World Wide Wounds

Honey as a topical antibacterial agent for treatment of infected wounds

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Published: December 2001
Last updated: November 2001
Revision: 1.0

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Keywords: honey; wound infection; wound dressings; vancomycin-enterococci (VRE); methicillin-resistant staphylococcus aureus (MRSA); Pseudomonas.

Key Points

1. Honey is a traditional topical treatment for infected wounds. It can be effective on antibiotic-resistant strains of bacteria.
2. Honey is produced from many different floral sources and its antibacterial activity varies with origin and processing. Honey selected for clinical use should be evaluated on the basis of antibacterial activity levels determined by laboratory testing.
3. The antibacterial properties of honey include the release of low levels of hydrogen peroxide. Some honeys have an additional phytochemical antibacterial component.
4. Many authors support the use of honey in infected wounds and some suggest its prophylactic use on the wounds of patients susceptible to MRSA and other antibiotic-resistant bacteria.

Abstract

Honey is an ancient remedy for the treatment of infected wounds, which has recently been 'rediscovered' by the medical profession, particularly where conventional modern therapeutic agents are failing. There are now many published reports describing the effectiveness of honey in rapidly clearing infection from wounds, with no adverse effects to slow the healing process; there is also some evidence to suggest that honey may actively

promote healing. In laboratory studies, it has been shown to have an antimicrobial action against a broad spectrum of bacteria and fungi. However, further research is needed to optimise the effective use of this agent in clinical practice.

Introduction

Honey was used to treat infected wounds as long ago as 2000 years before bacteria were discovered to be the cause of infection. In c.50 AD, Dioscorides described honey as being "good for all rotten and hollow ulcers" [1]. More recently, honey has been reported to have an inhibitory effect to around 60 species of bacteria including aerobes and anaerobes, gram-positives and gram-negatives [2]. An antifungal action has also been observed for some yeasts and species of *Aspergillus* and *Penicillium* [2], as well as all the common dermatophytes [3]. The current prevalence of antibiotic-resistant microbial species has led to a re-evaluation of the therapeutic use of ancient remedies, including honey[4].

Osmotic effect

The antibacterial property of honey was first recognised in 1892 by van Ketel [5]. It has often been assumed that this is due entirely to the osmotic effect of its high sugar content [6], [7], [8], [9], [10], [11], [12], [13]. Honey, like other saturated sugar syrups and sugar pastes, has an osmolarity sufficient to inhibit microbial growth [14], but when used as a wound contact layer, dilution by wound exudate reduces the osmolarity to a level that ceases to control infection [14], [15]. However, it has been shown that wounds infected with *Staphylococcus aureus* are quickly rendered sterile by honey [16], [17], [18], [19]. Honeys selected to have a median level of antibacterial activity have been found to prevent growth of *Staphylococcus aureus* if diluted by a further 7-14 fold beyond the point where their osmolarity ceases to be inhibitory [20].

The fact that the antibacterial properties of honey are increased when diluted was clearly observed and reported in 1919 [21]. The explanation for this apparent paradox came from the finding that honey contains an enzyme that produces hydrogen peroxide when diluted [22]. This agent was referred to as 'inhibine' prior to its identification as hydrogen peroxide [23]; the term 'inhibine number' was coined as a measure of the relative antibacterial potency of different honeys, it being the number of steps by which a honey could be diluted and still inhibit bacterial growth [24].

The importance of the additional antibacterial activity of honey is demonstrated in comparisons between the therapeutic effects of honey and sugar. In an experimental study conducted on burns created on the skin of pigs [25], there were fewer bacterial colonies seen histologically in wounds treated with honey compared with those treated with sugar, fewer micro-pustules in the neo-epidermis, and fewer bacteria seen in the eschar of the honey-treated wounds. There has also been a clinical case report of a discharging deep pressure sore not responding to various treatments, including dressing with sugar, which was completely healed in six weeks when dressed with honey [26]. Frequent changes of sugar dressings are also necessary to maintain a therapeutic action, compared with fewer changes of honey dressings [6].

