Methods of pain-reducing in diagnostic and therapeutic procedures in paediatric dermatology - a clinical study

Methoden van pijn-reductie bij diagnostische en therapeutische procedures in de kinderdermatologie - een klinisch onderzoek

Flora Bastiana van der Spek

COVER:

FIGURE 1. Skin Application Food Test (SAFT)

FIGURE 2. Skin biopsy procedure

FIGURE 3. Curettage of mollusca contagiosa

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Introduction

Chapter 1

Aspects of pain in medical care in children

INTRODUCTION

Fear and pain can make relatively simple investigations and treatments in children a traumatic experience. There is an increasing focus on the recognition, assessment, and management of pain in children [1]. Pain has been defined by the International Association for the Study of Pain Sub-Committee on Taxonomy as 'an unpleasant sensory and emotional experience connected with actual or potential tissue damage, or described in terms of such damage' [2]. They suggested that 'Pain is always subjective. Each individual learns the application of the word through experiences related to injury in later life' [2]. Children's previous experiences with pain will affect how they react to subsequent painful events. One should opt for a painless procedure whenever appropriate. Whenever possible pain-prevention or at least pain-reduction is very important to reduce children's distress. Studies on pain-reduction in various (dermatological) interventions and the choice of painless methods are presented in this thesis.

PAEDIATRIC PAIN: INTERACTING NEUROPHYSIOLOGICAL, DEVELOPMENTAL, BEHAVIOURAL AND PSYCHOLOGICAL FACTORS.

In pain there are two components: a neurophysiologically determined sensory component and an emotional one based on affective state, past experience, development, and a variety of other factors. The pain experienced by individuals is not linearly related to the amount of tissue damage they have incurred, but instead to a composite of the nociceptive stimulation from that damage plus a host of modifying factors that might diminish or magnify the pain [3]. In other words two critical dimensions of pain perception are the sensory components of the nociceptive stimulus and the affective and motivational components that underlie behaviours aimed at reducing or avoiding the noxious stimulus [4]. Zeltzer et al. summarised pain experiences and pain responses in a theoretical model (FIGURE 1) [4]. To understand and treat pain problems in children effectively requires knowledge of the maturation of somatosensory, emotional, and cognitive systems. Both the development of brain organisation and the interaction between the child and his or her environment is important [4]. The biological and behavioural capacities to respond to nociception develop relatively early in foetal life, and acute distress in response to tissue damage has been documented in pre-term and

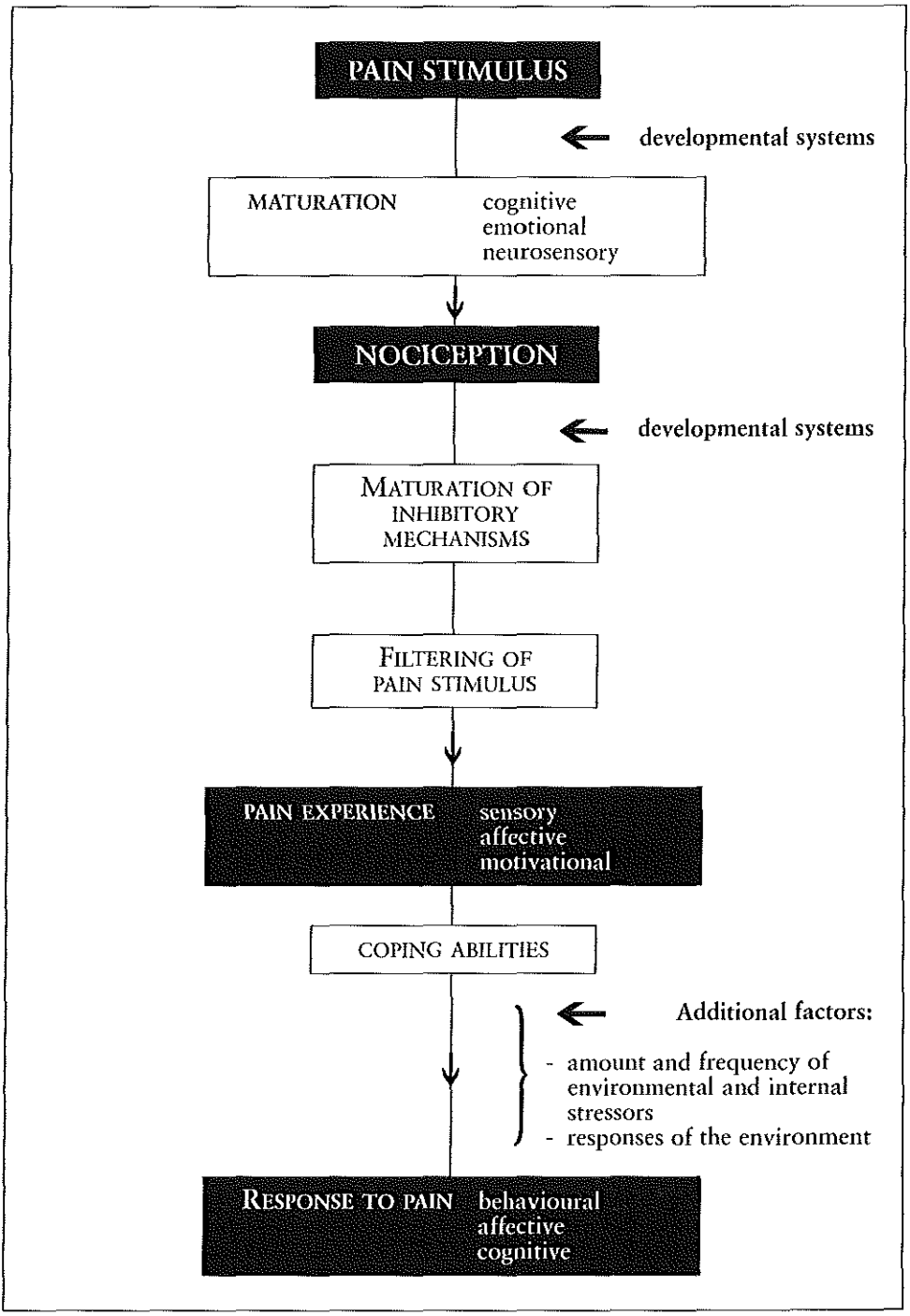

FIGURE 1. *Pain experiences and pain responses within a developmental framework: a theoretical model (from: Zeltzer et al. 1992).*

full-term neonates [5]. Nociception is present at birth. The activation of specific receptors in the periphery evokes reproducible responses within spinal cord dorsal horn neurones that in turn send projections to well demarcated cephalad loci. Certain areas of the nervous system are recognised to be particularly dense foci of processing and modulation of nociceptive inputs. Within each level, convergence and summation of incoming signals occurs in multiple time frames through both excitatory and inhibitory descending projections. In acute pain there is activation of two major types of nociceptors: high-threshold mechanoreceptors and polymodal nociceptors. Axons of high-threshold mechanoreceptors are myelinated and conduct in the A-delta velocity range (5-25 m/sec). These respond to strong pressure. Polymodal nociceptors respond to heat and algesic substances as well as to pressure. These axons are unmyelinated. They conduct slowly, in the C-fibre range (< 2 m/sec). Pain and pruritus are closely related sensations and are both carried in thin C-type nerve fibres, but why some sensations are interpreted as pain and others as pruritus is not known. Pain can usually be sharply localised to a particular part of the skin surface. Pruritus usually can only be attributed to a diffuse area of the skin. Pruritus is not a 'homogenous' sensation. Its qualities do vary. At times it has a burning quality and at other times it has an intense pain-like quality.
Nociceptors project to the spinal cord through primary afferents with cell bodies in dorsal root ganglia. Multiple incoming and descending stimuli combine to modulate the discharge patterns of dorsal horn cells. Neurotransmitters act as mediators within the many neural circuits. The nociceptive discharges are conveyed via axons that largely cross to ascend in the contralateral spinal cord. The spinothalamic tract, in the anterolateral cord, ascends to ventroposterior and medial thalamic nuclei and thence to associative and somatosensory areas of cerebral cortex that mediate the discriminative and somatosensory areas of cerebral cortex that mediate the discriminative and localising aspects of pain. Spinoreticular neurones project to the limbic system, and mediate arousal, affective responses, and neuroendocrine and autonomic sequelae of nociceptive input [6].

Maturation of cognitive, emotional, and neurosensory systems and their biological substrates in the growing infant will determine the capacity of the child to respond behaviourally and biologically to noxious stimuli. During maturation of inhibitory mechanisms the child's capacity of 'filtering' the environment will increase. Additional factors like the amount and frequency of environmental and internal stressors and the responses to the environment also influence the pain experience and response to pain [4]. In conclusion, there are many different influences on children's pain. Main influences are developmental stage, culture, gender, personality, family, society, religion and, very important, previous experiences of pain.

Pain is an important feature of children's life, no less than for adults. Clinical pain can never be seen primarily as a biological phenomenon or as only a psychological event, nor can pain be divorced from the social contact.

In the management of children's pain an appropriate assessment of pain in clinical settings is important. It is difficult to quantify the intensity of children's pain experience. The goal of pain assessment should be to provide accurate data to determine which actions should be taken to alleviate or abolish the pain and to evaluate the effectiveness of these actions. Knowing how much pain a child is experiencing is the first step towards offering appropriate treatment for his or her pain. The term 'measurement' is often used in a research context while 'assessment' is the preferred term in a clinical context. Measurement of pain refers to the quantification of various aspects of the experience. The assessment of pain needs to be appropriate for the individual child and his or her family.

A number of instruments which measure children's pain experiences are available. The QUESTT tool encompasses many of the important features of pain assessment. The acronym QUESTT stands for Question the child, Use pain rating scores, Evaluate behaviour and psychological changes, Secure parents' involvement, Take the cause of pain into account, and Take action and evaluate results [7]. An objective 'gold standard' of pain intensity is neither available at present nor expected to become available in the future. Pain can be measured by behaviour (what children do), biological markers (how their bodies react) and self-report (what children say) (TABLE 1).

	Self-report	Behavioural	Physiological
Infant		Cry characteristics Facial expression Body movement a.o.	Heart rate Respiratory rate Colour changes Hypoxia
Pre-schooler	Faces drawings Ladder scale a.o.	Different rating scales	
School-age	Visual analogue scales Numerical rating scales Word scales	Different rating scales	

TABLE 1. *Methods used in paediatric pain assessment.*

Children do not always tell the truth about their pain. Therefore, it is important to observe their non-verbal clues when assessing pain. A method for assessing and measuring pain relies on observation of behaviours, so-called behavioural measures. Behaviours associated with pain include facial expression, posture, and vocalisation or verbalisation.

Physiological measures have been useful in evaluating pain experiences associated with

short-term medical procedures. These are useful in combination with other data on pain-involving behaviours and pain-producing pathology. If pain persists over a period of time there is less increase in the sympathetic responses. This phenomenon is known as adaptation. Physiological signs only should not be used for assessing pain.
The introduction of appropriate tools of measurement into clinical practice creates a vision of a systematic approach for measuring pain. In this system personal belief, attitudes and subjectivity are reduced to a minimum. A number of pain assessment tools are available for use in clinical practice.
Pain is essentially a subjective experience. Assessment of pain should emphasise the child's perception of the experience. Tools are being developed to help children qualify their pain experience, so-called self-report measures.

Pain assessment in pre-school children is difficult. Few self-evaluation methods are reliable in older children. Behaviour scores are more appropriate in this population. Intuitive and global pain evaluation of parents, nurses or medical staff is mostly unreliable and insensitive. Therefore, behaviour observation pain scales have to be constructed. In recent years, patterns of behaviour in the neonate have been increasingly studied. The behaviours examined have been facial expression, body/limb movements and crying. Several observers have developed so-called facial coding systems with a view to aiding the classification of certain facial expressions. The evidence suggests that body movement in response to a painful stimulus can be used to assess pain in the pre-verbal child. Lack of response, however, does not indicate a lack of pain perception; it may indicate a higher intensity of pain. Research indicates that there is a typical cry in response to a painful stimulus. This is not considered a reliable indicator on its own. It should be used in combination with other indicators of pain. Again, lack of crying does not indicate lack of pain [7].
In infants, indirect measurements are used depending on infants' responses to presumably painful stimuli which can serve as indicators for pain. Some examples are cry spectrographic analysis and facial expression of infants undergoing a painful procedure. Stress scales are used for assessing distress in young children undergoing painful procedures. Examples for measuring pain in such infants are crying, grimacing and body movements. Scales with different behavioural items have been used.
There are three types of physiological indicators used to assess pain in the pre-verbal child: cardiovascular variables, respiratory variables and metabolic and endocrine variables. For pre-school children, researchers have devised many creative tools to help them indicate the degree of their pain. Examples are line drawings of faces, a photographic scale of facial expressions, a ladder scale, and linear analogue scales which include a straight, horizontal line with a happy, smiling face at one end and a sad, crying face at the other. The idea is that the child identifies varying levels of pain intensity using one of the numerous analogues [8].

