

ASPIRIN

The Golden Pill

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CHAPTER ELEVEN

Aspirin for Today

*In all things,
the supreme excellence is simplicity.*

— Henry Wadsworth Longfellow

In designing the ideal aspirin tablet, the following features are desired:

- Low dose of aspirin
- High bioavailability
- Gastrointestinal protection
- Rapid onset
- Pleasant flavor

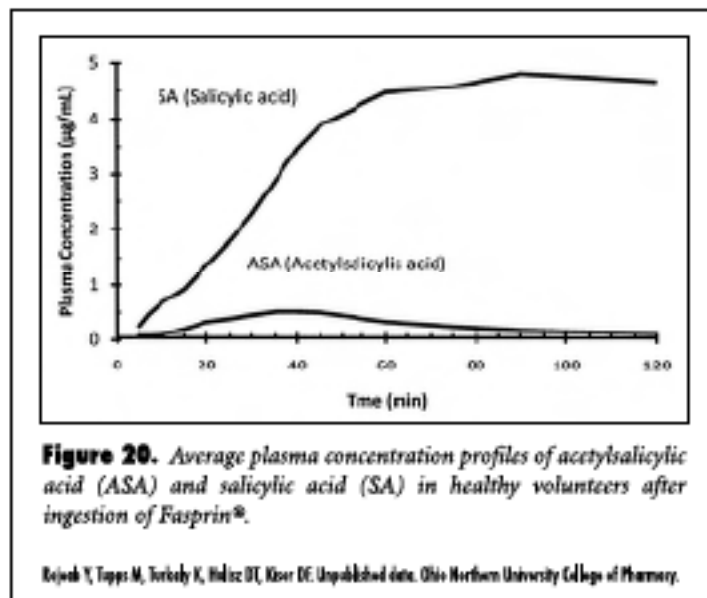
Low Dose of Aspirin

What is the optimal dose of aspirin? Theoretically, the optimal dose of aspirin should prevent a blood clot from forming yet allow endothelial cells lining the blood vessels to release prostacyclin to dilate and prevent occlusion of the vessel. Technically, the optimal dose of aspirin should generate a low thromboxane (TXA₂):prostacyclin ratio, allowing for antithrombotic effect yet sustained coronary artery vasodilation with minimal GI toxicities. Thromboxane A₂, generated by tissue injury, makes blood platelets stickier and more likely to form clots and constrict blood vessels. Prostacyclin is produced in vascular endothelial cells causes vasodilation and prevents the formation of platelet plugs leading to a clot. Higher doses of aspirin have antithrombotic benefits but prevent the

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release of prostacyclin and may be a potential mechanism by which cyclooxygenase (COX)-2 inhibitors produce a higher risk of MI.

Clinical trials of 10,000 patients, compared different dosages of aspirin (30 mg to 1300 mg) and included patients with virtually every clinical manifestation of atherosclerotic disease: stroke, transient ischemic attack (TIA), percutaneous coronary and peripheral interventions, carotid endarterectomy, and myocardial infarction. Low dose aspirin (30-300 mg) was as effective as higher doses of aspirin (> 325 mg) in all the trials. The daily treatment with 325 mg of aspirin would lead to an excess of more than 900,000 major bleeding events per year compared with a daily dose of 81 mg.



High Bioavailability

Aspirin is delivered in the form of tablets, powders, topical, intravenously or by suppository. More than 50 million patients take a daily aspirin pill for CVD prevention in the United States. About 40% of the population have difficulty swallowing tablets, which is a common condition with the elderly because of

weakened muscles of the esophagus. In the stomach, aspirin is not constantly stirred or in a suspended dispersed state. Gastroscopic studies show that most of the aspirin, especially when taken in tablet form, adheres to the stomach mucosa and settles in the stomach crevices (rugae) and thus largely escape suspension and agitation. Aspirin remaining undissolved for long periods of time causes damage to the gastrointestinal tract. Most of the GI bleeding occurs with the use of tablets that are poorly absorbed in the stomach. Options include placing a powdered aspirin in a glass of water, chewing a tablet and washing it down with water, or having an orally disintegrating tablet (ODT). An ODT dissolves in your mouth by saliva, with the aspirin absorbed by the lining of the mouth, absorbed directly into the blood stream.

