Clobetasol 17-Propionate Cream as an Effective Preventive Treatment for Drug Induced Superficial Thrombophlebitis

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Summary
Commonly used therapies for thrombophlebitis have a high failure rate. There are scant data on the application of topical corticosteroids to treat thrombophlebitis. The present study investigated if the potent topical corticosteroid clobetasol 17-propionate cream (Dermovate, Glaxo Wellcome) can be an effective treatment for drug-induced thrombophlebitis.
DP-b99, a neuroprotective agent currently undergoing development for acute stroke, can cause injection-site phlebitis. DP-b99 was administered at doses of 1 and 2 mg/kg by a 1 hour intravenous infusion into the lateral ear vein of groups of 6 and 5 rabbits, respectively. Each rabbit served as its own control by injecting both ears with DP-b99, while treating only one ear with clobetasol cream immediately after treatment, with subsequent applications twice daily for 3 days. Phlebitis was evaluated 1, 3, 5, 24, 32, 48, 56 and 72 hours after DP-b99 treatment using a clinical score ranging from 0 (no reaction) to 4. After 3 days the rabbits were sacrificed for histological analysis of the ears.
The phlebitis score was highest at 24 hours. Clobetasol treatment reduced the clinical scores at all time points and shortened the course of phlebitis. Maximal effect was observed 24-48 hours after the first application of clobetasol cream. Histologically, there were fewer cases of thrombophlebitis in the clobetasol-treated ears, and those seen were milder and more focal. To the best of the authors' knowledge this appears to be the only study to report a phlebitis-ameliorating effect of a topical corticosteroid.

Introduction
Drug-induced peripheral vein phlebitis or thrombophlebitis is a very common clinical complication that occurs in 25 to 70% of all patients receiving intravenous therapy (*Woodhouse, 1980; Tagalakis et al., 2002; Macklin, 2003*). Drug-induced phlebitis is a vascular and perivascular inflammatory reaction, characterised by polymorphonuclear cell infiltrate and thrombi. In severe cases the vessel wall becomes disorganised with intramural haemorrhages and necrosis. This inflammatory process may last up to 4 weeks (*Woodhouse, 1980*). Clinically, thrombophlebitis is characterised by pain, swelling, and erythema. In the more severe cases vein occlusion can develop, and secondary infection and septicaemia may ensue (*Woodhouse, 1980; Khan et al., 1997; Tagalakis et al., 2002; Macklin, 2003*). Peripheral thrombophlebitis is often refractory to treatment and frequently necessitates catheter removal and insertion of a new catheter in an alternative vein. Phlebitis is also a common, undocumented clinical problem in laboratory animals, especially rabbits.
The metal ion chelator DP-b99 is a newly developed lipophilic derivative of BAPTA (1,2-bis(2-aminophenoxy)ethane-N,N,N',N'-tetraacetic acid), which modulates the distribution of metal ions in hydrophobic media. DP-b99 is currently undergoing clinical development as an intravenously-administered neuroprotectant for acute ischemic

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stroke (*Rosenberg et al., 2004*). Phlebitis at the site of intravenous administration was DP-b99's most frequently reported adverse event in this drug's initial evaluation in healthy volunteers (*Rosenberg et al., 2005*), and the goal of the current study was to find an appropriate preventive treatment for DP-b99 induced phlebitis without interfering with its therapeutic effect in stroke patients.

Few systemic treatments have been tested for peripheral vein phlebitis, and even fewer were attempted as a prophylactic approach (*Dobbins et al., 2003*). These systemic studies usually employed heparin combined with cortisone (*Tighe et al., 1995; Dobbins et al., 2003*) or heparin alone (*Randolph et al., 1998; Marchiori et al., 2002*). Heparin aided fluid flow through the catheter and reduced the risk of phlebitis; however this effect was not always satisfactory and the haemorrhagic side effects of systemic anti-coagulation may be very serious (*Randolph et al., 1998; Marchiori et al., 2002*). Systemic treatment with the non steroidal anti-inflammatory drug (NSAID) diclofenac showed some benefit in reducing the clinical signs of phlebitis (*Becherucci et al., 2000*), but it also has potentially serious side effects.