For older children, a number of pain assessment tools are available for use in clinical practice that enable a systematic approach for pain assessment and management. The

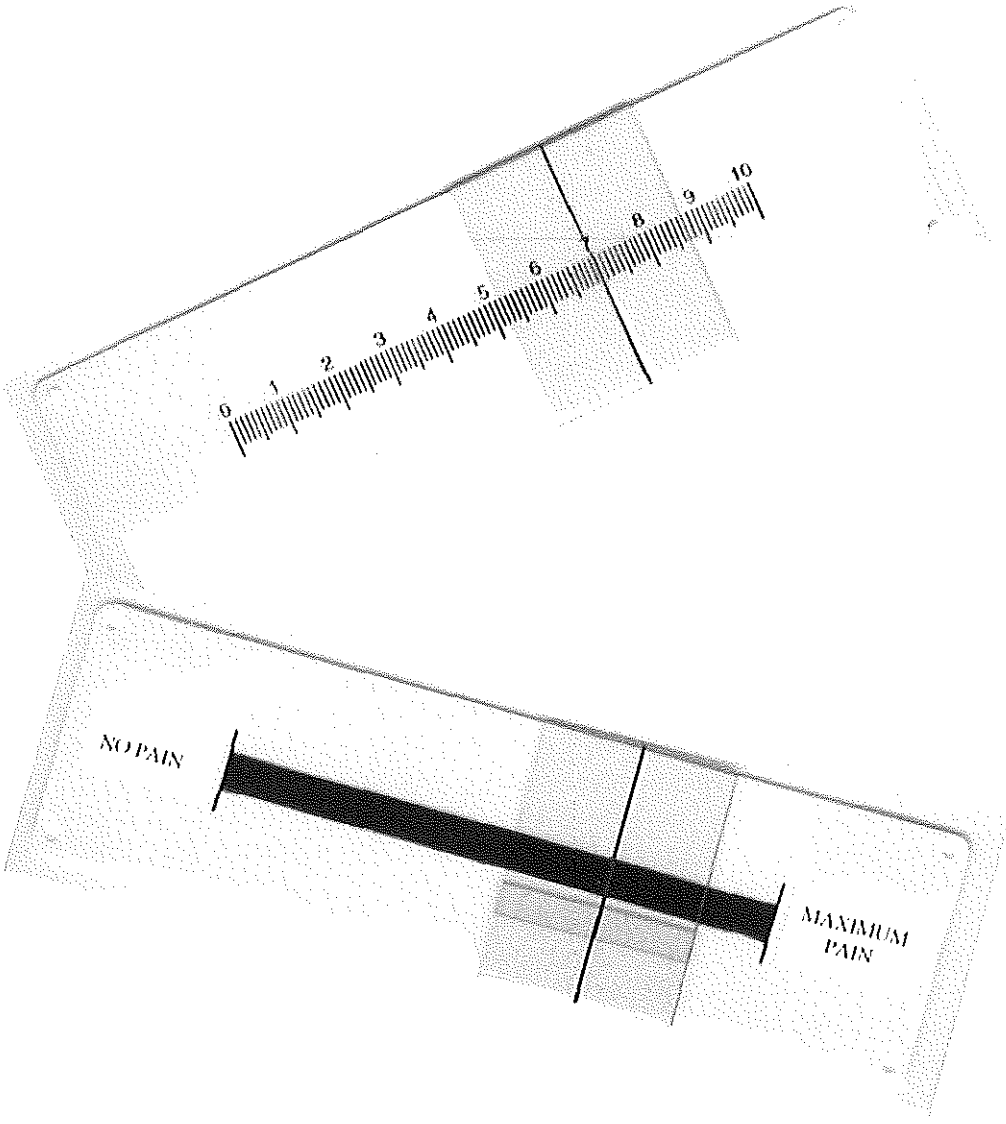

FIGURE 2A. *Visual analogue scale* [VAS].

selection of a pain assessment tool should be based on the child's age and cognitive ability and the time available to educate the child about the scale.

In children older than 4 years, visual analogue scales (VAS, FIGURE 2A) have been shown to be a reliable method for pain measurement. Such a scale may be a simple straight line extending from 'no pain' to the extreme limit of pain as defined by several phrases, e.g. 'pain as bad as it could possibly be'. In descriptive pain scales there is a limited number of categories such as 'mild, moderate and severe' and there is a considerable inter-individual variation in perception of these terms. In a study of 107 adult vol-

unteers, graded linear horizontal scales were both more reliable and preferred by participants. Visual analogue scales gave a more sensitive and accurate representation of pain intensity than did descriptive pain scales [9]. In a study of 100 children aged 2 to 17 years with juvenile chronic polyarthritis pain was measured using a visual analogue scale. Eleven percent failed to complete the scale, but this was particularly common below the age of 5. The authors observed that pain could be measured in most children and only a few of those over the age of 5 had any difficulty in understanding the concept of the visual analogue scale [10]. The visual analogue scale is useful for children with limited language skills, but the child needs the cognitive ability to translate experience into analogue format and to be able to understand proportionality.

Other assessment tools, among others, are a verbal graphic rating scale, a numerical rating scale for which children need to be numerate, thus excluding most children younger than five years, a poker chip tool in which four poker chips are placed in front of the child and described as 'pieces of hurt'. The Pain Assessment Tool for Children (PATCh) uses elements from five existing pain scales: faces, body outline, numerical visual analogue scale, descriptive words and behavioural scale. There are several faces scales. Different faces are shown depicting smiling to neutral to total misery (FIGURE 2B).

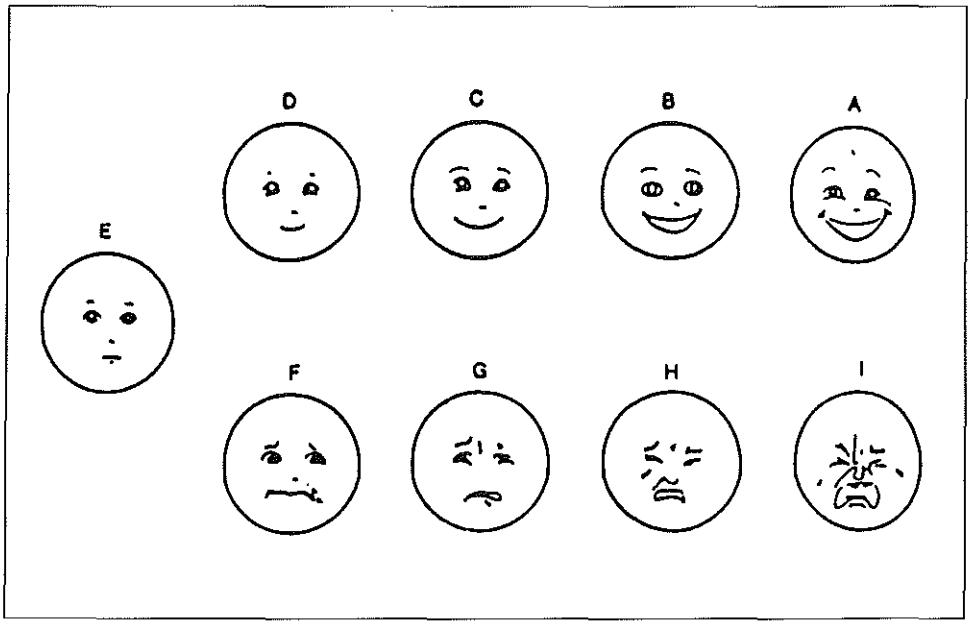

FIGURE 2B. *Visual analogue scale using facial expressions (From: McGrath PA, de Veber LL, and Hearn MT. Multidimensional pain assessment in children. In: Fields HL, Dubner R, and Cervero F (eds.). Advances in Pain Research and Therapy. Raven Press, New York 1985: 387-393).*

The 'Oucher' scale is made up of two scales: six photographs arranged vertically and a vertical numerical scale from 0 to 100. The scale of 0-100 means that the child needs

to be able to count to 100 in order to use it. Different questionnaires have also been developed. These are more appropriate for evaluating chronic pain.

PAIN AND LATER SEQUELAE

There used to be a misconception that very young children and neonates do not feel pain and do not have a memory for pain [11]. The biological and behavioural capacities to respond to nociception develop early in foetal life and acute distress in response to tissue damage has been documented in pre-term and full-term neonates [5]. Early pain experience is one of many relevant factors in the ontogeny of pain expression [5]. Very early painful experiences in life cannot be dismissed. They become embedded in a complex network of emotional experiences. Children's previous experiences with pain will affect how they react to subsequent painful events. Taddio et al. performed a randomised controlled trial of a topical anaesthetic cream (EMLA®) on pain in routine vaccination in infants aged 4 to 6 months. They observed that boys had higher pain scores than girls [12]. If this sex difference was a real effect, it may be partly related to previous experience of acute pain such as circumcision. They investigated post-hoc whether male neonatal circumcision was associated with a higher pain response to routine vaccination at 4 or 6 months. An observer and the paediatrician rated the infant's pain score on a 100 mm ungraded visual analogue scale. The infants were videotaped. A coder who was unaware of the treatments rated the pain responses on a modified behavioural pain scale (face, cry, and body movements). They noted that circumcision status was associated with increased infant pain response to routine vaccination at 4 to 6 months. Because memory of pain is believed to be important in subsequent pain perception and the main structures for memory are functional in the neonatal period, it is conceivable that pain from circumcision may have long-lasting effects on pain response and/or perception. In spite of the post-hoc nature of the analysis, and the relatively small sample size (42 boys received diphteria-pertussis-tetanus [DPT], and 18 also Haemophilus influenzae type b [HIB]), the authors suggested that analgesia should be routine for circumcision to avoid possible long-term effects in infant boys' pain responses [13].

Observation of the infants' facial expressions during immunisation injections indicated that by 6 months the children anticipated the event with fear and responded with pain and displayed some anger. Children's fear of pain changes with time. By the age of 20 months, children receiving needle injections display pain that is embedded in a complex matrix of the emotions of fear and anger. From the age of 2 years, many children fear a needle puncture more than anything else. For some the fear persists into adolescence and adulthood and may lead to actively avoiding necessary health care [11, 14]. One essential feature of a Pavlovian or classical conditioning paradigm is that an organism learns by associating neutral with non-neutral stimuli. One may learn to associate a previous neutral stimulus like visiting a doctor or dentist with non-neutral stimuli such as pain, fear and anxiety. Such an individual may then develop a phobic reaction to doctors or dentists because of their association with unpleasant stimuli [15].

PHOBIA: NEEDLES AND DENTISTS

According to the Diagnostic and Statistic Manual (DSM)-IV a phobia is defined as the presence of fear and avoidance behaviour. Needle phobia is not confined to children, is not an emotion-driven or transient phenomenon and is not a rare condition. Clinicians have to be aware of needle phobia because needle phobic individuals tend to avoid medical treatment which may lead to serious problems. The aetiology is rooted in an inherited vasovagal reflex that causes shock with needle puncture. With repeated needle exposure such individuals tend to develop a fear of needles. The avoidance of needles, doctors and dentists is central in the definition of needle phobia. Avoidance of health care is a health care problem [16]. There is evidence for a hereditary component to needle phobia. In addition to genetic factors, however, a learnt component to needle fear can also be identified. Needle fear often first comes into awareness after an adverse experience at the doctor's or the dentist's office. The learning of fear often becomes generalised in these individuals. Those who are initially fearful only of needles may develop fear of objects or situations associated with needles, for example blood, doctors, dentists, hospitals and even the antiseptic smell in offices or hospitals. Topical anaesthesia at the site of injection can be used to interrupt the vasovagal reflex at its origin so that the reflex is not triggered. If this is used consequently, then there is an intriguing possibility that needle phobia may be reduced or eliminated [16].

Studies have shown that child dental fear was related to age, general fears and dental fears of mothers. Traumatic medical experiences were also reported as important factors in the development of child dental fear. Dental fear and anxiety may lead to deterioration of dental health and avoiding of dental care. It may cause clinical behaviour management problems and more carious surfaces [17]. Dental anxiety was significantly related to pain reports [18]. Accomplishing painless treatment should be regarded as an important goal for the dentist [17].

PAIN-PREVENTION AND PAIN-REDUCTION

Children learn to be afraid of all kinds of injections at a very early age. Extreme fear can make minor procedures very traumatic for the child and time-consuming for the personnel involved. It is preferable to avoid this.

Health professionals often do not seem to appreciate fully the anxiety and fear that the needle provokes in their patients. In one survey of 119 children, 65 children thought that a 'shot' or 'needle' hurt more than anything else that they had ever experienced. Many children mistrust doctors and nurses who tell them that a needle will not hurt, but they become angry when it does. An anaesthetic cream, although not completely eliminating the fear associated with a needle puncture, should be a welcome adjunct to various psychological and pharmacological interventions available for reducing such fear in children [19].

HISTORICAL DEVELOPMENT OF LOCAL ANAESTHESIA

Local anaesthesia, the ability to reversibly block nerve transmission, permits a wide range of diagnostic and therapeutic procedures used in dermatology today. Modern local anaesthetics are the products of a rich history of evolution and progress, spanning more than 400 years. Peruvian Incas chewed coca leaves and dropped their saliva onto the wounds to relieve pain. In 1564 Ambroise Pare, a French surgeon, described selective local anaesthesia through nerve compression for amputation of an extremity. In 1784 James Moore, a British surgeon, developed a clamp to provide anaesthesia through nerve trunk compression. Charles-Gabriel Pravez and Alexander Wood concurrently developed hypodermic syringes in 1853. Wood was credited with the first subcutaneous injection of opiates to relieve pain. In 1855, Gaedcke from Germany isolated alkaloid extracts from the South American plant Erythroxylum coca. This was purified by Albert Neimann in 1858 and named cocaine. In 1869, Potain was first to observe that water could act as an effective cutaneous anaesthetic. In 1880, Vasilius von Anrep from Russia reported on the anaesthetic action of cocaine when applied to mucous membranes. William Stewart Halsted performed an inferior alveolar nerve block via hypodermic needle infiltration with cocaine in 1885. At the end of the 19th century Abel, Furth, Takamine and Aldrich produced adrenaline from extracts of the suprarenal gland. In 1897, Heinrich F.W. Braun recommended addition of adrenaline to cocaine solutions to reduce toxicity. Alfred Einhorn synthesised novicaine (procaine) in 1905. In 1918, Macht described the use of benzylalcohol as a local anaesthetic. Rosenthal and Minard reported on the anaesthetic effects of antihistamines in 1939. Xylocaine (lidocaine) was synthesised in 1946 by a Swedish chemist, Nils Loffgren. In 1948, the FDA application noted that the maximum dose for lidocaine was 'probably the same as for procaine'. Steffen, Zimmerman and Mihan reported in 1956 on the specific use of diphenhydramine as a local anaesthetic. In 1989, Jeffrey A. Klein presented his work on tumescent anaesthesia and liposuction to the Annual Meeting of the American Academy of Cosmetic Surgery. This shows the refinements of local anaesthesia from saliva to tumescent anaesthesia. The fields of anatomy, neurobiology, pharmacology, engineering and surgery are all integral to the development of today's anaesthetics and techniques [20].

