Studies in Phlebitis: Detection and Quantitation Using a Thermographic Camera

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A new method for the detection of acute phlebitis in superficial veins is investigated. A thermographic camera is utilized for the quantitation of temperature changes in a rabbit ear model. A control group receiving no injection is compared against each of five treatment groups receiving these commercially available parenterals: amiodarone hydrochloride, phenytoin sodium, mechlorethamine hydrochloride, cephalothin sodium, and diazepam. The vehicles of the above-mentioned drugs as well as several commonly used organic cosolvents are also investigated. Local tissue responses to the parenteral challenges are measured and a good correlation between the visual and the thermographic data was seen.

KEY WORDS: phlebitis; thrombophlebitis; thermography; detection; parenterals; inflammation.

INTRODUCTION

Background

Infusion-related phlebitis (or thrombophlebitis) is a complication resulting from the intravenous administration of many parenteral formulations. This condition may lead to thrombus formation and/or venous tissue destruction (1,2). Although its reported incidence and duration vary widely (1–3), phlebitis is a significant side effect of intravenous therapy.

The incidence and duration of phlebitis appear to be dependent upon a variety of factors. Chemical factors such as low pH (2,4,5), hypertonicity (6), and the inherent nature of the drug (1,2) have been shown to influence phlebitis. Physical factors such as the existence of particulates (7,8) and precipitation of the drug out of solution upon dilution are also known to influence this condition (9,10). Clinical factors involving injection technique (i.e., extravasation, type of needle, duration of infusion, etc.) can also contribute to the occurrence of phlebitis (1,2,11).

Infusion-related phlebitis is characterized by pain, tenderness, erythema, induration, edema, thrombus formation, and a local temperature increase (1,2). In some instances phlebitis may become suppurative and lead to sepsis (12). This condition may persist for weeks or, in some cases, months (1,2,13).

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Phlebitis is known to occur with the administration of infusions as well as from a single injection (1). Local reactions following injection of benzodiazepines have been observed by several investigators (14,15). Boon *et al.* (16), in a study involving 16 drugs commonly used in anesthetic practice, reported an incidence of injection related phlebitis of 36%.

Presently, the diagnosis of phlebitis is contingent upon manifestation of pain or visual symptoms. Therefore, detection requires a subjective evaluation of the injection site. This is usually accomplished by visualizing the above-mentioned symptoms and characterizing them on some numerical scale as to their severity (1,17,18). It is known that following venous insult, the main phase of the inflammatory response can take up to 24 hr to begin (19). If the symptoms of phlebitis are not immediately apparent, and therapy with an irritating drug is continued, considerable damage to the vascular tissues may occur. Treatments initiated after significant vascular damage may be of limited success.

In order to detect or predict phlebitis, accurate measurements of the symptoms are necessary. Many of these symptoms such as erythema, induration, and edema may be quantitated with a visual evaluation. The local temperature elevation present in this condition (resulting from chemically mediated, increased vascular permeability) may be more objectively measured with the aid of thermography (20,21). Thermographic evaluations are noninvasive and have been used in the past with success in the detection of deep vein thromboses (23), as well as for the assessment of blood flow in the dermis (20,21).

At the present time there is no objective quantitative method for detecting phlebitis. Focusing on injection-related phlebitis and using a rabbit ear model, a noninvasive method for the detection of acute injection-related phlebitis involving the use of a thermographic camera will be introduced. This model capitalizes on the local temperature elevation that is associated with the onset of the inflammatory response.

MATERIALS

The drugs used in this study were 0.9% sodium chloride inj., UPS (Abbott Laboratories, North Chicago, IL), amiodarone HCl (Cordarone, Labaz Laboratories, Ambares, France), phenytoin sodium (Dilantin, Parke-Davis, Morris Plains, NJ), diazepam (Valium, Roche Laboratories, Nutley, NJ), cephalothin sodium (Keflin, Eli Lilly and Company, Indianapolis, IN), and mechlorethamine (Mustargen, Merck Sharp & Dohme, West Point, PA). In addition, several commonly used cosolvents such as dimethyl acetamide (DMA), dimethyl sulfoxide (DMSO), ethanol (ETOH), dimethyl isosorbide (DMI), polyethylene glycol 400 (PEG 400), and propylene glycol (PG) were examined. All of the above mentioned cosolvents were purchased from either Aldrich or Sigma Chemical Company, Inc.

The injection rate was controlled with a syringe pump (Sage Instruments, Model 355). A Spectrotherm thermographic camera, Model 800, equipped with a Polaroid 200 camera was used for data collection.