As with systemic treatments, few topical drugs have been proposed for the treatment or prevention of peripheral vein thrombophlebitis. Preventive topical treatment with a glyceryl trinitrate patch showed benefit in prolonging the survival time of the cannula and in reducing the prevalence of phlebitis (*Wright et al., 1985; Khawaja et al., 1991*). Topical glyceryl trinitrate was tested in combination with systemic heparin and hydrocortisone (*Tighe et al., 1995*), but in a subsequent study its additional benefit was doubtful (*Dobbins et al., 2003*). The effect of glyceryl trinitrate is believed to be through vasodilatation, but even with a topical preparation this compound can lead to adverse systemic effects such as hypotension and headache (*Dobbins et al., 2003*). Topical heparin alone was also found to relieve the symptoms of phlebitis (*Mehta et al., 1975; Gorski et al., 2005*). Several topical NSAIDs including naproxen (*Cokmez et al., 2003*), felbinac gel (*Payne-James et al., 1992*), and diclofenac (*Becherucci et al., 2000*) were tried with some success in reducing the clinical signs of phlebitis and overall reduction in the incidence of thrombophlebitis. Surprisingly, topical treatment with steroids was hardly ever evaluated in peripheral vein phlebitis, with one exception of an early work with a preparation of adrenocortical extract and salicylic acid which reduced the incidence of thrombophlebitis by nearly 50% (*Woodhouse, 1979*).

Clobetasol cream, an ultra-high-potency corticosteroid, has been effective in treating difficult inflammatory skin conditions such as psoriasis (*Stein, 2005*), atopic dermatitis (*Breneman et al., 2005*) and bullous pemphigoid (*Fontaine et al., 2003*). In the current study we assessed the cream preparation of clobetasol as a topical treatment for DP-b99-induced phlebitis in a rabbit model. The marginal ear vein of the rabbit is an established model for assessment of drug-induced thrombophlebitis (*Johnson et al., 1989*), and previous studies have characterised this model clinically and histopathologically (*Kuwahara et al., 1998*). The phlebitogenic properties of several drugs such as diazepam (*Levy et al., 1989; White & Yalkowsky, 1991*), amioderone (*Ward et al., 1991*) and bisatrene (*Powis & Kovach, 1983*) were studied in this model. The current study utilized this model to asses the response to anti-phlebitis treatment following the use of DP-b99. The hypothesis of this study was that clobetasol will have a preventive effect on the development of DP-b99-induced phlebitis in the marginal ear vein of the rabbit.

Materials and Methods

The D-Pharm Institutional Animal Care and Use Committee, which works under the Israeli National Council for Experiments in Laboratory Animals, according to Israeli law and the U.S. National Institutes of Health guidelines for the care and use of laboratory animals, approved all the studies.

Eleven, pathogen-free, male, outbred New Zealand White rabbits *Oryctolagus cuniculus* (Harlan, Jeru-

salem, Israel), 14-15 weeks old and weighing 2.4-3 kg, were used in the study. The rabbits were quarantined 5 days for acclimatization before the study. All rabbits were clinically healthy prior to the study. They were housed in individual wire cages 65 x 65 x45 cm with a perforated plastic floor and collection pen (Tecniplast, Varese, Italy). The rabbits were housed in controlled environmental conditions: temperature 20º-22ºC, relative humidity 30-55% and a 12 hours light/dark cycle. The rabbits were fed standard rabbit diet (7078s Sterilizable Doe Rabbit Diet, Teklad, Madison, WI, USA) and fresh water *ad libitum*.

The rabbits were divided into 2 dose groups that received 1 mg/kg (n=6) or 2 mg/kg (n=5) DP-b99 to each ear. The drug substance was dissolved in normal saline (B.Braun, Germany) and was administered at a concentration of 0.4 mg/ml or 0.8 mg/ml. The marginal (lateral) ear veins of each rabbit were cannulated with a 24g venflon cannula (Romed, Wilnis, Holland) and 2.5 ml/kg of the test substance was administered as a continuous infusion over 1 hour, using an infusion pump (Harvard Apparatus, South Natick, Mass, USA). Cannulation and infusion were under general light anaesthesia: the rabbits were premedicated with acepromazine (C-Vet, Lancashire, UK) 1 mg/kg intramuscularly (IM) and anaesthetised with xylazine (VMD, Arendonk, Belgium) 3 mg/kg and ketamine (Fort Dodge, Iowa, USA) 50 mg/kg IM. Each rabbit served as its own control by infusing one ear with DP-b99 and the other ear with DP-b99 followed immediately by the application of clobetasol cream (0.05% w/w, Demovate, GlaxoWellcome, Uxbridge, UK). Additionally, clobetasol cream was applied twice a day throughout the 3 study days. The cream was applied gently to the infusion site, and the rabbits were restrained or guarded to prevent licking for an hour after the application.

