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Endotoxin Challenge: Optimizing Experimental Models for Antipyretic Drug Development

Nandita K Shankar[1] and Clayton A Dehn[2]*

[1]California Northstate University College of Medicine, USA
[2]Evolution Research Group (ERG), USA

***Corresponding author:** Clayton A. Dehn, Evolution Research Group (ERG) 430 Mountain Ave, Suite 302, New Providence, NJ 07974, USA

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Abstract

The endotoxin challenge serves as a valuable experimental model for antipyretic drug development, providing insights into systemic inflammatory responses and the efficacy of novel treatments. By inducing predictable physiological reactions, it mirrors the inflammatory profile of sepsis, allowing for investigations into the pathophysiology of fever and inflammation, as well as the evaluation of antipyretic therapies. This review examines the varied applications of endotoxin administration, particularly intravenous bolus dosing, and highlights the potential of combined bolus-infusion paradigms to sustain systemic responses and better align with therapeutic pharmacokinetics and pharmacodynamics. Furthermore, mathematical modeling and simulation techniques offer innovative approaches to optimizing experimental designs and data analysis. Despite its broad application, there remains a need for models that elicit a safe, sustained, and measurable systemic response, allowing for the thorough evaluation of antipyretics. Developing such models is crucial to enhancing the efficiency of drug development and improving clinical management of pyrexia across various settings.

Keywords: *Endotoxin challenge, Antipyretic drug development, Systemic inflammation, Experimental medicine models, Pharmacokinetic – pharmacodynamic optimization*

Introduction

The endotoxin challenge is an experimental medicine tool that has been used for over a century across a number of investigational efforts and in some settings even as a therapeutic. Kamisoglu et al. have shown that the plasma metabolomic profile following an endotoxin challenge is concordant with that from sepsis survivors, affirming the validity of the endotoxin challenge as a viable model to recapitulate homeostatic responses to inflammatory and pyrogenic challenges [1]. Uses of the endotoxin challenge in clinical investigation include attempts to characterize pathophysiology of pyrexia and inflammatory and anti-inflammatory pathways, describe time-course of clinical and molecular events as well as assessment of the degree of benefit of novel anti-pyretic and anti-inflammatory therapies. The doses and routes of endotoxin administration vary depending on the scientific question at hand. In turn, there are some challenges to design of an endotoxin challenge tailored to address specific questions, particularly in the context of definition of quantitative estimates of therapeutic benefit.

The innate risk of administering endotoxin especially to healthy volunteers is partly balanced by the somewhat predictable nature and time-course of the systemic response it elicits [2]. To further deliver on the twin need to ensure safe use of endotoxin for investigational purposes as well as to guide drug development, the NIH and FDA jointly oversaw an effort to develop a "national biological reference standard to be made available to pharmaceutical manufacturers and qualified biomedical investigators as an aid to standardization of bioassays and research with endotoxin". This standard developed using endotoxin from *Escherichia coli* O: 113: H10: K negative has also been adopted by the WHO as its reference for endotoxin assays [2].

Pyrexia or fever is defined as a state in which the central thermoregulatory set point is increased, primarily via disinhibition of thermogenesis, and pyrogens are agents that induce pyrexia [3,4]. In general, exogenous pyrogens such as bacterial and viral antigens or exotoxins activate the Toll-like receptor (TLR) pathway, that triggers a signal transduction cascade leading to increased generation of endogenous pyrogens such as prostaglandins, culminating in the pathophysiologic events that constitute the pyrexia response [3,5]. The purported teleologic role of pyrexia in the setting of disease, particularly infectious disease, is an adaptive response to inhibit microorganism proliferation and amplify endogenous immunological response [6]. However, this is accompanied by increases in metabolic demand as well as undue stress on the cardiovascular, respiratory and other systems that are less than welcome [6]. Timely and prudent use of antipyretics tailored to rein in the unwarranted systemic effects of pyrexia without impacting its benefits as an adaptive response relies heavily on clinical judgment [6]. However, there is limited standardization to guide the use of antipyretics, particularly so from a contextual perspective [6]. It is also important to note that antipyretics themselves may carry side-effects and there is a paucity of data and limited interest in developing newer antipyretics [6]. Given that fever is one of the commonest clinical symptoms and signs, there is an urgent need to develop newer antipyretics with optimized time-action and benefit-risk profiles to enable fit-for-purpose use based on the setting in which fever occurs.

