



Australia and New Zealand Horizon Scanning Network

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AN INITIATIVE OF THE NATIONAL, STATE AND
TERRITORY GOVERNMENTS OF AUSTRALIA
AND THE GOVERNMENT OF NEW ZEALAND

Australia and New Zealand
Horizon Scanning Network
SonoPrep[®]
Ultrasonic Skin Permeation System
Horizon Scanning Report

UNIVERSITY
OF
OTAGO



Te Whare Wānanga o Otago



NZHTA

NEW ZEALAND HEALTH TECHNOLOGY ASSESSMENT
DEPARTMENT OF PUBLIC HEALTH AND GENERAL PRACTICE
CHRISTCHURCH SCHOOL OF MEDICINE AND HEALTH SCIENCES
UNIVERSITY OF OTAGO
CHRISTCHURCH, NEW ZEALAND

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ISBN 0-642-82734-6

ISSN (Online)

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This Horizon Scanning Report was prepared by staff from the New Zealand Health Technology Assessment group, Department of Public Health and General Practice, Christchurch School of Medicine and Health Sciences, University of Otago, New Zealand. <http://nzhta.chmeds.ac.nz/> Mr Peter Day (Research Fellow) prepared the report. The literature search strategy was developed and undertaken by Mrs Susan Bidwell (Information Specialist Manager). Internal peer review was provided by Dr Robert Weir (Senior Research Fellow and Acting Director) and Mrs Susan Bidwell. Mrs Ally Reid (Administrative Secretary) provided document formatting.

The Health Policy Advisory Committee on Technology (Health PACT) oversaw the production of this Report. The Medical Services Advisory Committee (MSAC), the Australian Health Ministers' Advisory Council (AHMAC) and the New Zealand Ministry of Health provide the funding for these Horizon Scanning activities.

Publication approval number: 3698

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The New Zealand Health Technology Assessment Unit, Department of Public Health and General Practice, Christchurch School of Medicine and Health Sciences, University of Otago, on behalf of the Medical Services Advisory Committee (MSAC) and the New Zealand Ministry of Health, has undertaken an Horizon Scanning Report to provide advice to the Health Policy Advisory Committee on Technology (Health PACT) on the state of play of the introduction and use of the SonoPrep[®] ultrasonic skin permeation system (Register ID no. 000138).

The SonoPrep[®] ultrasonic skin permeation system utilizes low frequency ultrasonic energy for pretreating skin in children and adults prior to the application of topical anaesthetic to enhance rapid skin analgesia for needle insertion or IV procedure. It is offered by medical staff undertaking such procedures, and can also be self-administered. It is not currently in use in Australia and New Zealand but it may be introduced into Australia in 2005. Timing of its introduction into New Zealand is currently unknown.

This Horizon Scanning Report is intended for the use of health planners and policy makers. It provides an assessment of the current state of development of the SonoPrep[®] ultrasonic skin permeation system, its present use, the potential future application of the technology, and its likely impact on the Australian and New Zealand health care systems. This Horizon Scanning Report is a preliminary statement of the safety, effectiveness, cost-effectiveness and ethical considerations associated with the SonoPrep[®] ultrasonic skin permeation system.

Description of the technology

Development of the procedure

The skin's tough outer barrier known as the stratum corneum (the skin's outer most dead layer) acts as a strong impediment to transdermal drug delivery and fluid and analyte extraction. In order to overcome this limitation various technologies have been employed including iontophoresis, electroporation, photochemical waves and microneedle arrays (Lavon & Kost 2004). Research has found that non-invasive methods using the application of ultrasound enhance transdermal movement of various drugs (Machet & Boucaud 2002; Mitragotri & Kost 2004). The type of enhancement known as sonophoresis (also known as phonophoresis) is used to increase skin permeability to a variety of molecules by the use of ultrasonic frequency energy. Ultrasonic enhancement for the percutaneous absorption of drugs has been used, particularly in sports medicine, since the 1950's but without a sufficient research base showing an increase in transdermal transport (Mitragotri & Kost 2004; Machet & Boucaud 2002). The synergistic effects of chemical and electroporation (application of electric current) enhancement in combination with ultrasound have also been used to increase skin permeability to transdermal drug transport (Lavon & Kost 2004).

Despite a significant amount of research in recent years the process of sonophoresis is still not fully understood due to the occurrence of a number of phenomena in the skin that occur when exposed to ultrasound (Joshi & Raje 2002). These phenomena include cavitation (generation and oscillation of gas bubbles), thermal effects (temperature increase), induction of convective transport and mechanical effects (stresses from pressure variation due to ultrasound). Experimental and theoretical studies have shown the dominant phenomenon responsible for sonophoresis to be acoustic cavitation induced bilayer disordering which increases lipid bilayer permeability (Joshi & Raje 2002; Merino et al 2003; Mitragotri & Kost 2004). Recent studies indicate that cavitation plays an important role in the transdermal transport enhancement mechanism. Research has also been undertaken to establish a mathematical model describing the mechanism and predicting the enhancement ratio for different drugs and conditions (Joshi & Raje 2002; Lavon & Kost 2004).

Extensive research into low frequency sonophoresis using low-frequency ultrasound (20-100 kHz) has found better transdermal drug transport enhancement than at other frequencies (Mitragotri & Kost 2000; 2004). Two categories of low-frequency sonophoresis research, simultaneous sonophoresis and pretreatment sonophoresis, have been conducted over recent years. Simultaneous sonophoresis involves the simultaneous application of drug and ultrasound to the skin. This method requires a patient to wear an ultrasound device for the drug delivery. Pretreatment sonophoresis involves a short pretreatment of ultrasound to enhance drug delivery through the permeabilized skin and does not require the patient to wear an ultrasound device (Mitragotri & Kost 2004). Several drugs, including hydrocortisone and lidocaine (lignocaine)¹, have been used in clinical applications of sonophoresis as have blood glucose monitoring sensors. Pre-clinical research is ongoing into the use of sonophoresis and transdermal drug delivery including insulin (for diabetes treatment) (Smith et al 2003), low-molecular-weight heparin (DVT treatment), oligonucleotides (skin inflammation treatment) and vaccines (Mitragotri 2005).

