The alginogel Flaminal®: an overview of the evidence and use in clinical practice

KEY WORDS
- Antimicrobial
- Debridement
- Flaminal®
- TIME framework
- Wound bed preparation

The precise positioning of wound care products is an invaluable aid for the clinician, especially where there may be confusion due to the number of similar products. Flaminal® has been positioned as an 'enzyme alginogel' by an international panel of experts. In this respect it remains the only product in the category. Careful and accurate positioning is necessary in order that the maximum clinical value can be derived and products used to best effect. The components of Flaminal: alginate, enzymes, and glycol, are designed to provide antimicrobial broad-spectrum action, fluid uptake and moist wound conditions. To best illustrate clinical applications the T.I.M.E. framework is used to guide the clinician. Thus Flaminal may be used, after careful wound assessment, for bioburden control, creation of a moist environment, and promotion of autolytic debridement: a unique combination that will be appropriate for many chronic wounds, and optimal resource use.

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The concept of wound bed preparation (WBP) is a holistic approach to wound assessment that has stood the test of time and has been widely incorporated into routine clinical practice (Leaper et al, 2012). WBP has been refined and expanded into a clinical framework commonly known by the acronym TIME (Tissue, Infection/inflammation, Moisture imbalance, Edge of wound) to assist with clinical implementation by adding specifics to the assessment process (Dowsett and Newton, 2005). This is designed to target treatment of wound characteristics and patient-centred concerns, such as pain management, thus optimising the components of local wound care.

Where and how, in practical terms, does TIME guide the clinician? In essence, it is by focussing on specific wound characteristics, the requirement for the clinician to address priorities and implement treatments accordingly (Dowsett and Newton, 2005). Gone are the days when a single dressing can be claimed to act as a panacea, dealing with all requirements of the wound throughout its lifetime. With increasing understanding of wound healing biology, we appreciate that such products are fictional. Now we are urged to tailor the treatment according to the stage of healing and the needs of the patient. Furthermore, the focus has recently been on the function (mode of action) of the treatment, as opposed to its composition (van Rijswijk, 2006; Cutting, 2011). This does, however, depend on the clinician's awareness of treatment components and indications for use.

The Flaminal® (Aspen Pharmacare) products, available as Forte® (5% w/w [mass fraction] alginate) and Hydro® (3.5%) have a triple action attributable to the components of alginate, glucose oxidase/lactoperoxidase enzyme system, and to the physical gel formulation (White, 2006). They have been commercially available for 12 years, during which time a number of clinical and scientific studies have been conducted (Durante, 2012; Cooper, 2013; Grzela et al, 2014).

The Flaminal products have been designated 'enzyme alginogels' by a panel of experts convened to clarify their clinical positioning (Beele et al, 2012). This group went on to define precisely how the composition relates to the clinical mode of action — within the TIME construct — for the benefit of clinicians.

