

**Aspirin Effect...
a new dilemma**



Urinary 11-dehydro thromboxane B₂

Aspirin Effect... A New Solution

Aspirin, the foundation of antiplatelet therapy in cardiovascular medicine, is widely prescribed by physicians to prevent heart attack and stroke. It is estimated that more than 150,000 heart attacks each year could be prevented by the appropriate use of aspirin therapy.¹

Recently, physicians discovered that a significant number of individuals taking dosages of aspirin considered therapeutic were experiencing vascular thrombotic events including acute coronary syndromes, transient ischemic attacks, strokes and peripheral vascular events. In addition, clinical researchers, utilizing a variety of laboratory tests, discovered that some patients have a reduced or minimal response to aspirin administration.²

The observation that individuals do not respond identically to therapeutic aspirin dosage has been defined as "Aspirin Resistance", a relatively new but well documented concept in the medical literature.^{3,4}

Aspirin and Thromboxane Generation

Aspirin's therapeutic effect inhibits COX-1 and results in decreased production of thromboxane A₂ (TXA₂), which reduces the ability of platelets to aggregate (figure 1). TXA₂ is hydrolyzed in the liver into a number of metabolites including 11-dehydro thromboxane B₂ and cleared from circulation by the kidneys (figures 2A and 2B). Thus, high levels of urinary 11-dehydro thromboxane B₂ indicate

insufficient inhibition of thromboxane A₂ production, and a lack of aspirin effect.

Several factors (table 1) have been identified as potential mechanisms for influencing levels of 11-dehydro thromboxane B₂.^{5,6,7}

Table 1. Mechanisms of Variability in Aspirin Effect

- Reduced aspirin bioavailability
- Competitive interference by other NSAID's
- Increased platelet turnover
- Generation of thromboxane A₂ by COX-2
- Platelet polymorphisms
- Hyperlipidemia
- Diet and Lifestyle

of in-vivo platelet activation. Urinary 11-dehydro thromboxane B₂ is not subject to the preanalytical variables associated with other blood-based indirect measurements of platelet activation.

Methods requiring freshly drawn blood measure platelet function resulting from ex-vivo stimulation of the platelet utilizing a variety of platelet activating agents. Tests that require fresh blood are subject to preanalytical variables that can potentially influence patient results including specimen collection, storage and transportation. Inter-laboratory standardization of these tests is difficult.

Some researchers suggest that insufficient inhibition of thromboxane A₂ production most accurately represents the definition of true aspirin resistance.⁴

Summary

The ability to monitor aspirin effect allows healthcare providers to provide assurance to patients that their aspirin is working to inhibit platelet function. Dosage is important, as an ineffective response results in adverse events including an increased risk of death.^{8,9} Other antiplatelet therapy options such as clopidogrel may be utilized.

While there are several different methods available to detect platelet response to aspirin, urinary 11-dehydro thromboxane B₂ is a readily available marker that can quantify insufficient inhibition of thromboxane A₂ production by the platelets. Some researchers suggest that insufficient inhibition of thromboxane A₂ production most accurately represents the definition of true "aspirin resistance."⁴

Figure 1. Diagram of the cyclooxygenase platelet activation pathway.