Ultrasound has also been shown in a large number of studies to enhance uptake of low- and high-molecular mass molecules in cells and tissues (including tumour sites, brain and muscle tissue) either by compromising the integrity of cell tissues and membranes (sonoporation) or by encapsulating a drug in a carrier and using ultrasound to release the drug at the site of interest, or a combination of both. Experimental studies have also successfully shown the use of ultrasound to deliver DNA into various cells *in vitro* and *in vivo*. The underlying mechanisms involved in this process, though however, are not well understood (Mitragotri 2005). Other applications of ultrasound include the localised activation of drugs *in vitro* and *in vivo* to enhance the toxicity of chemotherapeutic compounds in various cancer cells (sonodynamic therapy) although the mechanisms by which it does this are not clear. Ultrasound has also been used in treatment to dissolve blood clots through either purely mechanical processes or by delivering thrombolytic agents to the site of a clot followed by targeted and non-targeted ultrasound (sonothrombolysis). Other uses include facilitating healing of wounds, and injuries to muscle, bone, and other tissue, osteoporosis treatment and ultrasound assisted lipoplasty (Mitragotri 2005).

¹ Used interchangeably in this report

There are numerous commercial diagnostic and therapeutic products now available that have used discoveries in biomedical ultrasound. Sontra Medical Corporation (Cambridge, MA) has developed the SonoPrep[®] ultrasonic skin permeation system for non-invasive and painless pretreatment sonophoresis for skin permeation to enhance transdermal drug delivery and fluid/analyte extraction.

The procedure

The SonoPrep[®] ultrasonic skin permeation device (Figure 1) comprises a battery operated power and control unit, a hand piece containing the ultrasonic probe, a disposable coupling medium cartridge, and a return electrode (Sontra Medical Corporation 2005a). In addition to the SonoPrep[®] device the accompanying SonoPrep[®] procedure tray (Figure 2) provides materials necessary for undertaking a skin permeation procedure. Each tray contains a single use disposable ultrasonic coupling medium cartridge, cleaning cartridge, locator ring, injection site marker, and skin prep pad (Sontra Medical Corporation 2005b).

The SonoPrep[®] device applies low ultrasonic frequency energy to the skin for up to 30 seconds duration. The ultrasonic horn within the hand piece vibrates at 55,000 times per second (55kHz) and transmits ultrasonic energy to the skin through a liquid coupling medium to generate gaseous bubbles (cavitation) that oscillate (expand and contract) in the coupling medium and the ordered bilayer of the outermost layer of skin, the stratum corneum. The ultrasonic cavitation in turn disorders the lipid bilayer of the stratum corneum, creating reversible micro-channels in the skin through which fluids and analytes can be extracted and large molecules, such as drug compounds, can also be delivered (Sontra Medical Corporation 2005a). Once the level of skin permeation is achieved, based on a reduction in skin impedance that is measured by current moving through the return electrode, the device automatically shuts itself off (Sontra Medical Corporation 2005a).

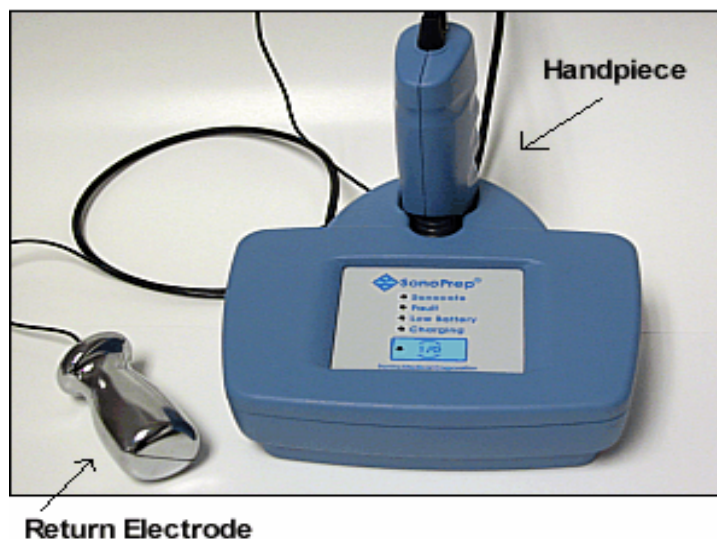


Figure 1. SonoPrep[®] Ultrasonic Skin Permeation Device (Sontra Medical Corporation, 2004)



Figure 2. SonoPrep® Procedure Tray (Sontra Medical Corporation, 2004)

A healthcare professional (nurse or clinician) administers the skin permeation treatment by marking the procedure site with a target ring plaster and applying the ultrasonic hand piece to the patient's skin. The treatment can also be self-administered by the patient. The hand piece is pushed down on the patient's skin in the target area to activate the ultrasonic horn. The patient holds the return electrode so that the device automatically shuts itself off, based on a drop in skin impedance (as measured by current moving through the return electrode) once the proper level of skin permeation is achieved. The permeation is achieved in under 30 seconds, the target ring is then filled with lidocaine topical anaesthetic cream, covered and approximately 5 minutes allowed for the anaesthetic to take effect, the cover and cream are removed, the skin is prepared and cutaneous procedures such as IV catheterization or injection are then undertaken. The effects of the skin permeation treatment remain for up to 24 hours (Sontra Medical Corporation 2005c).

Intended purpose

Topical anaesthetics are used to reduce local pain caused by procedures such as venipuncture injections, intravenous catheterization, skin biopsy, lumbar punctures and other cutaneous procedures and require at least 30 – 60 minutes to achieve analgesia. The SonoPrep® ultrasonic skin permeation system device aims to significantly reduce this waiting time to analgesia. The SonoPrep® ultrasonic skin permeation system is indicated for the rapid production of local dermal anaesthesia using topical over the counter (OTC) lidocaine (4%) prior to cutaneous procedures. It is also being developed to enhance transdermal drug delivery and/or to extract interstitial fluid for diagnostic purposes, e.g. continuous blood glucose monitoring.

Clinical need and burden of disease

SonoPrep® could potentially be applied to a wide range of patient groups. From published studies these populations include: patients requiring cutaneous anaesthesia in an Emergency Department setting (Becker et al 2005), adults receiving a eutectic mixture of local anaesthetic (EMLA) cream for cutaneous anaesthesia (Katz et al 2004), and diabetic patients requiring continuous glucose monitoring (Chuang et al 2004a;

Chuang 2004b). Given that needle insertion for cutaneous procedures is commonly used in clinical practice across many patient groups the potential scope for SonoPrep[®] is large, particularly in children, where injections can be difficult to administer, and in patients with diabetes who require continuous monitoring and metabolic control of blood glucose levels.

