS, NONDIHYDROPYRIDINE** (eg, **diltiazem**): The antiplatelet effects of aspirin may be increased with concurrent use increasing bleeding risk.
- **CORTICOSTEROIDS**: Corticosteroids may increase the clearance of salicylates, decrease salicylate serum levels, and increase gastrointestinal bleeding risk. One dog study showed no significant difference in gastric mucosal injury when ultra-low dose aspirin (0.5 mg/kg/d) was added to prednisone therapy. Adding aspirin did increase the incidence of mild, self-limiting diarrhea.[7]
- **DICHLORPHENAMIDE**: High-dose aspirin therapy used concurrently dichlorphenamide should be considered contraindicated as metabolic acidosis may result. Use caution with other carbonic anhydrase inhibitors.
- **DIGOXIN**: In dogs, aspirin demonstrates increased plasma levels of digoxin by decreasing digoxin clearance.
- **FUROSEMIDE**: Furosemide may compete with renal excretion of aspirin and delay aspirin excretion. Accumulated aspirin may cause clinical signs of toxicity in animals receiving high aspirin doses. Furosemide diuretic effect may be diminished.
- **GLUCOSAMINE**: Concomitant aspirin use may increase bleeding risk.
- **HEPARIN, ORAL ANTICOAGULANTS or ANTIPLATELET AGENTS** (eg, **clopidogrel**): Concomitant aspirin use may increase bleeding risk.
- **HYALURONIDASE**: The therapeutic benefits of hyaluronidase may be decreased; higher hyaluronidase doses may be required.

- **METHOTREXATE**: Aspirin may displace methotrexate from plasma proteins, increasing the risk for methotrexate toxicity.
- **NSAIDs**: Increased chances of developing gastrointestinal ulceration exists when used concomitantly. Animals on aspirin therapy that will be replaced with a COX-2 NSAID should probably have a "washout period" of 3 to 10 days between stopping aspirin and starting the NSAID.[8] Another recommendation for cats is a "washout period" of approximately 7 to 10 days when switching from aspirin to another NSAID.[9]
- **PENTOSAN POLYSULFATE SODIUM**: The antiplatelet effects of aspirin may be increased with concurrent use increasing bleeding risk.
- **PHENOBARBITAL**: Hepatic enzyme induction by phenobarbital may increase aspirin metabolism.
- **PROBENECID, SULFINPYRAZONE**: At usual doses, aspirin may antagonize the uricosuric effects of probenecid or sulfinpyrazone.
- **SPIRONOLACTONE**: Aspirin may inhibit the diuretic activity of spironolactone.
- **TETRACYCLINE**: Antacids in buffered aspirin may chelate tetracycline products if given simultaneously; space doses apart by at least one hour.
- **TILUDRONATE**: Serum concentrations of tiludronate may be decreased with concurrent aspirin therapy.
- **URINARY ACIDIFYING DRUGS** (eg, **methionine**, **ammonium chloride**, **ascorbic acid**): Urinary acidifiers can decrease urinary excretion of salicylates.
- **URINARY ALKALINIZING DRUGS** (eg, **acetazolamide**, **sodium bicarbonate**): Urinary alkalinizers significantly increase the renal excretion of salicylates; because carbonic anhydrase inhibitors (eg, **acetazolamide**, **dichlorphenamide**) may cause systemic acidosis and increase central nervous system levels of salicylates; toxicity may occur.
- **VALPROATE PRODUCTS**: Serum concentrations of valproate products may be increased with concurrent aspirin therapy.
- **VITAMIN E**: The antiplatelet effects of aspirin may be increased with concurrent use increasing bleeding risk.

Laboratory Considerations

- At high doses, aspirin may cause false-positive results for **urinary glucose** if using the cupric sulfate method (*Clinitest*®, Benedict's solution) and false-negative results if using the glucose oxidase method (*Clinistix*® or *Tes-Tape*®).
- **Urinary ketones** measured by the ferric chloride method (Gerhardt) may be affected if salicylates are in the urine (reddish-color produced). Salicylates may interfere with fluorescent methods for determining urine **5-HIAA** (**5-hydroxyindoleacetic acid**). Falsely elevated **VMA** (**vanillylmandelic acid**) may be seen with most methods used if salicylates are in the urine. Falsely lowered **VMA** levels may be seen if using the Pisano method.
- Urinary excretion of **xylose** may be decreased if aspirin is given concurrently. Falsely elevated **serum uric acid** values may be measured if using colorimetric methods.
- Aspirin can decrease serum concentrations of **total T4** (**thyroxine**).
- Aspirin may prolong bleeding time tests.