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EXPERIMENTAL METHODS

Parenterals

Several commercially available drugs that are known to cause phlebitis when injected intravenously are investigated along with their respective vehicles. The vehicles are of the same composition and pH as the commercial formulations reported in the *Physicians' Desk Reference*. The vehicle compositions are as follows: amiodarone hydrochloride (10% polysorbate 80, 2% benzyl alcohol); phenytoin sodium (PG:ETOH:H_2O, 40:10:50); diazepam (PG:ETOH:Na benzoate/benzoic acid buffer, 40:10:50); and mechlorethamine hydrochloride and cephalothin sodium (0.9% sodium chloride solution). In addition to the above, several commonly used organic cosolvents are included in the study.

Thermal Imaging Camera

The thermal imaging camera consists of an infrared radiation detector (cooled with liquid nitrogen for optimal sensitivity in the infrared spectral band, 2–5.6 μm), an optical scanning system, and a synchronized display unit. A signal is produced by the detector, then amplified and conveyed to the display unit, where it controls the electron beam of the monitor. The monitor operates synchronously with the scanning camera resulting in a high degree of spatial and thermal resolution. The temperature sensitivity of the thermal imager is ±0.1°C. Manual calibration was not necessary since this was an internal function.

Technique

Two New Zealand white rabbits of approximately equal weight (2–3 kg) were randomly assigned to each treatment group. The rabbits were anesthetized intramuscularly with 0.4 ml/kg of a solution containing 100 mg/ml ketamine HCl and 3 mg/ml acepromazine. The rabbit ears were then shaved, and one ear was assigned to the treatment group and the other ear served as a reference. A syringe pump was used to inject the lateral aspect of the marginal vein of the rabbit ear at a constant rate of 0.2 ml/min. A 27-gauge, 3/8-in. butterfly catheter attached to a 3-ml syringe was used for the injection. The doses and volume injected for each drug are given in Table I.

Baseline temperatures were then established for the artery and the marginal vein of each rabbit ear using the thermographic camera. Following the intravenous injection of the treatment ear, temperature readings of the artery and vein of both ears were taken at 0.0, 0.25, 0.50, 0.75, 1.0, 1.5, 2.0, 3.0, 4.0, 5.0, and 24 hr. Since the baseline temperature of each rabbit ear in the study was different, the temperatures were normalized by subtracting the vein–artery difference of the noninjected ear from that of the injected ear. This made it possible to determine the relative temperature change of the injected ear vein to that of the reference ear. A qualitative comparison of the temperature change between the control group, which received no injection, and the normal saline treatment group was then made. The normal saline treatment group was then compared with the remaining treatment groups and the commercial drugs were also compared against their vehicles.

The treatment groups were monitored visually for the presence of phlebitis around the injection site. The criterion for a positive phlebitis score was the presence of erythema or edema in a region not less than 5 mm in diameter. Any involved area of the ear smaller than this was deemed a negative response. The presence or absence of phlebitis was recorded 24 hr following the injection.

Table I. Dose and Volumes Administered

Drug	Dose		
	mg/kg	mg/ml	ml
Amiodarone	10	50	0.6
Diazepam	0.3	5	0.2
Phenytoin	3.3	50	0.2
Cephalothin	6.6	100	0.2
Mechlorethamine	0.1	1	0.3
All cosolvents and vehicles	—	—	0.4

RESULTS

Figure 1 is a typical recording from the thermal imaging camera. The upper portions of the recordings show the thermal profile of the rabbit ears. The line passing through the ears corresponds to the point of thermal measurement. The lower portions of the thermograms is where the data is displayed. The baseline in these two cases is at 34.0°C and each line above it represent a 0.5°C increase in temperature. Four peaks are present in each thermogram; the smaller, outer peaks are the venous temperatures and the larger, inner peaks are the arterial temperatures. Recording A is of a subject just prior to injection. Recording B is of the same rabbit, 10 min after an amiodarone injection into the right lateral vein. Note the 1.5°C increase in temperature shown by the elevated right outer peak.

Each data point (in all of the graphs) represents the mean of two subjects. Figure 2 is a plot of the mean temperature change between the experimental and the reference ears versus time for the untreated rabbits and those treated with normal saline. From this graph, it can be seen that there is no increase in temperature for the normal saline treatment group. The control-group data show some small temperature

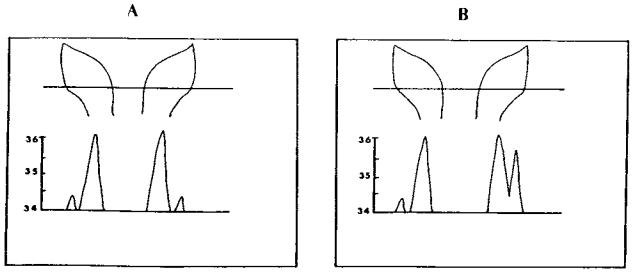

Fig. 1. Copy of a typical thermographic output. The venous and arterial temperatures are read directly from the thermogram which is a plot of the temperatures along the scanning line. Each horizontal line in the thermal profile represents 0.5°C. Inner peaks are the arterial temperatures; outer peaks are the venous temperatures. (A) Subject prior to injection. (B) Same subject 10 min after receiving an injection of amiodarone HCl in the right lateral vein.