It was not possible to quantify the number of patients in Australia and New Zealand requiring cutaneous anaesthesia prior to a needle insertion or intravenous procedure. Estimates of sub-populations likely to benefit from SonoPrep[®] were available for the numbers of hospital inpatient discharges who were children (aged 14 years or less) and the population prevalence of type 1 and type 2 diabetes. Australian and New Zealand data on the number of consults for emergency anaesthesia was not available.

The total number of hospital separations in 2001/02 in Australia for children (aged 14 years or less) was 550,076, comprising 8.6% of all hospitalisations (Australian Institute of Health and Welfare 2004). The total number of inpatient separations of children (aged 14 years or less) from public hospitals in New Zealand in 2001/02 was 171,663 and from private hospitals was 6,455, a total of 178,118 separations (New Zealand Health Information Service 2004).

An estimate of the number of patients who could benefit from continuous glucose monitoring was possible based on estimates of diabetes prevalence. The AIHW estimates, based on self-reported information, that 95,000 (0.5%) of Australian's have type 1 diabetes based on the 2001 National Health Survey and that a further 900,000 (7%) of adults aged 25 years and over had type 2 diabetes based on 1999/2000 data (Australian Institute of Health and Welfare 2004). The New Zealand population of adults aged 15 years and over in 2002/03 was estimated at 3,124,690 (Statistics New Zealand 2005). Self-reported diabetes information from the 2002/03 New Zealand Health Survey indicated that the diabetes prevalence rate in adults aged 15 years and over was 4.2%, of which 85-90% were type 2 diabetes (Ministry of Health 2004).

Stage of development

The SonoPrep[®] ultrasonic skin permeation system to accelerate the delivery of topical anaesthetics for local dermal anaesthesia prior to needle insertion or IV procedure is not currently approved for use outside of the United States. It was not possible to ascertain the diffusion of the SonoPrep[®] device in the United States as it was only recently approved by the FDA, first for use in electrophysiology applications in February 2004 and for skin permeation for dermal anaesthesia in August 2004. The company is seeking international approval for use in other countries, including possibly Australia in 2005 (personal communication, Sontra company representative, 22.12.04). Whether or not approval is to be sought for its introduction into New Zealand is not known.

Ongoing research efforts have been made into developing minimally invasive and continuous blood glucose monitors to improve patient compliance and metabolic control. Two phase 1 clinical trials have been completed into the feasibility of continuous transdermal glucose monitoring using SonoPrep[®] as part of a blood glucose monitoring system that uses glucose flux biosensors through ultrasonically permeated skin (Chuang 2004a; Chuang et al 2004b). Other clinical studies are planned in 2005 focusing on improvements to the glucose flux biosensor and the development of a wireless radio

frequency (RF) interface between the biosensor and glucose meter. Larger clinical studies for FDA marketing approval are planned for 2006². A Phase 1 human clinical study (unpublished) has also demonstrated the feasibility of SonoPrep[®] ultrasonic skin permeation for enabling the topical delivery of large molecular weight vaccines using the recall protein antigens for tetanus toxoid and candida albicans to pass through treated skin and induce a skin immune response. Additional studies are planned for influenza and hepatitis A vaccines³. Other clinical studies involving ultrasound pretreatment with SonoPrep[®] and the application of lidocaine topical anaesthesia have been completed involving children aged 3-7 years and adults undergoing iontophoresis of topical anaesthetic but results have not yet been published (Sontra Medical Corporation 2005e; 2005f).

Treatment Alternatives

Existing comparators

The existing comparators for the SonoPrep[®] device are conventional topical anaesthetic without pre-treatment with ultrasonic skin permeation, usual drug delivery methods such as oral administration and subcutaneous injection, and standard methods for the measurement of blood analytes, such as blood glucose self-monitoring in patients with type 1 and type 2 diabetes. Increasing skin permeability (sonophoresis) to allow for transdermal drug delivery has some advantages compared to conventional drug delivery methods. These include steady delivery and better patient compliance, reduced gastrointestinal degradation in the patient and/or reduced necessity for a first-pass metabolism by the liver (Lavon and Kost 2004). Greater efficiency in transdermal drug delivery may allow for lower doses of drugs and improved safety. The limitations of transdermal drug delivery include low skin permeability, the use of high potency drugs only (so low doses attain required effect), the inability to deliver large molecule drugs (>500 Da), lag time and possible skin irritation and sensitisation (Lavon and Kost 2004).

EMLA cream, a commonly used eutectic (5%) mixture of lidocaine and prilocaine (2.5% each), requires 60-90 minutes to provide cutaneous anaesthesia. Newer products have reduced this to 30 minutes through the incorporation of liposomes (lipid bilayers in an aqueous solution) to facilitate absorption of 4%-5% liposomal lidocaine cream (LMX, Ferndale Labs, Ferndale, MI). Other topical anaesthetic formulations including tetracaine and combination agents such as S-caine (lidocaine and tetracaine) have been evaluated with effective anaesthesia onset reported to be in the range of 30-60 minutes (Friedman et al 2002).

The disadvantages of conventional EMLA and other variants include the long application time required, which limits their use in ED and primary care settings because of time constraints, relative expense, cannulation difficulty from underlying vein constriction and possible toxicity especially from agents used in combination (Becker et al 2005).

Other accelerants that have been used include pressurized helium to enable lidocaine particles to penetrate the skin using a Powerjet device but its effectiveness is dependant

² Information provided by Sontra Medical Corporation 2005

³ Information provided by Sontra Medical Corporation 2005

upon skin site (Wolf et al 2002). Lidocaine has also been delivered using iontophoresis (application of electric current to increase penetration of drugs into surface tissues) but discomfort during delivery, limitations in suitable drug molecules, and reliance upon existing transdermal pathways such as hair follicles means the effectiveness of iontophoresis may be slow, unreliable and dependent upon skin type (Wallace et al 2001). Unlike iontophoresis, ultrasound does not need to be continuously applied during drug delivery. The skin can instead be briefly pretreated before drug application.

