Studies in Phlebitis. III. Evaluation of Diazepam and Phenytoin

Milissa White[1] and Samuel H. Yalkowsky[1,2]

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INTRODUCTION

Phlebitis occurs as the result of inflammation of the walls of a vein. The process of inflammation begins with tissue injury. The damaged tissue immediately releases histamine and other chemical mediators. The released histamine causes vasodilation, which results in increased blood flow to the area. This increase in blood flow results in warmth surrounding the damaged tissue (1).

Previous studies performed in this laboratory have shown that this local increase in temperature resulting from phlebitis can be detected before the appearance of visual indicators (such as redness and swelling) (2,3). It is the purpose of this study to determine if diazepam phlebitis and phenytoin phlebitis are detected early in the rabbit ear/thermocouple model (3) and if there is a relationship between thermal measurements and the severity of phlebitis. Another objective was to determine if there is a connection between precipitation and phlebitis.

MATERIALS AND METHODS

The following methodology was adapted from the previous studies done by Ward *et al.* (3).

New Zealand white rabbits weighing approximately 3.5 kg were anesthetized intramuscularly using 0.2 ml/kg of a solution containing 250 mg/ml ketamine hydrochloride, 10 mg/ml acepromazine, and 50 mg/ml xylazine. The rabbit ears were shaved to facilitate injection and visualization of symptoms. One ear was chosen as a reference, and the lateral vein of the opposite ear was injected at the midpoint with either diazepam (5 mg/ml), phenytoin (50 mg/ml), or placebo (0.9% normal saline). A summary of the injection conditions is shown in Table I.

Each injection was performed via a 27-gauge, ⅜-in. butterfly catheter (Abbott Hospitals, Inc.) attached to a syringe. A syringe pump (Sage Instruments, Model 355) was used to control the rate of injection.

After injection, one type T thermocouple (Sensortek, Model 2102) interfaced with a digital thermometer (Cole and Palmer, Model 8500-40) was placed directly over the vein approximately 2 cm downstream from the injection site. A second thermocouple was placed at the corresponding point on the reference ear. Figure 1 shows the experimental setup for this study. The temperature differences between the reference ear and the injected ear were measured at the following time intervals: every 10 min for the first 2 hr after injection, every 30 min for the next 2 hr, and at 24 and 48 hr. At each time interval, the rabbits were also checked for any visual indications of phlebitis (such as redness and swelling).

Table I. Summary of Injection Conditions

Drug	Injection volume (ml/kg)	Approximate rate (ml/min)
Phenytoin	0.3	0.7
Diazepam	0.18	0.4
Normal saline	0.3	0.7

RESULTS

The mean temperature differences are plotted against

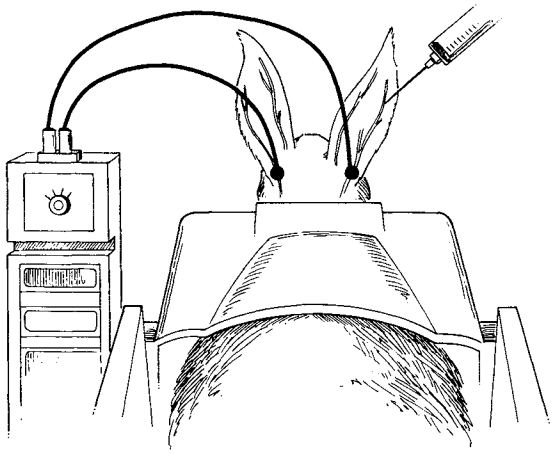

Fig. 1. Schematic diagram of the experimental setup.