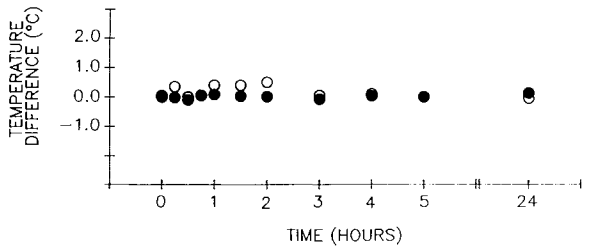

Fig. 2. Temperature elevation produced by the control (○) and normal saline treatment groups (●).

fluctuations indicating that some deviation about the mean of zero can occur. However, the control group is very similar to that of the rabbits receiving normal saline and there is no apparent difference between them. The local visual tissue response for both treatment groups was negative for the presence of phlebitis.

The data presented in Fig. 3 represent the amiodarone and phenytoin treatment groups as well as their respective vehicles. It can be seen that for the amiodarone treatment group there is a significant temperature increase within 15 min of the injection. This elevation in temperature peaks at a value of 1.6°C and remains elevated at 1°C for 24 hr. Positive signs of phlebitis were present locally at 24 hr. The amiodarone vehicle exhibits no such temperature elevation or local tissue response (paralleling the untreated and normal saline treatment groups) for any of the recorded time points. Although not as large, the phenytoin treatment group shows significant temperature changes relative to the treatment groups in Fig. 2. Here the temperature peaks at 1.3°C and averages 1.0°C for the duration of the study, and as in the case of amiodarone, there is a local inflammatory response at 24 hr. As in the previous case the vehicle produces no significant temperature increase or tissue reaction.

The data recorded for the diazepam, cephalothin, and mechlorethamine treatment groups, as well as their respective vehicles, are given in Fig. 4. Rabbits from both diazepam and cephalothin treatment groups show a slight early thermal response that diminishes after about an hour. However, this appears to be insignificant. No temperature changes are seen for either of the vehicles. Near-baseline

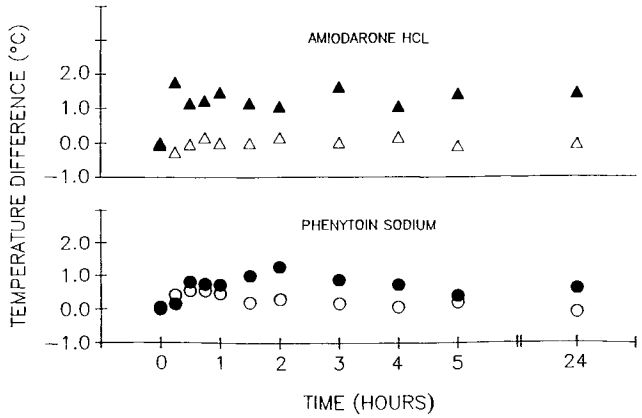

Fig. 3. Temperature elevation produced by amiodarone HCl (▲), the amiodarone vehicle (△), phenytoin sodium (●), and the phenytoin vehicle (○).

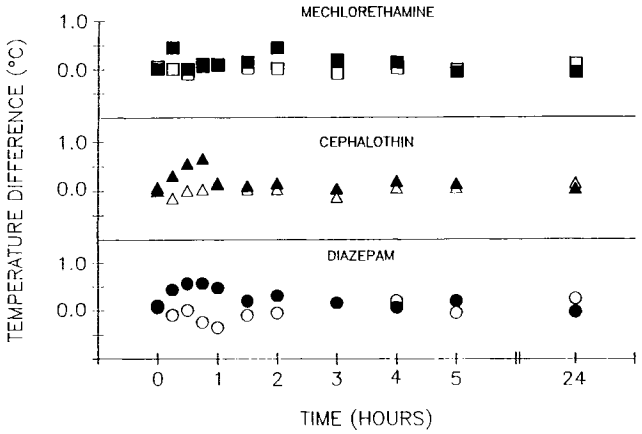

Fig. 4. Temperature elevation produced by mechlorethamine HCl (■), the mechlorethamine vehicle (□), cephalothin sodium (▲), the cephalothin vehicle (△), diazepam (●), and the diazepam vehicle (○).

readings were observed for both mechlorethamine and its vehicle for the duration of the study. Neither diazepam, cephalothin, nor mechlorethamine produced phlebitis locally at the 24-h time point.

