Adverse Reactions and Interactions with Aspirin
Considerations in the Treatment of the Elderly Patient

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Summary
Aspirin (acetylsalicylic acid) is probably the most frequently used medication, and its
use is generally uneventful. However, aspirin is also noted for numerous side effects and
drug interactions that can complicate the course of therapy. The elderly, especially those
with complicated medical histories, are more prone to the adverse effects of salicylates
and may develop gastrointestinal tract bleeding, renal insufficiency, asthma and CNS
toxicity. In the clinical situation, important drug interactions can occur with concurrent
use of anticoagulants, sulphonylureas, diuretics, methotrexate and antacids.

In long term aspirin therapy, enteric-coated or nonacetylated forms of aspirin are
associated with fewer side effects and may be better tolerated. Monitoring of therapy
(especially in the higher risk patient), with frequent assessments of the clinical state and
measurements of serum creatinine, electrolytes and salicylate concentrations, may di­
minish the likelihood of toxicity.

Aspirin (acetylsalicylic acid) is probably the most commonly used medication. It is inexpensive and
an effective analgesic, antipyretic and anti-inflammatory agent. Its occasional use in adults is well
tolerated and not expected to be associated with side effects, even in the elderly. However, chronic and painful rheumatic diseases are common in the elderly and the long term commitment to aspirin, especially in dosages used to treat inflammatory diseases such as rheumatoid arthritis, must be expected to be associated with the development of predictable side effects. Apart from therapeutic nihilism there are no real alternatives to the use of aspirin in many patients. Paracetamol (acetaminophen) is not an anti-inflammatory drug and is not expected to provide adequate therapy for inflammatory arthritis. Other nonsteroidal anti-inflammatory drugs (NSAIDs) are essentially no less toxic than aspirin; corticosteroids have their own gamut of side effects which can be devastating at any age, and particularly for the elderly. Thus, in the absence of contraindications, the practitioner should not hesitate to use aspirin. Rather, a method should be established to monitor the effects of aspirin on the patient and to adjust the course of therapy when desirable results occur or undesirable results intervene. This review is not intended to discuss all the toxicities of aspirin and related NSAIDs; rather, it concentrates on those toxicities of aspirin that may be enhanced by age, and the interactions of aspirin with the other medications that the elderly frequently require for diverse medical problems.

1. Pharmacokinetics of Aspirin

The advantageous and detrimental effects of aspirin can be related loosely to the serum concentration of its principal metabolite, salicylate, the deacetylated form of the drug. Therefore, a knowledge of the salient features of aspirin pharmacokinetics would be useful in understanding why toxicity may have occurred in a patient (Flower et al. 1985; Kimberly & Plotz 1989). In brief, orally ingested aspirin is absorbed rapidly (a minor proportion from the stomach and the majority from the upper small intestine), metabolised in the liver by several pathways and excreted by the kidney (Furst et al. 1977; Gupta et al. 1975; Levy et al. 1975).

1.1 Formation of Salicylate

The capacity of the gastrointestinal tract to absorb aspirin is large, and therefore plays little role in determining plasma concentrations of salicylate. Aspirin can be measured in the plasma within minutes of ingestion, but the half-life ($t_{1/2}$) of aspirin itself is very short ($t_{1/2} = 15$ minutes) because of deacetylation to salicylate, which occurs via 3 mechanisms:

1. Spontaneous deacetylation in plasma.
2. Enzymatic hydrolysis of the acetyl group in the liver.
3. Loss of the acetyl group by acetylation of proteins such as prostaglandin synthetase, albumin and haemoglobin.

1.2 Distribution of Salicylate

Salicylate is 80 to 90% bound to plasma proteins, predominantly albumin, and is distributed widely throughout the body. Unbound salicylate rapidly diffuses across cell membranes, primarily by a pH-dependent passive process. With increasing dose the proportion of drug in the plasma that is unbound increases, providing more free drug to the tissues. Thus, increments in the free plasma concentration of salicylate are greater at higher doses of drug – especially when plasma albumin is low, as may occur in active rheumatoid arthritis and other conditions associated with hypoalbuminaemia. Small upward dosage modifications in such patients may be associated with large increases in plasma salicylate concentrations, with attendant toxicity.

1.3 Metabolism and Excretion of Salicylate

Salicylate is metabolised in the liver. The majority pathway converts salicylic acid to its glycine conjugate salicyluric acid; there are in addition 2 glucuronide conjugates of salicylic acid. Salicylates are excreted via the kidney as free salicylate (10%), salicyluric acid (75%) and glucuronide conjugates (15%). Because the metabolised salicylate products