Hydrogen peroxide activity

Hydrogen peroxide is a well-known antimicrobial agent, initially hailed for its antibacterial and cleansing properties when it was first introduced into clinical practice [27]. In more recent times it has lost favour because of inflammation and damage to tissue [28], [29],

[30]. However, the hydrogen peroxide concentration produced in honey activated by dilution is typically around 1 mmol/l [2], about 1000 times less than in the 3% solution commonly used as an antiseptic. The harmful effects of hydrogen peroxide are further reduced because honey sequesters and inactivates the free iron which catalyses the formation of oxygen free radicals produced by hydrogen peroxide [31] and its antioxidant components help to mop up oxygen free radicals [32]. Studies in animal models have demonstrated that honey reduces inflammation (seen histologically), compared with various controls, in deep [25] and superficial [33] burns and in full-thickness wounds [34], [35], [36], [37].

Although the level of hydrogen peroxide in honey is very low it is still effective as an antimicrobial agent. It has been reported that hydrogen peroxide is more effective when supplied by continuous generation with glucose oxidase than when added in isolation [38]. A study with *Escherichia coli* exposed to a constantly replenished stream of hydrogen peroxide, showed that bacterial growth was inhibited by 0.02-0.05 mmol/l hydrogen peroxide, a concentration that was not damaging to fibroblast cells from human skin [39].

Phytochemical component

In some honeys treated with catalase to remove the hydrogen peroxide activity, additional non-peroxide antibacterial factors have been identified [40], [41], [42], [43], [44]. Manuka (Leptospermum scoparium) honey from New Zealand has been found to have substantial levels of non-peroxide antibacterial activity [40]. This is associated with an unidentified phytochemical component, although further investigations are still to be completed. A similar finding has been made in honey from an unidentified Leptospermum species in Australia, 'jellybush' [C. Davis, Queensland Department of Primary Industries: personal communication].

Increased lymphocyte and phagocytic activity

The clearing of infection seen when honey is applied to a wound may reflect more than just antibacterial properties. Recent research shows that the proliferation of peripheral blood B-lymphocytes and T-lymphocytes in cell culture is stimulated by honey at concentrations as low as 0.1%; and phagocytes are activated by honey at concentrations as low as 0.1% [45]. Honey (at a concentration of 1%) also stimulates monocytes in cell culture to release cytokines, tumour necrosis factor (TNF)-alpha, interleukin (IL)-1 and IL-6, which activate the immune response to infection [46].

In addition, the glucose content of honey and the acid pH (typically between pH3 and pH4) may assist in the bacteria-destroying action of macrophages [47].

Anti-bacterial potency

Honey is produced from many different floral sources and its antimicrobial activity varies with origin and processing. Dioscorides (c.50 AD) stated that a pale yellow honey from Attica was the best [1]; Aristotle (384-322 BC), when discussing different honeys, referred to pale honey as being "good as a salve for sore eyes and wounds" [48]. Today, the strawberry-tree honey of Sardinia is valued for its therapeutic properties [49]; in India lotus honey is said to be a panacea for eye diseases [50]; honey from the Jirdin valley of Yemen is revered in Dubai for its therapeutic properties [51]; and manuka honey has a long-standing reputation in New Zealand folk-lore for its antiseptic properties.

A wide range of MIC values (the minimum concentration of honey necessary for complete inhibition of bacterial growth) have been reported in studies comparing different honeys

tested against single species of bacteria: from 25% to 0.25% (v/v) [52]; >50% to 1.5% (v/v) [5]; 20% to 0.6% (v/v) [53]; 50 to 1.5% (v/v) [54].

A survey of 345 samples of New Zealand honeys from 26 different floral sources found a large number with low activity (36% of the samples had activity near or below the level of detection in an agar diffusion assay), the activity of the rest being distributed over a 30-fold range of activity [40]. An unpublished survey of 340 samples of Australian honeys from 78 different floral sources found 68.5% of the samples had activity below the level of detection in an agar diffusion assay [C. Davis, Queensland Department of Primary Industries: Personal communication].