Dosages

Note: There are no FDA-approved products and dosages for veterinary patients; all dosages are extra-label.

- **DOGS**:

  Decrease platelet aggregation; antithrombotic (extra-label): The ideal aspirin dosage, if any, for prevention of thromboembolism in dogs is unknown (eg, data conflicts, study limitations).[10] Commonly, dosages of 0.5 – 1 mg/kg PO every 24 hours are recommended, but some recommend up to 10 mg/kg PO every 24 hours. A preliminary report demonstrated platelet activity is increased in dogs with immune-mediated hemolytic anemia (IMHA) compared to normal dogs. The same report found neither low-dose PO aspirin (0.5 mg/kg/d) nor individually dosed heparin suppresses platelet thromboxane release in vivo.[11]

  Analgesic/antipyretic/anti-inflammatory (extra-label): Anecdotal dosages range from 10 – 20 mg/kg of buffered aspirin PO every 12 hours. Anecdotal anti-inflammatory dosages are slightly higher (20 – 30 mg/kg PO every 8-12 hours), but canine-approved NSAIDs generally have significantly fewer gastrointestinal effects and are usually preferred.

- **CATS**:

  Analgesic/antipyretic/anti-inflammatory (extra-label): Anecdotal dosage recommendation is 10 mg/kg PO every 48 to 72 hours; practically: half to one 81-mg tablet ("baby aspirin") Monday, Wednesday, and Friday weekly.

  Antithrombotic (extra-label): Two basic dosage regimens have been recommended, "high dose" and "low dose"; it is unknown if one is superior to the other regarding efficacy. "High dose" appears to significantly increase the risk for gastrointestinal side effects. High-dose: 10 mg/kg PO every 24 to 72 hours; half to one 81-mg tablet ("baby aspirin") every 48 to 72 hours (ie, Mondays, Wednesdays, Fridays). Low-dose: 5 mg per cat PO every 72 hours. A randomized, prospective multicenter study of cats with a prior thromboembolic event found that high-dose aspirin at 72 mg/cat PO every 72 hours was inferior to clopidogrel in reducing the risk for recurrent arterial thromboembolism, though both drugs were well tolerated.[12]

- **FERRETS**:

  As an analgesic (extra-label): 10 – 20 mg/kg PO every 24 hours (has short duration of activity).[13]

- **RABBITS/RODENTS/SMALL MAMMALS**:

  Note: All are extra-label.

  - **Rabbits**: 5 – 20 mg/kg PO every 24 hours for low-grade analgesia.[14]
  - **Mice, Rats, Gerbils, Hamsters**: 100 – 150 mg/kg PO every 4 hours. **Guinea pigs**: 87 mg/kg PO.[15]

- **HORSES**: (NOTE: ARCI UCGFS CLASS 4 DRUG)

Antiplatelet adjunctive treatment of laminitis (extra-label): 5 – 10 mg/kg PO every 24 to 48 hours or 20 mg/kg PO every 96 to 120 hours.[16]

Monitoring

- Analgesic effect and/or antipyretic effect.
- Bleeding times if indicated.
- Packed cell volume (PCV) and fecal occult blood (eg, guaiac) tests if indicated.

Client Information

- Contact veterinarian if gastrointestinal bleeding symptoms or distress occur (eg, black, tarry feces; anorexia, vomiting).
- Aspirin predates formal FDA approval regulations for its use in animals. There are no listed meat or milk withdrawal times listed for food-producing animals. In the interest of public health of salicylate-sensitive people, this author suggests a minimum of one day withdrawal time for either milk or meat.

Chemistry / Synonyms

Aspirin is the salicylate ester of acetic acid. The compound occurs as a white, crystalline powder or tabular or needle-like crystals. As a weak acid with a pK_a of 3.5, aspirin is slightly soluble in water and freely soluble in alcohol. Each gram of aspirin contains approximately 760 mg of salicylate.

Aspirin may also be known as ASA, acetylsal acid, acetylsalicylic acid, acidum acetylsalicylicum, polopiryna, or salicylic acid acetate; many trade names are available.

