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Possible therapeutic use of vasodilator iontophoresis

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Abstract

Background. Investigation into the effects of a novel vasodilator delivery method (for the eventual treatment of scleroderma related digital ulceration) on healthy controls is reported. When Raynaud's phenomenon (episodic cold-induced colour changes of the fingers) occurs in the context of scleroderma, it can be extremely severe, leading to ulceration and sometimes gangrene. The current treatment of choice for scleroderma-related critical digital ischaemia and/or ulceration is intravenous prostanoid therapy, necessitating hospitalisation. However, iloprost is often poorly tolerated and may be ineffective.

Methods. This study utilises a newly designed iontophoresis chamber which has the potential to allow a therapeutic, rather than diagnostic application for vasodilatory iontophoresis. Ten healthy controls underwent whole finger iontophoresis with 1% acetylcholine chloride for 2 min at 100 μA. Iontophoresis with varying treatment times and currents was carried out on a subset of subjects to determine the effect on perfusion increase.

Results. A significant increase in perfusion following iontophoresis was found, compared to the adjacent, untreated finger ($P < 0.001$). Maximum increase as a percentage from baseline, mean [SD] = 100 [66]%. Both treatment time and current have an approximately linear relationship with perfusion increase.

Conclusions. Iontophoresis of the whole finger administers drugs locally with no systemic effects and warrants further investigation as a therapy.

Keywords: Acetylcholine chloride; Blood flow; Iontophoresis; Ischaemia; Laser Doppler imaging; Non-systemic; Raynaud's phenomenon; Scleroderma; Ulceration; Vasodilation

Introduction

Iontophoresis is the non-invasive process of driving ionised drugs or chemicals into the skin by means of an applied electric field, generated by low dc currents (μA). Iontophoresis enhances the absorption of drugs, either as a diagnostic tool or a therapeutic, alternative method of drug delivery.

Iontophoresis has been used in many pathophysiological studies to determine whether microvascular reactivity is impaired with reference to healthy controls. The choice of drug or chemical is dependent on the specific outcome desired and the area to be treated. Iontophoresis of both acetylcholine chloride (ACh, endothelial-dependent) and sodium nitroprusside (NaNP, endothelial-independent) cause a rapid and dramatic increase in dermal blood flow and are popular choices to determine circulatory impairment due to endothelial dysfunction. Algotsson et al. (1995) performed iontophoresis of ACh, NaNP and isoprenaline sulphate on the forearms of patients with Alzheimer's disease and age-matched healthy controls to determine whether Alzheimer's could be a systemic disease. Caballero

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et al. (1999) demonstrated, again with ACh and NaNP, that abnormalities in vascular reactivity were present in individuals at risk of developing Type 2 diabetes (relatives of present sufferers) before other indicators were present. Similar studies to quantify endothelial dysfunction with ACh and NaNP have been carried out on patients with hypertension (Farkas et al., 2004), reflex sympathetic dystrophy (Gorodkin et al., 2004), fibromyalgia (Al-Allaf et al., 2001), peripheral arterial disease (Jagren et al., 2002, Rossi et al., 2002) and to investigate the role of nitric oxide and prostaglandins in endothelial blood flow regulation (Kvandal et al., 2003). The above blood flow responses were all measured with single point laser Doppler flowmetry (LDF) or laser Doppler imaging, over an area (LDI).

The technique of iontophoresis to examine microvascular responses to endothelial-dependent and endothelial-independent vasodilation in patients with Raynaud's phenomenon (episodic cold-induced colour changes of the fingers) and scleroderma (a multisystem connective tissue disease also known as systemic sclerosis, SSc) has been studied by several groups including our own (Anderson et al., 1996; 1999; Khan and Belch, 1999; Khan et al., 1997; La Civita et al., 1998). Perfusion increase due to iontophoresis of ACh and NaNP, as quantified by laser Doppler, has been demonstrated even in patients with SSc who have very thickened skin (Anderson et al., 1996, 1999). The aim of these pathophysiological iontophoresis studies was primarily to assess whether vasodilation was impaired in patients with Raynaud's phenomenon and SSc, and if so, whether this was primarily endothelial-dependent. However, their results raised the question as to whether we might apply iontophoresis therapeutically in patients with severe Raynaud's.

When Raynaud's phenomenon occurs secondary to SSc, it can be very severe, and may progress to irreversible tissue ischaemia with scarring, ulceration and sometimes gangrene, necessitating digital amputation. Treatment is unsatisfactory—while intravenous prostacyclin analogues are the treatment of choice in patients with severe digital ischaemia (Pope et al., 2000), these require admission to hospital, can be associated with troublesome vasodilatory side effects (hypotension, dizziness, headache), and are not always effective (Wigley et al., 1994). To emphasise the scale of the problem, a review, carried out in 2001, of the case records of 171 patients with SSc attending Hope Hospital, Salford, UK showed that 28 (16%) had at least one digital amputation and 73 (43%) had experienced at least one episode of severe digital ischaemia as defined by requirement for intravenous vasodilator therapy, surgical debridement and/or amputation (Hider et al., 2001). Previous laser Doppler studies have demonstrated that microvascular flow in the digits is reduced in patients with SSc (Clark et al., 1999), reflecting the dermal microvascular damage which is well recognised in SSc. Thus, we need to identify therapies which will increase microvascular flow, preferably locally in the digits without causing systemic adverse effects.

Rather than iontophoresis of a chemical over a small area (as in earlier pathophysiological studies), we have developed a method to iontophorese chemicals over a whole finger. The purpose of this preliminary investigation was to test the hypothesis that vasoactive drugs (in this case ACh) could be administered to large areas without systemic side effects. Blood flow changes were monitored with laser Doppler imaging.

Materials and methods

Iontophoresis chamber

The iontophoresis chamber, constructed from two concentric cylinders (Figs. 1 and 2), is manufactured from PTFE. The outer, cylinder (140 mm height × 80 mm diameter) forms a solid container for the iontophoresis solution. The inner cylinder (120 mm × 40 mm) has a grid of holes to allow liquid to flow easily between this and the outer cylinder. The finger to be treated sits within the inner cylinder and the electrode (50 cm, 0.2 mm diameter, platinum wire, Goodfellow, Huntingdon, UK) is wrapped, in a spiral around the outside of the inner cylinder, to avoid patient contact. A lid fits over the top of the two cylinders and has an aperture over the inner cylinder ensuring that the finger cannot come into contact with the electrode.

Subjects

Ten healthy controls, 3 men, 7 women, median age 29 (range 24–40) years, participated in this pilot study. No subjects were known to suffer from cardiovascular disease. All patients and controls were asked to abstain from any vasoactive medication for 24 h prior to the study and from smoking and caffeine on the day of the study. The study was approved by the Salford and Trafford Local Research Ethics Committee.

All ten subjects were acclimatised to room temperature (23°C) over a 20-min period. Once acclimatised, the index finger of the non-dominant hand (2 right, 8 left) was

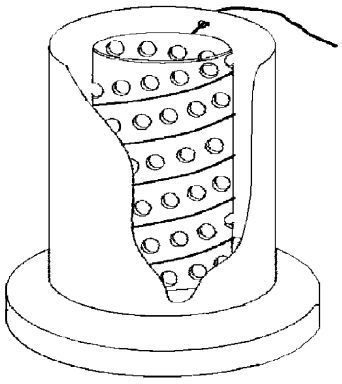

Fig. 1. Cutaway schematic of the iontophoresis chamber.