Phlebitis was evaluated twice daily by means of clinical score according to the following scale (*Levy et al., 1989*):

0 = no reaction.

1 = changes in vein colour and thickness without changes surrounding the vein.

2 = changes in vein colour and thickness accompanied by erythema or oedema limited to the proximity of the vein.

3 = changes in vein colour and thickness accompanied by wide erythema or oedema around the vein up to the level of the central artery.

4 = changes in vein colour and thickness accompanied by erythema or oedema surrounding the vein, reaching and exceeding the central artery.

The clinical score was evaluated 1, 3, 5, 24, 32, 48, 56 and 72 hours after drug administration. Seventy-two hours after the infusion the rabbits were anaesthetised with xylazine (VMD, Arendonk, Belgium) 3 mg/kg and ketamine (Fort Dodge, Iowa, USA) 50 mg/kg IM and then euthanaised with pentobarbitone (CTS, Kiryat Malachi, Israel) 200 mg/kg intra cardiac. Samples of 3 centimetres of the ear vein from the point of the tip of the cannula and distally were excised and subjected to pathological microscopic analysis. Samples for histology were prepared by a standard procedure and were stained with Hematoxylin Eosin. Histology was performed under light microscopy. The pathologist (AM) was blinded to the treatment procedure. The lateral ear vein was specifically evaluated for the presence of thrombus and phlebitis. The histology findings were graded according to the following criteria, that were adapted from *Kuwahara (1998)*:

Thrombus

None

Small – <1/3 of the vein in cross-section

Medium – 1/3 – 2/3 of the vein in cross-section

Large – >2/3 of the vein in cross-section

Phlebitis:

None

Mild – Few inflammatory cells in venous wall or perivascular tissue

Moderate – Many inflammatory cells in venous wall or perivascular tissue

Severe – Diffuse and denser inflammatory cells in venous wall or perivascular tissue

Statistical analysis

The clobetasol treatment effect was calculated by firstly subtracting the clobetasol-treated ear score from the non-treated ear score. The multiple measures over time were converted to a single continuous parameter by calculating the area under each rabbit curve. We then did a standard ANOVA with dose as a factor. Since dose was not significant ($F_{1,9}$ = 2.365, P = 0.1584) it was deleted from the model. We then only tested (by ANOVA) whether the mean response to clobetasol treatment was significantly different from 0 for the overall area under the curve (overall time). For specific time points we used the Sign Rank Test. The effect of clobetasol over time was also assessed via a quadratic model allowing random effects for the linear and quadratic coefficients. The differences in prevalence of histological lesions between groups were evaluated by chi-square test. A p-value of 0.05 was considered significant.

Results

DP-b99 1 mg/kg induced mild phlebitis with mean peak score (± standard error) of 1.58 ± 0.27 after 24 hours (Fig. 1). When treated with clobetasol the phlebitis almost disappeared, with a 24 hours peak score of 1.00 ± 0.26 (Fig. 1), which represents a very mild phlebitis that would hardly be detected in a clinical setting. With DP-b99 dose of 2 mg/kg, the mean 24 hours score observed without clobetasol treatment was 1.90 ± 0.40 and with clobetasol 1.00 ± 0.00 (Fig. 2). The time courses of the phlebitis in the untreated ears for the 2 doses were similar. There was an early small peak in the score 3 hours after drug administration - probably due to both mechanical irritation from the cannulation and a reaction to DP-b99. However, this initial irritation subsided after 5 hours and then the signs of inflammation increased again, probably as a reaction to the drug substance. The highest clinical score was obtained 24 hours post-administration for both doses. After 24 hours the clinical score decreased slowly in both clobetasol treated and non-treated ears. The difference in score-time area under the curve between the rabbit's clobetasol treated non–treated ears revealed significant differences ($F_{1,11}$ = 23.128, P < 0.001), indicating the overall effect of the clobetasol. The analysis of the effect revealed significant effects at 3 (p=0.016), 24 (p=0.031), 32 (p=0.008) and 48 (p=0.016) hours. To estimate the slope of the clobetasol effect at various times, a quadratic model which allows for random effects was used. It yielded slope estimates of 0.022 at 5 hours (p=0.002), 0.018 at 10 hours (p=0.003), 0.015 at 15 hours (p=0.005), -0.010 at 48 hours (p=0.023) and –0.016 at 56 hours (p=0.005). These results indicate that there is a slower development of phlebitis (significantly positive slope prior to 32 hours) with clobetasol, and an expedited healing process after 32 hours

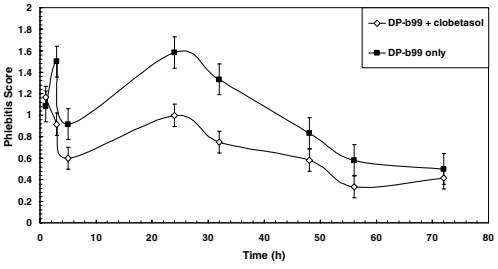

Figure 1. Phlebitis score monitored over 72 hours post administration of DP-b99 1 mg/kg/ear with or without topical clobetasol. Data presented as mean ± standard error (n=6).

