Flaminal®: a novel approach to wound bioburden control

It is now widely accepted that wound bioburden, in chronic wounds in particular, will often require control. This is best achieved by the use of appropriate topical agents, available in safe, sustained release, broad-spectrum forms. The ancillary functions, if any, of a topical antimicrobial are becoming important health economic factors. Resistance and its development is also of great interest. The new Flaminal® products are novel formulations with broad-spectrum antimicrobial activity which have the capacity to control exudate and promote rapid wound healing. These will be available on the Drug Tariff from October 2006.

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KEY WORDS
Topical antimicrobial Glucose oxidase Lactoperoxidase Hydrogen peroxide Wound bioburden

Modern wound management requires that systematic assessment and treatment approaches be adopted in order to address the needs of the wound in a logical way. The frameworks of wound bed preparation using the TIME acronym (Dowsett and Ayello, 2004) and Applied Wound Management (Gray et al, 2006) are two such systems. Both require the assessment and management of the tissues in the wound (e.g. slough, necrosis), the control of exudate and an assessment and control of bioburden, as appropriate.

In recent years, research has increased our understanding of the role bacteria play in the chronic wound. For example, the wound bioburden has been ranked according to the Wound Infection Continuum (Kingsley, 2001) and to the principles of Wound Bed Preparation (Schultz et al, 2003). It is recognised that under certain circumstances, the bioburden will be a contributing factor to delayed healing (White, 2006) in the state now known as critical colonisation (White et al, 2006), or to overt infection. Wound bioburden in these states can be controlled by topical or systemic therapy with topical antimicrobials being the approach of choice for critical colonisation and local infection (Kingsley, 2003; White et al, 2006).

Bacteria in chronic wounds have been associated with the development of an ‘immunopathological’ state (Heinzelmann et al, 2002). The various virulence determinants of typical wound bacteria e.g. Pseudomonas aeruginosa and Staphylococcus aureus (Bowler et al, 2001) have been listed and linked, to some degree, with the signs and symptoms of the wound (Cooper, 2003). Notable among these is the development of the biofilm.

Complex communities of microorganisms encased in slime and attached to surfaces are known as biofilms (Costerton et al, 1995; 1999). They probably represent the most common form of existence for microbes in natural environments (Cooper, 2006). Biofilms have been described in wounds (Serralta et al, 2001; Boutli-Kasapidou et al, 2006). It is likely that many — possibly all — chronic wounds will harbour biofilms (Costerton, 2006), and in the typical chronic wound, slough is associated with biofilm formation. However, not all biofilms in wounds will necessarily be formed in the presence of slough. It has been shown that some wound antimicrobials, notably silver, iodine compounds, honey (Akyama et al, 2004; Chaw et al 2005; White, 2005) maggots and electrical current (Van der Borden et al, 2004a,b) have the capacity to disrupt the biofilm.

Antimicrobial wound dressings
Hydrogel dressings are either sheet presentations or amorphous gels supplied in tubes. They are intended to create a moist wound environment in dry wounds, and absorb exudate in exuding wounds to promote autolytic debridement, i.e. they either donate or absorb moisture (Thomas and Hay, 2006).

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Figure 1. Flaminal® and Flaminal® Hydro are available in 15g tubes.
1996). Both presentations have been available in the UK for more than 20
years and both have become widely
used in clinical practice (Flanagan, 1995).
Flaminal® hydrogels are different because
they are based upon gelled alginate and
not on other polymers (Figure 1).

The recent developments in
antimicrobial wound dressings have
tended to follow the prevailing fashion,
i.e. the use of silver (Silver et al, 2006).
The arrival of medical-grade honey,
with a CE mark and Drug Tariff listing,
have been a welcome alternative
(White, 2005). Flaminal® hydrogels
use the enzymes glucose oxidase
and lactoperoxidase to control the
bioburden in a similar way to honey.
Honey works as an antimicrobial
by using its ‘built-in’ glucose oxidase
enzyme system for generating hydrogen
peroxide (Figure 2) (Molan, 2005).
Hydrogen peroxide is a non-specific
antimicrobial that kills all micro-
organisms (Russell, 2002). This agent,
used for many years as a solution to
clean sloughy wounds (O’Brien 2002), is
an antimicrobial by virtue of its
oxidising activity. The use of hydrogen
peroxide in solution form is now
largely history. It is, however, the basic
mechanism employed by phagocytic cells
in fighting micro-organisms (Baboir, 1984; O’Brien, 2000).

Phagocyte antimicrobial action
Phagocytes (neutrophils, macrophages,
eosinophils) destroy pathogens in part
by ‘respiratory burst’ which is the rapid
production of oxygen metabolites
such as superoxide, peroxide, hydroxyl
radicals and possibly singlet molecular
oxygen (Baboir, 1984; Clark, 1990).
The antimicrobial effectiveness of
hydrogen peroxide is increased
greatly by peroxidase. One enzyme
that can be used for this purpose is
myeloperoxidase; this is present in
neutrophils and monocytes but is lost
when the monocyte matures into a
macrophage. Further, peroxidase-coated
organisms are more readily
killed when ingested by macrophages
than are uncoated organisms (Klebanoff
et al, 1983).