CONCLUSION

The management of pain associated with paediatric procedures is not a simple task. Clinical judgement will always be necessary. A reliable, valid and measurable assessment should be performed on a regular basis to manage pain in children. There are many different influences on children's pain including developmental stage and previous experiences of pain. Pain assessment should evaluate the effectiveness of pharmacological and non-drug interventions. The QUESTT approach encompasses the important aspects of pain assessment. Pain can be measured by behaviour, biological markers and self-report.

Psychological or pharmacological approaches are available for pain relief. The decision to use one of them or both will depend on the knowledge of the procedure, an understanding of the child and the expected pain and anxiety in the child undergoing that procedure. The goal of pain management for paediatric procedures is to minimise distress and permit a successful procedure. Producing a co-operative child is an insufficient goal if the child suffers 'in silence' [21]. It should be emphasised that whenever possible pain-prevention or at least pain-reduction, is very important to reduce children's distress. This is also true for diagnostic and therapeutic procedures in paediatric dermatology.

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Chapter 2

Aims of the study

Considerable proportions of the patients who consult a dermatologist are children. A special approach is required in order to examine a child thoroughly. Children are often afraid of doctors and hospitals. This may be based on an unpleasant experience. Moreover, undertaking additional examination in children for further diagnostics or for further advice is also sometimes exhausting. TABLE I shows diagnostic and therapeutic procedures in (paediatric) dermatology, preventive procedures and other indications in which pain-reduction or pain-prevention is desired. Simple treatment of dermatological problems in a child may lead to serious problems because of pain and anxiety and may even become impossible.
Therefore, the initial investigations that were pursued focused on the evaluation of pain-reducing measures at the paediatric dermatological clinic, whereby the diagnostic interventions and treatment may be approached in a child-friendly manner. One should preferably opt for a painless procedure whenever appropriate. This has several advantages. The dermatologist can conduct the examinations more thoroughly which contributes towards better diagnostics. If certain interventions can be carried out easily then these would be more efficient. Moreover, the child will have less traumatic memories of the visit to the physician, whereby examinations and therapy at subsequent visits would be easier.

The studies described in the first part of the thesis consist of the investigations into pain-reducing measures for superficial (dermatological) interventions. A local anaesthetic only was used in all investigations. It was investigated whether the application of an emulsion provided adequate pain-reduction for various indications. Adverse side effects of this emulsion were also investigated.

The second part of the thesis deals with studies into painless (child-friendly) diagnostic investigations in children with atopic dermatitis. A painless skin test (SAFT: Skin Application Food Test) was developed for establishing food allergy in children. This test was used to investigate food allergy in children. The test was investigated further and compared with prick-prick test and oral challenge.

❑ DIAGNOSTIC PROCEDURES

- Skin biopsy procedure for histological examination (FIGURE 1)
- Skin tests in evaluating (food) allergy (FIGURE 2)

❑ THERAPEUTIC PROCEDURES

- Curettage of mollusca contagiosa (FIGURE 3)
- Treatment of condylomata acuminata (FIGURE 4)
- Laser treatment of port-wine stains (FIGURE 5)
- Debridement of leg ulcers (FIGURE 6)

❑ PREVENTIVE PROCEDURES

- Vaccination

❑ OTHER INDICATIONS IN CHILDREN DESIRING PAIN-PREVENTION OR -REDUCTION

- Venipuncture
- Intravenous cannulation
- Heel lances
- Prick tests
- Circumcision
- Separating preputial adhesions
- Lumbar punctures

TABLE 1. *Diagnostic and therapeutic procedures in (paediatric) dermatology, preventive procedures and other indications in which pain-reduction or pain-prevention is desired.*

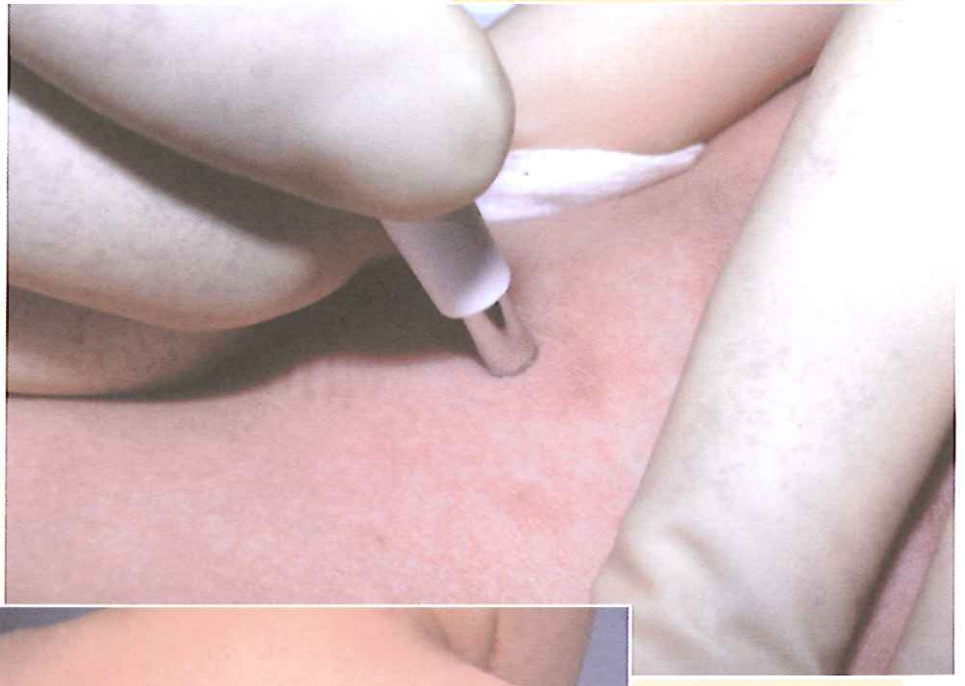

FIGURE 1.
Skin biopsy procedure.

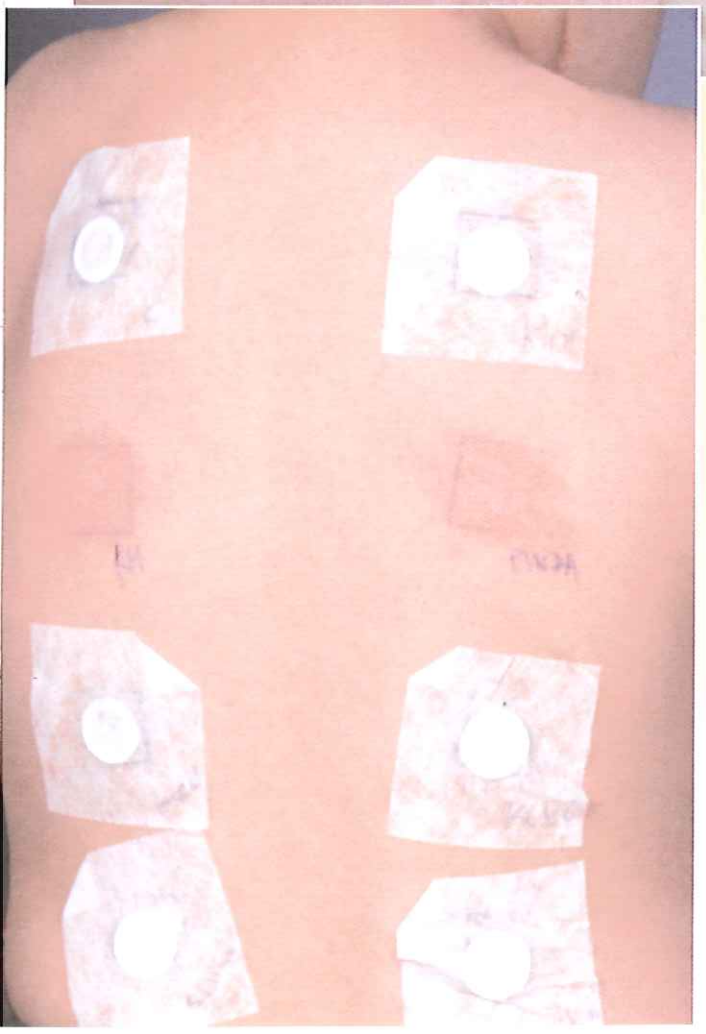

FIGURE 2.
The Skin Application Food Test (SAFT).

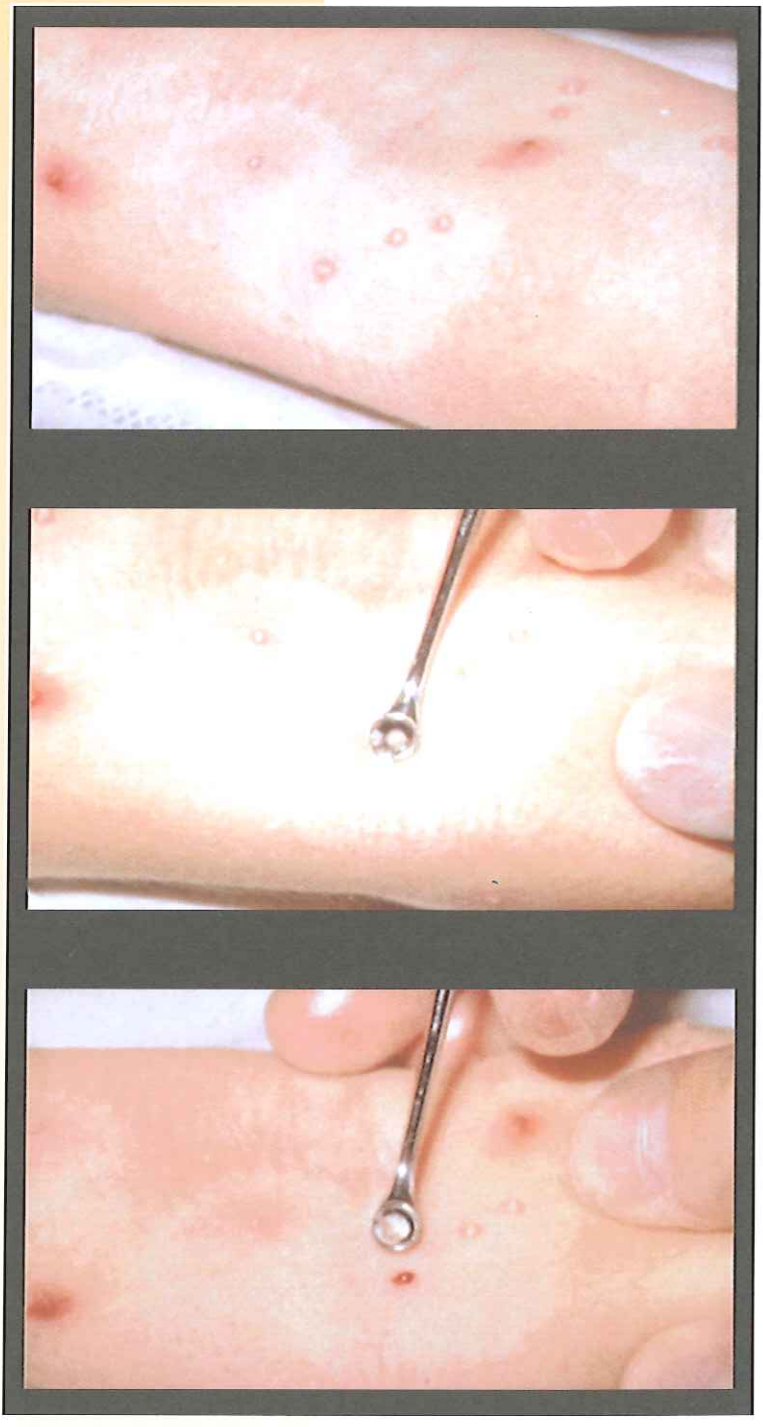

FIGURE 3. *Curettage of mollusca contagiosa.*

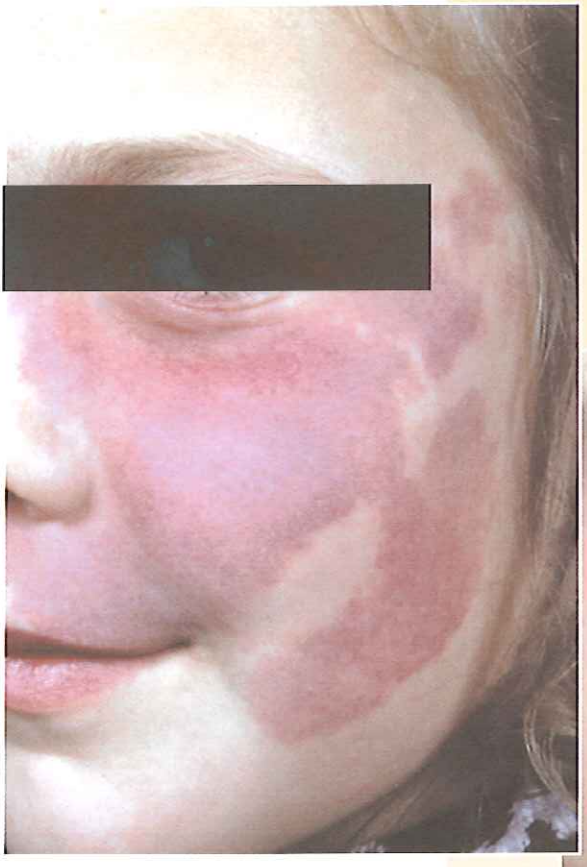

FIGURE 5. *Port-wine stain.*

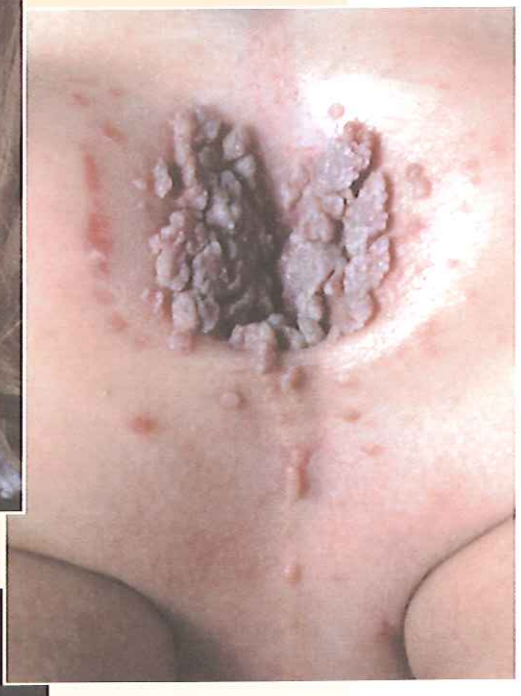

FIGURE 4.
Condylomata acuminata.

