Nitric oxide donors and the skin: useful therapeutic agents?

**ABSTRACT**

Nitric oxide (NO) is involved in several processes in the skin, including wound healing, pigmentation and regulation of apoptosis. Pharmacological intervention with NO donors appears to be a promising treatment for conditions such as diabetic ulceration. In this issue of *Clinical Science*, Khan et al. describe the synthesis of a number of NO donors, based on nitrosylated thiosugars, structural changes in which altered the rate of NO release. The *in vivo* behaviour of one of the donors was then measured by laser Doppler blood flow measurements on the skin. The ability to tailor the pharmacokinetic behaviour of these drugs should be of interest in developing NO donors for clinical use.

Nitric oxide (NO) is surely the most protean of biological messengers, with examples of functions described ranging from control of vasodilatation [1] to cell cycle regulation, with effects on apoptosis [2], proliferation and differentiation [3], protein chemistry with matching of oxygen delivery to local anoxia [4], and even microbicidal activity [5]. The apparent simplicity of NO, and its biological potency, rapidly suggested it as a promising pharmacological agent, but capitalizing on the immense increase in knowledge in NO-related biology has been frustratingly slow. Structurally, there is no simpler biological agent, yet serendipity has played a larger part than design in developing therapies based on NO biology. Sildenafil was initially developed as an anti-hypertensive agent based on the known cGMP-enhancing effects of NO, until found to have an altogether different clinical role. The use of sublingual nitrates to treat angina was pioneered with no knowledge of NO release, and the centuries old use of nitrite, which releases NO and is microbicidal [6], to preserve meat is more thought of as a cultural and culinary practice than a practical use of NO effects. Salami and advanced biotech seem odd bedfellows.

The ubiquity of NO in mammalian physiology, although promising many pharmacological benefits, is at the same time an Achilles heel. The two major practical problems have been lack of specificity, resulting in numerous unwanted effects, and the lack of adequate pharmacokinetically appropriate and localized means of NO delivery. An example of the problems caused by lack of specificity has been the use of NO synthase (NOS) antagonists to treat septic shock. Although many of the altered haemodynamics are corrected, overall mortality is not reduced [7]. Targeting drug delivery to the site of action has involved such experimental technologies as adenoviral delivery, which, although effective in animal models [8], has all the practical and regulatory problems associated with gene therapy.

Using the skin as a target organ in pharmacological studies has many advantages. Topical administration delivers drugs directly to the site of action, at an effective dose, and usually with clinically insignificant systemic absorption. Indeed, many drugs applied to the skin in clinical practice, including corticosteroids, fluorouracil and retinoids, have significant side effects when used systemically, but minimally so as topical agents. Pharmacological and clinical effects can be easily measured in the skin, often without the need for complex instruments. Beyond this, though, the skin is an excellent organ for proof of concept studies. Using this paradigm, the effectiveness of high output NO as treatment for human infectious disease has been shown in studies in which topical acidified nitrite cured cutaneous fungal and viral disease [5,9], and clinically significant vasodilatation has been demonstrated by the reversal of the vasoconstriction of Raynaud’s disease and localized systemic sclerosis with topical NO-releasing formulations [10,11].

Specific functions of NO are dictated by localization and kinetics of release. Briefly, high output bursts of NO, such as are released by the chemical reduction of nitrite, seem ideal for microbicidal purposes [12], but not necessarily for other roles. In this issue of *Clinical Science*

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Science, Khan et al. [13] describe the synthesis of a range of NO donors offering different pharmacokinetic properties, and in which a sensitive bioassay, laser Doppler imaging, was used to define the NO release properties of one of the synthesized donors. S-Nitrosated thiosugars release NO spontaneously, which, in theory, should ensure more consistent NO release than donors such as glyceryl trinitrate (GTN) which need to be metabolized. By altering the number of acetyl side arms, lipophilicity and thus NO release could be modified. The importance of the paper by Khan et al. [13] is that it offers the possibility of designing an NO donor, based on a safe thiosugar base, and tailored to specific clinical requirements.

NO donors have a range of potential uses in the skin. The benefits of topical NO have already been demonstrated in Raynaud’s syndrome [11], but other conditions with diminished skin blood flow, such as poorly vascularized skin grafts, could also benefit. An exciting prospect is the potential to improve diabetic wound healing. Diabetic foot ulcers are an enormous and growing problem, having cost Medicaid in the U.S.A. $1.5 billion [14] in 1995. Wound healing is delayed in both inducible NOS (iNOS)- [15] and endothelial NOS (eNOS)- [16] knockout mice, and poor wound healing in diabetic mice is associated with reduced eNOS protein [17] and wound NO synthesis [18]. Wound healing in diabetic mice is improved by both supplementation with l-arginine, the precursor of NO [19], and by application of a topical NO donor [20]. With such a widespread clinical problem, a treatment producing even a small improvement in healing would be significant [14], and this animal data is highly suggestive of NO-based therapies being worthy candidates for clinical studies.

eNOS-knockout mice, as well as poor wound healing, also show greatly increased dermal and epidermal apoptosis on UVB irradiation [2]. Whether NO reduces DNA damage, and thus the need for safe disposal of potentially malignant cells, or deleteriously blocks apoptosis of mutated cells remains under investigation, but again suggests clinical roles for NO donors. On a purely cosmetic level, topical NO may be a novel tanning agent. In vitro data [21] show that keratinocyte-derived NO drives melanogenesis, and guinea-pigs treated with topical NOS antagonists have reduced pigmentation [22]. Could topical NO offer a sun and skin cancer-free path to a tan and at the same time prevent UV-induced cell death?

This is an exciting time to be engaged in applied clinical skin research. The paper by Khan et al. [13] adds to the armamentarium of NO donors with discrete, but well defined, characteristics. A number of cutaneous diseases in which NO is involved have been described. The stage is now set for the clinical studies answering the which, what and how questions. Which disease, what NO donor, and how it should be used.

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REFERENCES


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