Flaminal® and Flaminal®
Hydro both contain an
enzyme complex containing
glucose oxidase and
lactoperoxidase that protects
against microbial colonisation
and combats infection.
Thus both gels can be used
clinically to address the
tissues in the wound, exudate
or moisture, and bioburden.

Flaminal® and Flaminal®
Hydro alginate
gel dressings
Flaminal® and Flaminal® Hydro (Flen
Pharma, Belgium; Ark Therapeutics,
UK) are new antimicrobial, amorphous
alginate gel dressings which are based
upon alginate, an agent well-known
in modern wound management for
its capacity to form moist gels in the
presence of fluids such as wound
exudate. Both Flaminal® and Flaminal®
Hydro are available in 15g tubes
(Figure 1). Flaminal® is designed for
use on moderate to heavily exuding
wounds and has a high alginate content,
whereas Flaminal® Hydro is intended
for more lightly exuding wounds and
contains less alginate. Both contain an
enzyme complex containing glucose
oxidase and lactoperoxidase that
protects against microbial colonisation
and combats infection. Thus both
gels can be used clinically to address
the tissues in the wound, exudate or
moisture, and bioburden.

Flaminal® hydrogels possess some of
the attributes of the ideal antiseptic, such
as slow-release and sustained release of
the antimicrobial, non-toxic, and unlikely
to select for resistance.

Both are intended to promote
moist wound healing and, by association,
antulotic debridement. In addition, and
by virtue of the content of glucose
oxidase and lactoperoxidase both
will also have the capacity to control
the bioburden of the wound in a safe,
sustained fashion. This is useful for the
management of all wounds left to heal
by secondary intent, particularly chronic
wounds, as they are invariably colonised.

Lactoperoxidase
Flaminal® contains lactoperoxidase
which is an enzyme extracted from
milk and acts as an important natural
antimicrobial (Banks et al, 1986). It
has been shown to be bacteriostatic
against Gram-positive organisms and
exhibits pH-dependent bactericidal
action against Gram-negative organisms
in the presence of hydrogen peroxide
and thiocyanate. Lactoperoxidase offers
the following benefits in chronic wound
management:

\begin{itemize}
  \item Antimicrobial properties
  \item Resistance to proteolysis
\end{itemize}

Peroxidases are enzymes that belong
to the natural non-immune defence
systems (Tafazoli and O’Brien, 2005)
found in milk and in the secretions of
exocrine glands such as saliva, tears,
testinal secretions, cervical mucus and
the thyroid.

The mammary fluids colostrum
and milk, deliver nature’s first host
defences upon the first feed after birth.
Lactoperoxidase also helps maintain
the sterility of milk (Clare et al, 2003; Florisa
et al, 2003). In tears it provides, together
with lysozyme, mechanisms for keeping
the eye free from infection (Bron and
Seal, 1986). In the Airways the secretion
of mucus provides a defence against
infection. Mucus contains enzymes,
including lactoperoxidase which is

Figure 2. Glucose oxidase and its mode of action.
identical to that found in breast milk; this, in conjunction with secretions containing thiocyanate (SCN\textsuperscript{–}), form a peroxidase system that protects against infection from bacteria, fungi and viruses (Conner et al, 2002).

The salivary gland is a rich source of peroxidases (Banerjee and Datta, 1986; Ihalin et al, 2006). Lactoperoxidase in saliva (Banerjee and Datta, 1986) serves to combat bacteria, particularly Streptococcus mutans (Thomas et al, 1983) and to inhibit acid formation in dental plaque (Tenovuo et al, 1981).

Activity
Peroxidases have no antimicrobial activity themselves, but in the presence of the specific co-factors they constitute an important defence system when they are in liquid solution. These co-factors are hydrogen peroxide and a halide (e.g. iodine, chlorine) or pseudo-halides (e.g. thiocyanate) depending on the specific enzyme. The oxidation product OX \textsuperscript{−} is a short-lived oxidizing agent which will react with thiol groups (\textsuperscript{−}SH) of the enzymes essential for the metabolism of bacteria. This defence mechanism plays a key role in protecting mucus membranes against bacterial invasion.

Lactoperoxidase system
The lactoperoxidase system can produce, in appropriate conditions, molecules such as hypothiocyanite (OSC\textsubscript{N} \textsuperscript{−}), hypoiodide (OI\textsuperscript{−}) or a mixture of both (Ghibaudi and Laurenti, 2003). These molecules are powerful antimicrobial agents against bacteria, viruses and yeasts. A non-exhaustive list of susceptible organisms includes the following:

Bacteria:

\begin{itemize}
  \item Escherichia coli
  \item Yersinia enterocolitica
  \item Klebsiella pneumoniae
  \item Streptococcus agalactiae
  \item Streptococcus mutans
  \item Staphylococcus aureus (including methicillin-resistant S. aureus)
  \item Salmonella species
  \item Shigella sonnei
  \item Listeria monocytogenes
  \item Acinetobacter species
  \item Neisseria species
  \item Haemophilus influenzae
\end{itemize}

Viruses:

\begin{itemize}
  \item Herpes simplex virus
  \item Immunodeficiency virus
  \item Respiratory syncytial virus
\end{itemize}

Yeast: Candida albicans.