Storage / Stability

Aspirin tablets should be stored in tight, moisture-resistant containers. Do not use products past the expiration date or if a strong vinegar-like odor is emitting from the bottle.

Aspirin is stable in dry air but readily hydrolyzes to acetate and salicylate when exposed to water or moist air; it then exudes a strong vinegar-like odor. The addition of heat will speed the hydrolysis rate. In aqueous solutions, aspirin is most stable at a pH of 2 to 3 and least stable at a pH of <2 or >8. Should an aqueous solution be desirable as a dosage form, the commercial product *Alka-Seltzer*® will remain stable for 10 hours at room temperature in solution.

Compatibility / Compounding Considerations

Compounded preparation stability: Aspirin is hydrolyzed by water to degradative byproducts, acetic acid, and salicylic acid.

Effervescent buffered aspirin tablets (*Alka-Seltzer*®) dissolved in water are demonstrated to be stable for 10 hours at room temperature and 90 hours refrigerated.[17] Although pharmacists compound aspirin suspensions in fixed oils, the long-term stability of these preparations is unknown.

Dosage Forms / Regulatory Status

VETERINARY-LABELED PRODUCTS:

Note: No known products are FDA approved for use in animals.

Aspirin Tablets (Enteric-Coated): 81 mg; (OTC). Labeled for use in dogs.

Aspirin Tablets (Buffered, Microencapsulated, Chewable for dogs): 60 mg, 120 mg, 150 mg, 300 mg, and 450 mg; *Canine Aspirin Chewable Tablets for Small & Medium* (150 mg) or *Large Dogs*® (450 mg); (OTC). Labeled for use in dogs.

Aspirin Tablets 60 grains (3.9 g): Aspirin 60 Grains (OTC & Rx); Rx is labeled for use in horses, foals, cattle, calves, sheep, and swine; not for use in horses intended for food or in lactating dairy animals.

Aspirin Boluses 240 grains (15.6 g): Aspirin 240 Grains Boluses, Aspirin Bolus (various); (OTC). Labeled for use in horses, foals, cattle, and calves; not for use in lactating animals.

Aspirin Boluses 480 grains (31.2 g): Aspirin 480 Grains Boluses (various); (OTC). Labeled for use in mature horses and cattle.

Aspirin Powder: 1 lb (various); (OTC); Aspirin Powder Molasses-Flavored 50% acetylsalicylic acid in base; Aspirin USP 204 g/lb (apple flavored); Acetylsalicylic acid; (OTC). Labeled for use in horses, foals, cattle, calves, sheep, swine, and poultry.

Aspirin Granules: 2.5 gram per 39 mL scoop (apple and molasses flavor); *Arthri-Eze Aspirin Granules*®; (OTC); Labeled for use in horses.

Aspirin Liquid Concentrate (equiv. to 12% aspirin) for Dilution in Drinking Water in 32 oz. bottles; (OTC). Labeled for addition to drinking water for swine, poultry, beef cattle, and dairy cattle.
There are no listed meat or milk withdrawal times listed for food-producing animals, but because of salicylate-sensitive people, in the interest of public health, this author suggests a minimum of 1 day withdrawal time for either milk or meat.

The ARCI (Association of Racing Commissioners International) has designated this drug as a class 4 substance.

HUMAN-LABELED PRODUCTS:

Aspirin, Tablets; Chewable: 81 mg (1.25 grains); many trade names, generic; (OTC).

Aspirin, Tablets; Plain Uncoated: 325 mg (5 grains), & 500 mg (7.8 grains); many trade names, generic; (OTC).

Aspirin, Tablets; Enteric Coated: 81 mg, 325 mg, 500 mg, & 650 mg (10 grains); many trade names, generic; (OTC).

Aspirin, Tablets; Extended-Controlled Release: 81 mg, 650 mg; many trade names, generic; (OTC).

Aspirin, Tablets; Buffered Uncoated: 324 mg (5 grains) & 325 mg (5 grains), with aluminum &/or magnesium salts; many trade names, generic; (OTC).

Aspirin, Tablets; Buffered Coated: 325 mg & 500 mg; many trade names, generic; (OTC).

Rectal suppositories, chewing gum, and effervescent oral dosage forms are commercially available for humans.

References / Revisions

Reviewed and updated by David J. Laffrenzen, PharmD, BCP, and Brian A. Scansen, DVM, MS, DACVIM (Cardiology), FVIR. Last update August 2017.

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