Studies in Phlebitis. II. Early Detection of Amiodarone-Induced Phlebitis in a Rabbit Model

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INTRODUCTION

Infusion thrombophlebitis (ITP) is well recognized as a significant complication of intravenous therapy (1). The symptoms vary and include pain, erythema, induration, edema, and thrombus formation. The exact etiology of ITP differs among formulations but the pathophysiological events following the injection of an irritating parenteral are similar to that of any inflammatory response. The main phase of this inflammatory response usually does not begin until several hours following venous insult and the visual symptoms may not be apparent for several hours to days (2). The increased blood flow from the early as well as the late stages of inflammation causes a local rise in temperature (3,4), which was found (5) to be detectable well before the appearance of the visual symptoms accompanying venous tissue destruction.

In the first study in this series (5) we introduced a new method for the detection of ITP using a rabbit ear model and a thermographic camera. This method of detection utilized the local temperature elevation associated with the inflammatory process as a quantitative marker for detecting phlebitis. It is the purpose of this study to refine and extend our previous model toward the goal of early detection and prediction of severity. In these experiments the thermographic camera has been replaced with a simple, inexpensive thermocouple monitoring system. The model drug used in this study was amiodarone HCl. Amiodarone is an antiarrhythmic drug commonly administered as a bolus injection followed by a short-term infusion. In addition, a more objective method for visually quantitating the extent of phlebitis produced by a single amiodarone injection is introduced.

MATERIALS AND METHODS

Twenty-four New Zealand-strain white rabbits of approximately equal weight (3.0 kg) were divided into three groups. Each treatment group received a different parenteral. The three treatments used were as follows: (1) a placebo injection of 0.9% normal saline (Abbott Laboratories, Chicago, IL); (2) an amiodarone vehicle of 10% polysorbate 80 with 2% benzyl alcohol (Sigma, St. Louis, MO, and Aldrich, Milwaukee, WI, respectively); and (3) amiodarone HCl, 50 mg/ml, (Labaz Laboratories, Ambare's France). The amiodarone vehicle was prepared in a laminar flow hood, passed through 0.22-μm filters into sterile, pyrogen-free vials, and then autoclaved.

In preparation for iv injection, the rabbits were mildly sedated with 0.3 ml/kg of a solution containing 250 mg/ml ketamine HCl, 10 mg/ml acepromazine, and 50 mg/ml xylazine by intramuscular injection. Both ears were then shaved to facilitate injection as well as visualization of veins and symptoms. One of the ears was assigned as a reference, while the other received the injection in the lateral vein at the midpoint of the ear.

The injections were given via a 27-gauge, ⅜-in., butterfly catheter (Abbott Hospitals, Inc., Chicago, IL) attached to a 1-ml syringe. A syringe pump (Sage Instruments, Model 355, Cambridge, MA) was used to control the rate to a uniform level of 1 ml/min. The dose was determined by individual rabbit weight and scaled to the standard human quantity of 10 mg/kg (usually resulting in a volume near 0.6 ml).

Immediately following the injection, one type T thermocouple (Sensortek, Model 2102, Clifton, NJ) interfaced with a digital thermometer (Cole and Palmer, Model 8500-40, Chicago, IL) was secured at a point directly over the vein and 2 cm proximal (downstream) to the injection site. A second thermocouple was attached to the corresponding point on the reference ear. The temperature difference between the experimental and the reference ears was then recorded at the following time intervals: every 10 min for the first 2 hr after the injection; every 30 min for the next 4 hr; and at 24, 48, and 72 hr.

Visual data were collected by actual physical measurement of the length of the region of inflammation and erythema along the injected vein. These measurements were recorded in centimeters and collected at the same time points.

Statistical evaluation of the thermal data was accomplished through the use of a repeated measures ANOVA for calculation of the mean square error terms. These values were used for a Fischer Protected LSD test at the 0.05 level.

RESULTS

The recorded temperature differences between the experimental and the reference ears for all three treatment groups are plotted against time in Fig. 1. Each data point, up to 24 hr, represents the mean of no fewer than six rabbits. The 48- and 72-hr time points have fewer rabbits due to histological studies performed at 24 hr.

Contrasts for significant differences between the three treatment groups for each time point yielded the following results:

(1) a significant difference between amiodarone and normal saline from 1 hr up to and including 24 hr,
(2) a significant difference between amiodarone and the polysorbate vehicle from 1 hr up to and including 24 hr, and
(3) no significant difference between the vehicle and the normal saline for any of the measured time points.

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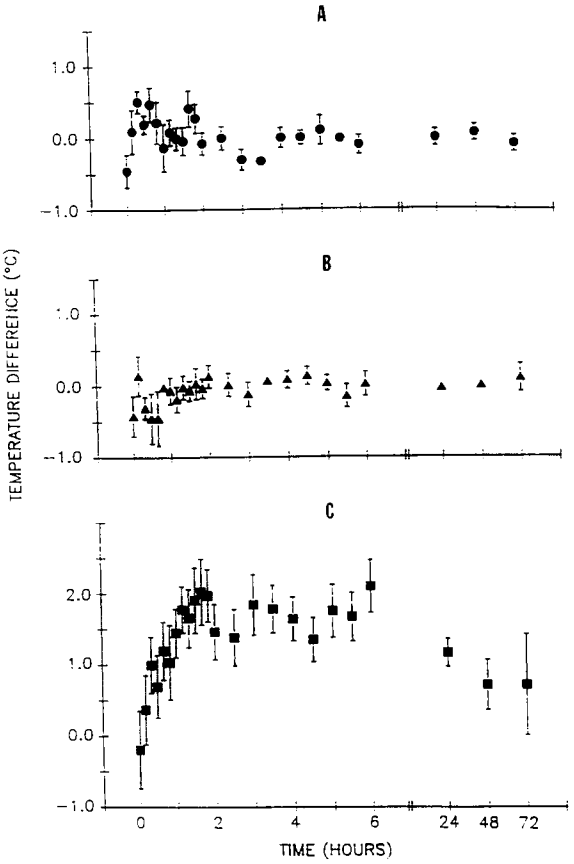