The sterile inflammatory state induced by an endotoxin challenge makes it especially valuable to characterize pyrexia and evaluate antipyretics. Although endotoxin may be administered by various routes, in the context of pyrexia, given the need to elicit a measurable systemic response, intravenous (IV) administration remains the preferred route. Systemic responses have been reported in settings of high and low dose administration. Following an IV endotoxin (*E. coli* O: 113) bolus in the range of 2 to 4 ng/kg body weight in healthy volunteers, Suffredini et al. and others reported a monophasic febrile response with onset 1 to 2 hours after administration, peaking at 3 to 4 hours to reach a maximal rise in body temperature over baseline with spontaneous resolution of the febrile response between 8 and 12 hours after the bolus administration [2,7]. In a placebo-controlled study, Pernerstorfer et al. were able to successfully demonstrate superiority of the antipyretic effects of acetaminophen over aspirin using a 4ng/kg IV endotoxin bolus challenge [8]. Dose-limiting toxicities at doses greater than 4ng/kg have generally precluded their routine use. The brisk and robust febrile response following IV endotoxin at the 2-4ng/kg dose is preceded by flu-like symptoms (chills, rigors, malaise, nausea and headache) starting one hour after administration and resolving spontaneously within 3 to 5 hours [2]. Other systemic changes accompanying the febrile response include a drop in blood pressure and increases in heart and respiratory rates with alterations in various blood-based measures including leukocytosis, cytokines and hormones [7]. It is important to note that while the rapid-onset responses are a direct effect of endotoxin, some of the other observed responses are a result of triggering of the inflammatory and cytokine cascade rather than a direct effect of the endotoxin itself, whose half-life when administered as an IV bolus is short lived. The IV bolus endotoxin challenge therefore allows for insights into the inflammatory event cascade and its mediators and at the same time also sheds light on whether a novel therapeutic has antipyretic or anti-inflammatory benefits. However, its ability to inform on the magnitude and duration of such benefit is particularly dependent on the synchrony between the temporal profile of action of the investigational agent and that of the responses to the endotoxin challenge. This is especially true for a novel antipyretic.

An alternate option would be administration of endotoxin as a continuous IV infusion to attempt to synchronize temporal profiles across the endotoxin challenge and investigational agent. However, the pharmacokinetics of a continuous infusion may limit the ability to achieve a peak challenge that is sufficiently robust to trigger a measurable systemic response. And indeed, Andreason et al. [9] have reported that lower doses of endotoxin in the range of 0.06-0.08 ng/kg, achieved via IV bolus or continuous IV infusion elicit what appears to be a submaximal inflammatory response with no detectable changes in vital signs including body temperature.

There is a need for development of a reliable yet feasible endotoxin challenge model that enables elicitation of a peak systemic response that is sustained over several hours, while not exceeding the total amount of endotoxin that can be safely administered and in a paradigm that is flexible enough to investigate a range of PK-PD profiles across agents and escalating doses. This need is particularly urgent in the context of novel antipyretics where onset and offset of effects and synchrony with the febrile response are critical parameters of success. One potential option would be a combined bolus-infusion approach, where a bolus administration of endotoxin is followed by a continuous infusion such that the total dose of endotoxin does not lead to dose-limiting toxicities. Van Lier et al. have proposed that a continuous infusion of endotoxin may better reflect the prolonged systemic responses including fever observed in the setting of infection and inflammation in man [10]. In a model of endotoxin challenge with a bolus dose of 1mg/kg followed by an infusion at 0.5ng/kg/hour for 3 hours, Jansen et al. were able to successfully demonstrate the beneficial anti-inflammatory effects of Cytosorb hemoperfusion in a group of healthy volunteers [11]. In a study with endotoxin challenges on two separate occasions, using a paradigm that combined a bolus administration of endotoxin at 1ng/kg followed by an infusion at 1ng/kg/hour for 3 hours in a group of healthy volunteers, Leijte et al. were able to show endotoxin tolerance and reversal, confirming that the total dose administered in such a paradigm is safe and that the model is able to successfully detect treatment differences [12]. In a head-to-head comparison of a bolus only paradigm (2ng/kg) versus a combined bolus-infusion paradigm (1ng/kg bolus followed by a 3-hour infusion at 1ng/kg/hr) in the context of experimental endotoxemia, Kiers et al. found that subjects attained comparable peak levels and exhibited more prolonged and sustained duration of symptoms including fever during the endotoxin challenge model of a bolus followed by a continuous infusion vs bolus only method [13]. Kiers et al. also found that subjects attained higher peak cytokine levels that were sustained for longer durations following the combined bolus-infusion paradigm vs the bolus only paradigm [13]. Hence it is possible that a carefully developed combined bolus-infusion paradigm may permit administration of higher total amounts of endotoxin that could lead to a temperature response with slower onset but more sustained duration. Yet another novel approach would be to use modeling and simulation tools either as standalone approaches or in combination with *in vivo* efforts to optimize experimental paradigms and data analyses strategies. Using mathematical modeling of data collated across multiple endotoxin challenge experiments and investigator groups, Windoloski et al. showed that a continuous infusion elicits a stronger response that lasts longer than a bolus only paradigm, while potentially allowing for delivery of maximal total doses of endotoxin that can be safely administered [14]. Liu et al. have used mathematical modeling to describe and predict the dynamics of responses to endotoxin challenges with intent to inform on novel clinical trial design, particularly in the context of drug development [15].

Taken together, a combined bolus-infusion paradigm coupled with a mathematical modeling and simulation strategy may be the optimal solution to provide an experimental model of endotoxin challenge that is safe but provides a measurable response while allowing for synchronization with the PK-PD properties of a novel therapeutic. Although there is evidence that speaks to each component of the above approach, data to confirm validity of the approach and develop an integrated strategy are currently lacking. Therefore, there is an urgent need for targeted experimentation to address the above gaps and provide a consolidated strategy that integrates human *in vivo* experimentation and modeling and simulation tools that delivers on a fit-fit-for-purpose endotoxin challenge design.

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