Salicylate Salts

Choline Magnesium Trisalicylate

Triethanolamine **Salicylate**

magnesium **salicylate**

choline **salicylate**

Introduction

Choline **salicylate**, magnesium **salicylate**, sodium **salicylate**, and trolamine (triethanolamine) **salicylate** are nonsteroidal anti-inflammatory agents (NSAIAs), and are salts of salicylic acid that dissociate to **salicylate** in vivo.

Uses

Although the uses included in the labeling approved by the US Food and Drug Administration (FDA) vary from one preparation to another, oral **salicylate** salts (choline **salicylate**, magnesium **salicylate**, sodium **salicylate**) are generally used for anti-inflammatory and analgesic effects in the symptomatic treatment of conditions for which **salicylate** therapy is indicated (e.g., pain, rheumatoid arthritis, osteoarthritis). There are relatively few controlled comparative studies of oral **salicylate** salts and aspirin, but the anti-inflammatory, analgesic, and antipyretic effects of **salicylate** salts are generally considered to be comparable to those of aspirin. However, since **salicylate** salts do not inhibit platelet aggregation, they should not be substituted for aspirin in the prophylaxis of thrombosis.

There is no evidence that one oral **salicylate** salt is therapeutically superior to another; however, **salicylate** salts containing magnesium or sodium should be avoided in patients in whom excessive amounts of these electrolytes might be harmful. (See Cautions: Precautions and Contraindications.) In the treatment of rheumatoid arthritis or osteoarthritis, there is some evidence that the anti-inflammatory and analgesic effects of usual dosages of oral **salicylate** salts are about equal to those of usual dosages of other currently available NSAIAs. Oral **salicylate** salts may be particularly useful in patients with GI intolerance to aspirin or in patients in whom interference with normal platelet function by aspirin or other NSAIAs is considered undesirable. Oral solutions of choline **salicylate** or choline **salicylate** and magnesium **salicylate** may be useful in patients who are unable to take tablets or capsules of aspirin or other salicylates.

Trolamine **salicylate** is applied topically alone or as an adjunct to systemic therapy in the treatment of mild muscle or joint pain, such as that associated with inflammatory disease (e.g., rheumatoid arthritis). However, the evidence that topical trolamine **salicylate** is an effective analgesic is inconclusive. In one double-blind, placebo-controlled crossover study in patients with osteoarthritis of the knee, the analgesic effect of topical trolamine **salicylate** did not differ from that of placebo when trolamine **salicylate** or placebo was used alone or as an adjunct to systemic therapy with a NSAIA. In another study, the analgesic effect of topical trolamine **salicylate** was reported to be at least equal to that of 650-mg oral doses of aspirin in patients with muscle and joint pain secondary to inflammatory disease (e.g., osteoarthritis) or with nonarticular inflammation. The conflicting results may be due in part to problems in study design and differences in the type and severity of diseases present in the study populations. One manufacturer states that data from unpublished studies support the efficacy of topical trolamine **salicylate** as an analgesic. Further published studies are needed.

Dosage and Administration

Administration

Choline **salicylate**, magnesium **salicylate**, sodium **salicylate**, and combination preparations containing choline **salicylate** and magnesium **salicylate** are administered orally. The drugs should usually be given with food or a large quantity (240 mL) of water or milk to minimize gastric irritation. Although rarely necessary, sodium **salicylate** may also be administered by slow IV infusion. Trolamine **salicylate** is applied topically.

Dosage

Dosage of **salicylate** salts must be carefully adjusted according to individual requirements and response, using the lowest possible effective dosage.

Choline **salicylate** and combination preparations containing sodium **salicylate** should not be used for self-medication of

pain for longer than 10 days in adults or 5 days in children, unless directed by a physician, since pain of such intensity and duration may indicate a pathologic condition requiring medical evaluation and supervised treatment. A manufacturer of magnesium **salicylate** recommends that the drug not be used for self-medication of pain for longer than 5 days in adults.