Fig. 1. Mean temperature differences and the within-treatment group standard errors for each time point. (A) Normal saline; (B) polysorbate 80 vehicle; (C) amiodarone HCl.

Figure 1A is a representation of the normal saline treatment group data plotted as the means and standard errors versus time. It can be seen from this graph that, following the first hour, the averaged thermal readings are consistently near zero and the error terms small. At no time after the first hour is there any deviation from the zero line larger than 0.4°C.

The data for the polysorbate treatment group (Fig. 1B) are quite similar to those for the normal saline treatment group. For the first hour there is some erratic thermal behavior, followed by near-zero averaged temperature differences for the remainder of the study. Here the largest deviation from the zero line is approximately 0.2°C. The small standard errors associated with each time point indicate good agreement within the treatment group.

Figure 1C contains the data from the amiodarone treatment group. It can be seen from the graph that after the injection there is an initial drop below the point of zero temperature difference, however, this is not significant (the early erratic thermal behavior may be due to the effect of the trauma that is caused by the injection procedure itself since it is seen in all three treatment groups). The initial drop is followed by a steady temperature increase. This increase in temperature difference between the experimental and the reference ears peaks with a value of 2.03°C at 1 hr 40 min and reaches a relatively constant value of about 1.7°C through to the 6-hr time point. At 24, 48, and 72 hr the temperature differences begin to diminish, however, the experimental ears are still nearly a full degree warmer than the reference ears after 3 days.

The length of erythema and swelling surrounding the vein is assumed to be representative of the severity of phlebitis present. Figure 2 shows the relationship between the length of inflammation (at 24 hr) and the temperature difference between the experimental and the reference ears early in the study (1 to 2 hr postinjection). Each data point represents one rabbit. There is a correlation (r = 0.75) between large temperature differences at early measurements and the severity of the phlebitis manifested at later times.

Visual and physical examination of the rabbits in the amiodarone treatment group at the 24-hr time point revealed symptoms of phlebitis in all rabbits. However, measurements of phlebitis taken at the 3-hr time point for this same treatment group showed the presence of this condition in only 1 of 10 subjects. Nearly all rabbits in this study had a measurable amount of erythema. In the vehicle and saline treatment groups, however, these regions were quite small (generally circular in shape and less than 1 mm in diameter) and attributed to the local trauma of the venipuncture. Furthermore, the severity of these reddened areas decreased with time after 3 hr, whereas the condition worsened for the amiodarone treatment group.

DISCUSSION

Infusion of injection related phlebitis is similar to any inflammatory process in that it generates heat at the site of inflammation. We have demonstrated that a simple thermocouple system can be used as a convenient, noninvasive means of quantitating the early temperature changes accompanying the onset of venous inflammation and phlebitis.

The rabbit model for examining phlebitis has been used by several investigators (6–8); however, not until now has a predictive model been introduced. As shown in Fig. 1C large temperature differences are detected well in advance (several hours) of visual symptoms. Not only is early detection of phlebitis possible, but also it may be possible to predict the severity of the condition from the magnitude of the temperature differences (see Fig. 2).

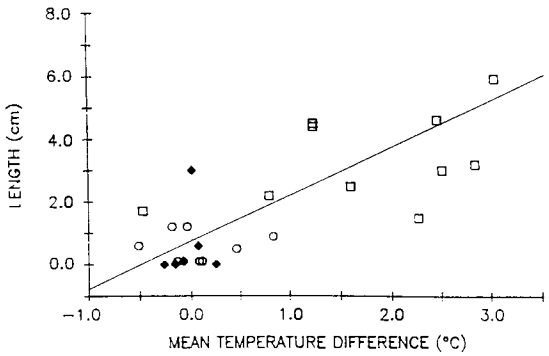

Fig. 2. Length of inflammation present surrounding the ear vein at 24 hr versus the mean experimental/reference temperature difference for the time course of 1–2 hr. Each data point represents one subject in the study. The line represents the best-fit linear regression equation, (r = 0.75). (□) Amiodarone HCl; (○) normal saline; (◆) polysorbate 80 vehicle.

Using this model it was shown that amiodarone itself, and not its polysorbate 80 vehicle, is responsible for the phlebitis that often accompanies its administration. The rabbit ear/thermocouple model may be useful for identifying the specific agent that is responsible for producing phlebitis.

The potential of a drug to induce ITP must be a concern for those involved in parenteral formulation; therefore, industrial applications of this technique should be significant. By using this model one may know within 1 to 2 hr of the phlebitis potential of a parenteral, thereby providing a fast, inexpensive, and accurate method for preformulation screening of parenteral medications and of their potential vehicles. Further, clinical applications of this technique may lead to more effective treatment. Knowing in advance that phlebitis is imminent would allow early therapeutic intervention.

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