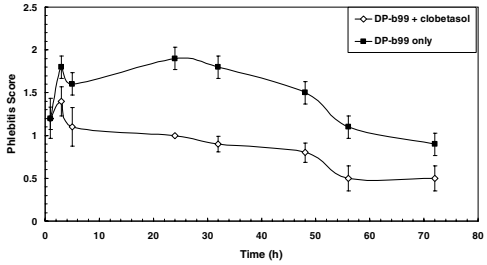

Figure 2. Phlebitis score monitored over 72 hours post administration of DP-b99 2 mg/kg/ear with or without topical clobetasol. Data presented as mean ± standard error (n=5).

(a negative slope). Similar results were obtained while analysing each dose (either 1 mg/kg or 2 mg/kg) separately (Fig. 3).

On histological assessment of the 1 mg/kg DP-b99 treated rabbits, only 1 ear treated with clobetasol and 1 ear without clobetasol showed mild perivascular inflammatory cellular infiltrate. However, thrombus was evident in 2/6 clobetasol and 4/6 non-clobetasol treated ears (Table 1). This was in agreement with the minimal clinical scores observed in this group 72 hours post drug administration. The histological analysis of the ears after the 2 mg/kg dose revealed phlebitis in 3/5 (1 mild, 2 moderate) of the control ears and mild phlebitis in 1/5 of rabbits that was treated with clobetasol. This is in agreement with the clinical results that show a positive effect for clobetasol in reducing DP-b99-induced phlebitis. The inflammatory infiltrate was a mixture of granulocytes and macrophages consistent with a sub-acute reaction (Table 1). Chi square analysis of the histological findings was not significant.

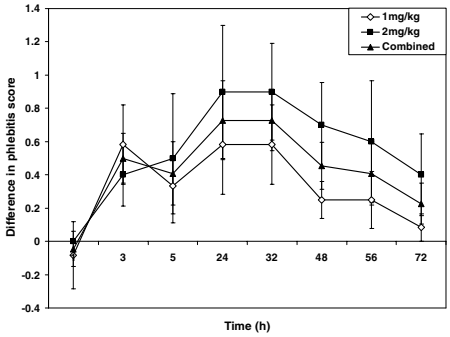

Figure 3. Difference in phlebitis score between ears treated with DP-b99 without clobetasol cream and with clobetasol over time. Three plots are presented; treatment with DP- b99 1 mg/kg/ear (n=6), DP-b99 2 mg/kg/ear (n=5) and a combined plot of the 2 treatments (n=11). Data presented as mean ± standard error. Note the positive slope until 24 hours indicating reduced phlebitis reaction and the negative slope after 32 hours indicating expedited healing process.

Table 1. Prevalence of histopathological lesions 72 hours post administration of DP-b99 1 mg/kg or 2 mg/kg with or without clobetasol.

Treatment	Number of rabbits	Prevalence of phlebitis	Prevalence of thrombus	Prevalence of no pathology
DP-b99 1 mg/kg With clobetasol	6	1/6 (1 mild)	2/6 (2 medium)	4/6
DP-b99 1 mg/kg Without clobetasol	6	1/6 (1 mild)	4/6 (1 small, 3 medium)	2/6
DP-b99 2 mg/kg With clobetasol	5	1/5 (1 mild)	2/5 (1 small, 1 large)	3/5
DP-b99 2 mg/kg Without clobetasol	5	3/5 (1 mild, 2 moderate)	3/5 (3 large)	2/5

Phlebitis was graded as: mild – few inflammatory cells in the venous wall or perivascular tissue; moderate – many inflammatory cells in the venous wall or perivascular tissue; or severe – diffuse and denser inflammatory cells in the venous wall or perivascular tissue. Thrombus was graded as: small – <1/3 of the vein in cross-section; medium – 1/3 – 2/3 of the vein in cross-section; or large – >2/3 of the vein in cross-section.

