



Can chronic use of anti-inflammatory agents paradoxically promote chronic inflammation through compensatory host response?

John D. Doux^a, Kimberly A. Bazar^b, Patrick Y. Lee^a, Anthony J. Yun^{a,*}

^a *Stanford University, 470 University Ave., Palo Alto, CA 94301, USA*

^b *San Mateo Medical Center, CA, USA*

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Summary A higher relative risk of thrombotic cardiovascular complications has recently emerged in studies evaluating the use of non-steroidal anti-inflammatory drugs (NSAIDs) such as rofecoxib, celecoxib, and naproxen. Direct pro-thrombotic effects of selective cyclooxygenase-2 inhibition were originally speculated to be the potential mechanism behind these results, but this proposal fails to explain the pro-thrombotic effects of non-selective NSAIDs. We hypothesize that the paradoxical pro-inflammatory, pro-thrombotic effects associated with chronic use of anti-inflammatory agents are attributable to compensatory host response rather than direct effects of the drugs. Chronic pharmacologic inhibition of inflammation may induce physiologic dependence, and cessation of therapy has been shown to produce rebound effects in aspirin, statins, and other immunomodulatory agents. By down-regulating inflammatory pathways in a pulsatile fashion, chronic use of NSAIDs may promote compensatory up-regulation of these same pathways and shift the host baseline equilibrium towards an inflammatory state. The host may be susceptible to inflammation between intermittent doses and after withdrawal of therapy. Inflammation is a promoter of adrenergia and thrombosis, and the constellation of these effects may predispose to excess risk of acute cardiovascular events. © 2005 Elsevier Ltd. All rights reserved.

Non-steroidal anti-inflammatory drugs (NSAIDs) are the single most commonly used type of medication, with over 13 million regular users [1]. A higher relative risk of thrombotic cardiovascular complications has recently emerged in studies evaluating the use of NSAIDs, such as rofecoxib, celecoxib,

and naproxen [2–4]. These studies have been met with surprise given that inflammation is considered a cornerstone in the pathogenesis of cardiovascular disease. Direct pro-thrombotic effects of selective cyclooxygenase-2 (cox-2) inhibition were originally speculated to be the potential mechanism behind these results, but this proposal fails to explain the pro-thrombotic effects of non-selective NSAIDs. We hypothesize that the paradoxical pro-inflammatory, pro-thrombotic effects associated with

* Corresponding author. Tel.: +1 650 387 6667; fax: +1 650 325 5028.

E-mail address: ayun@stanford.edu (A.J. Yun).

chronic use of anti-inflammatory agents are attributable to compensatory host response rather than direct effects of the drugs.

Many drugs promote physiologic dependence, and cessation of therapy can produce rebound effects [5]. The unintended effects observed with anti-inflammatory agents may also operate through this mechanism. By down-regulating inflammatory pathways in pulsatile fashion, chronic use of NSAIDs may promote compensatory up-regulation of these same pathways. NSAIDs likely exert their anti-inflammatory effects via the inhibition of cox-2, an enzyme that normally converts arachidonic acid to prostaglandins [6]. It should be noted, however, that cox-2 production is an inducible process, and inhibition of cox-2 activity increases synthesis of the cox-2 enzyme [7]. Thus, an extended period of inhibition could potentially lead to significant elevation of latent cox-2 activity. Upon release of inhibition, increased cox-2 levels could theoretically lead to increased production of prostaglandins and thus exaggerated inflammation.

The relatively short half-lives of the specific cox-2 inhibitors may explain the findings found in association with their use. The half-life of rofecoxib is 17 h; that of celecoxib, 11 h. Naproxen, albeit a non-specific inhibitor, may act via a similar mechanism, as it possesses a half-life of 13 h. Any intermittent or non-compliant use of these medications, or simply individual variation in elimination patterns, would produce periods when serum levels dip below that required for functional inhibition. During periods when inhibition did occur, latent cox-2 activity would have undergone marked elevation as a result of increased production of enzyme. Prostaglandin conversion would consequently increase at those times when inhibition fails to occur, producing an increase rather than a decrease in inflammation. Without a period where the inductive pathway can reset to baseline, a vicious cycle may occur where intermittent inhibition of cox-2 activity leads to stepwise escalation of cox-2 production. Such intermittent induction may in turn provoke progressively greater degrees of inflammation until drastic consequences result. Support for this mechanism also stems from the observation that issues with celecoxib occurred at higher dosages, suggesting that induction to produce the witnessed effects may require a threshold magnitude of inhibition.

Inflammation is a promoter of adrenergia and thrombosis, and the constellation of these effects may predispose to excess risk of acute cardiovascular events. Inflammatory cytokines such as IL-1, IL-6, and TNF-alpha promote coagulation and potential vasoocclusion, possibly through chemo-

kines such as CCL17 and CCL22 [8–10]. Thrombin and other components of the coagulation cascade such as factor Xa and tissue factor–factor VIIa complex not only further promote inflammation, but also increase sympathetic activity [11–16]. Increased sympathetic activity in turn can further promote inflammation by inciting T helper (Th)2 bias, as well as increasing the oxygen demand on the heart by inducing vasoconstriction and tachycardia [17]. All of these factors can also lead to an increased risk of cardiovascular events [18].

The currently observed examples may represent specific manifestations of a much broader phenomenon. Indeed, many different pharmacologic methods of inhibiting inflammation can induce physiologic dependence, and cessation of therapy often produces rebound effects. Withdrawal following sustained chronic use of NSAIDs can produce analgesic rebound headache [19]. In the case of aspirin, withdrawal following chronic use has yielded observations of increased risk of cardiac events [20] and acute lower limb ischemia [21]. These phenomena may result from vascular inflammation induced by increased prostaglandin synthesis following withdrawal of longstanding cyclooxygenase inhibition. Similar processes may operate with regards to withdrawal syndromes for HMG CoA-reductase inhibitors in the setting of acute coronary episodes [22,23] and efalizumab in the treatment of psoriasis [24].

Validation of our hypothesis requires more empiric studies. Numerous studies involving anti-inflammatory agents have reported absence of excess cardiovascular risk, in contrast to the recent group of studies revealing the presence of such risk. A number of factors may account for the apparently conflicting observations. It would be useful to determine if the proposed pro-inflammatory rebound phenomenon is sensitive to dosing amount and frequency. Variation in effects may not only be due to heterogeneity amongst study members in response to the medication, but also due to variations in patterns of use not captured by the study protocol. The key may be with how these medications were intended for use as opposed to how they have become used. As use of these agents has extended beyond the indication of acute relief to that of a permanent solution, compensatory induction may mitigate any effects exerted by the medication and produce a higher baseline level of chronic inflammation. Confirmation of our hypothesis would dictate a significant re-examination of when and how anti-inflammatory agents are to be deployed. Perhaps pulsed administration of short-acting pro-inflammatory agents would represent a counterintuitive strategy to

treat inflammatory conditions by harnessing host compensatory mechanisms.

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