Conventional methods of blood glucose monitoring in patients with type 1 and type 2 diabetes have helped reduce microvascular complications and associated co-morbidities. Self-monitoring has become an important practice in diabetes management. Patients with type 1 diabetes require intensive management with multiple blood glucose measurements, insulin injections or continuous delivery with an external pump. Current self-management methods require painful finger sticks, and low patient compliance with intermittent measurement can miss important peaks and troughs in blood glucose level trends and result in severe hypoglycemic events (Anonymous - Diabetes Control and Complication Research Group 1993). Continuous monitoring could better control blood glucose fluctuations and improve patient compliance, hence the development of continuous and minimally invasive blood glucose monitoring devices. These new technologies include the MiniMed[®] continuous blood glucose monitor (CGMS[®]; Medtronic MiniMed, Northridge, CA) and the minimally invasive GlucoWatch[®] Biographer (GWB; Cygus, Inc., Redwood City, CA). Shortcomings in the monitoring mechanics of these technologies have led to the development of the Symphony[®] blood glucose monitoring system using a flux biosensor and meter and the SonoPrep[®] ultrasonic skin permeation device that senses glucose flux through ultrasonically permeated skin (Sontra Medical Corporation 2005d; Chuang et al 2004a; 2004b).

Clinical Outcomes

Effectiveness

Few clinical studies have been conducted investigating transdermal drug delivery using low frequency sonophoresis. A number of early clinical studies looked at the effects of ultrasound on the percutaneous absorption of lignocaine (McElnay, et al 1985), lignocaine and prilocaine as a EMLA cream (Benson, et al 1988). A recent Randomised Controlled Trial examined the effects of low frequency ultrasound on the latency of topical EMLA anaesthetic cream (Zhang et al 2004). The early studies applied ultrasound to the site of already applied topical anaesthetic rather than as a treatment prior to topical anaesthetic application. The ultrasound parameters were of much greater frequency and applied for a much longer duration than SonoPrep[®]. There was no significant difference in onset time between those participants who had ultrasound for percutaneous lignocaine absorption and those who had not (McElnay, et al 1985). With the absorption of EMLA cream, the application of ultrasound resulted in no significant difference in onset times between control data and those using ultrasound at different frequencies (Benson, et al 1988). However, low frequency ultrasound applied to EMLA cream was considered to accelerate skin permeation and the effectiveness time of EMLA cream with a significantly longer EMLA latency period than controls (Zhang et al 2004). Recent clinical studies incorporating newer research on sonophoresis (phonophoresis) using the SonoPrep[®] ultrasonic skin permeation system have been undertaken evaluating

its effectiveness in permeabilized skin preparation for the rapid onset of topical local anaesthetics, transdermal delivery of vaccine (unpublished)⁴, and the extraction of interstitial fluid for blood glucose monitoring.

Topical anaesthesia

Two Randomised Controlled Trials reported on pretreatment with SonoPrep[®] to enhance skin permeability for rapid onset and pain reduction with topical anaesthesia. Both studies found that SonoPrep[®] ultrasonic pretreatment greatly reduced the time to anaesthesia for topical EMLA and lidocaine anaesthetic creams. There were also significant reductions in subjects' pain perception scores compared to control subjects.

The SonoPrep[®] device was tested in a prospective randomised controlled trial (level II evidence) in an Emergency Department setting on 104 mild or moderately ill adult patients prior to receiving intravenous cannulation (Becker et al 2005). This study compared one group of patients who received brief SonoPrep[®] treatment (frequency 53-56 kHz, average 15.5 seconds) and a five minute application of topical anaesthetic (4% liposomal lidocaine cream) prior to cannulation, to the control group who received IV insertion with no ultrasound or topical anaesthetic. The cannulation site was observed after ultrasound treatment, after removal of the topical anesthetic, and 20 to 36 hours following ultrasound treatment. Participants' subjective pain scores were rated on a visual analog scale and dichotomised for analysis using an arbitrary cut-off of >3 versus ≤ 3 (Table 1).

Table 1. Comparison between SonoPrep[®] pretreatment and EMLA cream versus standard treatment for pain perception of IV cannulation: Pain score

	Control (n = 49)	Sonoprep [®] treated (n = 45)
Pain ≤ 3	18 (37%)	36 (80%)
Pain > 3	31 (63%)	9 (20%)

P <0.0001

The authors concluded that treatment with SonoPrep[®] decreased the time to effective anaesthesia from 30 minutes to five minutes as the perceived pain in the treatment group after 5 minutes of topical anaesthetic application indicated significantly (p<0.0001) lower pain scores than the standard care group. The EMLA cream used for this study was intended to take at least 30 minutes to achieve localised numbness. The study was supported by a grant from Sontra Medical Corporation. The main limitations with this study were that it was non-placebo controlled (no placebo ultrasound or EMLA cream), the possible selection bias resulting from patient dropouts, possible pain perception bias, and lack of objective outcome measurements.

A randomised, double-blinded placebo controlled crossover trial (level II evidence) compared speed of onset and the effectiveness of cutaneous anaesthesia using ultrasound pre-treatment with SonoPrep[®] or no pre-treatment in 42 healthy adult volunteers (Katz et al 2004). This study assessed four treatment groups: ultrasound pretreatment with the SonoPrep[®] (55 kHz, average 9 seconds) and onset of cutaneous analgesia with 1g EMLA cream at 5, 10 and 15 minutes and the application of EMLA cream at 60 minutes, without SonoPrep[®] pretreatment. A placebo cream was applied to the control group, utilising the same pre-treatment (or no pre-treatment) and time conditions. Cutaneous

⁴ Information provided by Sontra Medical Corporation 2005

analgesia was assessed by pain score with a 20 gauge needle prick and patient preference for EMLA or placebo cream. Study results are presented in table 2.