Discussion

The pathogenesis of DP-b99-induced phlebitis is unclear. In humans the phlebitis was mostly mild and was observed more frequently in young subjects than in the elderly (*Rosenberg et al., 2005*). In the present study, the mild inflammatory histological signs do not hint clearly at the mechanism underlying the DP-b99 pro-phlebitic effect; however, the relatively high prevalence of thrombi may indicate endothelial injury. The mixed inflammatory infiltrate indicates a response to an acute irritation and possibly endothelial injury. No precipitation of the drug substance was observed microscopically.

The rabbit's marginal ear vein is a very sensitive model for peripheral phlebitis (*Kuwahara et al., 1998*) as the veins are very superficial and thin, the interstitium has limited space, and the lack of pigment in albino animals makes the inflammation easily discernible. This model was frequently used to demonstrate local toxicity after intravenous administration, but has not been used routinely to assess thrombophlebitis therapy. For the same reasons, mentioned above, it should be just as sensitive in demonstrating resolution of phlebitis. Indeed, to our knowledge the current study is the first to employ this model to such an end.

Clobetasol reduced both the peak score of the phlebitis and shortened the healing process. To the best of our knowledge apart from an early study using adrenocortical extract (*Woodhouse, 1979*), this appears to be the only study to report a phlebitis-ameliorating effect of a topical corticosteroid. In our study the phlebitis was self limiting even without treatment, as may be expected after a single administration of an irritating agent; however, this may not be the case with repeated administrations, e.g. when administering parenteral nutrition, where the phlebitis can progressively worsen. Clobetasol has the potential to prevent this perpetuating cascade with minimal side effects after being applied locally. Few local treatments have been attempted for phlebitis in human patients. Trinitrates have potentially serious side effects, especially in elderly people (*Wright et al., 1985*) and their benefit is questionable (*Dobbins et al., 2003*). The topical NSAID felbinac showed only reduction in hardness around the cannula, but not in erythema pain or oedema (*Payne-James et al., 1992*). In topical or systemic administration it showed improvement in all clinical parameters tested, namely hardness, eryrthema, heat and pain, but adverse reactions were reported following either mode of administration (*Cokmez et al., 2003*). A topical heparin formulation was reported to reduce erythema and pain and to induce thrombus regression (*Gorski et al., 2005*). Another study with topical heparinoid ointment showed a quicker relief of the clinical signs (*Mehta et al., 1975*). The evaluation in the current study combined a variety of clinical and histological parameters and demonstrated the efficacy of topical clobetasol. The study has a few limitations: the clinical scoring was not blinded, the group size was small and the irritant was mild; therefore, further investigations, with larger study groups and other drugs with phlebitogenic potential should be performed. Clearly, one cannot directly transpose animal-based data to human patients but our study warrants an evaluation of topical steroids in human chemical thrombophlebitis. Local application of potent corticosteroids, if found effective in humans, have the potential to replace or supplement the current treatment with heparin or NSAIDs.

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References

Becherucci A, D Bagilet, J Marenghini, M Diab & H Biancardi: [Effect of topical and oral diclofenac on superficial thrombophlebitis caused by intravenous infusion]. Med Clin (Barc). 2000, *114*, 371-373.

Breneman D, AB, Fleischer Jr., D Kaplan, M Lebwohl, B Miller, D Pariser, T Rist, L Swinyer, Y Liu & V Foley: Clobetasol propionate 0.05%

lotion in the treatment of moderate to severe atopic dermatitis: a randomized evaluation versus clobetasol propionate emollient cream. J Drugs Dermatol. 2005, *4*, 330-336.

Cokmez A, S Gur, H Genc, S Deniz & E Tarcan: Effect of transdermal glyceryl trinitrate and anti-inflammatory gel in infusion phlebitis. ANZ J Surg. 2003, *73*, 794-796.

Dobbins BM, JA Catton, MJ Tighe, GV Miller, IG Martin & MJ McMahon: Randomized clinical trials to determine the role of topical glyceryl trinitrate in peripheral intravenous nutrition. Br J Surg. 2003, *90*, 804-810.

Fontaine J, P Joly & JC Roujeau: Treatment of bullous pemphigoid. J Dermatol. 2003, *30*, 83-90.

Gorski G, P Szopinski, J Michalak, A Marianowska, M Borkowski, M Geremek, M Trochimczuk, J Brotanek, S Sarnik, J Semenka, D Wilkowski & W Noszczyk: Liposomal heparin spray: a new formula in adjunctive treatment of superficial venous thrombosis. Angiology. 2005, *56*, 9-17.