Choline **salicylate** and combination preparations containing sodium **salicylate** should not be used in adults or children for self-medication of marked fever (greater than 39.5°C), fever persisting longer than 3 days, or recurrent fever, unless directed by a physician, since such fevers may indicate serious illness requiring prompt evaluation and treatment by a physician.

To minimize the risk of overdosage, no more than 5 doses of any of these drugs should be administered to children for analgesia or antipyresis in any 24-hour period, unless directed by a physician.

Choline **Salicylate**

Choline **salicylate** oral solution may be mixed with fruit juice, a carbonated beverage, or water just before administration; it should not be mixed with an antacid. (See Chemistry and Stability: Choline **Salicylate**.)

For analgesia or antipyresis in adults or children older than 11 years of age, the usual oral dosage of choline **salicylate** is 435-870 mg (2.5-5 mL of the oral solution) every 4 hours as necessary. In children 2-11 years of age, the usual oral dosage for analgesia or antipyresis is 2 g (11.5 mL) per m^2 daily, administered in 4-6 divided doses. Alternatively, children may receive the following approximate oral doses every 4 hours as necessary: children 11 years of age, 653 mg (3.8 mL); children 9-10 years of age, 544 mg (3.1 mL); children 6-8 years of age, 435 mg (2.5 mL); children 4-5 years of age, 327 mg (1.9 mL); and children 2-3 years of age, 218 mg (1.3 mL). Dosage in children younger than 2 years of age must be individualized.

For the symptomatic treatment of rheumatoid arthritis, osteoarthritis, or other polyarthritic or inflammatory conditions, the usual oral dosage of choline **salicylate** is 4.8-7.2 g (28-41 mL) daily in adults and 107-134 mg (0.6-0.8 mL) per kg daily in children, administered in divided doses; up to 174 mg (1 mL) per kg daily may be required in some children. Dosage should be adjusted according to the patient's response, tolerance, and serum **salicylate** concentration.

Choline **Salicylate** and Magnesium **Salicylate** Combination

Choline **salicylate** and magnesium **salicylate** oral solution may be mixed with fruit juice just before administration; it should not be mixed with an antacid. (See Chemistry and Stability: Choline **Salicylate**.) Dosage of combination preparations containing choline **salicylate** and magnesium **salicylate** is expressed in terms of **salicylate** content. For the **salicylate** content of the currently available combination preparations, see Chemistry and Stability: Choline **Salicylate** and Magnesium **Salicylate** Combination.

For the symptomatic treatment of rheumatoid arthritis, osteoarthritis, or other polyarthritic or inflammatory conditions, the usual initial adult dosage of oral combination preparations containing choline **salicylate** and magnesium **salicylate** is 1.5-2.5 g of **salicylate** daily, administered as a single daily dose or in 2 or 3 divided doses. The usual oral adult maintenance dosage is 1-4.5 g of **salicylate** daily. Dosage should be adjusted according to the patient's response, tolerance, and serum **salicylate** concentration.

Magnesium **Salicylate**

Dosage of magnesium **salicylate** is expressed in terms of anhydrous magnesium **salicylate**.

For analgesia or antipyresis in adults or children older than 11 years of age, the usual oral dosage of magnesium **salicylate** is 300-600 mg every 4 hours as necessary. Alternatively, for self-medication of pain, adults or children older than 11 years of age may receive an initial oral dose of 500 mg to 1 g, followed by 500 mg every 4 hours as necessary, not to exceed 3.5 g in any 24-hour period. Children may receive the following approximate oral doses every 4 hours as necessary, not to exceed 5 doses in any 24-hour period: children 11 years of age, 450 mg; children 9-10 years of age, 375 mg; children 6-8 years of age, 300 mg; children 4-5 years of age, 225 mg; and children 2-3 years of age, 150 mg. Dosage in children younger than 2 years of age must be individualized.

