Letter to the Editor

The Anti-inflammatory Action of Locally Injected Ketorolac

To the Editor:

I am writing with regard to the article published in the October 1997 issue of the Journal titled “The Anti-inflammatory Action of Locally Injected Ketorolac” by Joel W. Brook, Alan Boike, Roger L. Zema, Michael Weaver, and Paul Postak (the winner of the 1997 William J. Stickel Silver Award). I take exception to this flawed research that managed to sacrifice 86 rabbits while offering little or no possibility of achieving any meaningful results.

I admit that I am sensitive to animal experimentation, although I understand its importance in medical research. However, the results anticipated must justify the sacrifice of animal life, and in this case they do not.

This article reveals many errors and omissions, as well as a lack of good judgment. First, there is no mention of this research, which involved the death of 86 rabbits, being approved by any hospital animal research board. What was the result of the initial pilot study that justified the death of an additional 80 rabbits?

I am unclear as to the fate of the 11 rabbits whose skin was perforated by the bludgeoning of their Achilles tendons. I assume they were killed. I do not believe that a loss of 11 out of 80 animals—a rate of 14%—is acceptable. This is an unnecessary sacrifice of animals that served no purpose at all. No humane scientist would condone this without adjusting the protocol to prevent further unnecessary injury.

Next, I am unclear as to the need to sacrifice 80 animals. Rabbits have two hind legs, both available for use. Why not use one leg for the control and the other leg for the experimental injection? That would have saved 40 animals and perhaps produced a more uniform result.

I am also puzzled by the authors' statement that “the slides were scanned at ×100 to locate the area with the greatest concentration of mononuclear inflammatory cells.” Does this mean they “looked around a little?” The authors then state that they counted all inflammatory cells in one high-power field twice, and took an average. Does this mean they were unable to accurately count between 3 and 285 cells in any given high-power field? Shouldn’t the two counts be the same, without a need for averaging? Exactly how far off were the two counts? Most important, why was only one high-power field examined? Wouldn’t it make sense to count the cells in many high-power fields for each rabbit and average the results? It does not make sense to sacrifice an entire animal for one high-power field (1 mm of tissue) when there was more information to be gleaned—specifically, from the other leg and more high-power fields. This shows an utter disregard for life.

Furthermore, Table 1 requires comment. It shows a wild spread of data for the number of chronic inflammatory cells per high-power field per specimen. I took the liberty of graphing the four series, and the result was a remarkable absence of any clear trend. For example, the control group average is 62, but the range is from 4 to 285; That makes the mean worthless. The authors proceed to suggest that the reason for the huge spread is that they used too many animals: “Another potential explanation for the variation in data could be the sample size of the groups. A review of the literature revealed that similar studies have all used groups of 10 to 20 subjects.” The use of a smaller group of subjects with such a marked spread of data would make a meaningless conclusion downright incorrect.

Most important is the authors’ choice of assay to determine the level of inflammation. If this cell-count method is standard procedure, it should be clearly referenced. I believe their technique was flawed and is not an accurate indication of the degree of inflammation. Did they do any control work using a known injectable anti-inflammatory agent such as Hexadrol? Why was no trial conducted using an injectable steroid? That is a critical omission. Did they demonstrate in any way that performing a cell count is an adequate method of determining the level of inflammation? I saw no proof of the reliability of this technique. I believe that this experiment never had a chance for success. In fact, one of the references cited by the authors, by Chellman et al., indicates that all injectable nonsteroidal anti-inflammatory drugs cause some degree of muscle damage as assessed histopathologically, although ketorolac causes less damage than other drugs. So, in fact,
direct injection can actually increase the cell count!

It has been well documented that ketorolac is a potent injectable analgesic with minimal anti-inflammatory activity. What, then, was the purpose of this study? While it is true that negative results can be useful, this study had no meaningful result at all. I think that this line of research is objectionable and ill-advised. It alarms me that this was only a pilot study and that the authors plan to slaughter more animals for a project that has no chance of success. I believe that great pressure should be brought to bear on this research group by the podiatric medical profession and by animal-rights groups to ensure that this project be discontinued and that all future animal research be approved by a research board. The credibility of our profession depends on it.

STUART PLOTKIN, DPM
2 Medical Dr, Ste C
Port Jefferson Station, NY 11776

Reference

Authors’ Response

To the Editor:
We would like to thank Dr. Plotkin for his remarks. Podiatry is still a relatively young profession, and it is important that we not only carry out research but critically evaluate it. The concerns raised about the use of animals in our study are understandable but unfounded. This study was not conceived, planned, or performed in a vacuum. All facilities in which animal studies are performed are required to have an Institutional Animal Care and Use Committee (IACUC) to evaluate needs and protocols. The research was approved and the number of animals deemed appropriate by our institution’s IACUC, as well as the HAAS Fund Committee, which financed the project. Both bodies raised a number of issues that were satisfactorily addressed prior to final approval. The broad issues of animal rights and the use of animals in scientific research, although important, are beyond the scope of this response. However, we are happy to address the scientific issues raised by Dr. Plotkin.

As stated in our article, the initial pilot study involving six animals was conducted to establish measurable parameters (position, force, etc.), not to determine whether or not the study should be performed. The background information outlining the need for a local anti-inflammatory agent that does not produce the side effects seen with corticosteroids is clearly documented and well referenced within the body of the article.

The possibility of using the contralateral leg as either a control or an experimental limb was given due consideration, and rejected for the following reasons: First, ketorolac has systemic effects. Second, the IACUC did not allow subjecting both hind legs to trauma.

The method used to test the level of inflammation present was thoroughly valid. Counting the number of inflammatory cells present in a maximally involved area is a technique used by practicing pathologists every day. Not only was this modeled on the methods used by McWhorter et al., but it was approved by our team pathologist, who is the director of cytology at PHS Mt. Sinai.

The high degree of variability of our data was attributed to a number of factors, all of which were explained in the body of the article. Dr. Plotkin’s “conclusion” that the data yielded no result is grossly incorrect. The negative result was definitive. Ketorolac has moderate rather than minimal anti-inflammatory action when used systemically. Therefore, a study designed to test its action locally is not only justified but completely valid.

JOEL W. BROOK, DPM, MS
ROGER L. ZEMA, DPM
MICHAEL WEAVER, MD
PAUL POSTAK, BS
PHS Mt Sinai
One Mt Sinai Dr
Cleveland, OH 44106

ALAN BOIKE, DPM
The Cleveland Clinic Foundation
9500 Euclid Ave
Cleveland, OH 44195

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