The failure to take into account the large variance in antibacterial potency of different honeys may contribute, in part, to the large discrepancy in results reported between hospitals using honey in similar ways. Some have reported rapid clearance of infection in a range of different types of wound, with all wounds becoming sterile in 3-6 days [17], [19], 7 days [16], [55], [56] or 7-10 days [18]. Others have reported bacteria still present in wounds after 2 weeks [57], [58], 3 weeks [59], [60], [61], and 5 weeks [62].

A randomised controlled trial found early tangential excision and skin grafting to be superior to honey in controlling infection in the treatment of moderate burns [63]. The honey used in this trial however was not standardised and the same author had reported good results with honey in the treatment of burns in a previous study [64].

Laboratory investigations

The only studies that give a reasonable indication of the likely usefulness of honey for treatment of infected wounds are those conducted with standardised honeys. Two types of standardised honey have been subjected to laboratory investigations. These are a typical (near median activity) manuka honey from New Zealand, with activity due to a phytochemical component and a typical (near median activity) multifloral honey with activity due to hydrogen peroxide. In one study the hydrogen peroxide component was removed from the manuka honey, but generally manuka honey was selected for its phytochemical component and low hydrogen peroxide component. The antibacterial potency of these two honeys are described below.

The non-peroxide antibacterial activity of the typical (near median activity) manuka honey was tested against seven species of bacteria and compared with the typical (near median activity) honey with hydrogen peroxide activity. The MIC (minimum inhibitory concentration) of the honeys was found to range from 1.8% to 10.8% (v/v), indicating that the honeys had sufficient antibacterial potency to stop bacterial growth if diluted at least nine times, and up to 56 times in the presence of *Staphylococcus aureus* [65], the most common wound pathogen. In another study with 58 clinical isolates of *Staphylococcus aureus* [20] the MIC ranged from 2% to 4% (v/v). In a study of 20 isolates of *Pseudomonas* from infected wounds [66] the MIC of these two honeys was found to range from 5.5% to 9.0%.

Antibiotic-resistant strains have also been studied and found to be as sensitive to honey as the antibiotic-sensitive strains of the same species. The MIC for 82 epidemic strains of methicillin-resistant staphylococcus aureus (MRSA) was found to range from 3% to 8% (v/v) [67]. In this study 56 strains of vancomycin-resistant enterococci (VRE) were also examined, and the MIC values were found to range from 5% to 10% (v/v) for the manuka honey and from 8% to 20% for the second honey. In a further study the MIC values for eight strains of MRSA isolated from swabs collected from acute and chronic wounds, and 16 strains of VRE isolated from the hospital environment were all below 10% (v/v) for both honeys, as were the MIC values for 15 strains of beta-haemolytic streptococci, and seven

strains of vancomycin-sensitive enterococci isolated from swabs collected from acute and chronic wounds [68].

Overall in these studies, other than those with enterococci, there was no marked difference in effectiveness between the two types of honey used. However, further research is needed to fully evaluate the effectiveness of these results.

Clinical observations

Honey has been used to treat infections in a wide range of wound types. These include burns [16], venous leg ulcers, leg ulcers of mixed aetiology, diabetic foot ulcers, pressure ulcers, unhealed graft donor sites, abscesses, boils, pilonidal sinuses, infected wounds from lower limb surgery [69], necrotising faciitis [55] and neonatal postoperative wound infection [61]. In many of these and other cases, honey has been used to heal wounds not responding to treatment with conventional antibiotics and antiseptics [16], [26], [57], [58], [61], [62], [69], [70], [71], [72], [73], [74].

One study, for example, reported treatment with honey dressings of 59 patients with recalcitrant wounds and ulcers, 47 of which had been treated for between one month to two years with no signs of healing. Some had increased in size. The ulcers had been treated with a chlorinated lime and boric acid solution (Eusol) and dressed with acriflavine, framycetin-impregnated dressing (Sofra-Tulle) or neomycin-zinc bacitracin (Cicatrin) [16]. Swabs from the 51 wounds with bacteria present became sterile within one week and the others remained sterile. All but one wound (a Buruli ulcer) showed signs of healing.