For the symptomatic treatment of rheumatoid arthritis, osteoarthritis, or other polyarthritic or inflammatory conditions, the usual initial oral adult dosage of magnesium **salicylate** is 545 mg to 1.2 g 3 or 4 times daily. Dosage should be adjusted according to the patient's response, tolerance, and serum **salicylate** concentration.

Sodium **Salicylate**

For analgesia or antipyresis in adults or children older than 11 years of age, the usual oral dosage of sodium **salicylate** is 325-650 mg every 4 hours as necessary. In children 2-11 years of age, the usual oral dosage for analgesia or antipyresis is 25-50 mg/kg daily or 1.5 g/m^2 daily, administered in 4-6 divided doses. Alternatively, children may receive the following approximate oral doses every 4 hours as necessary: children 11 years of age, 480 mg; children 9-10 years of age, 400 mg; children 6-8 years of age, 325 mg; children 4-5 years of age, 240 mg; and children 2-3 years of age, 160 mg. Dosage in children younger than 2 years of age must be individualized.

For the symptomatic treatment of rheumatoid arthritis, osteoarthritis, or other polyarthritic or inflammatory conditions, sodium **salicylate** has been given in an oral dosage of 3.6-5.4 g daily in adults and 80-100 mg/kg daily in children, administered in divided doses; up to 130 mg/kg daily may have been required in some children. For the symptomatic treatment of rheumatic fever, sodium **salicylate** has been given in the same dosage as that employed with aspirin. Because of the high sodium content of sodium **salicylate** preparations, use of the drug for rheumatic fever generally was avoided, particularly if congestive cardiac complications were present; high dosages were used with extreme caution in patients with carditis since congestive heart failure or pulmonary edema could have been precipitated.

Trolamine **Salicylate**

For the topical treatment of mild muscle or joint pain in adults, trolamine **salicylate** cream, lotion, or stick should be applied liberally and gently rubbed into the cleansed, affected area 2-4 times daily, preferably with one application at bedtime. Supervised therapy is usually continued for as long as a satisfactory response is obtained and no severe or intolerable adverse effect occurs. However, trolamine **salicylate** should not be used for self-medication of pain for longer than 10 days, unless directed by a physician, since pain of such intensity and duration may indicate a pathologic condition requiring medical evaluation and supervised treatment. If pain persists or worsens, the patient should discontinue topical trolamine **salicylate** therapy immediately and notify a physician.

Cautions

For further information on cautions, precautions, and contraindications associated with the use of **salicylate** salts, see Cautions in the Salicylates General Statement 28:08.04.

Precautions and Contraindications

Like other salicylates, oral or IV (parenteral preparations containing **salicylate** salts are no longer commercially available in the US) **salicylate** salts should be used with caution in patients with impaired renal function and with extreme caution, if at all, in patients with advanced chronic renal impairment. The manufacturers caution that patients who generally consume 3 or more alcohol-containing drinks per day should ask their clinician whether to use oral salicylates (e.g., choline **salicylate**, magnesium **salicylate**) or an alternative analgesic for self-medication since salicylates may increase the risk of GI bleeding.

A specific **salicylate** salt preparation is contraindicated in patients with known hypersensitivity to that preparation or any of the ingredients in the formulation and should be used with extreme caution, if at all, in patients with known hypersensitivity to salicylates. For further information on sensitivity reactions to salicylates, see Cautions: Sensitivity Reactions, in the Salicylates General Statement 28:08.04.

Choline **Salicylate**

The manufacturers caution that patients who generally consume 3 or more alcohol-containing drinks per day should ask their clinician whether to use choline **salicylate** or another analgesic for self-medication since choline **salicylate** may increase the risk of GI bleeding.

Magnesium **Salicylate**

Because of the risk of hypermagnesemia, preparations containing magnesium **salicylate** are generally contraindicated in patients with advanced chronic renal impairment. If magnesium **salicylate** is used in patients with any degree of renal impairment, other drugs containing magnesium may need to be discontinued. If high dosages of magnesium **salicylate** are administered, serum magnesium concentration should be monitored.