Table 2. Comparison between effectiveness of EMLA and placebo creams with SonoPrep® pretreatment: Pain score

	5 min (with SonoPrep®) (n = 20)	10 min (with SonoPrep®) (n = 22)	15 min (with SonoPrep®) (n=20)	60 min (without SonoPrep®) (n = 22)
Pain score				
EMLA cream	0.30 (0.31)	0.20 (0.26)	0.12 (0.20)	0.30 (0.38)
Placebo cream	0.74 (0.29)	0.64 (0.31)	0.74 (0.31)	0.65 (0.33)
Treatment difference				
Mean difference	- 0.44	- 0.44	- 0.62	- 0.35
95% CI	- 0.69 to - 0.20	-0.67 to - 0.20	-0.87 to - 0.38	- 0.58 to -0.12
Difference P value				
ANOVA test	0.0004	<0.0001	<0.0001	0.001
Van Elteren test	0.004	0.0006	0.0002	0.006

Data for pain score are mean (SD). The pain score was the mean of 5 individual pin pricks, each scored by the subject either 1 ("sharp"), 0.5 ("less sharp"), or 0 ("dull"). Treatment difference in mean pain score (EMLA cream – placebo cream). A negative value indicates less pain (better efficacy) with EMLA than placebo cream.

The study authors concluded that the SonoPrep® device produced rapid onset of topical anaesthesia with EMLA cream as early as five minutes compared to the standard time of 60 minutes without ultrasound treatment. The study was supported by Sontra Medical Corporation, was not performed in a clinical setting and used healthy volunteers. The main study limitation was that the testing was done over different sessions and results combine two different groups of participants with two different treatment regimes, rather than all four treatment regimes tested in the same patient in one session. The lack of objective outcome measurements and no placebo ultrasound treatment were other limitations.

Although both of these studies assessed the rapid onset of local anaesthesia through the stratum corneum, the SonoPrep® device has not been tested in clinical procedures requiring deeper penetration of the cutaneous structures.

Blood glucose monitoring

Two clinical studies were identified and both showed high correlation between glucose flux biosensor output readings through SonoPrep® ultrasonically permeated skin and standard blood glucose measurements in completed data sets. However, a significant limitation with these two studies was the relatively high error rate in the biosensor data sets.

The SonoPrep® ultrasonic skin permeation system has been tested (level IV evidence) in diabetic patients to assess the feasibility of transdermal glucose monitoring through ultrasonically permeated skin (Chuang et al 2004a). This clinical pilot study compared data collected every 5 seconds over 20 skin sites pretreated using SonoPrep® (55 kHz, average 6.8 seconds), with blood glucose readings taken every 20 minutes over an 8-hour period. Ten (three type 1 and seven type 2) diabetic patients were included in the study. Sensor output readings data were compared to blood glucose measurements and a correlation co-efficient of $r=0.84$ in completed data sets (12/20) after removing erroneous data was calculated with 95% of sensor data pairs in the Clark error grid analysis A+B region parameter⁵. The study was supported by Sontra Medical

⁵ An error grid analysis describing the clinical accuracy of self-monitoring blood glucose systems as a function of the entire range of system and reference absolute blood glucose levels.

Corporation and was not performed in a clinical setting. Limitations with this study include the high error rate in the biosensor data due to mechanical arrangements of the apparatus and biosensor sensitivity variations. The study was a very small pilot study. Although the SonoPrep[®] device was shown to enable transdermal glucose monitoring with the use of the glucose flux biosensor in this study, the accuracy of this approach to measuring blood glucose was not compared with other continuous measurement devices or the self-monitoring method.

A follow-up Phase 1 clinical study tested the SonoPrep[®] ultrasonic skin permeation system in diabetic patients (level IV evidence) to assess improved transdermal glucose monitoring activity with a glucose flux biosensor through ultrasonically permeated skin (Chuang et al 2004b). This clinical study compared data collected by glucose flux biosensors placed over 36 skin sites pretreated with SonoPrep[®] (average 15 seconds) (the Symphony[®] Diabetes Management System), with reference blood glucose readings over 7.5 hours from a standard glucose analyser in 12 (nine type 1 and three type 2) diabetic patients. Additionally each patient had three other commercial continuous glucose monitoring devices attached, two implanted MiniMed CGMS Gold[®] and one Cygnus G2 Biographer Glucowatch[®] device.

Table 3. Comparison between SonoPrep[®] pretreatment with Sontra glucose flux biosensor and other commercially available glucose monitoring devices

Device	N readings	R ²	Std Deviation
SonoPrep & biosensor	30	0.88	0.083
MiniMed CGMS	23	0.67	0.245
Cygnus G2 Biographer	13	0.49	0.291

Sensor output readings data were compared to standard blood glucose measurements (total of 2039 sensor-BG data pairs) and a correlation co-efficient of $r=0.90$ in completed data sets (29/36) after removing erroneous data was calculated with 96% of sensor data pairs in the Clark error grid analysis A+B region parameter. Hypoglycaemic events were predicted with 77% sensitivity and 96% specificity. SonoPrep[®] pretreatment and biosensor glucose monitoring was shown to be more highly correlated with standard blood glucose measurements than other glucose monitoring devices (Table 3). The study was supported by Sontra Medical Corporation. Limitations with this study include the reduced but still high error rate in the biosensor data sets, limited data as the study was presented as a conference presentation and the small study sample.

Safety

Safety issues arise from ultrasound interactions with biological tissues and the selection of frequency, intensity, duty cycle, application time, tissue type and environmental factors are parameters used to determine conditions for safe use (Mitragotri 2005). There has been extensive research into the physical, chemical and biological effects of ultrasound and because of this ultrasound has been used much more effectively and safely in medicine (Nyborg 2001). Much of this research and clinical application has been in diagnostic ultrasound but this is now being adopted in therapeutic ultrasound applications such as transdermal drug delivery. Safety concerns remain concerning the auditory effects from airborne ultrasound and direct effects on tissues. There is a dose-response relationship between the frequency and amplitude (intensity or power) of ultrasound and increased transdermal transport and also the severity of effects on skin tissue (Machet & Boucaud 2002). Ultrasound effects on tissues are quantified using two parameters: thermal and mechanical indexes. The thermal index is defined by the

amount of energy required to raise tissue temperature by 1°C and the mechanical index is defined by a combination of pressure amplitude and frequency. The FDA has defined upper limits for these indices for safety purposes in diagnostic ultrasound. However, their application to therapeutic ultrasound is problematic and questionable, because many relevant parameters are excluded from these definitions. Another difficulty is that therapeutic ultrasound relies on tissue interaction whereas the goal in diagnostic ultrasound is to minimize tissue interaction (Mitragotri 2005). Further research is required to better understand the safety of therapeutic ultrasound and to develop generalised rules for a window of parameters within which the safe application of therapeutic ultrasound can be practiced.