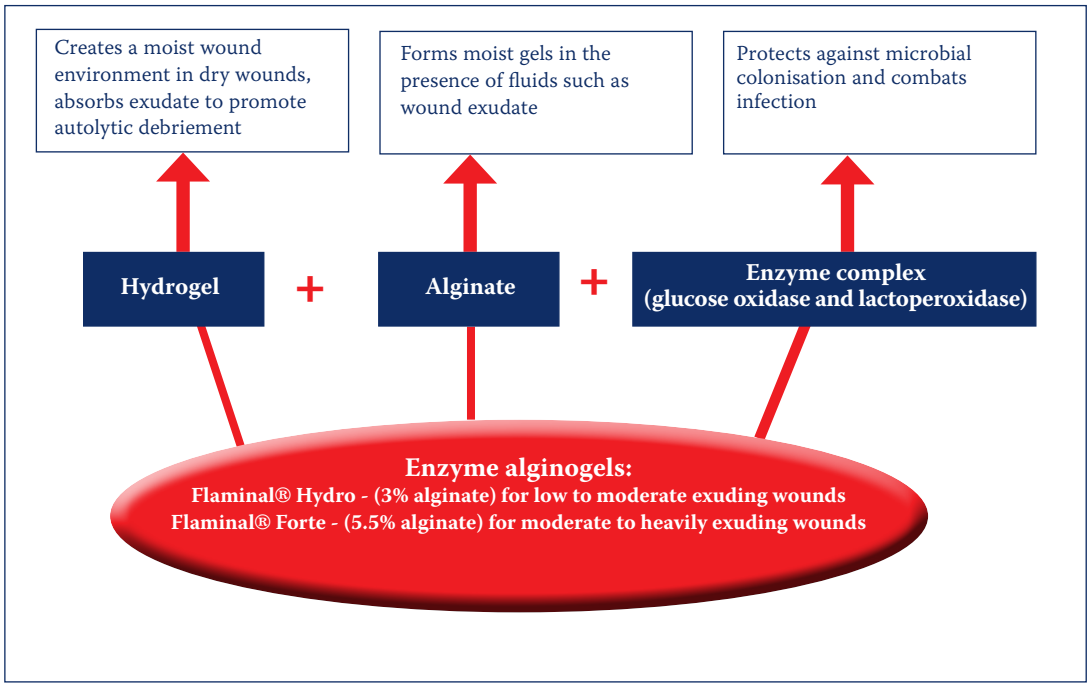

Figure 1. The Flaminal® enzyme system of glucose oxidase and lactoperoxidase generates naturally occurring antibacterial and anti-biofilm agents

THE ACRONYM — LETTER BY LETTER

The 'T' in TIME signifies 'tissues within the wound'. The Flaminal alginate component interacts with exudate to form a moist gel; an environment conducive for autolytic debridement (Durante, 2011). This is further enhanced by the humectant properties of polyethylene glycol in the Flaminal formulation.

The 'I' of TIME denotes inflammation and/or infection. The Flaminal enzyme system of glucose oxidase and lactoperoxidase generates naturally occurring antibacterial and anti-biofilm agents (*Figure 1*). Furthermore, the action to inhibit matrix metalloproteases (MMPs), known to be contributing factors in wound 'chronicity' via uncontrolled inflammation (Walcott et al, 2008; Bjarnsholt, 2013) is also a significant clinical factor (Grzela et al, 2014).

The 'M' refers to 'moisture imbalance', or 'maceration'. The high fluid absorbency capacity of the alginate incorporates excess exudate into a gel — thus 'controlling' the fluid balance within the wound (Thomas, 2000; Cutting and White, 2002; White and Cutting, 2003).

Finally, the 'E' focuses on the 'edge of the wound', or 'epithelium'. This physical feature is a marker of healing as a well-defined and advancing epithelium is a positive sign the wound is progressing towards closure. The delicate new tissues in such wounds are friable and must be protected.

FLAMINAL — SCIENTIFIC EVIDENCE

Using the TIME framework once more, scientific studies can be used to show antimicrobial and anti-inflammatory actions *in vitro* and *ex vivo*. Moisture control or fluid uptake can also be measured *in vitro,* according to standardised test methods. The 'E' edge or epithelium aspect of TIME can be supported by *in vitro* cytotoxicity studies on cells and tissues that show Flaminal to be safe, non-toxic to the advancing new growth (Vandenbulke et al, 2006).

The antimicrobial action of Flaminal has been tested exhaustively using combinations of *in vivo* and *in vitro* experiments, and clinical isolates (Vandenbulcke et al, 2006; De Smet et al, 2009).

Since the identification of bacterial biofilms in chronic wounds (Serralta et al, 2001), there has been considerable debate as to their clinical

Table 1. Average cost of burns and scalds treatment	
Cost of a bed day in a specialist burns facility, to treat a minor burn or scald	£750
Cost of a bed day in a burns centre intensive care unit, to treat a very serious burn or scald	£2,500
Average cost of inpatient treatment for a minor scald (covering less than 10% of the body)	£1,850

significance. It is widely accepted that the majority of chronic wounds will contain some degree of biofilm (Walcott et al, 2008), and that this delays healing. It must, therefore, be inhibited, or disrupted, if healing is to proceed normally (Walcott et al, 2009).