Another study used honey on nine infants with large infected surgical wounds that failed to heal with intravenous antibiotics, cleaning the wound with aqueous 0.05% chlorhexidine solution and application of fusidic acid ointment [61]. Marked clinical improvement was seen in all cases after five days of treatment with honey, and all wounds were closed, clean and free of infection after 21 days of application of honey.

In a randomised control trial 26 patients with postoperative wound infections had their wounds treated with honey and 24 had their wounds washed with 70% ethanol and povidone iodine applied [75]. The group treated with honey had infection eradicated and achieved complete healing in less than half the time compared with the antiseptic-treated group.

Two randomised controlled clinical trials have compared honey with silver sulfadiazine ointment on partial-thickness burns [59], [64]. Both of these showed that honey gave better control of infection.

In a comparative trial 20 consecutive cases of patients with Fournier's gangrene were treated conservatively with topical application of honey and compared retrospectively with 21 similar cases, managed using the orthodox method of wound debridement, wound excision, secondary suturing, and in some cases scrotal plastic reconstruction [55]. The average duration of hospitalisation was slightly longer with the honey treatment group, but response to treatment and alleviation of morbidity were faster. Systemic antibiotics were administered to both groups, but in the honey-treated groups these were given routinely whereas in the control group they were selected on the basis of sensitivity testing. Although some of the bacteria isolated from the honey-treated patients were not sensitive to the antibiotics used, all the wounds in this group became free of infection within one week.

Wounds infected with *Pseudomonas*, not responding to other treatment, have been rapidly cleared of infection using honey, allowing successful skin grafting [71], [74].

In patients with wounds infected with antibiotic-resistant strains of bacteria, not responding to antibiotic therapy, good results have been achieved after five weeks of application of honey [62]. The bacteria infecting the wounds were found to be resistant to ampicillin, oxytetracycline, gentamicin, chloramphenicol and cephadine. Wounds infected with MRSA have also been cleared of infection and healed by application of honey including a leg ulcer [73], cavity wounds resulting from haematomas [72] and surgical wounds [69].

Adverse reactions

Allergic reactions to honey are rare [76] and have been attributed in some cases to a reaction to a specific pollen in the honey [77], [78]. Honey processed for use in wound care is passed through fine filters which remove most of the pollen. In more than 500 published reports on the clinical usage of honey in open wounds [63], [69], [71], [72], [73], [74], [75], there have been no adverse reactions noted other than a localised stinging sensation described by some patients. This may be due to the acidity of honey as it has not been reported when the acidity is neutralised [69].

A transient stinging sensation was also observed in 102 cases in a trial of honey for ophthalmological use [79], although this was never severe enough to stop treatment. In papers describing the application of honey to open wounds it has been reported to be soothing [80], to relieve pain [80], be non-irritating [17], [81], [82], be pain free on application [83], and with no adverse effects [58]. A number of histological studies examining wound tissues also support the safe use of honey [25], [36], [84], [85].

Practical aspects of using honey on wounds

Substantial amounts of honey need to be applied to a wound to achieve adequate potency. Although it may be very viscous or even solid at room temperature, honey becomes very fluid at body temperature and even more fluid if diluted with proportionally small volumes of exudate. It is therefore very important that sufficient honey is applied to a wound and it is kept in place if a good therapeutic effect is to be obtained. For the optimal MIC of the antibacterial components of honey to be reached at the deepest sites of infection there needs to be the highest concentration possible on the surface, and a 'reservoir' of sufficient quantity that it is not substantially depleted by diffusion into the wound tissues.