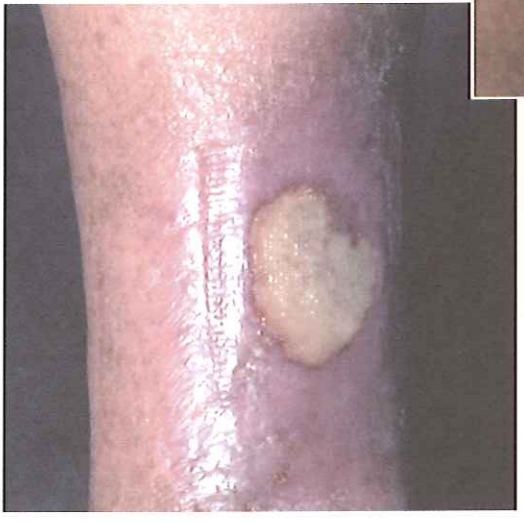

FIGURE 6. *Leg ulcer.*

Part I
Pain-reduction

Chapter 3

Topical anaesthetics in dermatology; indications for EMLA®

based on:

Waard-van der Spek FB de, Berg GM van den, Oranje AP. Lidocaïne-prilocaïne-crème: een aanwinst bij lokaal anaesthesie. Nederlands Tijdschrift voor Geneeskunde 1991; 135: 1343-1345

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Chapter 3

Topical anaesthetics in dermatology; indications for EMLA®

LOCAL (TOPICAL) ANALGESIC DRUGS

Painful interventions may have serious adverse psychological impact particularly in children. Injection of analgesics such as lidocaine and other related substances is quite painful. Local anaesthesia plays a useful role in simple or superficial interventions. An overview of the historical development of local anaesthesia is given in chapter 1. Lesions can be frozen by refrigerants such as ethylchloride spray. The same effect may be achieved by liquid nitrogen, but its lower temperature may cause greater post-operative discomfort. Local anaesthetics are generally ineffective when applied to intact human skin because they are poorly absorbed. EMLA® is a topical anaesthetic cream developed by Broberg and Evers for use on intact skin [1]. The acronym EMLA® stands for Eutectic Mixture of Local Anaesthetics. EMLA® is a mixture of lidocaine 25 mg/g and prilocaine 25 mg/g. EMLA® cream comprises the following ingredients: 25 mg lidocaine, 25 mg prilocaine, arlatone 289 (emulsifier), carbapol 934 (thickener), and distilled water in 1 ml cream. Other local anaesthetics that are used, among others, include 10% lidocaine gel containing glycerrhetinic acid monohemiphtalate disodium as an absorption promoter, amethocaine and 4% tetracaine containing cream (TABLE 1).

- Amethocaine patch
- Ethylchloride spray
- Lidocaine gel
- Lidocaine gel + glycerrhetinic acid monohemiphtalate disodium (absorption promoter)
- Lidocaine Adrenaline Tetracaine (LAT) gel
- Lidocaine/prilocaine eutectic mixture (EMLA®)
- Liquid nitrogen
- Tetracaine Adrenaline Cocaine (TAC) gel
- Tetracaine cream

TABLE 1. *Some topical anaesthetics used in dermatology.*

GENERAL PRINCIPLES, CLASSIFICATION AND STRUCTURE

A local anaesthetic cream consists of hydrophilic groups, usually a tertiary amine, and hydrophobic groups, generally an aromatic residue. An alkyl chain separates these groups. They may be separated into two groups: those containing an ester linkage (e.g. procaine, tetracaine and cocaine), and those containing an amide linkage (e.g. lidocaine and prilocaine) [2]. The linkage is responsible for the pathway by which the molecule is metabolised and excreted.

MECHANISM OF ACTION

Local anaesthetics act on sodium channels in the nerve membranes. The conduction is decreased via interaction with specific binding sites and total inhibition of conduction is achieved with increasing concentration of the local anaesthetic [2]. The base that is used in EMLA® makes it possible to achieve high concentrations of lidocaine and prilocaine in an aqueous solution, allowing a good absorption through intact skin. A high concentration of the drug is also necessary for optimal penetration through diffusion barriers. The emulsion droplets of EMLA® cream contain a high concentration of the local anaesthetics, although the total concentration in the emulsion is relatively low (5%). Local anaesthetics such as lidocaine are available in an uncharged base form and a water-soluble salt form. The salt form dissociates into cations, anions, and the uncharged base when dissolved in water. Penetration and diffusion of the local anaesthetic through the tissues are possible by the uncharged base form. The cations induce the impulse-blocking effect in the nerves.

(DERMATOLOGICAL) INDICATIONS

EMLA® produced effective analgesia in the skin prior to a variety of superficial skin interventions. Ethylchloride spray (ECS) caused more local irritation in a study in which the analgesic efficacy and local tolerance of EMLA® and ECS before intravenous cannulation in pre-medicated children were compared [3]. Several more local anaesthetics are available and have been evaluated. For example, a 10% lidocaine gel containing glycerrhetinic acid monohemiphtalate disodium as an absorption promoter reduced the pain upon venous cannulation in adults and in children, although further improvement seemed necessary in order to achieve ideal conditions [4].

Tetracaine adrenaline cocaine (TAC) gel was effective in laceration repair, but serious adverse reactions have been reported. Lidocaine adrenaline tetracaine (LAT) gel was as effective as TAC gel in topical anaesthesia for facial and scalp lacerations in a randomised double-blind study in 95 children aged 5 to 17 years, but additional studies on its safety are necessary [5].

Amethocaine in the form of a self-adhesive patch was evaluated in an open study in

children before venous cannulation. A satisfactory anaesthesia was achieved in 80% of the patients, but 20% of the patients felt moderate to severe pain [6].
EMLA® cream was compared with a 4% tetracaine containing cream for preventing venipuncture induced pain in children. EMLA® was noted to reduce the pain more effectively [7].
EMLA® used with glyceryl trinitrate (GTN) ointment that promotes venous dilatation made intravenous cannulation technically easier in adults. However, side effects of GTN include headaches and hypotension. Further studies are necessary, especially in children, for establishing the efficacy and the safety of this combination [8].
In fact, EMLA® is the only registered topical anaesthetic for use in children from the age of 3 months. Studies indicated that EMLA® was also safe to use in neonates. In the Netherlands, a registration request for use in neonates has been submitted. At present, we prefer to use EMLA® for inducing local anaesthesia for superficial interventions. Indications for EMLA® cream are discussed in the following section.
EMLA® cream produced effective analgesia in both intact and diseased skin before a variety of clinical procedures. Several studies on different indications in children (mollusca contagiosa, skin biopsy and MMR vaccination) are described in this thesis. Other indications are summarised below.

The efficacy of EMLA® cream was compared with that of lidocaine infiltration in alleviating pain during arterial cannulation in a double-blind, double-dummy study. Forty non-premedicated adults were allocated randomly to four groups receiving EMLA® cream alone, EMLA® and 0.9% saline infiltration, EMLA® and 1% lidocaine infiltration, or placebo cream and 1% lidocaine infiltration. In the three EMLA® groups, the pain scores by both patients and observers were significantly lower than that in the placebo-lidocaine group [9].

TABLE 2 presents a selection of studies in which EMLA® cream was used as a topical anaesthetic in children. We chose several representative trials (double-blind and placebo-controlled, known application time) involving a relatively large number of patients. Smaller studies with promising results in specific indications are also described.

VENIPUNCTURE, INTRAVENOUS CANNULATION AND LUMBAR PUNCTURE

The efficacy of EMLA® cream in venipuncture and its analgesic effect based on length of application were studied by Hallén et al. [13]. In that double-blind, randomised study of 114 children aged 4 to 17 years, application times were 20 minutes or longer. The product's analgesic effect became evident at or about 60 minutes. For shorter application times there was no difference in analgesic effect between the cream and placebo. In a double-blind study of 40 children aged 3-13 years, EMLA® reduced the pain after application time of at least 60 minutes [15]. However, in a study of 111 children aged between 1 and 5 years, a minimum application time of 30 minutes was required to obtain effective analgesia [16].

Author/Study design	Number of patients	Application time (min)	Result
Molluscum contagiosum			
Rosdahl et al./open (1988)	55	60	Effective >90% no pain
Wagner et al./open (1989)	40	30	Effective
de Waard-van der Spek et al./ double-blind (1990)	83	15,30,60	Already effective after 15 min
Venipuncture			
Hallén et al./double-blind (1984)	114	>20	Effective after 60 min
Dohlwitz et al./double-blind (1985)	110	>20	Effective
Cooper et al./double-blind (1987)	40	60	Effective
Hopkins et al./double-blind (1988)	120	30-300	Already effective after 30 min
Intravenous infusion insertion			
Ehrenström et al./double-blind (1983)	60	60	Effective
Hallén et al./double-blind (1984)	111	60	Effective
Maunuksela et al./double-blind (1986)	60	>60	Effective
Manner et al./double-blind (1987)	40	65-280	Effective
Lumbar puncture			
Halperin et al./double-blind crossover (1989)	14	60-100	Effective
Cutaneous hypersensitivity (heel lances)			
Fitzgerald et al./open (premature infants) (1989)	17	? (probably a few minutes)	Reversible hypersensitivity by EMLA®
Separation of preputial adhesions			
MacKinley/open (1988)	39	60	Completely pain-free in 32 boys

TABLE 2. *Studies on indications in children for the use of* EMLA® *cream as a topical anaesthetic.*

Other indications are injections, intravenous cannulation and lumbar punctures in which the cream significantly reduced pain [17,19,20,23]. The acceptable application times in these studies ranged from 30 to 60 minutes and for intravenous cannulation it was at least 45 minutes.

HEEL LANCES

A double-blind study was performed in 17 premature infants in whom the flexion reflex threshold was used as a measure of sensation. In an area of local tissue damage as a result of routine heel lances, the threshold was one-half of that in the intact other heel. This hypersensitivity to tissue damage was reversed by treating the damaged area with EMLA® cream. Treatment with placebo had no effect [21].

PREPUTIAL ADHESIONS

In an open study, EMLA® was successfully used for separating preputial adhesions in 39 boys [22].

CONDYLOMATA ACUMINATA (CA)

Condylomata acuminata (CA) are anogenital warts that are widespread in adolescents and adults. The infection, which is caused by human papillomavirus (HPV), is usually sexually transmitted. To date, about 60 HPV types have been identified, but only some of these are responsible of CA infections [24]. Condylomata acuminata have also been reported in children [25,26]. CA are removed by cauterisation or laser treatment and the efficacy of EMLA® analgesia during this treatment has been investigated in a number of clinical studies.

A preliminary study by Hallén et al. [27] suggested that EMLA® cream provided effective analgesia for the cautery of genital warts in 96% (n=57) of men and in only 40% of the 51 women in the study. However, a study by Ljunghall and Lillieborg [28] found that EMLA® cream was effective on vulval mucosa provided that the application time was optimised. Ten women were enrolled in a pilot study for establishing the time of onset of analgesia as determined by a pinch test. Anaesthesia was found to occur after application times of only 5 to 7 minutes. A further 42 women underwent cautery of genital warts following application of EMLA® cream for 10, 15 or 20 minutes. A 10-minute application provided sufficient anaesthesia for the cautery of genital warts in 92% of the women. However, longer application times resulted in less effective analgesia [28] which may explain the apparent failure of EMLA® cream to provide adequate analgesia in studies in which it was applied to female genital mucosa for longer periods. Rylander et al. [29] assessed the time of onset and application time required for EMLA® induced local anaesthesia in a double-blind trial involving 80 women with CA on the genital mucosa. EMLA® (n=60) or placebo (n=20) cream was applied 1 to 75 minutes prior to carbon dioxide laser treatment of a test site with a CA lesion. The degree of pain experienced was assessed by the patient using a Visual Analogue Scale (VAS). Analgesia was discernible after only 4 to 5 minutes, although the most effective

analgesia was achieved after applying EMLA® cream for 5 to 15 minutes. Patients receiving EMLA® cream, regardless of application time, recorded significant lower pain scores than the placebo group. Additional analgesia was required for 7 patients (12%) in the EMLA® group and for all 20 patients in the placebo-treated group.