The concept of biofilm-based wound care, achieved through robust debridement and subsequent use of specific anti-biofilm agents, has emerged (Rhoads et al, 2008), but is yet to gain universal acceptance. While evidence supports debridement, clinicians often appear reticent to use aggressive approaches, perhaps through an innate desire not to damage the wound bed. In which case, debridement by non-traumatic means can be effective, but slower, depending on the degree of devitalised tissues in the wound. In such cases, autolysis is recommended (Hofman, 2007). This can be achieved using an enzyme alginogel, as has been demonstrated in numerous clinical reports on a variety of wounds (Durante, 2011).

As there are no valid means of evaluating agents for anti-biofilm activity *in vivo*, *in vitro* laboratory studies have been used. Flaminal has been evaluated in a study of biofilms of *Staphylococcus* (S) *aureus*, meticillin-resistant *S aureus* and *Pseudomonas aeruginosa* (Cooper, 2013). The enzyme system was found to prevent the formation of biofilms at low concentration (≤0.5% w/v [mass concentration]) and, at higher concentration, to inhibit established biofilm. The concentration in Flaminal exceeds this comfortably.

The uncontrolled inflammation observed in 'chronic' wounds is attributed the excess activity of matrix metalloprotease enzymes (MMPs; especially MMPs -2 and -9) in the wound bed, resulting in compromised healing (Rayment and Upton, 2009; Amato et al, 2013). In recent years, a number of dressing products have been claimed to have a modulating action on MMPs, but there are very few studies which monitor MMPs *in vivo* and correlate levels with clinical changes in the wound. Flaminal has been evaluated for MMP modulation in a clinical study on venous leg ulcers, and from *in vitro* biochemistry studies (Grzela et al, 2014). Results show a steady, sustained decrease in MMPs 2 and -9 over the 4-week treatment period, which coincided with a decrease in wound area.

RECENT FLAMINAL CLINICAL EVIDENCE

A number of purely clinical and clinical-scientific studies have now been published, including Lacarrubba et al, 2005; Dela Brassinne et al, 2006; Van den Plas et al, 2009; and Kyriopoulos et al, 2010. There also exists long-term experience in major wound centres, where wound care, dermatology and burns specialists have amassed a wealth of knowledge through the treatment of many hundreds of patients over the past decade (White, 2006, Beele et al, 2012; White, 2014).

In a single-centre case series, 23 patients with wounds of diverse aetiology were treated with the enzyme alginogel 6 (Durante, 2012). Flaminal was applied to patients who were treated through a scheduled protocol and assessed at 14 days, 30 days and 60 days. The median wound age before application of the enzyme alginogel was 292 days, with 18 of the 23 wounds being distinctly 'chronic' in aetiology. Four wounds were clinically infected at baseline; of these, three were negative by day 14 and the fourth by day 30. After 2 months, a pronounced decrease in surface and volume of all treated wounds was noted ($p<0.001$).

In a retrospective study on two groups of 30 patients with burns, Hoeksema et al (2013) stratified burns to be treated with either Flaminal or with silver sulfadiazine 1% cream, according to depth. Both the superficial burns ($p=0.013$) and deep partial thickness burns ($p=0.04$) healed faster with Flaminal. This was a key factor in achieving a mean 7-day reduction in hospital stay with the associated potential cost savings (*Table 1*).

DISCUSSION

Matching the choice and use of wound dressings to the requirements of the wound is a challenge. The varied presentations of wounds make prioritising the treatment complicated. Wound exudate and infection, or at least critical colonisation, are the most common management problems. The clinician will often be confronted with a wound that requires debridement, bioburden control, and exudate management. Dressing selection becomes difficult, one dressing or more may be required. It is not uncommon to encounter wounds that contain a variety of tissues. Typically, clinicians will employ the logic of dealing with the most pathological feature first. Failure to do this leads to compromise with wound dressing selection or multiple dressings being applied.

The alginogel Flaminal, in its two-concentration of alginate presentations, is designed to make wound management simpler without compromising clinical efficacy. The various modes of action outlined, supported by clinical and scientific evidence, makes Flaminal an ideal product for use in conjunction with the WBP and TIME frameworks. An extensive body of scientific and clinical evidence now exists to support these products. WUK

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