Several studies examining the safety of low-frequency sonophoresis report that it appears to be safe in enhancing the topical delivery of medications with minimal detectable changes in skin structure and that it is well tolerated by patients in clinical studies. In clinical studies where low frequency ultrasound using SonoPrep[®] has been used for treating skin prior to the application of topical anaesthesia no adverse events were reported. There were only minor needle marks, redness, pallor and irritation reported and all resolved subsequently without treatment (Becker et al 2005; Katz et al 2004). In studies using SonoPrep[®] ultrasonic skin permeation in conjunction with glucose monitoring sensors some patients experienced slight erythema and swelling, and redness associated with the adhesive used for the procedure but no pain or irritation during SonoPrep[®] and sensor operation (Chuang et al 2004a; Chuang et al 2004b).

In the study by Becker et al (2005) (level II evidence) visual inspection of the IV site for skin irritation in both intervention and control groups was graded on a four point scale as 1) no observable effect, 2) minor redness, 3) significant redness, or 4) major redness after ultrasound application, after IV insertion, and at 20-36 hours follow-up later. There was no difference between treatment and control groups in the assessment of irritation and no participants experienced any significant irritation or major redness. No adverse events associated with application of the SonoPrep[®] device and/or the topical lidocaine were reported at any stage.

In the study by Katz et al (2004) (level II evidence) each person was assessed for adverse events and any notable effect on skin appearance immediately after the intervention and at 24-48 hours after treatment. Changes in skin appearance were classified into pallor, redness, piloerection, and other cutaneous change and were rated as mild, moderate or severe. After the intervention no severe cutaneous changes were observed although several moderate and mild cases of pallor, redness, piloerection and needle marks were observed and resolved without treatment. Mild or moderate pallor was more evident at all 4 observation times with EMLA than placebo cream treatment. The most common cutaneous change at follow-up was mild needle marks. There were no adverse events arising from the application of the SonoPrep[®] device.

In the study by Chuang et al (2004a) (level IV evidence) skin sites were examined and photographed at both the end of the study and the next day for irritation due to biosensor contact and SonoPrep[®] ultrasonic permeation. Patients rated ultrasonic application discomfort levels on a scale of '0' = no sensation to '3' = painful. There was 'barely perceptible' to 'slight' erythema in most biosensor sites and half of the sites had slight swelling immediately after removal. There was more redness associated with the adhesive used to define each target site than the actual skin permeation and biosensor gel

site. On the next day all test sites improved, and 65% of sites showed no evidence of erythema or edema. No pain or irritation was reported by patients at any time during the study. An additional study by Chuang et al (2004b) reported that patients experienced no pain or irritation during SonoPrep[®] and the sensor operation.

Potential Cost Impact

Cost Analysis

No specific cost-effectiveness studies were identified for the horizon scanning report and it was not possible to estimate the costs to the health system for SonoPrep[®]. In terms of unit costs the cost of a single SonoPrep[®] system has a list price of \$US 1,995 and procedure trays are \$US 8. Each tray is for single patient use and provides the materials for treating up to three sites on the same patient. The lidocaine is sold separately at \$US 200 for a case of 50 – 1 gram pouches, enough for treating between three and four locations. The manufacturer allows the SonoPrep[®] system to be available on a loan basis: when \$US 2,400 is spent on procedure trays and/or lidocaine pouches the purchaser receives the use of the SonoPrep[®] free on the condition that product is used. The reduction in time to achieving cutaneous analgesia could potentially result in quicker treatment times in a hospital setting.

Ethical Considerations

Informed Consent

It is worth noting the ethical imperative to reduce pain in people when it is possible to do so. In addition, the reduction in pain resulting from adequate anaesthesia in the management and treatment of conditions in children would result in relieving anxiety associated with cutaneous penetration with needle sticks. In the clinical studies evaluating the SonoPrep[®] device, participant volunteers gave informed written consent to participate and study protocols underwent ethics approval.

Access Issues

Commercial therapeutic ultrasound products are being produced by numerous companies for a growing range of medical indications and their use is becoming increasingly common in clinical practice. Sontra Medical Corporation has developed the ultrasound based transdermal drug delivery product SonoPrep[®] and gained FDA market clearance for clinical use in the USA. The actual uptake of SonoPrep[®] in the USA is not known but there is potential for its uptake in clinical practice given the benefits for paediatric patients, patients requiring emergency anaesthesia, and patients requiring blood glucose monitoring. Its potential utilisation may be as an optional adjunctive procedure to existing cutaneous procedures requiring conventional topical anaesthetic. Standard methods for blood glucose measurement will remain until limitations in minimally invasive continuous blood glucose monitoring technology are resolved.

Training

There is no formal training in the use of SonoPrep[®] other than vendor instructions included with the product on its use. Vendors may include a demonstration and/or provide training when supplying of the product. In Australia and New Zealand formal medical or nursing training is required in needle insertion for fluid/analyte extraction and to administer infusions via injection using hypodermic, subcutaneous, intramuscular, intradermal, and intravenous methods.

Clinical Guidelines

No clinical guidelines on using ultrasonic skin permeation systems for pre-treating skin for topical anaesthesia or any transdermal drug transport were identified in terms of when and how ultrasonic skin permeation devices should be used in clinical practice.

Limitations of the Assessment

Methodological issues and the relevance or currency of information provided over time are paramount in any assessment carried out in the early life of a technology.

Horizon Scanning forms an integral component of Health Technology Assessment. However, it is a specialised and quite distinct activity conducted for an entirely different purpose compared to a comprehensive systematic review. The rapid evolution of technological advances can in some cases overtake the speed at which trials or other reviews are conducted. In many cases, by the time a study or review has been completed, the technology may have evolved to a higher level leaving the technology under investigation obsolete and replaced.

An Horizon Scanning Report maintains a predictive or speculative focus, often based on low level evidence, and is aimed at informing policy and decision makers. It is not a definitive assessment of the safety, effectiveness, ethical considerations and cost effectiveness of a technology.

In the context of a rapidly evolving technology, an Horizon Scanning Report is a 'state of play' assessment that presents a trade-off between the value of early, uncertain information, versus the value of certain, but late information that may be of limited relevance to policy and decision makers.