Honey produced as a food often is not well filtered, and may contain various particles in it. Also, although honey does not allow vegetative bacteria to survive, it does contain viable spores, including clostridia. Honey that has been treated by gamma-irradiation is available commercially; this processing kills clostridial spores [86], [87] without loss of any of the antibacterial activity [86]. Various brands of honey with standardised antibacterial activity, processed as a medical product and sterilised by gamma-irradiation are available commercially. New Zealand manuka (Leptospermum scoparium) honey is sold with the activity of its phytochemical antibacterial component rated on a 'UMF' scale, with the 'UMF' number being the equivalent concentration of phenol with the same antibacterial activity against Staphylococcus aureus (i.e. UMF 15 = 15% phenol). Australian Leptospermum honey, Medihoney, is a listed product with the Therapeutic Goods Administration in Australia and has a standardised level of this antibacterial component. In addition, practical guides on the clinical use of honey in infected wounds are now available [69], [88]. The main considerations are summarised in Box 1.

Box 1: Practical considerations for the clinical use of honey

1. The amount of honey required on the wound relates to the amount of fluid exuding from the wound diluting it. The frequency of dressing changes required will depend on how rapidly the honey is being

diluted by exudate. If there is no exudate, dressings need to be changed twice-weekly to maintain a 'reservoir' of antibacterial components as they diffuse into the wound tissues.
2. To achieve best results the honey should be applied to an absorbent dressing prior to application. If applied directly to the wound, the honey tends to run off before a secondary dressing is applied to hold it in place.
3. Honey will not soak readily into absorbent dressings. Soaking is facilitated by warming the honey to body temperature and/or adding 1 part water to 20 parts honey to make the honey more fluid.
4. In some situations a 'blister' of honey can be held on a wound using an adhesive film dressing. Honey can be used to treat cavity wounds in this way, although this approach is not suitable for heavily exuding wounds.
5. For moderately to heavily exuding wounds, a secondary dressing may be needed to contain seepage of diluted honey from the primary dressing. An occlusive dressing such as polyurethane film is best, as an absorbent secondary dressing tends to draw the honey away from the wound surface.
6. A low-adherent dressing helps prevent the honey dressing sticking to the wound in cases where this is a problem. This dressing is placed between the wound and the honey dressing, but must be porous to allow the antibacterial components of the honey to diffuse freely into the wound bed.
7. Alginate dressings impregnated with honey are a good alternative to cotton/cellulose dressings, as the alginate converts into a honey-containing soft gel.
8. Any depressions or cavities in the wound bed need to be filled with honey in addition to using a honey-impregnated dressing. This is to ensure the antibacterial components of the honey diffuse into the wound tissues.
9. Honey can safely be inserted into cavities and sinuses. It is water-soluble and easily rinsed out; any residues are bio-degradable (honey filtered in processing does not contain any foreign bodies). For sinuses with small openings a catheter on a syringe filled with honey is an effective way of applying honey.
10. Since infection may lie in the tissues underlying the wound margins, honey dressings need to extend beyond the inflamed area surrounding a wound.

Conclusion

The use of honey to treat infected wounds, is viewed with sceptism by some. For example, an editorial in the Archives of Internal Medicine in 1976 on medical folk-lore [89] ridiculed the use of honey, placing "honey from selected geographic areas" in the category of "worthless but harmless substances". However, it is excepted that the clinical significance of the antibacterial activity in honey will be unequivocally proven only if a clinical trial is conducted to compare dressings of sugar and selected honeys [90]. Although more research is needed, as with many of the therapeutic interventions used in modern wound care, in the absence of data from well controlled clinical trials, it is necessary to draw on clinical experience and anecdotal reports to make sensible clinical decisions.

A recent review on the successful usage of honey as a dressing on infected wounds shows that many authors support the use of honey in infected wounds and some suggest the prophylactic use of honey on the wounds of patients susceptible to MRSA and other antibiotic-resistant bacteria, [16], [64], [80], [83], [84]. Whichever honey is used on a wound, consideration needs to be given to its quality and further evidence and understanding of the therapeutic and chemical properties of honey is needed to optimise the use of this product in the clinical management of wounds.

For further information about the Honey Research Unit, University of Waikato, its research activities and details of where to obtain honey for medical use, visit http://honey.bio.waikato.ac.nz

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