Letters to the Editor

Pain on Intravenous Injection

Since numerous pharmaceutical compounds used by anesthesiologists are known to cause pain on intravenous injections, we were pleased with the endeavor to develop an *in vivo* model for "predicting human responses to infusion of intravenously administered materials" (1). Nevertheless, based on our own investigations in this field, we feel it necessary to make some supplementary remarks.

1. Unphysiological osmolality and/or pH have been hypothesized to be responsible for pain on injections. Recently, we were able to prove this hypothesis in humans (2). Unphysiological osmolality and/or pH of pharmaceutical formulations seem to be more relevant as pain-evoking stumuli than the agents themselves with the exception of propofol, which causes pain (3). Therefore, testing of pharmaceutical compounds with unphysiological pH and/or osmolality in a model as described by the authors is hardly necessary. Costs and efforts should be concentrated on pharmaceutical research to develop vehicles and solvents with appropriate physicochemical properties. As demonstrated in the case of diazepam, the use of fat emulsion as a vehicle instead of propylene glycol and ethanol reduces osmolality from 8.0 to 0.3 osmol $\cdot$ kg^{-1} and thus reduces incidence of pain and thrombosis from 40 to 0% (4).

2. An "additional study into the innervation of peripheral veins," as requested by the authors was done in humans recently. Intravenously-applied mechanical, electrical, thermal, and chemical stimuli evoke pain via polymodal nociceptors which are located within the vein wall and in all likelihood are connected to thinly myelinated A∂-fibers (5).

3. For good reasons, we perfused vascularly-isolated vein segments in order to avoid possible systemic effects of the substances. Scrutiny of the data of Marcek and coworkers presented in Fig. 3 (1) reveals a latency of 25 seconds from the beginning of the acetate vehicle infusion to the onset of struggling, i.e., an interval, where systemic actions, if present, should have started. Possible systemic effects of new compounds might interfere with the physical response measured in this model, hence the struggle might be caused by pain, but may also reflect other side effects like nausea, hypotension, or even central excitation. In contrast, sedatives and hypnotics may prevent or reduce the struggling although evoking pain.

False positive as well as false negative results are therefore not unlikely to result from this method, which might not be suited for "objectively measuring the pain response to intravenously administered substances," at least in case of compounds that act as described above.

4. The authors tested five different compounds in their experiment 1 with a pH between 1.3 and 4.7 which is in the pain-evoking range also in humans (2). At first glance, it is surprising that solutions with lower pH did not consistently evoke greater responses as shown in Fig. 4 (1). Since Marcek and co-workers did not account for differences in ionic strength, buffer capacity, and osmolality of the solutions as well as of dilution and buffering with blood, they were not able to demonstrate a clear stimulus/response-relation which is a "conditio sine qua non" for the validation of such a new model.

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Reply to the Comments by Drs. Klement and Kindgen-Milles

1. Efforts are being made to develop vehicles and solvents with appropriate physicochemical properties to reduce negative effects of drug administration as indicated in point No. 1. However, many pharmacologic agents have inherent problems associated with stability, solubility, etc., which direct formulation development outside desired limits. Strict regulatory guidelines concerning stability, safety, and other issues as well as compliance with company goals may force a decision to use a less than ideal formulation, making the use of the model described valuable and necessary. Additionally, changes in formulations designed to reduce pain may have further unintended consequences. As an example, the use of a fat emulsion instead of propylene glycol and ethanol in the formulation of diazepam has been shown to reduce the incidence of pain and thrombosis; however, this change in formulation also reduces potency relative to other formulations (1).

2. We are currently unaware of any procedure for isolation of vein segments in conscious animals and therefore chose to infuse test substances directly into the systemic circulation. Data presented in Fig. 3 of our manuscript contains an example of a response to infusion of an acetate vehicle. The latency of the initial response to infusion of this material ranged from 4 to 37 seconds (20.1 $\pm$ 3.5, mean $\pm$

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SE), indicating that for some animals little, if any, time was allowed for expression of side effects. We feel it is reasonable to assume that, while polymodal nociceptors are present in the vein wall, it would take some time for offending substances to penetrate and reach the receptors.

We believe it may be possible to find compounds or solutions which lead to false positive or false negative results. We have tested D-amphetamine in the screen to determine if such a stimulant would result in a false positive result. Negative results were obtained in five of five rats treated with 1 mg/kg D-amphetamine in an initial investigation. We believe results from this model should not be interpreted without additional information. Should other studies on a test substance show the material to be an emetic, hypotensive, etc., via other routes, these factors should be considered in interpreting results.

3. Point No. 4 indicates that, although solutions tested varied greatly in pH, differences in other physical characteristics of the test solutions were not identified and thus a clear stimulus response was not demonstrated. The objective of this study was not to identify and investigate any one characteristic of intravenous solutions which may or may not invoke the pain response, but was instead aimed at objective measurement of an animal's response to infusion. Further, carefully designed study into each component or characteristic of an intravenous solution is obviously necessary to determine its role in the pain response. The model will greatly aid in this endeavor.

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Obituary for Razia Zaman and Shahanara Zaman Saroya

Razia Zaman was born on February 24, 1955 and Shahanara Zaman Saroya was born on April 17, 1957. They were the beloved daughters of Dr. Masood Zaman and Ms. Rabia Zaman. Razia obtained her Ph.D. in Clinical Pharmacology at the University of Birmingham and completed a postdoctoral program at the University of Georgia before taking a Senior Research position with Hazleton Laboratories in Madison, Wisconsin. Shahanara obtained her Ph.D. in Toxicology at the University of Michigan and was carrying out postdoctoral studies at the University of Wisconsin.

Razia and Shahanara died tragically in an automobile accident on July 11 of this year. Both Razia and Shahanara were loved and respected by all those who were fortunate enough to meet them, know them, and work with them. They were taken from us at the prime of their lives and words cannot express the terrible loss. They grew up together, played, and worked together. Now they lie in peace, together. Razia and Shahanara are survived by their parents and their sister Samina, and Shahanara by her husband Naeem.

L. Bernstam, *University of Michigan*

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Many friends at Hazleton Laboratories and the University of Wisconsin