Van den Berg et al. [30], in an open study of 60 men, compared the analgesic efficacy achieved by EMLA® cream and by lidocaine injection for punch biopsy and electrocoagulation of CA on the genital area and/or perianal area. EMLA® cream (n=31) was applied for 13 to 45 minutes, or lidocaine infiltration (n=29) carried out 0.5 to 4 minutes prior to removal of the warts by electrocoagulation. Pain was assessed by the patient using a 4-point verbal scale and a VAS. Lidocaine injection itself was reported to be slightly (59% of the patients) or moderately (34%) painful, whereas application of EMLA® cream was painless. EMLA® cream had a lower analgesic efficacy than lidocaine infiltration for electrocoagulation (satisfactory analgesia achieved in 62% versus 100% of patients, respectively), but EMLA® cream proved very useful for taking punch biopsies (effective analgesia achieved in 94% of patients) or as pre-medication to alleviate the pain of infiltration.

A similar study, comparing EMLA® cream (application time 10 minutes) with lidocaine infiltration, was carried out by Lassus et al. [31]. This study assessed the pain experienced during administration of anaesthesia and during laser surgery of genital warts in 100 male patients. Although the efficacy of infiltrated anaesthetic was slightly better than EMLA® cream in alleviating pain during surgery, the overall treatment (administration and surgery) pain score was significantly lower in the EMLA® group as a result of the higher pain scores for the infiltration process. The authors therefore suggested that EMLA® cream should be the treatment of choice in laser surgery of genital warts.

A more recent study by Frega et al. [32] also recommended EMLA® cream as the anaesthetic of choice for laser surgery of genital warts. Pain during administration of anaesthesia and during surgery was assessed in 180 patients (90 females and 90 males) receiving EMLA® cream and 90 patients (45 females and 45 males) receiving 2% Carbocaine® infiltration. The application time for EMLA® cream was 5 to 18 minutes (median 7 minutes). Unlike the study by Lassus et al. [31], the results of this study indicated that pain was significantly less in the EMLA® group than in the infiltration group, both during administration of anaesthesia and during laser surgery. Side effects such as pallor and/or oedema occurred more often in the infiltration group. This together with occasional bleeding could affect the efficacy of laser treatment.

PORT-WINE STAINS

In the past, the use of argon and carbon dioxide lasers for removing port-wine stains resulted in very painful operations. The infiltration of lidocaine to alleviate the laser pain was itself painful. In addition, argon lasers could cause scarring and were not effective for pale port-wine stains. The more recently available pulsed-dye laser can be used for pale port-wine stains and is less painful than treatment with other types of

lasers. Thus, this type of laser therapy is now available for young children.

Lasers have been used in models to compare the efficacy of different anaesthetics. For example, Arendt-Nielssen and Bjerring [33] reported a study in which the efficacy of EMLA® cream was compared with that of lidocaine infiltration, using an argon laser for experimental pain stimulation. Three parameters were measured: pain threshold (i.e. when no pain was felt but other sensations could be detected), sensory threshold (no sensations felt) and pain-related cortical responses. The effect of EMLA® cream application time on the efficacy and duration of analgesia was determined. With application times of less than 2 hours, the analgesic effect of EMLA® increased after removal of the cream. Lidocaine infiltration provided total sensory block almost immediately after injection. A similar degree of efficacy was achieved with EMLA® cream, either immediately after an application time of 100 or 120 minutes or 20 minutes after the removal of the cream following an application time of 80 minutes.

Several studies on the clinical use of EMLA® cream for the treatment of port-wine stains has been reported. These have shown that EMLA® provides pain-free administration of effective analgesia without affecting the degree of lightening of the port-wine stain achieved during treatment.

Lanigan and Cotteril [34] reported the effect of EMLA® cream in the treatment of facial port-wine stains with a tunable dye laser. The cream provided adequate analgesia in 8 of the 10 treated patients and was well tolerated. The results of the laser treatment were not different in the EMLA® group compared with those given conventional infiltration analgesia, and the authors concluded that EMLA® cream could be recommended for use during port-wine stain removal.

Ashinhoff and Geronemus [35] investigated whether pre-treatment with EMLA® cream, which is thought to cause vasoconstriction of cutaneous blood vessels, affects the efficacy of subsequent pulsed-dye laser treatment of port-wine stains. Eight patients, aged 4 to 32 years, received test treatments on two sites in the same area of port-wine stain. One of the test sites was pre-treated with EMLA® cream (60 minutes application under occlusion followed by 15 minutes unoccluded). The other site was not pre-treated. EMLA® cream was found to provide effective topical analgesia during treatment. Examination of the test sites 6 to 8 weeks after laser treatment showed that EMLA® pre-treatment did not affect the degree of lightening of the port-wine stain. Thus EMLA® cream can be used to alleviate the pain of pulsed-dye laser treatment without affecting the efficacy for the removal of the port-wine stain.

Tan and Stafford [36] assessed the efficacy of EMLA® cream versus placebo or no treatment in a study involving 73 children (aged 5 to 16 years) with port-wine stain who were treated with pulsed-dye laser. Three test sites within one area of port-wine stain were pre-treated with EMLA® cream, placebo cream or no cream and covered with an occlusive dressing for 60 minutes. Laser treatment was then carried out on each area and the degree of pain experienced assessed by the patient, physician and an independent observer, using a modified VAS that included diagrams ranging from happy to crying faces. The pain scores for the three individuals carrying out the assessments were in good agreement. The mean pain scores for no treatment, placebo and EMLA® were

38.6, 32.1 and 10.9, respectively. These values were significantly different from one another ($p<0.0001$). The investigators also reported that 52% of the EMLA® treated sites were pain-free during laser therapy, compared with only 11% of the placebo-treated sites ($p<0.001$).
However, our own experience was that the analgesic efficacy of EMLA® was not adequate in the treatment of port-wine stains in young children.

LEG ULCERS

Effective analgesia was achieved with EMLA® for surgical debridement of leg ulcers of venous or arterial origin [37].

ACNE

Whiteheads, a common symptom in acne, not only are disfiguring but may also develop into painful inflamed lesions. Application of EMLA® cream for 60 to 180 minutes has been shown to provide adequate pain-relief for such inflamed lesions [38]. In a study reported by Bottomley et al. [39] EMLA® cream was used during light electocautery and fulguration of whiteheads in 12 patients. The pain scores (VAS) varied considerably between individuals in the study. One patient who was unable to tolerate either electrocautery or fulguration without analgesia was found to tolerate fulguration when EMLA® was provided.

HIRSUTISM

All the currently available methods for hair removal, such as electrolysis, thermolysis and temporary methods (e.g. wax) are painful or uncomfortable. Induction of analgesia by infiltration can be very painful in some areas of the face, such as the upper lip, where excess hair is commonly located. The use of EMLA® cream in epilation therefore has great potential. Only one clinical trial has been reported to date. Hjorth et al. [40] investigated 21 patients in a double-blind, placebo-controlled crossover study. EMLA® or placebo cream (5 g) was applied to the upper lip for 1 hour and then hair was removed by thermolysis over a period of 10 minutes. Pain was assessed by the subject and the cosmetologist on a 4-point scale. Significantly less pain was experienced with EMLA® compared with placebo, and 90% of the patients expressed a preference for EMLA® cream.

COMMON WARTS

A study reported by Vesterager et al. [41] showed that EMLA® cream does not provide effective analgesia for the removal of common warts by curettage. A total of 89 patients

were evaluated. Forty-seven received lidocaine infiltration and 42 received EMLA® cream (2.5 g, 120 minutes application time). Although the pain rating for administration of anaesthetic was significantly lower for the EMLA® group (100% reported 'no pain', compared with 25% in the lidocaine group), the overall rating for EMLA® was significantly less than that for lidocaine ('very good' overall impression reported by 33% and 62% of the patients, respectively; $p<0.001$) owing to the less effective analgesia provided during curettage. The efficacy of EMLA® did not depend on the size of the wart. The results suggested that EMLA® does not penetrate the highly hyperkeratotic wart area at a rate sufficient to allow accumulation of EMLA® in the skin and the authors concluded that EMLA® could not be recommended for curettage of warts.
Oranje and de Waard-van der Spek (unpublished observation) have also noted that EMLA® analgesia is not sufficient for cryotherapy of common warts.

SKIN TESTS

Intradermal skin testing is a proven technique for determining the presence of specific IgE-mediated reactions in atopy. However, the pain and apprehension associated with intradermal testing cause many parents to hesitate in letting their child undergo the procedure. An alternative reliable painless test or the use of a topical anaesthetic prior to skin testing would seem an ideal solution for this dilemma. The product should be safe and efficacious and not interfere with the test response. Wolf et al. [42] in an open study evaluated the anaesthetic properties of EMLA® prior to intradermal skin testing. They also evaluated the possible effect of EMLA® on the extent of the wheal and flare reaction. In 40 children, aged 4 to 9 years, complete anaesthesia was obtained after one hour application with EMLA® in 36 cases (90%). There were no significant differences in wheal or flare reactions between treated and untreated skin.
However, there are reports on suppression of the flare response when histamine or allergen is injected into EMLA®-treated skin. Sicherer et al. [43] evaluated the effect of EMLA® in terms of pain perception and effects on the wheal and flare responses for prick and intradermal allergen skin tests and intradermal histamine tests in 20 adults in a masked, placebo-controlled study. The subjects had a history of positive allergen tests. EMLA® significantly reduced the pain associated with diagnostic allergy skin testing. There was no effect on the size of the wheal response. EMLA® reduced the flare response and in some cases inhibited it completely. This must be taken into consideration in interpreting the results.

VACCINATION

Several studies into the application of EMLA® for vaccinations have been reported [44-47]. In the present studies, the application of EMLA® cream for subcutaneous injection with NaCl, intramuscular influenza vaccination and intramuscular Diphtheria,

Pertussis, Tetanus (DPT) vaccination was investigated. All studies were randomised, double-blind and placebo-controlled. These studies are summarised in TABLE 3. Taddio et al. [44] reported that EMLA® cream reduced the pain during insertion of the needle in 20 adult volunteers. However, in the same study, EMLA® cream had no effect on the pain resulting from injection of the physiological saline solution subcutaneously. In adults EMLA® reduced the pain of both the puncture and injection of intramuscular Fluzone® vaccination [45]. Studies were also performed in intramuscular DPT vaccinations in children [46,47]. In both studies lower pain scores and lowered intensity of crying was observed after EMLA® application.

Author	Indication	Size of the study	Age	Appl. time minutes	Scoring method	Results
Taddio et al.[44]	s.c. 0.9% NaCl	20	19-46 yrs (aver. 30 yrs)	60-75	VAS	Insert needle:after EMLA® pain << Injection: no difference
Taddio et al.[45]	i.m. Fluzone® vaccination	60	22-65 yrs (aver. 35 yrs)	60-90	VAS	Both puncture and injection: after EMLA® pain <<
Taddio et al.[46]	i.m. DPT vaccination	96	4-6 months (aver. 5 months)	60-120	behaviour	pain score and crying: after EMLA® <<
Uhari[47]	i.m. DPT vaccination	155	3-28 months (aver. 9 months)	3-145 (9 < 50 min)	VAS (parents & nurses)	pain and crying: after EMLA® << anxiety: no difference

TABLE 3. *Studies on the application of* EMLA® *cream for administering subcutaneous (s.c.) and intramuscular (i.m.) injections.*

CONCLUSION

Used correctly, EMLA® cream is a safe and effective topical anaesthetic. Application times required for the cream range from about 10 minutes for mucous membranes to 2 hours for the skin. The main dermatological indications, at present, in our opinion, are curettage of molluscum contagiosum (chapter 3), cauterisation of condylomata acuminata, laser therapy of port-wine stains and superficial surgical procedures at the mucous membranes (TABLE 4). For procedures on mucous membranes and genitals, data are available only in adults and studies in children are warranted. It is disappointing that analgesia with EMLA® cream is not sufficient for cryotreatment of common warts.

Indication	Application time (minutes)
Molluscum contagiosum	30 - 60 (15 in atopic dermatitis)
Skin biopsy (pre-treatment)	60
Condylomata acuminata	5 - 15
Port-wine stains (pulsed-dye laser)	60
Debridement leg ulcers	30
Vaccination	60

TABLE 4. *Indications and the recommended application times for* EMLA®.

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Chapter 4

EMLA® in molluscum contagiosum

based on:

Waard-van der Spek FB de, Oranje AP, Lillieborg S, Hop WCJ and Stolz E. Treatment of molluscum contagiosum using a lidocaine/prilocaine cream (EMLA®) for analgesia. J Am Acad Dermatol 1990; 23: 685-688

Chapter 4

EMLA® in molluscum contagiosum

INTRODUCTION

Treatment of molluscum contagiosum with a comedo extractor or a curette is widely used, although removal is usually painful. An anaesthetic cream containing 2.5% lidocaine and 2.5% prilocaine (EMLA® [*e*utectic *mi*xture of *l*ocal *a*naesthetics]) has been developed for topical application. The use of an oil-in-water emulsion ensures adequate absorption by intact skin [1]. Several studies [1-6] have shown significant alleviation of the pain associated with venipuncture and intravenous cannulation after application of EMLA® cream to the puncture site. The successful use of EMLA® cream has also been reported for other superficial procedures such as removal of tattoos [1] cutting of split-skin grafts [7] and cautery of condylomata acuminata [8]. In most studies the duration of application of the cream under occlusion was 60 minutes or more. Ehrenström et al. [3] reported a minimal effective application time of EMLA® cream of 45 minutes for intravenous cannulation in adults. This study was performed to evaluate the efficacy and minimal effective application time of EMLA® cream for the removal of molluscum contagiosum in children.