This report provides an assessment of the current state of development of the SonoPrep[®] ultrasonic skin permeation system, its present and potential use in the Australian and New Zealand public health systems, and future implications for the use of this technology.

Availability and Level of Evidence

The medical literature (Table 4) was searched utilising the search terms outlined (Table 5) to identify relevant studies and reviews, until 19 April 2005. In addition, major international health technology assessment databases were searched.

Table 4. Literature sources utilised in assessment

Source	Location
<i>Electronic databases</i>	
Cinahl	Ovid - University library
Cochrane Library – including, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, the Cochrane Central Register of Controlled Trials (CENTRAL)	Ovid - University library
Current Contents	Ovid - University library
Embase	Ovid - University library
Pre-Medline and Medline via Ovid	Ovid - University library
Medline (via PubMed last 60 days)	Ovid - University library
International Pharmaceutical Abstracts	Ovid - University library
Web of Science – Thomson ISI Citation Indexes	Ovid - University library
The Health Technology Assessment Database, the NHS Economic Evaluation Databases	http://www.york.ac.uk/inst/crd/crddatabases.htm
<i>Internet</i>	
Etext on Health Technology Assessment Information Resources. Chapter 15. Emerging health technologies	http://www.nlm.nih.gov/nichsr/ehta/chapter15.html
Sontra Medical Corporation	http://www.sontra.com
US Food & Drug Administration (FDA) Center for Devices & Radiological Health	http://www.fda.gov/cdrh
MAUDE database Manufacturer and User Facility Device Experience Database - (MAUDE)	http://www.fda.gov/cdrh/maude.html
Eucomed	http://www.eucomed.be
Medgadget: International Journal of Emerging Medical Technologies	http://www.medgadget.com
Medscape	http://www.medscape.com
University Health Consortium Clinical Technology Advisory	http://public.uhc.edu/uhcmail/CTA
Popular Science	http://www.popsci.com
American Medical News	http://www.amednews.com
Medical Post	http://www.medicalpost.com
Medical Device Daily	http://www.medicaldevicedaily.com
Doctors' Guide	http://www.docguide.com
UK National Horizon Scanning Centre	http://www.publichealth.bham.ac.uk/horizon
Canadian Coordinating Office for Health Technology Assessment Emerging Technology List	http://www.ccohta.ca
Blue Cross Blue Shield Technology Evaluation Center	http://www.bcbs.com/tec/tecassessments.html
Google Search Engine and Google Scholar Search	http://scholar.google.com

Table 5. Search terms utilised

Search terms
<p>MeSH & EMBASE headings phonophoresis, ultrasonics, skin absorption, administration cutaneous, lidocaine, anesthesia local, anesthesia topical, blood glucose self-monitoring, blood glucose level, ultrasound, skin penetration, skin permeability</p> <p>Text words sonoprep, sonophoresis, phonophoresis, lignocaine, cutaneous, percutaneous, absorption, permeation, permeability, skin permeation, skin absorption, skin penetration, skin permeability, percutaneous administration, percutaneous absorption, percutaneous penetration, percutaneous permeability, percutaneous permeation, cutaneous administration, cutaneous absorption, cutaneous penetration, cutaneous permeability, cutaneous permeation</p> <p>Limits No limits</p>

Sources of Further Information

One randomised controlled trial has examined the combination of SonoPrep[®] ultrasonic skin permeation and iontophoretic transport for 2 minutes with 2% topical lidocaine anaesthetic compared with sham ultrasound for 2 minutes with 2% topical lidocaine and iontophoretic transport alone for ten minutes in thirty adults. Equivalent pain scores were reported for SonoPrep[®] treatment followed by two minutes of iontophoresis and the ten minute iontophoresis alone treatment. Results are still to be published (Sontra Medical Corporation 2005e).

Another prospective controlled clinical study (still to be published) of 70 young children aged 3-7 years has been undertaken to demonstrate the analgesic effect of a 5-minute application of LMX lidocaine anaesthetic cream after SonoPrep[®] ultrasonic pretreatment compared with usual treatment of 30-minute application of LMX cream in children presenting for venipuncture at an urban outpatient clinic (Sontra Medical Corporation 2005f).

Impact Summary

Commercial therapeutic ultrasound products are becoming increasingly common in clinical practice. Sontra Medical Corporation has developed the ultrasound based transdermal drug delivery product SonoPrep[®] and gained FDA market clearance for clinical use in the USA. The company may seek approval in 2005 for its use in Australia. Its introduction into New Zealand is unknown. The actual uptake of SonoPrep[®] in the USA is not known but there is large potential for its uptake in clinical practice given its benefit for inducing rapid analgesic onset of topical anaesthetic and increased patient throughput for paediatric patients and its potential for enhancing continuous monitoring of diabetic patients using non-invasive blood glucose monitoring technology. The cost of the SonoPrep[®] system is known in terms of unit costs, but no cost-effectiveness studies are yet available to determine overall cost versus effectiveness. Its utilisation at this stage until more substantial clinical research on safety and effectiveness is published is likely to be as an optional adjunctive procedure rather than standard practice, with conventional cutaneous procedures utilising topical anaesthetic treatment for drug delivery and analyte/fluid extraction remaining the standard procedure. There are ongoing research efforts into developing improved minimally invasive continuous transdermal blood glucose monitors utilising SonoPrep[®] ultrasonic skin permeation but these will not replace standard monitoring methods until efficient, affordable and portable systems become available.

Conclusions

Research into non-invasive methods using the application of ultrasound has been found to enhance transdermal movement of various drugs. Sonophoresis (phonophoresis) is used to increase skin permeability to a variety of molecules by the use of ultrasonic frequency energy. Experimental and theoretical studies have shown the dominant

phenomenon responsible for sonophoresis to be acoustic cavitation induced bilayer disordering which increases lipid bilayer permeability and the transdermal transport enhancement mechanism. Low ultrasonic frequency sonophoresis has been shown to produce more optimal transdermal drug transport.