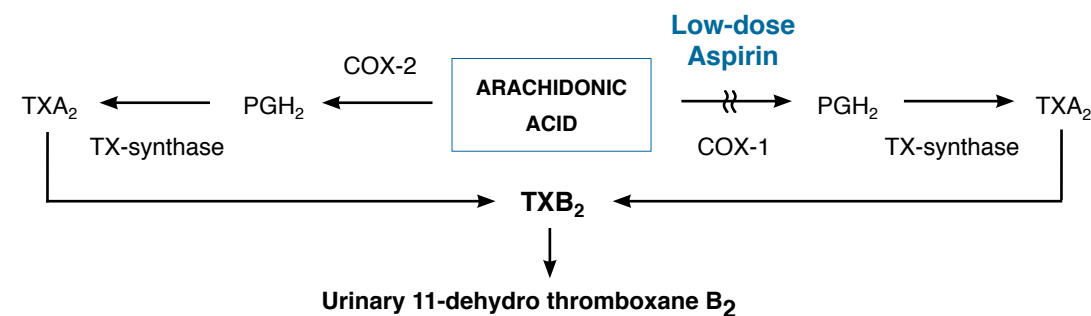


Figure 2A. Aspirin Effect

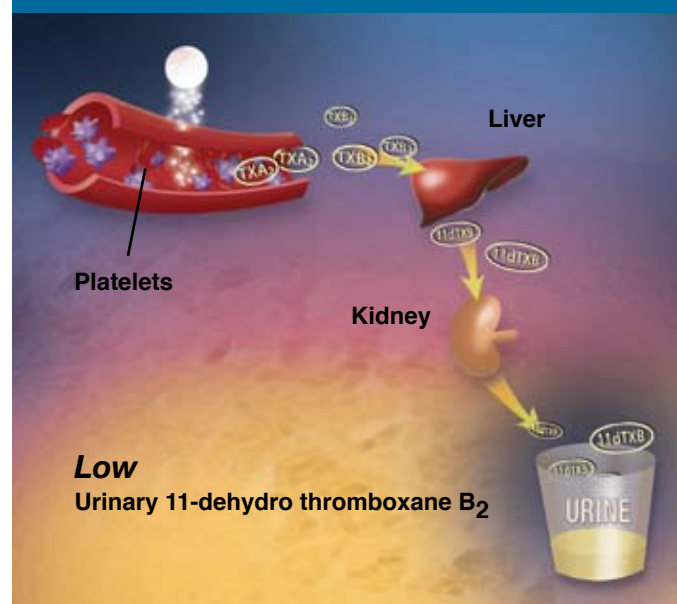
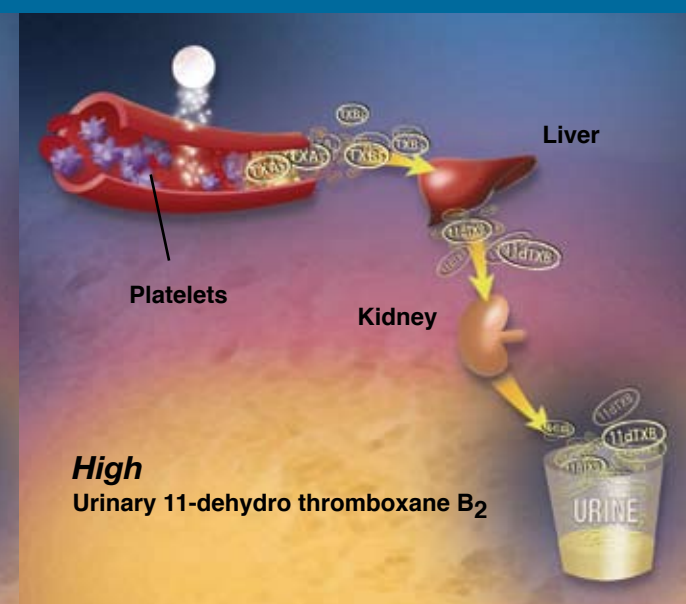


Figure 2B. Lack of Aspirin Effect



Clinical Importance

In 2002, a clinical outcomes study was published evaluating patients at high risk for cardiovascular events. Urinary 11-dehydro thromboxane B₂ was used in the study as a marker for in-vivo platelet activation. Results analyzed by quartile showed that patients in the 4th quartile (lack of aspirin effect) had a 3.5 times greater risk of cardiovascular death than those in the 1st quartile (aspirin effect).⁸

A second clinical outcomes study evaluating "aspirin resistance" in patients with cardiovascular disease was published utilizing platelet aggregometry. It also demonstrated a greater than 3 times risk of death in those patients not responding to aspirin.⁹

Urinary 11-dehydro thromboxane B₂ is not subject to the preanalytical variables associated with other blood-based indirect measurements of platelet activation.

Laboratory Measurement of Aspirin Effect

Several tests may be utilized to measure the effect of aspirin on platelets. Urinary 11-dehydro thromboxane is a stable metabolite of thromboxane A₂ and an indicator

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