MATERIALS AND METHODS

STUDY DESIGN AND PATIENTS

The study was double-blind and placebo-controlled and included 83 children aged 4 to 12 years with five or more molluscum contagiosum lesions. The patients were randomly allocated to four groups: active treatment with EMLA® cream for 15, 30, or 60 minutes, or placebo. Power calculations had led to minimum group sizes of about 20 patients each (significance level 5%, power 90%). To obtain blinding, the placebo group was randomly subdivided into the same three application times as the active treatment group. The trial was stratified for the presence of atopic dermatitis. The study was approved by the Medical Ethical Committee of Erasmus University and University Hospital Rotterdam. Informed consent was obtained in writing from one of the parents of each patient before enrolment in the study.

TREATMENT PROTOCOL

EMLA® cream (Astra AB, Södertälje, Sweden), containing lidocaine, 25 mg, and prilocaine, 25 mg/g with polyoxyethylene (Arlatone 289) as emulsifier and carboxypolymethylene (Carbopol 934) as thickener, was used. In the placebo cream the active agents were replaced by fractionated coconut oil (Miglyol 812).

On the day of treatment an envelope containing the application time was opened. A thick layer of cream, approximately 1 g/10 cm^2 was applied to the lesions. A plastic dressing (Tegaderm®) was applied to provide occlusion. A maximum of 10 g of cream was used for each child. After the assigned application time, the cream was wiped off. The lesions were removed with a comedo extractor or curette, and iodine was applied. A maximum of 15 lesions was treated in each child. Side effects, if any, were recorded as follows: erythema, oedema, or other; severity was indicated as slight, moderate, or severe.

Pain was assessed directly after completion of treatment by the patient and the physician on a verbal scale as no, mild, moderate, or severe pain. In addition, the patient indicated the pain on a 100 mm ungraded line (visual analogue scale [VAS]) where 0 mm represented 'no pain' and 100 mm 'the worst pain you can imagine' [9,10]. All patients were treated and scored by the same physician (FBWS).

STATISTICAL ANALYSIS

The differences between the placebo-treated and the EMLA®-treated groups with regard to VAS scores and verbal pain assessment were analysed with the Mann-Whitney rank-sum test. Significance levels at repeated comparisons with the placebo group were adjusted according to a sequentially rejected Bonferroni procedure [11]. The differences among the 15-, 30-, and 60-minute groups within the EMLA® cream and placebo groups were analysed with the Kruskal-Wallis test and the Terpstra-Jonckheere test [12]. The increase in the percentage of EMLA®-treated patients who had a local reaction with increasing application time was tested for statistical significance by Mantel's test [13]. All p values given are two-sided.

RESULTS

PATIENTS

The study comprised 83 patients, of whom 15 had atopic dermatitis. Fifty-eight patients received EMLA® cream and 25 patients placebo cream. One (atopic) child in the placebo-treated group was withdrawn from the analysis of analgesic efficacy because she had only three lesions. There were no significant differences among the groups with regard to sex (EMLA® cream: 25 girls, 33 boys; placebo: 16 girls, 9 boys), age (median 7 years, range 4 to 12 years in both groups), weight (median EMLA® cream: 26 kg, range 15 to 44 kg; placebo: median 25 kg, range 16 to 55 kg), and number of patients with atopic dermatitis. In the EMLA®-treated children 31% had 5 to 10 lesions and the corresponding percentage in the placebo-treated group was 29%.

ANALGESIC EFFICACY

No significant differences in pain scores were observed among the 15-, 30-, and 60-minute EMLA®-treated groups, nor were any significant differences observed among the 15-, 30-, and 60-minute placebo groups. The latter were thus added into one placebo group in the continued analysis. EMLA® cream significantly prevented the pain compared with placebo cream after all three application times, according to all assessments (VAS, verbal scale, patient and doctor; $p<0.01$). No significant differences were observed in either the EMLA®-treated or placebo-treated group in the VAS scores of atopic and non-atopic patients. According to the patients' verbal assessments, the frequency of no pain increased from 36% in the 15-minute group to 61% in the 60-minute EMLA®-treated group (not significant). In the placebo group only one of 24 children (4%) reported no pain. Altogether, 91% of the children given EMLA® cream felt either no or slight pain compared with 54% of the children given placebo. The result of the physician's assessment was similar. Curettage was interrupted because of pain in 1 of 24 patients in the placebo group and 1 of 58 patients in the EMLA®-treated patients.

ADVERSE REACTIONS

No general side effects or serious local reactions were noted. In all, 496 separate skin areas in the EMLA®-treated patients and 217 in the placebo-treated patients were evaluated for local reactions. Transient local redness was the only reaction observed. The percentage of patients with redness in at least one location increased from 0% (0/22) in the 15-minute EMLA®-treated group, to 28% (5/18) in the 30-minute EMLA® group, to 56% (10/18) in the 60-minute EMLA® group ($p<0.001$). This was also the case when only non-atopic patients were considered. No such increase was found in the placebo group. In the placebo-treated patients, redness was seen in only two patients.

DISCUSSION

In an open study, Rosdahl et al. [14] treated 55 children with molluscum contagiosum with curettage after a 1-hour application of EMLA® cream. Ninety-three percent of the children felt no pain or only slight pain. In our study 91% of all the children treated with EMLA® cream felt no pain or slight pain compared with 54% of the children given placebo. No significant difference was observed among the 15-, 30-, and 60-minute EMLA®-treated groups, and an application time of less than 60 minutes is satisfactory. In the placebo group, only one of the 24 children reported no pain (4%). An explanation could be that in this case a placebo effect, a well-known phenomenon, is illustrated in an extreme way.

A number of studies of the relationship between dermal analgesia and application time of EMLA® cream have been performed in adults [3,15]. In children, three double-blind, placebo-controlled studies have explored the effect of application time. Dohlwitz and Uppfeldt [2] observed no difference in analgesia between 20 and 75 minutes in a study of venipuncture in children aged 4 to 16 years. Hallén et al. [4] reported that the effect

of EMLA® cream in venipuncture in children of the same age became evident at about 60 minutes. Hopkins et al. [16] noted no difference in analgesia between 30 and 300 minutes in children aged 1 to 5 years scheduled for venipuncture. In these studies, however, the application time was not randomised. Our study is the first time-response study in children in which the patients were randomly allocated to groups with different application times.

Measurement of pain is difficult because pain is a subjective phenomenon and only the patient can give a true measure of its severity. Scott and Huskisson [9] described the use of a VAS for measuring pain in adults. VAS has a higher sensitivity than a traditional verbal scale (e.g., no, slight, moderate, severe pain) [9,10]. Several investigators later reported that analogue scales were also useful in children from the age of about 4 years [5,6,14]. In our study the use of both a verbal scale and a VAS resulted in significant differences between the EMLA®-treated and placebo groups. It was not possible to detect a significant difference among the EMLA® groups with neither of the scales. With both scales, however, the largest proportion of children reporting no pain (VAS score 0) was in the 60-minute EMLA®-treated group.

In our study in children, transient local redness was the only adverse reaction observed. The incidence of redness is increased with application time of EMLA® as reported in adults [7]. Ohlsén et al. [7] suggested that the redness may be caused by the vasoactive properties of lidocaine and prilocaine. One case of methaemoglobinemia after a 5-hour application of 5 g EMLA® cream has been reported in a 3-month-old prematurely born infant. This infant had concomitant trimethoprim-sulfamethoxazole therapy which is also capable of inducing methaemoglobinemia [17]. Engberg et al. [18] later showed that application of 2 g EMLA® cream on a 16 cm^2 area for 4 hours in infants aged 3 to 12 months without concomitant medication resulted in methaemoglobin levels that were within the normal range. Haugstvedt et al. [19] measured plasma concentrations of lidocaine and prilocaine in children 2 to 8 years old after 2 hours' application of 10 to 16 g EMLA® cream under occlusion to a total skin area of 100 to 160 cm^2. Plasma levels of the local anaesthetics were 10 to 15 times lower than those associated with toxicity.

CONCLUSION

EMLA® cream effectively prevented the pain of curettage of mollusca contagiosa after 15, 30, and 60 minutes application in children aged 4 to 12 years ($p<0.01$). No significant difference in pain was observed among the 15-, 30-, and 60 minute EMLA®-treated groups, but the proportion of children reporting no pain on the verbal scale increased from 36% in the 15-minute group to 61% in the 60-minute group. Transient local redness was the only skin reaction noted. In conclusion, an application time of EMLA® cream of less than 60 minutes is satisfactory for the curettage of molluscum contagiosum in children.

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Chapter 5

EMLA® in skin biopsies

based on:

Waard-van der Spek FB de, Mulder PGH, Oranje AP. Prilocaine/lidocaine patch (EMLA®) as a local premedication for skin biopsy in children. J Am Acad Dermatol 1997; 37: 418-421

Chapter 5

Prilocaine/lidocaine patch (EMLA®) as a local pre-medication for skin biopsy in children.

INTRODUCTION

A skin biopsy usually requires the infiltration of a local anaesthetic, a process that itself is often painful and causes anxiety. Use of topical prilocaine-lidocaine cream (EMLA®) has been successful in patients undergoing superficial procedures such as venipuncture, lumbar punctures, and curettage of mollusca contagiosa [1-5]. Use of this cream as a local anaesthetic in patients undergoing a skin biopsy procedure has been examined. In a study in 12 adult volunteers, the maximal depth of anaesthesia achieved with use of the cream was 5 mm; this depth was reached 30 minutes after application of the cream for 90 minutes, and during the 60-minute period after application for 120 minutes [6]. In another study, ten patients reported pain deep in the dermis during a skin biopsy procedure after application of the cream [7]. In a study by Jones et al. [8] a 60 minute application of cream was not effective in eliminating the pain caused by injection of a local anaesthetic in 60 adult patients. To enhance the ease of application, a single-unit-dose package of lidocaine/prilocaine 5% emulsion has been developed which might eliminate the possibility of incorrect application that leads to lack of analgesic effect. In a study of 108 patients undergoing either excisional biopsy procedures or curettage with electrosurgery, EMLA® cream/Tegaderm® and patch formulations were shown to be equally effective. This study also showed that the cream provided effective anaesthesia in 87% of subjects after 110 to 180 minutes application [9].
No reports exist of serious side effects after the application of the anaesthetic emulsion, although a temporary local redness or paleness of the skin may occur.

The purpose of this study was to investigate the analgesic effect of the patch as a local anaesthetic for children undergoing a skin biopsy procedure. The effect on both the pain at the injection site and the pain of the biopsy was investigated. We also evaluated the differences in pain experienced by boys and girls.

MATERIALS AND METHODS

The protocol for the study was approved by the Medical Ethical Committee of the

University Hospital Rotterdam. The study group consisted of children who required a skin biopsy procedure for investigation of a skin disorder. The children's parents gave signed informed consent after they had received verbal and written information about the study. The study was randomised, double-blinded and placebo-controlled. Two parallel groups were used; 31 children received an EMLA® patch and 32 children received a placebo patch at the site of the biopsy for 60 minutes. After removal of the patch the physician examined the skin for side effects and then infiltrated the skin with 1 ml of lidocaine and performed the biopsy with a 4 mm punch.

The child and the physician indicated the level of pain on a verbal scale as 'no pain', 'mild pain', 'moderate pain' or 'severe pain'. The child also indicated the level of pain on a 100 mm ungraded line (visual analogue scale [VAS]). 0 mm represented 'no pain' and 100 mm represented 'the worst pain you can imagine'. The Visual Analogue Scale (VAS) is used extensively and is considered to be as reliable as an objective pain score. It is suitable for use in patients aged 4 years or older [10,11]. The pain was scored after the lidocaine was injected and after the biopsy was taken.

The difference in the distribution of pain scores between groups was examined with the Mann-Whitney test for the VAS scores because of their positive skewness. The four-point verbal pain scores were compared between groups in a 4 x 2 cross table and tested using an exact-trend test.

RESULTS

Sixty-three children were randomly recruited into the study. Three children were withdrawn from the study because two had excessive anxiety and scores were missing in one child. Thus 60 children were evaluated.

The study included 29 girls (15 in the EMLA® group and 14 in the placebo group) and 31 boys (13 in the EMLA® group and 18 in the placebo group). The age of the subjects varied from 4 years to 15 years (mean 9.6 years) in the EMLA® group and from 4 years to 18 years (mean 8.5 years) in the placebo group. The groups were balanced with regard to ages and gender of the subjects.

TABLES 1 and 2 show the characteristics of the distributions of the VAS pain scores and verbal pain sores for the injection and for the biopsy in the EMLA® group and the placebo group. The distribution of VAS pain scores for the injection in the EMLA® group was significantly lower than in the placebo group (z=3.06; p=0.002). The VAS scores for the biopsy did not show a significant difference (z=1.47; p=0.142).

A significant difference existed between both treatment groups in the distribution of the verbal pain scores for the injection scored by the patient and by the physician. In the

1A

	INJECTION	
	VAS	
	EMLA®	PLACEBO
MEDIAN	0.80	2.80
IQR *	0.13-2.25	1.23-6.65
p-VALUE MANN-WHITNEY TEST	0.002	

* IQR = INTERQUARTILE RANGE

TABLE 1 - *Statistical analysis of the difference in* VAS *scores after the injection* (1A) *and the biopsy* (1B) *between the* EMLA® *group and the placebo group.*

1B

	BIOPSY	
	VAS	
	EMLA®	PLACEBO
MEDIAN	0.00	0.00
IQR *	0.00-0.45	0.00-2.03
p-VALUE MANN-WHITNEY TEST	0.142	

* IQR = INTERQUARTILE RANGE

EMLA® group the verbal pain scores were significantly lower (p=0.004 respectively p=0.001, two-sided, exact-trend test). In the placebo group, 3 children reported 'no pain' after the injection as compared with 8 children in the EMLA® group (TABLE 2A).