The advantages of increasing skin permeability to allow for transdermal drug delivery include steady delivery, better patient compliance, reduced gastrointestinal degradation in the patient and/or reduced necessity for a first-pass metabolism by the liver. Greater efficiency in transdermal drug delivery may allow for lower doses of drugs and improved safety. The limitations of transdermal drug delivery include low skin permeability, the use of higher potency drugs only, the inability to deliver large molecule drugs (>500 Da), lag time and possible skin irritation and sensitisation. Current blood glucose self-management methods for patients with diabetes often require painful finger sticks, are subject to low patient compliance, and intermittent measurement may mean possible severe hypoglycaemic events. Continuous monitoring using minimally invasive blood glucose monitoring devices through permeated skin may better control blood glucose fluctuations and improve patient compliance.

There are numerous commercial products now available that have used discoveries in biomedical ultrasound for diagnostic and therapeutic purposes. Sontra Medical Corporation (Cambridge, MA) has developed the SonoPrep[®] ultrasonic skin permeation system which utilizes short applications (~30 seconds) of low frequency ultrasonic energy (~55 kHz) for skin permeation prior to the application of topical anaesthetic to enhance rapid skin analgesia for needle insertion or IV procedure in children and adults. It is also being developed to enhance transdermal minimally invasive transdermal blood glucose monitoring.

Few clinical studies have been conducted investigating transdermal drug delivery using low frequency sonophoresis. A number of earlier clinical studies looked at the effects of ultrasound on the percutaneous absorption of topical anaesthetic utilising the research of the time but this involved ultrasonic treatment of the already applied topical anaesthetic rather than pretreatment and different ultrasound parameters (higher intensity and longer duration) from those now used for low frequency sonophoresis. Recent clinical studies have incorporated newer research on sonophoresis using the SonoPrep[®] ultrasonic skin permeation system. Pre-clinical research is ongoing into the use of sonophoresis for transdermal drug delivery including insulin, low-molecular-weight heparin, oligonucleotides and vaccine delivery.

Two RCT studies (Level II evidence) reported on SonoPrep[®] effectiveness in enhancing skin permeability for rapid onset and pain reduction with topical anaesthesia. Both studies found that SonoPrep[®] ultrasonic pretreatment greatly reduced the time to anaesthesia for topical EMLA and lidocaine anaesthetic creams. Significant reductions in pain perception scores were also found compared to control subjects. There were limitations in the methodology and outcome measurements of both studies and both studies were supported by Sontra Medical Corporation.

Two clinical studies (Level IV evidence) examined the effectiveness of SonoPrep[®] used in combination with a glucose flux biosensor for minimally invasive transdermal blood glucose monitoring and both studies showed a high correlation between glucose flux biosensor output readings through SonoPrep[®] ultrasonically permeated skin and standard

blood glucose measurements in completed data sets. However, a significant limitation with these two studies was the relatively high error rate in the biosensor data sets and limitations in study methodology. Both studies were supported by Sontra Medical Corporation.

Safety issues arise from ultrasound interactions with biological tissues and the selection of parameters used to determine conditions for safe ultrasound use. The application of existing diagnostic ultrasound safety parameters to therapeutic ultrasound is problematic and questionable, because some parameters are unsuited to therapeutic ultrasound. Further research is required to better understand the safety of therapeutic ultrasound and to develop generalised rules for a window of parameters within which the safe application of therapeutic ultrasound can be practised. In clinical studies where low frequency ultrasound using SonoPrep[®] has been used for pretreating skin prior to the application of topical anaesthesia no adverse events were reported. There was only minor skin trauma reported and all resolved subsequently without treatment. In studies using SonoPrep[®] in conjunction with glucose monitoring sensors some patients experienced slight erythema and swelling, and redness associated with the adhesive used for the procedure but no pain or irritation during SonoPrep[®] and sensor operation.

There were no specific cost-effectiveness studies identified for the horizon scanning report and it was not possible to estimate the costs to the health system for SonoPrep[®]. The unit cost of a SonoPrep[®] system has a list price of \$US 1,995 and procedure trays are \$US 8.

The results of two recently completed clinical trials are due for publication on the effectiveness of SonoPrep[®]. These examined the rapid onset of topical LMX lidocaine cream in young children and the use of SonoPrep[®] in combination with iontophoretic transport for 2-minutes with 2% topical lidocaine for ultra-rapid analgesic effect from topical anaesthetic in adults. Other clinical studies are planned by Sontra Corporation in 2005 focusing on improvements to the glucose flux biosensor technology used with SonoPrep[®] for blood glucose monitoring and larger clinical studies are planned for 2006 for FDA marketing approval. A Phase 1 human clinical study (unpublished) has also demonstrated the feasibility of SonoPrep[®] ultrasonic skin permeation for enabling the topical delivery of large molecular weight vaccines with additional studies planned for influenza and hepatitis A vaccines.

HPACT Advisory: that the results of pending clinical trials using SonoPrep[®] ultrasonic skin permeation system technology be monitored and that a more substantial body of additional non-stakeholder clinical research on the safety and effectiveness of SonoPrep[®] is necessary to improve the quality of evidence currently available.

Appendix: Levels of Evidence

There were published articles included for assessment in this report. All studies were graded according to the dimensions of evidence defined by the National Health and Medical Research Council (NHMRC, 2000) (Table 6). There were two level II grade RCTs (Becker et al 2005; Katz et al 2004) which evaluated the safety and effectiveness of cutaneous anaesthesia using ultrasound pre-treatment with Sonoprep[®] and two level IV grade case series studies (Chuang et al 2004a; Chuang 2004b) evaluating the ultrasonic pretreatment with Sonoprep[®] and continuous transdermal glucose monitoring included in the assessment.

Table 6. Designations of levels of evidence

Level of evidence	Study design
I	Evidence obtained from a systematic review of all relevant randomised controlled trials
II	Evidence obtained from at least one properly-designed randomised controlled trial
III-1	Evidence obtained from well-designed pseudorandomised controlled trials (alternate allocation or some other method)
III-2	Evidence obtained from comparative studies (including systematic reviews of such studies) with concurrent controls and allocation not randomised, cohort studies, case-control studies, or interrupted time series with a control group
III-3	Evidence obtained from comparative studies with historical control, two or more single arm studies, or interrupted time series without a parallel control group
IV	Evidence obtained from case series, either post-test or pre-test/post-test

Modified from: National Health and Medical Research Council (1999). *A guide to the development, implementation and evaluation of clinical practice guidelines*, Commonwealth of Australia, Canberra, ACT.

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