The safer form of aspirin is in the form of an Orally Disintegrating Tablet (ODT). ODTs are intended to dissolve and disintegrate rapidly in the mouth when the tablet comes in

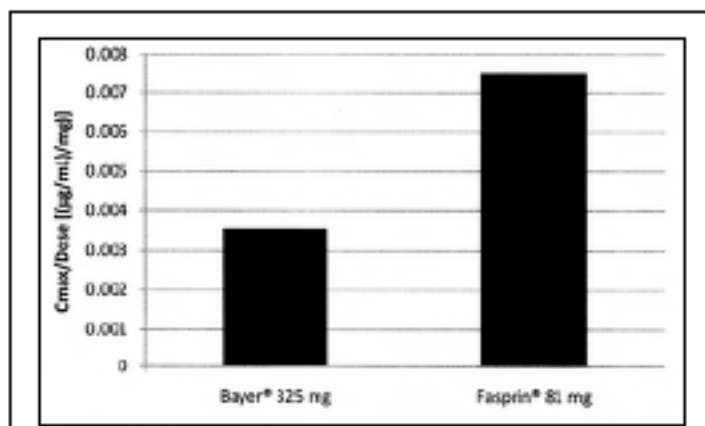


Figure 21. Dose normalized maximum concentration (C_{max}) of acetylsalicylic acid (ASA) from Bayer® and Fasprin® products administered to healthy volunteers. The data suggests that there is a greater percentage of ASA released from the dosage form relative to the dose.

Rajesh V, Toppo M, Turky F, Haddad DT, Kiser DE Unpublished data. Ohio Northern University College of Pharmacy.

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contact with the saliva on the tongue, forming a soluble aspirin that is absorbed by the buccal mucosa. Aspirin is absorbed more rapidly through the oral mucosa since the drug enters directly into the bloodstream and avoids hepatic first pass metabolism. Bioavailability is improved with the ODT, therefore the drug can be administered in smaller doses, which can lead to fewer side effects and improved patient compliance.

A recent study to determine the absorption of ODT low dose aspirin (Fasprin®; 81 mg) demonstrated that ASA was detected in the blood as early as five minutes. Fasprin® provided high bioavailability, since aspirin concentrations at 5 minutes were 5-fold greater than previously reported studies with low dose (baby; 81 mg) aspirin, and that maximum blood concentrations of salicylic acid were 30% greater than those previously reported.

Gastrointestinal Protection

Two approaches to provide GI protection involve the addition of an amino sugar to enhance the gastric mucosal barrier and the addition of a zinc compound to treat and prevent gastric ulcers.

Glucosamine is an amino sugar and a major constituent of gastric mucus. Glucosamine is a small molecule, very soluble in water, and 90% absorbed in the GI tract. Glucosamine appears linked to its ability to stimulate the synthesis of proteoglycans needed to stabilize cell membranes and increase intracellular ground substance. Evidence indicates a combination of glucosamine with an NSAID, such as aspirin can enhance the salicylate blood level.

One of the GI side-effects of NSAIDs is aggravating or initiating colitis type disorders, explained by the hypothesis that NSAIDs inhibit glucosamine synthetase resulting in a reduction of the glucoaminoglycan (GAG) layer of the GI tract. The GAG layer is mechanical, located in the pre-endothelial and sub-endothelial area in the arterial network, and is an electrostatic barrier, due to the negative charges from the highly anionic GAGs. The neutralization of the electrostatic barrier, results in a breakdown of the GAG defense, resulting in an increase in extravasation of body fluids into the intestinal lumen and also the passage of toxins and large foreign molecular weight antigens into the circulation. Glucosamine also

directly inhibits the secretion of inflammatory molecules.

Zinc compounds have proved their efficacy in treating or preventing NSAID-induced GI injuries. The zinc ions augment the mucus and strengthen the mucosal barrier. Mucosal ulcerations were completely prevented by pre-treatment with zinc sulphate. These protective effects result from the inhibition of lipid peroxidation and the preservation of mucosal nitric oxide synthase. Zinc carnosine has been shown to protect the small intestine from NSAID-induced injury and stimulate mucosal repair.

Zinc compounds have anti-inflammatory and anti-infective properties. Zinc can inhibit the growth of *Streptococci* and *Actinomyces* bacteria when used as a dentifrice. Zinc compounds have antiseptic, antifungal, antiviral and astringent properties. As an astringent, zinc can be used therapeutically to arrest hemorrhage by coagulating blood, check diarrhea, reduce inflammation of mucus membranes, promote healing, toughen skin and decrease sweating. Zinc's dominant biological action is membrane stabilization.