2A

	PATIENT		PHYSICIAN	
	EMLA®	PLACEBO	EMLA®	PLACEBO
NO PAIN	8	3	12	4
MILD PAIN	16	14	13	15
MODERATE PAIN	3	8	3	10
SEVERE PAIN	1	7	0	3
p-VALUE EXACT TREND TEST	0.004		0.001	

TABLE 2 - *Distribution of the verbal pain scores of the patients and the physician and statistical analysis of the difference in verbal pain scores after the injection* (2A) *and the biopsy* (2B) *between the* EMLA® *group and the placebo group.*

Two of these 3 children in the placebo group were boys, aged 5 and 6 years, and one of them was a girl aged 7 years. In the EMLA® group 1 child, an 8-year-old girl, reported severe pain after the injections as compared with 7 children in the placebo group. In the distribution of verbal pain scores of the biopsy no significant difference existed between the EMLA® and the placebo groups.

A difference in pain scoring was noted between boys and girls in the EMLA® and placebo groups. In the placebo group the girls scored significantly higher on the VAS scores of the injection than did the boys (z=2.11; p=0.035). In this group there was no difference in VAS scores of the biopsy.
In the EMLA® group the girls scored higher on the VAS than the boys, although the difference was not significant (injection z=1.69; p=0.091; biopsy z=1.85; p=0.065).
On the verbal scales of the patient and the physician for the injection in the EMLA®

2B

	PATIENT		PHYSICIAN	
	EMLA®	PLACEBO	EMLA®	PLACEBO
NO PAIN	24	21	23	26
MILD PAIN	1	7	5	5
MODERATE PAIN	3	3	0	1
SEVERE PAIN	0	1	0	0
p-VALUE EXACT TREND TEST	0.226		0.781	

group the girls scored significantly higher than the boys (p=0.017 resp. p=0.044, two-sided, exact-trend test). The other verbal scores showed a trend of girls scoring higher than boys but the differences were not significant.
No serious side effects were observed in any of the children.

DISCUSSION

The results of this study showed that the anaesthetic patch significantly reduced the pain at the site of lidocaine infiltration before a skin biopsy procedure was performed in children. In the 3 children who reported 'no pain' after the injection in the placebo group, one could hypothetise that in them the 'placebo-effect' was illustrated.
Thune et al. compared use of the anaesthetic cream and infiltration with prilocaine in 51 adults. The cream was an effective local anaesthetic after a mean application time of 2 hours. After a shorter application time, and in case of a large biopsy site in several patients, prilocaine infiltration was necessary after the cream application to obtain adequate anaesthesia [12].

Jones et al. showed that the anaesthetic cream was not effective in eliminating pain upon injection of the local anaesthetic when it was applied for one hour in 60 adults. They suggested that a longer application could improve the analgesic effect, but this would limit its use for routine procedures [8]. Gupta and Sibbald found that the cream provided effective anaesthesia in 87% of patients after application for 110 to 180 minutes [9].
The anaesthetic cream may be a useful local anaesthetic for children undergoing kidney biopsy procedures. Ogborn reported that the cream was used as a substitute for dermal infiltration of local anaesthetic in eight children who underwent a percutaneous kidney biopsy procedure. Five children reported no sensation upon the initial skin puncture. Only one child felt 'a sharp object' [13].

In our study no difference existed in the pain scores of the EMLA® and placebo groups for the biopsy. This is not surprising, because infiltration with lidocaine, although painful itself, provides adequate anaesthesia. All children received lidocaine infiltration after removal of the patch.

In our study girls appeared to experience more pain than boys. This finding corroborates our observations in a previous study on use of the cream as a local anaesthetic in mumps/measles/rubella (MMR) vaccination in children [14]. In contrast, Taddio et al. reported a lower pain score in girls than in boys [15].

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Chapter 6

EMLA® in Mumps/Measles/Rubella (MMR) vaccination

based on:

Waard-van der der Spek FB de, Bernsen JC, Mulder PGH, Kleij-Troost BW van der, Berg J van den, Oranje AP. EMLA® cream as a local anaesthetic in MMR vaccination. International Journal of Clinical Practice 1998; 52(2): 136

Waard-van der der Spek FB de, Bernsen JC, Mulder PGH, Kleij-Troost BW van der, Berg J van den, Oranje AP. EMLA® crème als lokaal analgeticum bij BMR vaccinatie bij kinderen. Tijdschrift voor Jeugdgezondheidszorg 1998; 1: 9-10

Chapter 6

EMLA^R cream as a local anaesthetic in MMR vaccination in children

INTRODUCTION

The local anaesthetic prilocaine-lidocaine emulsion (EMLA^R) has been used with increasing success in superficial dermato-surgical interventions such as venipuncture, for inserting infusions, lumbar punctures and curettage of mollusca contagiosa [1-5]. The anaesthesia can penetrate up to a depth of 5 mm [6].
No serious side effects have been reported after the application of the anaesthetic emulsion. A temporary local redness or paleness of the skin may occur.
Several studies into the application of EMLA^R for vaccinations have been reported [7-10]. In those studies the application of EMLA^R cream for subcutaneous injection with NaCl, intramuscular influenza vaccination and intramuscular Diphtheria, Pertussis, Tetanus (DPT) vaccination was investigated. Those studies were randomised, double-blind and placebo-controlled and are summarised in TABLE 1. The aim of this study was to investigate the analgesic effect of EMLA^R cream for the subcutaneous administration of Mumps/Measles/Rubella (MMR) vaccination in children aged about 9 years. These children were vaccinated according to the government vaccination programme.

Author	Indication	Size of the study	Age	Appl. time minutes	Scoring method	Results
Taddio et al.[7]	s.c. 0.9% NaCl	20	19-46 yrs (aver. 30 yrs)	60-75	VAS	insert needle:after EMLA^R pain << injection: no difference
Taddio et al.[8]	i.m. Fluzone^R vaccination	60	22-65 yrs (aver. 35 yrs)	60-90	VAS	both puncture and injection: after EMLA^R pain <<
Taddio et al.[9]	i.m. DPT vaccination	96	4-6 months (aver. 5 months)	60-120	behaviour	pain score and crying: after EMLA^R <<
Uhari[10]	i.m. DPT vaccination	155	3-28 months (aver. 9 months)	3-145 (9<50 min)	VAS (parents & nurses)	pain and crying: after EMLA^R << anxiety: no difference

TABLE 1. *Studies on the application of* EMLA^R *cream for administering subcutaneous (s.c.) and intramuscular (i.m.) injections.*

MATERIALS AND METHODS

SUBJECTS

The protocol was approved by the Medical Ethical Committee of the University Hospital Rotterdam. The study group consisted of children aged about 9 years who were required to undergo MMR vaccination according to the government vaccination programme. Written permission for taking part in this study was requested from their parents.

PRODUCT INFORMATION

The EMLA® patch per gram consisted of 25 mg lidocaine base, 25 mg prilocaine base, 19 mg Arlatone 189. 2 mg Carbopol and approximately 1 mg NaOH till pH 9.2 made up with water.

The placebo patch per gram consisted of 19 mg Arlatone 189.2 mg Carbopol and approximately 1 mg NaOH till pH 9.2 made up with water.

The MMR vaccine consisted of live attenuated mumps- measles and rubella virus, neomycin and solvent.

PROCEDURE

The study was randomised, double-blind and placebo-controlled. There were two parallel groups. Forty-seven children received an EMLA® patch and 48 children received a placebo patch in the upper arm at the site of vaccination during 60 minutes before vaccination.

The skin was examined for eventual side effects after the patch was removed. Each child was then vaccinated subcutaneously with 0.5 ml MMR vaccine. The angle between the skin surface and the needle was 10 to 15 degrees.

EVALUATION

The effect of EMLA® and placebo on the vaccination was determined by the pain experienced by each child.

The child and the investigator indicated the level of pain on a verbal scale as no, mild, moderate or severe pain. The child also indicated the level of pain on a 100 mm ungraded line (visual analogue scale [VAS]). 0 mm represented 'no pain' and 100 mm 'the worst pain you can imagine'.

STATISTICAL ANALYSIS

The average difference in the scores of the pain between both the treatment groups was examined using the Mann-Whitney test for the Visual Analogue Scale (VAS) scores and the Trend test for the verbal scores. The difference in the observed side effects was tested with the Chi-square test and the Fisher's exact test.

RESULTS

Ninety-six children were randomly assigned into the study. One child was withdrawn from the study because of excessive anxiety expressed by the mother and the child. The mother influenced the child very negatively.

There were 42 girls (22 in the EMLA® group and 20 in the placebo group) and 53 boys (25 in the EMLA® group and 28 in the placebo group). There was no significant difference among the groups with regard to sex.

The age varied from 8 years and 3 months to 9 years and 2 months in the EMLA® group and the placebo group. The groups were balanced regarding the distribution of the ages.

The time of application of the patch varied from 60 to 90 minutes in the EMLA® group. The average was 62 minutes and the median 60 minutes.
In the placebo group, the time of application varied from 55 to 90 minutes with an average of 65 minutes and a median of 62 minutes. There was no difference between the two groups.

There were no significant differences between the verbal pain scores of the children in the EMLA® and the placebo groups.
There were also no significant differences between the girls and the boys in the EMLA® and the placebo groups.

No significant differences in the investigator's verbal pain scale values between the EMLA® and the placebo groups were observed. There were also no significant differences between the investigator's verbal pain scale values for girls and boys in the EMLA® and the placebo groups.

The scores of the children in the visual analogue scale are depicted as histograms and dot plots in FIGURE 1.
In the dot plots, a strip represents median value in the EMLA® group and the placebo group.

There was a significant (p=0.017) difference in VAS pain scores between the EMLA® and the placebo groups in girls. This difference in boys was clearly not significant (p=0.514). In the whole group, the difference in VAS scores between the EMLA® and the placebo groups was not significant, but almost reached significance (p=0.052).

None of the children showed serious side effects. There was no significant difference in the adverse events between the EMLA® group and the placebo group.

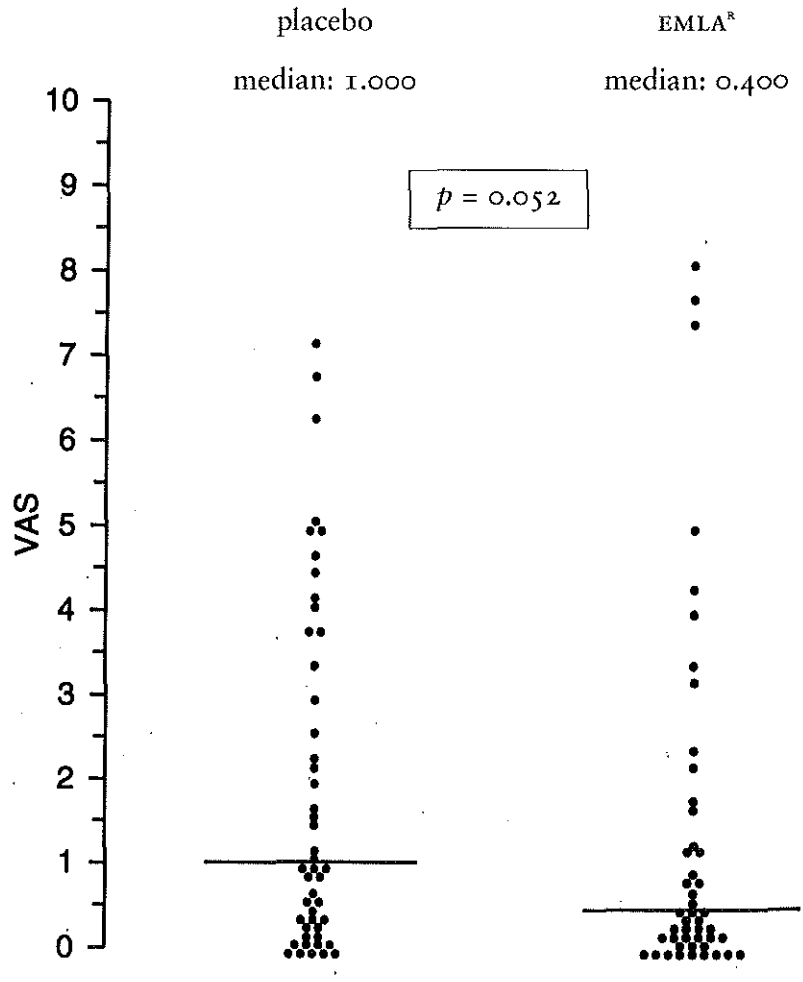

FIGURE 1: *Visual analogue scale [VAS] scores of individual patients in the* EMLA® *and Placebo groups. Each dot represents the score in* 1 *patient. The median of the groups is shown as a strip. The difference between the groups is not, although almost significant in de Mann-Whitney test* (p = 0.052).

DISCUSSION

Mumps/Measles/Rubella (MMR) vaccination is painful. EMLA® has not been used previously for MMR vaccination. In our study we observed that EMLA® cream did not significantly reduce the pain of MMR vaccination in 9-year-old children as measured using the VAS score. The difference almost reached significance. The difference in VAS scores in the girls was statistically significant.