Johnson JV, AH Jeske, HK McDaniel & GQ Herrera: Development of an in vivo model for assessment of drug-induced vascular injury. J Oral Maxillofac Surg. 1989, *47*, 819-822.

Khan EA, AG Correa & CJ Baker: Suppurative thrombophlebitis in children: a ten-year experience. Pediatr Infect Dis J. 1997, *16*, 63-67.

Khawaja HT, JD Williams & PC Weaver: Transdermal glyceryl trinitrate to allow peripheral total parenteral nutrition: a double-blind placebo controlled feasibility study. J R Soc Med. 1991, *84*, 69-72.

Kuwahara T, S Asanami & S Kubo: Experimental infusion phlebitis: tolerance osmolality of peripheral venous endothelial cells. Nutrition. 1998, *14*, 496-501.

Levy MY, L Langerman, S Gottschalk-Sabag & S Benita: Side-effect evaluation of a new diazepam formulation: venous sequela reduction following intravenous (i.v.) injection of a diazepam emulsion in rabbits. Pharm Res. 1989, *6*, 510-516.

Macklin D: Phlebitis. Am J Nurs. 2003, *103*, 55-60.

Marchiori A, F Verlato, P Sabbion, G Camporese, F Rosso, L Mosena, GM Andreozzi & P Prandoni: High versus low doses of unfractionated heparin for the treatment of superficial thrombophlebitis of the leg. A prospective, controlled, randomized study. Haematologica. 2002, *87*, 523-527.

Mehta PP, S Sagar & VV Kakkar: Treatment of superficial thrombophlebitis: a randomized, double-blind trial of heparinoid cream. Br Med J. 1975, *3*, 614-616.

Payne-James JJ, MJ Bray, S Kapadia, SK Rana, D McSwiggan & DB Silk: Topical nonsteroidal anti-inflammatory gel for the prevention of peripheral vein thrombophlebitis. A double-blind, randomised, placebo-controlled trial in normal subjects. Anaesthesia. 1992, *47*, 324-326.

Powis G & Kovach JS: Disposition of bisantrene in humans and rabbits: evidence for intravascular deposition of drug as a cause of phlebitis. Cancer Res . 1983, *43*, 925-929.

Randolph AG, DJ Cook, CA Gonzales & M Andrew: Benefit of heparin in peripheral venous and arterial catheters: systematic review and meta-analysis of randomised controlled trials. Bmj. 1998, *316*, 969-975.

Rosenberg G, I Angel & A Kozak: Clinical pharmacology of DP-b99 in healthy volunteers: first administration to humans. Br J Clin Pharmacol. 2005, *60*, 7-16.

Rosenberg G, I Angel, A Kozak & D Schnelder: Evaluation of safety and changes in the NIH stroke scale, rankin, and Barthel scores following DP-b99 administration in acute stroke patients. Stroke. 2004, *35*, 338.

Stein L: Clinical studies of a new vehicle formulation for topical corticosteroids in the treatment of psoriasis. J Am Acad Dermatol. 2005, *53*, S39-49.

Tagalakis V, SR Kahn, M Libman & M Blostein: The epidemiology of peripheral vein infusion thrombophlebitis: a critical review. Am J Med. 2002, *113*, 146-151.

Tighe MJ, C Wong, IG Martin & MJ McMahon: Do heparin, hydrocortisone, and glyceryl trinitrate influence thrombophlebitis during full intravenous nutrition via a peripheral vein? JPEN J Parenter Enteral Nutr. 1995, *19*, 507-509.

Ward GH, PE, Nolan Jr., M White & SH Yalkowsky: Studies in phlebitis. II. Early detection of amiodarone-induced phlebitis in a rabbit model. Pharm Res. 1991, *8*, 801-803.

White M & SH Yalkowsky: Studies in phlebitis. III. Evaluation of diazepam and phenytoin. Pharm Res. 1991, *8*, 1341-1342.

Woodhouse CR: Movelat in the prophylaxis of infusion thrombophlebitis. Br Med J. 1979, *1*, 454-455.

Woodhouse CR: Infusion thrombophlebitis: the histological and clinical features. Ann R Coll Surg Engl. 1980, *62*, 364-368.

Wright A, JF Hecker & GB Lewis: Use of transdermal glyceryl trinitrate to reduce failure of intravenous infusion due to phlebitis and extravasation. Lancet. 1985, *2*, 1148-1150.