Clinical evidence for the effectiveness of Flaminal\textsuperscript{®} gels
Both Flaminal\textsuperscript{®} gels have been tested in vitro and in vivo for antimicrobial activity, and for cytotoxicity in vitro (Vandenbulcke et al, 2006) and in a randomised comparative clinical trial. In the clinical trial, de la brassinne et al (2006) compared Flaminal\textsuperscript{®} with IntraSite gel\textsuperscript{®} (Smith & Nephew, Hull) in patients with leg ulcers. Two groups of 10 patients that had a balanced total wound size were treated for 28 days. Each wound was assessed weekly for the surrogate endpoints of area and volume. Results show both groups to have area reduction over time with Flaminal\textsuperscript{®} having a statistically significant reduction at day 14 (p<0.01) and at day 28 (p<0.01), representing a 63\% reduction in size for Flaminal\textsuperscript{®} vs 19\% for IntraSite (Figure 3). Similarly, the volumes of both groups also decreased over time. However, for this parameter the difference was greater for Flaminal\textsuperscript{®} at day 7 (p<0.001), and at days 14 (p<0.001) up to day 28 (p=0.02), representing an 80\% vs 41\% total volume reduction. The correlation between volume and area was highly significant, expressed as a Pearson coefficient for the Flaminal\textsuperscript{®} group 0.843; p<0.001 (Figures 3 and 4).
In vitro cytotoxicity assays, conducted on human keratinocytes in culture, showed Flaminal® gels to be essentially non-toxic. The antimicrobial activity in vitro showed that both Flaminal® gels reduced a range of Gram-negative and Gram-positive organisms by more than seven log_{10} units in 48 hours. E. coli and S. aureus were both reduced by over two log_{10} values in 45–60 minutes while C. albicans was reduced by two log_{10} in three hours (Figures 5, 6, 7). In vivo, the sampling of wounds before and after treatment with Flaminal® showed a significant decrease in the eradication of species isolated (p=0.018). This included complete eradication of C. albicans, P. aeruginosa and S. pyogenes among others (Vandenbulcke et al, 2006).

Conclusions
From the available laboratory and clinical evidence it is clear that the Flaminal® products are safe and effective both clinically and microbiologically. They offer an alternative to the current antimicrobials insofar as they have exudate absorptive capacity, they promote autolytic debridement, they have a broad spectrum of antimicrobial activity with a very low propensity for resistance, and are safe to use on the newly-growing tissues of the wound bed.

The combination of glucose oxidase with lactoperoxidase serves to provide a sustained source of safe and effective broad-spectrum antimicrobial action in a manner similar to our own natural white cell defences. These new and unique additions to the UK Drug Tariff offer the clinician practical alternatives to existing wound treatments.


Banks JG, Board RG, Sparks NH (1986) Natural antimicrobial systems and their

Key Points

- Flamin® hydrogels offer a novel antimicrobial action with exudate control.
- The control of wound bioburden by topical applications is important in critical colonisation, and local infection in wounds healing by secondary intent.
- Flamin® has a broad spectrum of antimicrobial action including rapid kill of MRSA.
- Clinical data indicates that Flamin® is effective in reducing wound depth and area in chronic leg ulcers.
- Flamin® has a very low propensity for resistance selection.
In drier/granulating wounds, Flaminal should be changed every 34 days. The dressing can stay in place for as long as the gel structure is intact: 14 days, depending upon the amount of exudate. [1] White R. Flaminal: A novel approach to wound bioburden control, Wounds UK 2006, 2 (3): 6469. TAPS No. PP7788 FD10115. www.aminalaustralia.com ALWAYS READ THE LABEL AND USE AS DIRECTED. If symptoms persist consult your doctor or healthcare professional. Flen Pharma NV Blauwesteenstraat 87, B-2550 Kontich, Belgium www.enpharma.com : Trademark of Flen Pharma Aspen Pharmacare Australia Pty Limited ABN 51 Flaminal®: A novel approach to wound bioburden control. Article. Sep 2006. Richard White.Â Models such as the TIME framework â€“ Tissue management, Inflammation and infection control, Moisture balance, Epithelial (edge) advancement â€“ offer a logical and systematic approach to wound bed assessment (Falanga, 2004; Dowsett and Ayello, 2004). Table 1 summarises the disturbances in wound bed remodelling associated with each stage of the TIME framework and the relevant treatment approaches. However, the clinical reality is that clinicians often have to deal with several aspects of the TIME framework at the same time, which requires ongoing assessment and realignments in treatment, often usi