Sodium **Salicylate**

Because of the high sodium content, sodium **salicylate** preparations should be used with extreme caution, if at all, in patients with congestive heart failure or other conditions in which a high sodium intake would be harmful.

Trolamine **Salicylate**

When used in appropriate dosage, topically applied trolamine **salicylate** appears to have a low order of toxicity. When the drug is used extensively, moderate peeling of the skin may occur but does not necessarily require discontinuance of therapy. Contact with the eyes and mucous membranes should be avoided and trolamine **salicylate** should not be applied to acutely inflamed skin or raw, weeping surfaces. If excessive irritation develops, the drug should be discontinued and the patient should notify a physician. Since only trace amounts of **salicylate** are detected in serum following topical application of trolamine **salicylate**, it is probably not necessary to consider the effect of percutaneous trolamine **salicylate** absorption on total serum **salicylate** concentration in most patients who are concurrently receiving systemic salicylates.

Pediatric Precautions

For information on salicylates and Reye's syndrome, see Cautions: Pediatric Precautions, in the Salicylates General Statement 28:08.04.

Safety and efficacy of choline **salicylate** and magnesium **salicylate** combination preparations and magnesium **salicylate** preparations in children have not been established. Trolamine **salicylate** should be used in children only under the direction and supervision of a physician.

Pharmacokinetics

For information on the distribution and elimination of **salicylate**, see Pharmacokinetics in the Salicylates General Statement 28:08.04.

Absorption

In general, **salicylate** salts are rapidly absorbed from the GI tract. Choline **salicylate** oral solution and choline **salicylate** and magnesium **salicylate** oral solution are the most rapidly absorbed. Trolamine **salicylate** also is rapidly absorbed percutaneously following topical application. There are few published studies determining the extent of absorption of **salicylate** salt preparations.

Choline and Magnesium Salicylates

In one study in fasting healthy adults given 870 mg of choline **salicylate** as an oral solution, average peak plasma **salicylate** concentrations of 39 mcg/mL were attained within 20 minutes. In one crossover study in adults given daily doses of choline **salicylate** oral solution and uncoated plain aspirin tablets that were approximately equivalent in **salicylate** content, average blood **salicylate** concentrations attained after 7 days on either regimen were nearly equal, suggesting that the extent of absorption of both preparations is similar.

In one crossover study in fasting healthy adults comparing uncoated plain aspirin (two 325-mg tablets), anhydrous magnesium **salicylate** (one 524-mg tablet), and the combination preparation containing choline **salicylate** and magnesium **salicylate** (one Trilisate 500 tablet), average peak plasma **salicylate** concentrations of 33 mcg/mL, 37 mcg/mL, and 37 mcg/mL, respectively, were attained within 1.5-2 hours. Based on the areas under the plasma concentration-time curves (AUCs) and on the percentage of the dose excreted in the urine in 24 hours as salicyluric acid, there were no apparent differences in the extent of absorption among these **salicylate** preparations. In another crossover study in patients with rheumatoid arthritis given daily doses of uncoated plain aspirin tablets, buffered aspirin tablets, and Trilisate 500 tablets that were equivalent in **salicylate** content, average steady-state serum **salicylate** concentrations achieved with any of these preparations were nearly equal, suggesting that the extent of absorption of the preparations is similar.

In one crossover study in fasting healthy adults that compared equivalent single doses of the combination preparation containing choline **salicylate** and magnesium **salicylate** as the oral solution (10 mL of Trilisate Liquid) and tablets (2 Trilisate 500 tablets), peak plasma **salicylate** concentrations averaged 85 mcg/mL within 35 minutes with the oral solution and 78 mcg/mL within 1.5 hours with the tablets. Based on the AUCs observed in this study, there was no apparent difference in the extent of absorption between these dosage forms. Following oral administration of 4 Trilisate 500 tablets as a single dose in healthy adults in one study, average peak blood **salicylate** concentrations of 170 mcg/mL were attained within 2 hours.