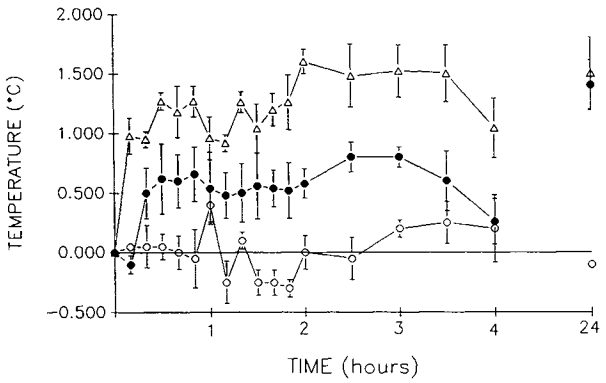

Fig. 2. Mean temperature differences (±SE) verses time for rabbits injected with either phenytoin (△——△), diazepam (●——●), or placebo (○——○). Six rabbits were injected with phenytoin, six with diazepam, and three with placebo.

[1] Department of Pharmaceutical Sciences, College of Pharmacy, University of Arizona, Tucson, Arizona 85721.
[2] To whom correspondence should be addressed.

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Table II. Comparisons of Treatment Groups

Drug	Water solubility (2)	Precipitation *in vitro* (5,6)	Temperature increase *in vivo*	Phlebitis *in vivo*
Amiodarone	Not miscible	Yes	Largest	Severe
Phenytoin	Not miscible	Yes	Moderate	Moderate
Diazepam	Not miscible	Rate dependent	Slight	Slight
Normal saline	Miscible	No	None	None

time for all three treatment groups in Fig. 2. Following the injection of either diazepam or phenytoin, there is an increase in temperature for both treatment groups. Phenytoin shows a larger temperature elevation than diazepam. Further, rabbits injected with placebo (normal saline) show no significant temperature difference.

For rabbits injected with diazepam and phenytoin, visual indications of phlebitis are not apparent until the 24-hr time interval. For rabbits injected with normal saline, no visual indicators of phlebitis are seen at any of the time intervals. These results are in good agreement with those obtained by thermography (2).

Table II shows that amiodarone produced the largest temperature elevation from 1 to 2 hr (3). Further, rabbits injected with amiodarone show the largest degree of venous involvement at the 24-hr time period (3). On the other hand, diazepam causes only slight temperature elevations from 1 to 2 hr, with only slight indications of phlebitis after 24 hr. These results suggest that early temperature measurements indicate the severity of phlebitis that will be seen hours later.

DISCUSSION

The rabbit ear/thermocouple model established for the early detection of phlebitis is not limited to amiodarone; phenytoin and diazepam also show temperature increases preceding visual symptoms. Therefore, our method of early detection will have significant clinical and industrial applications. Presently, the detection of phlebitis is dependent upon the appearance of visual symptoms (qualitative) after extensive tissue damage has occurred. By detecting phlebitis in its early stages, clinical measures can be taken to lessen its severity. Additionally, parenterals can be quickly screened during the preformulation stage for their potential to produce phlebitis.

Previous investigators have identified precipitation as a possible cause of phlebitis (4). Yalkowsky *et al.* (5) developed an *in vitro* method for the detection of precipitation of parenterals after injection. For example, when diazepam is injected at slow rates, little or no precipitation is detected; however, at more rapid injection rates, precipitation of diazepam occurs. The manufacturer indeed recommends that diazepam should be injected at a very slow rate. Rapid injection of poorly water-soluble drugs accompanied by slow dilution provides an ideal situation for the formation and growth of crystal nuclei. These crystals can irritate the vein wall and, subsequently, initiate the inflammatory process. In this study, injection rates into the bloodstream were arbitrarily chosen. Since diazepam and phenytoin have poor water solubility and are formulated in cosolvents, the phlebitic response may have varied with different injection rates.

Our results show that initial temperature elevations correlate with the visual indications of phlebitis that are seen hours later. The larger temperature increases correspond to greater degrees of venous involvement.

Instead of thermal imaging (2), which is expensive and rather inconvenient, we now use thermocouple monitoring, which has proven to be simple, and inexpensive. Both methods may serve to predict phlebitis quantitatively.

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