The results from the various organic cosolvents studied are shown in Figs. 5 and 6. Of the six cosolvents tested (50% DMI, 70% DMSO, 70% DMA, 50% PEG 400, 40% PG, and 50% ETOH), none produced a significant deviation from the untreated control group either thermally or visually.

DISCUSSION

Drugs that are poorly soluble in water when formulated with cosolvents can precipitate when injected (9). This can cause acute phlebitis. Drugs that have higher aqueous solubility may tend to cause phlebitis only on prolonged or chronic administration. Phenytoin, amiodarone, and to some extent, diazepam are known to cause acute phlebitis when administered intravenously. These drugs are poorly soluble (see Table I). In the case of amiodarone and phenytoin our data confirm an acute response. Cephalothin and mechlorethamine usually cause phlebitis when administered for extended periods of time. They are both freely soluble, and therefore, chemical irritation rather than precipitation is

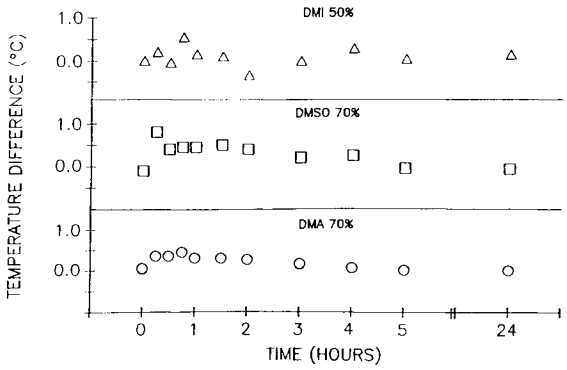

Fig. 5. Temperature elevation produced by the following cosolvents: 50% dimethylisosorbide (△), 70% dimethyl sulfoxide (□), and 70% dimthylacetamide (○).

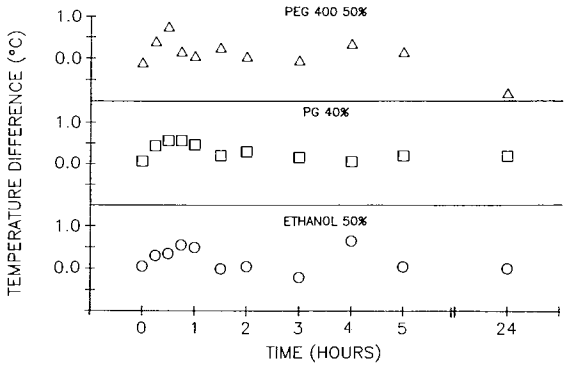

Fig. 6. Temperature elevation produced by the following cosolvents: 50% polyethylene glycol 400 (△), 40% propylene glycol (□), and 50% ethanol (○).

more likely the cause of phlebitis. The purpose of their inclusion in this study of acute phlebitis was that of a negative control. Since only a single injection was given, one would not expect to see temperature increases or phlebitis, as was the case.

In viewing the data in Fig. 3 it can be seen that only amiodarone hydrochloride and phenytoin sodium show a sustained increase in temperature exceeding 0.5°C. In several of the cosolvents early temperature increases were noted. These increases fell off to near-baseline levels after 1 to 1.5 hr. Since no visual response was seen in any of these cases, it is likely that these small, early thermal responses may be due to the local trauma of the venipuncture. Of the cosolvents tested, none gave an appreciable sustained thermal response. Visual examination of the rabbits in the cosolvent treatment groups revealed the absence of symptoms of phlebitis. A summary of the thermal and visual data is provided in Table II.

Table II. Thermal and Visual Response Data of Systems Studied

Drug or cosolvent	Thermal response	Visual response	Solubility (H_2O)
Normal saline	None	None	Miscible
Phenytoin	Positive	Positive	Not miscible
Phenytoin vehicle	None	None	Miscible
Diazepam	None	None	Not miscible
Diazepam vehicle	None	None	Miscible
Amiodarone	Positive	Positive	Not miscible
Amiodarone vehicle	None	None	Miscible
Cephalothin	None	None	Miscible
Mechlorethamine	None	None	Miscible
50% ethanol	None	None	Miscible
50% DMI	None	None	Miscible
70% DMSO	None	None	Miscible
70% DMA	None	None	Miscible
50% PEG 400	None	None	Miscible
40% PG	None	None	Miscible

Thermography has been used very successfully in the past for the detection of deep vein thromboses (22). Skin temperatures measured by thermography have been shown to be a direct measure of tissue blood perfusion (20). It appears that thermography may also be useful in detecting superficial venous phlebitis caused by the injection/infusion of many parenteral formulations as well as their vehicles. This project has demonstrated good agreement between the venous temperature increase detected by thermography and the visual signs of phlebitis observed in the rabbit. This model could prove to be extremely useful in preformulation studies allowing early changes in the formulation so that expensive delays could be avoided.

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