Sodium **Salicylate**

In one crossover study in healthy adults comparing uncoated plain aspirin tablets and uncoated sodium **salicylate** tablets (no longer commercially available in the US), sodium **salicylate** was absorbed more rapidly than aspirin. Following administration of a single 650-mg oral dose of sodium **salicylate** (as two 325-mg uncoated tablets [no longer commercially available in the US]) in this study, average peak plasma **salicylate** concentrations of 65 mcg/mL were attained within 40 minutes. As part of the same study, 3.9 g of sodium **salicylate** (no longer commercially available in the US as a single-entity preparation) was administered orally in 4 divided doses daily for 7 days; based on the average percentage of the daily dose excreted in the urine in 24 hours after 5-7 days, sodium **salicylate** was at least 85% absorbed. In one study in healthy adults given sodium **salicylate** IV (no longer commercially available in the US) and as an oral aqueous solution (no longer commercially available in the US), it was shown that the solution was completely absorbed. In another study in fasting healthy adults given a single 975-mg oral dose of sodium **salicylate** (as three 325-mg enteric-coated tablets) (no longer commercially available in the US), an average peak serum **salicylate** concentration of 68 mcg/mL occurred at 6 hours.

Trolamine **Salicylate**

Trolamine **salicylate** is rapidly and well absorbed percutaneously following topical application. Following topical application of 10 g of 10% trolamine **salicylate** cream (1 g of trolamine **salicylate**) to intact skin over one knee in a group of patients with rheumatoid arthritis, **salicylate** concentrations in synovial fluid after 1-2 hours were 0.16-0.25 mcg/mL and were approximately 60% of those attained after a 500-mg oral dose of aspirin; blood **salicylate** concentrations after topical application of trolamine **salicylate** were less than 1% of those after oral administration of aspirin.

Chemistry and Stability

Chemistry

Choline **salicylate**, magnesium **salicylate**, sodium **salicylate**, and trolamine (triethanolamine) **salicylate** are nonsteroidal anti-inflammatory agents (NSAIAs) that are salts of salicylic acid. A combination preparation containing a mixture of choline **salicylate** and magnesium **salicylate** (choline magnesium trisalicylate) also is commercially available. **Salicylate** salts dissociate to **salicylate** in vivo.

Choline **Salicylate**

Choline **salicylate** occurs as a white, crystalline, very hygroscopic powder and is very soluble in water and in alcohol. Each gram of choline **salicylate** contains approximately 570 mg of **salicylate** (equivalent to 750 mg of aspirin).

Choline **Salicylate** and Magnesium **Salicylate** Combination

The **salicylate** contents of the commercially available combination preparations containing choline **salicylate** and magnesium **salicylate** are as follows: 5 mL of Trilisate Liquid or each Trilisate 500 tablet contains 500 mg of **salicylate** (equivalent to 650 mg of aspirin), each Trilisate 750 tablet contains 750 mg of **salicylate** (equivalent to 975 mg of aspirin), and each Trilisate 1000 tablet contains 1000 mg of **salicylate** (equivalent to 1300 mg of aspirin).

Magnesium **Salicylate**

Magnesium **salicylate** occurs as a tetrahydrate, white, crystalline powder that effloresces on exposure to air and is soluble in water and in alcohol. Each gram of anhydrous magnesium **salicylate** contains approximately 6.7 mEq of magnesium and 920 mg of **salicylate** (equivalent to 1.2 g of aspirin).

Sodium **Salicylate**

Sodium **salicylate** occurs as an amorphous or microcrystalline powder, or scales, and is freely and slowly soluble in water and slowly soluble in alcohol. Sodium **salicylate** may have a faint characteristic odor and a faint-pink tinge. Each gram of sodium **salicylate** contains 6.25 mEq of sodium and approximately 860 mg of **salicylate** (equivalent to 1.1 g of aspirin). Sodium **salicylate** currently is commercially available in the US only as a combination preparation with analgesics, antihistamines, antitussives, decongestants, expectorants, or caffeine.