Rapid Onset

Rapid onset of blood aspirin levels is important when one is having a heart attack, stroke or migraine headache. The myocardium (heart muscle) begins to undergo irreversible injury within 20 minutes of ischemia and a wavefront of death sweeps from the inner to the outer layers of myocardium during a 3 to 6 hour period. The repair process requires two months to complete. During a stroke, 1.9 million nerve cells die each minute and the ischemic brain, due to a lack of oxygen, ages about 3.6 years each hour, emphasizing the need for rapid treatment of this disorder. During a migraine attack, gastric stasis and delayed gastric emptying occurs and absorption of solid aspirin formulations or any other medication may be impaired.

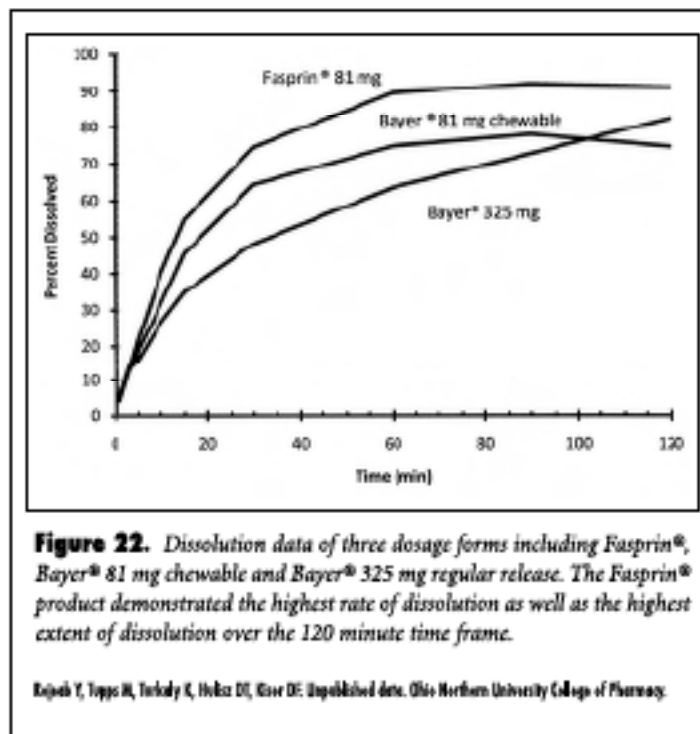
Regular 325 mg aspirin tablets reach peak blood levels in 30 to 40 minutes and only about 50% of the aspirin tablet is absorbed. Enteric coated aspirin tablets take about 2 to 4 hours to reach peak blood levels, and only half of the aspirin is absorbed.

Orally Disintegrating Tablets (ODT) are intended to dissolve and disintegrate rapidly in the mouth when the tablet comes in contact with the saliva on the tongue, forming a soluble aspirin that

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is absorbed by the buccal mucosa. Bioavailability is improved with the ODT and the drug can be administered in smaller doses, which can lead to fewer side effects and improved patient compliance.

Fasprin® provided high bioavailability, since aspirin concentrations at 5 minutes were 5-fold greater than previously reported studies with low dose (baby; 81 mg) aspirin, and that maximum blood concentrations of salicylic acid were 30% greater than those reported previously.



Pleasant Flavor

Most aspirin tablets don't have a pleasant flavor, so chewing an aspirin tablet to obtain rapid absorption by the buccal mucosa leaves one with an unpleasant vinegar taste and aftertaste. Fasprin® a low-dose aspirin ODT has a pleasant natural lemon flavor and leaves one with a very pleasant taste.

Conclusion

During the past century indications for aspirin have exploded, but the tablet design has been stagnant. With the exception of the development of the enteric coated tablet the only new advance has been the orally disintegrating tablet. Today, the only aspirin tablet that meets the criteria for the ideal tablet is Fasprin.

Fasprin® is: (1) a low dose 81 mg aspirin tablet, (2) with high bioavailability since the aspirin level is 5-fold greater than previously reported studies with low dose aspirin, (3) with gastrointestinal protection since it contains glucosamine and a zinc compound, (4) rapid onset because it is in the form of an orally disintegrating tablet which enters the blood stream in 5 minutes, and (5) has a pleasant lemon flavor.

Chapter Eleven – References

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