Trolamine **Salicylate**

Trolamine **salicylate** occurs as a waxy solid and is miscible with water and with alcohol. Each gram of trolamine **salicylate** contains approximately 480 mg of **salicylate** (equivalent to 630 mg of aspirin).

Stability

Choline **Salicylate**

Aqueous solutions of choline **salicylate** are easily discolored by traces of iron. Addition of an alkali (e.g., an antacid) to an aqueous solution of choline **salicylate** liberates choline and gives the solution a fishy odor.

Sodium **Salicylate**

Sodium **salicylate** becomes pink on exposure to light; therefore, preparations containing the drug should be protected from light. Sodium **salicylate** is incompatible with ferric salts and mineral acids.

For further information on chemistry and stability, pharmacology, pharmacokinetics, uses, cautions, chronic toxicity, acute toxicity, drug interactions, laboratory test interferences, and dosage and administration of **salicylate** salts, see the Salicylates General Statement 28:08.04.

Preparations

Choline **Salicylate**
Oral
Solution
870 mg/5 mL
Arthropan
Purdue Frederick

Choline **Salicylate** and Magnesium **Salicylate** Combination (Choline Magnesium Trisalicylate)
Oral
Solution
293 mg/5 mL Choline **Salicylate** and 362 mg/5 mL Magnesium **Salicylate**
Trilisate Liquid
Purdue Frederick

Tablets, film-coated
293 mg Choline **Salicylate** and 362 mg Magnesium **Salicylate***
Tricosal
Qualitest Vintage

Trilisate 500 (scored)
Purdue Frederick

440 mg Choline **Salicylate** and 544 mg Magnesium **Salicylate***
Tricosal
Qualitest Vintage

Trilisate 750 (scored)
Purdue Frederick

587 mg Choline **Salicylate** and 725 mg Magnesium **Salicylate***
Tricosal
Qualitest Vintage

Trilisate 1000 (scored)
Purdue Frederick

*available by nonproprietary name

Magnesium **Salicylate**
Oral
Tablets
325 mg (of anhydrous magnesium **salicylate**)*
Doan's Regular Caplets

Novartis

467 mg (of anhydrous magnesium **salicylate**)
Backache Pain Relief
Bristol-Myers Squibb Chain Drug

Momentum
Medtech

500 mg (of anhydrous magnesium **salicylate**)*
Doan's Extra Strength Caplets (with propylene glycol)
Novartis

545 mg (of anhydrous magnesium **salicylate**)
Magan
Savage

600 mg (of anhydrous magnesium **salicylate**)
Mobidin (scored)
Ascher

650 mg (of anhydrous magnesium **salicylate**)
Keygesic-10
Key

Magnesium **salicylate** also is commercially available in combination with an antihistamine, a decongestant, and minerals and vitamins.

*available by nonproprietary name

Sodium **Salicylate**
Sodium **salicylate** is commercially available in combination with other analgesics, antihistamines, antitussives, caffeine, decongestants, and expectorants.

Trolamine **Salicylate** (Triethanolamine **Salicylate**)
Topical
Cream
10%
Arthricream
Bergen Brunswig CVS Leader Major McKesson Medalist
Valu-Rite
Arthricreme
Osco Rite Aid Sav-On

Arthritis Pain Medicine
Goldline

Aspercreme (with parabens)
Thompson

Mobisyl Creme (with parabens)
Ascher

Myoflex Creme (with propylene glycol)
Novartis

Sportscreme Cream
Thompson

Lotion
10%
Aspercreme (with parabens and propylene glycol)
Thompson

Sportscreme Lotion
Thompson

Stick
10%
Sportscreme Stick
Thompson