Taddio et al. [7] reported that EMLA® cream reduced the pain during insertion of the needle in 20 adult volunteers. However, in the same study, EMLA® cream had no effect on the pain resulting from subcutaneous injection of the physiological saline solution.
In our investigations, there was no significant difference between the verbal pain scores of the children and the investigators in the EMLA® group and the placebo group. It is possible that a more objective pain score is obtained using visual analogue scale (VAS). This scoring system is used very extensively and is regarded as very reliable. It is suitable for use from the age of 4 years [12,13]. Studies were also performed for intramuscular DPT vaccinations [9,10]. In both studies lower pain scores and lowered intensity of crying was observed after application with EMLA®.

Many variables may influence the pain score upon an injection. Such variables include anxiety for the procedure, the temperature, the volume, the pH, the constituents, the osmolarity of the solution, the injection technique and various environmental factors. It is important to keep the variables as constant as possible and to use a scoring system that is as objective as possible. We have attempted to keep the variables as constant as possible.

It is recommended to investigate the effect of EMLA® cream more thoroughly and also examine the value of newly developed local anaesthetics on MMR vaccination. If it is at all possible to make such vaccinations less painful, then some of the children who must undergo additional vaccinations according to the government vaccination programme may benefit from this. This is especially important because stressful events in the early childhood may influence the development of a child. The children that we target are those with extreme anxiety. Another study would be necessary to evaluate the efficacy of EMLA® in anxious children.

No adverse events occurred in the EMLA® and the placebo groups. A temporary redness or paleness of the skin was observed. This agrees with the data reported in the literature. Local purpura may be rarely observed after the application of EMLA® cream, even when only applied for 30 minutes [14]. Patch tests did not show any allergic contact reaction. A vesicular reaction developed in 1 patient, but it too resolved spontaneously within several days [14]. Despite a widespread and frequent use of EMLA® cream as a local anaesthetic, we only found 2 cases of reported allergic contact dermatitis caused by EMLA® in literature. In both patients patch tests were positive for EMLA® and prilocaine [15,16].
In conclusion, it can be stated that EMLA® cream significantly relieved pain upon MMR vaccination in the group of girls investigated in the present study. However, the difference in VAS score in the whole group was not significant. Probably the pain of MMR vaccination is not upon skin penetration, but during the injection of the liquid in the subcutaneous space.

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Chapter 7

Side effects of EMLA®

partly based on:

Waard-van der Spek FB de, Oranje AP. Purpura caused by EMLA® is of toxic origin. Contact Dermatitis 1997; 36: 11-13

Chapter 7

Side effects of EMLA®

INTRODUCTION

The most commonly observed side effects of EMLA® are not serious and consist of blanching or erythema. These effects may be due to effects of the anaesthetics on vascular smooth muscle and may be concentration dependent. At very low concentrations (e.g. short application times), they may produce vascular contraction, whereas at higher concentrations which would be achieved after long application times, the vascular and bronchial smooth muscle are relaxed and thus may induce erythema. Side effects that are more serious are only incidentally reported. Methaemoglobinemia and toxic purpura because of a high level of absorption are described. Other side effect is allergic reactions.

THIS CHAPTER HAS BEEN SUB-DIVIDED INTO TWO SECTIONS:

- *part a* deals with purpura
- *part b* deals with absorption, methaemoglobinemia and allergic reactions.

Part a: Purpura

INTRODUCTION

During the past 10 years, we have used EMLA® cream in at least 4000 patients as an anaesthetic for removing molluscum contagiosum and for other indications without serious side effects. We observed purpura in 4 patients with molluscum contagiosum 30 minutes after the application of EMLA® cream. Purpura was observed after application of EMLA® cream for 60 minutes in another patient in whom it was used as a local anaesthetic for taking a lip biopsy. The purpura disappeared within several days.

Purpura is a discoloration of the skin or mucous membranes due to extravasation of red blood cells. It is a physical sign depending on many causes. Purpura can be divided into purpura by platelet disorders, vascular or non-thrombocytopenic purpura, coagulation disorders and several miscellaneous clinical syndromes of varying aetiology such as painful bruising syndrome and purpura simplex. A direct toxic or (contact) allergic effect or some immunological disturbance may cause vessel damage. There is a wide variety of substances capable of causing capillary damage with or without any change in platelets. They may be directly toxic or cause an allergic reaction.
Various textile fabrics, rubber, anti-oxidants, other chemicals and pressure may cause non-thrombocytopenic purpura. Wool, textile finishers, optical whiteners in washing powders, fibreglass and pressure may induce clothing purpura [1-3]. Allergic contact purpura may be produced by the rubber anti-oxidant N-isopropyl N-phenylparaphenylenediamine (IPPD) and paraphenylenediamine used as hair and fur dyes. It has been suggested that IPPD acts as a toxin or allergen with an affinity for vascular endothelium [4,5]. Purpuric drug reactions may also occur. Exposure to d-limonene, the predominant monoterpene in citrus oil caused a purpuric reaction in a healthy 39-year-old man who was exposed to d-limonene for 2 hours by immersing his left hand in a glass jar of the solvent [6]. A purpuric contact dermatitis to benzoyl peroxide in which a primary and selective toxic effect on the capillary endothelium may have led to a peri-capillary infiltration was reported. Alternatively, those authors also suggested a primary antigen-induced lymphocytic reaction in the peri-capillary region which could have liberated toxic lymphokines and may have been directly responsible for the endothelial damage [7].
We investigated whether the purpura that we had observed was of an allergic nature using patch tests.

MATERIALS AND METHODS

PATIENTS AND STUDY DESIGN

All 5 patients were recalled for patch test investigation. All patients and their parents were provided verbal and written information on the study and were willing to parti-

cipate. Four of the 5 patients had atopic dermatitis. These 4 patients were treated for molluscum contagiosum.

METHODS

All the individual ingredients of the EMLA® cream, EMLA® cream itself, placebo cream (EMLA® without lidocaine and prilocaine) and Tegaderm® (3M) plaster were applied to the skin using big Finn-chambers® (Bipharma). The series consisted of: Carboxypolymethylene 0.1 mg/ml - 1 mg/ml - 10 mg/ml; Arlatone 289 0.1 mg/ml - 1 mg/ml - 10 mg/ml; Prilocaine (ASTRA) 0.25 mg/ml - 2.5 mg/ml - 25 mg/ml; Lidocaine (ASTRA) 0.25 mg/ml - 2.5 mg/ml - 25 mg/ml; Placebo cream; EMLA® cream and Tegaderm® plaster.

The tests were read for the first time 30 minutes after application of the test substances to the skin. The tests were read for the second time after 48 hours after which the test substances were removed. The tests were read for the third time after 72 hours.

RESULTS

The tests were negative in all the 5 patients at the first reading after 30 minutes as well as after 48 and 72 hours.

DISCUSSION

Blanching and redness are commonly observed side effects of EMLA® application [8,9]. In the literature, purpura has not been described, although anecdotal oral communications confirm that it develops sometimes after prolonged application of EMLA®. To our knowledge, purpuric reactions after EMLA® application have not been reported previously by other authors [8]. Purpura is not mentioned as possible side effect in the product information provided by the manufacturer.

Purpura reactions were observed once after application of EMLA® cream in the 5 patients in our study. The 4 patients with mollusca contagiosa also had atopic dermatitis. Since the barrier function of the skin is reduced in atopic dermatitis, an increased penetration of substances may occur [10]. In the fifth patient, EMLA® was applied on the lip. The locally applied anaesthetics are absorbed very rapidly through the mucous membranes [11].

In our patients, the purpura reaction was seen 30 minutes after EMLA® application on the skin and after 60 minutes application on the lip. Since this purpura reaction could not be reproduced upon patch testing, we concluded that the reaction was not of an allergic nature. It may be possible that the purpura were caused by a toxic effect on the capillary endothelium inducing the extravasation of the erythrocytes. One of the explanations for the purpura reaction may be that EMLA® was applied for too long in these selected cases. However, we did not observe any purpuric reaction after application of

EMLA® during patch testing. An eczematous skin often surrounds mollusca contagiosa. The epidermal barrier function is disturbed in an eczematous skin, permitting a more rapid penetration of the local anaesthetics. In contrast to the skin, mucous membranes allow faster penetration of local anaesthetics. This may be an explanation for the purpuric reaction in only one case after EMLA® application for taking a lip biopsy.

Part b: Absorption, methaemoglobinemia and allergic reactions

ABSORPTION

Absorption is not a real 'side effect' on its own, but may cause several problems. Severe lidocaine intoxication was reported by cutaneous absorption in a 55-year-old woman. This patient had extensive cutaneous T cell lymphoma. Her painful skin lesions were treated with 5% lidocaine in lanette wax cream twice daily (approximately 60% of the body surface). Five hundred grams of the cream were used daily (25 gram of lidocaine base). Toxic reactions occurred after 5 days (see also later). She had visual disturbances, became dizzy and confused and delirious. On day 8, she had several generalised seizures and became drowsy. The next day she had a cardiac arrest shortly after an intramuscular injection of promethazine. The suspected systemic intoxication with lidocaine as a result of cutaneous absorption was confirmed retrospectively by very high serum concentrations of lidocaine (21.2 mg/l). The patient remained comatose even after lidocaine was stopped and she died on day 14. Apart from the amount of cream used and the percentage of body surface on which it was applied, the erosive nature of the lesions also seemed to be an important factor which influenced absorption [12].

The absorption of lidocaine and prilocaine after application of EMLA® cream to normal and abnormal skin was studied by Juhlin et al. [13]. The cream was applied under occlusion to 25 to 100 cm^2 skin of adults for one to two hours. In normal skin, the absorption on the face was faster than on the upper arm. Absorption for abnormal adult skin (psoriasis or eczema) was faster than that in normal skin. Plasma levels of lidocaine and prilocaine in the former were higher, and a more rapid but shorter anaesthesia was obtained. Anaesthesia resulted and persisted for 15 to 30 minutes after application for 15 minutes. Application for 60 minutes was necessary for complete anaesthesia in normal skin. Plasma levels in the systemic circulation were 100 times lower than those associated with toxicity.

EMLA® cream acted rapidly in children with atopic dermatitis. Analgesia occurred more quickly in those with dry eczematous skin than in children with normal skin [14].

Skin is a diffusion barrier between the internal and external milieus in humans. This barrier function is provided by the stratum corneum. Transepidermal water loss (TEWL) is often used as a measure of the state of the diffusion barrier. In 48 patients with atopic dermatitis (age 18-30 years), an increased TEWL was observed both in dry non-eczematous skin and in clinically normal skin [15]. This may indicate a primary defect in the epidermal barrier permitting more rapid penetration of local anaesthetics through the skin.

Haugstvedt et al. [16] determined plasma levels of lidocaine and prilocaine in children (younger than 9 years) after application of 10 to 16 g EMLA® cream under occlusion for

2 hours. Plasma levels were far below the toxic level before and after application at 2, 3, 4 and 5 hours.

METHAEMOGLOBINEMIA

Plasma levels of lidocaine and prilocaine together with the formation of methaemoglobin were also determined in infants aged 3 to 12 months. Investigations were conducted after application of 2 g EMLA® cream to 16 cm² skin for 4 hours [17]. In all cases, plasma levels were clearly below the toxic level. A minimal increase in methaemoglobin was noted in only a few children. This is of importance since a 12-week-old infant with methaemoglobinemia after application of 5 g EMLA® cream for 5 hours was reported [18]. This infant had also been treated for over two months with trimethoprim-sulfamethoxazole. Sulfonamides may also cause methaemoglobinemia. In this infant it was more likely that the combination of the antibiotic and the long application time of EMLA® cream caused the methaemoglobinemia.

Nilsson et al. determined plasma levels of local anaesthetics and the fraction of methaemoglobin in infants younger than 3 months in whom 2 g EMLA® cream was applied over 16 cm² skin for 4 hours. Plasma levels of the local anaesthetics were low. Methaemoglobin levels were higher than those before application of the cream. However, there was no clinically significant increase in methaemoglobin. The activity of erythrocyte methaemoglobin reductase did not reach adult levels until after the age of 3 months. The enzyme capacity may be overloaded when EMLA® is administered concomitantly with other methaemoglobin-inducing agents. Use of EMLA® should be restricted in infants in this age group [19]. Frayling et al. [20] also reported a slight increase in methaemoglobin in children aged 1 to 6 years after application of 5 g EMLA® cream for 2 hours. The peak level of methaemoglobin remained considerably below the toxic level. A minimum effective dose is recommended for children treated daily with the EMLA® cream. A slightly increased methaemoglobin level was sometimes still present after 24 hours and a cumulative effect may occur.

ALLERGIC REACTIONS TO LOCAL ANAESTHETICS

Local anaesthetics are structurally divided into three parts: a lipophilic aromatic group, an intermediate chain linkage and a hydrophilic amine group. Local anaesthetics are classified into two groups based on the intermediate chain. These are ester type and amide type local anaesthetics.

Ester type local anaesthetics (TABLE 1) are metabolised in the plasma by pseudocholinesterase. Patients with genetically abnormal pseudocholinesterase are predisposed to adverse effects of ester type local anaesthetics. During the degradation process a p-aminobenzoic acid (PABA) metabolite is formed which is associated with allergic reactions. Amide type local anaesthetics (TABLE 1) do not undergo such metabolism. However,

preservative (methylparaben) used in the preparation of amide type local anaesthetics are metabolised to PABA. Amide type local anaesthetics are metabolised in the liver by microsomal enzymes. Patients with decreased hepatic functions are predisposed to adverse effects of amide type local anaesthetics.
Patients allergic to ester type local anaesthetics should be treated with a preservative-free amide type local anaesthetic. Patients who are allergic to PABA may show cross-reactivity with ester and amide type local anaesthetics which contain methylparaben [21]. Patients who are allergic to amide type local anaesthetics may use ester type local anaesthetics provided they are not allergic to these. If there is an allergy to both types of local anaesthetics, which is very rare, or if skin testing cannot be performed, alternatives such as diphenhydramine, opioids, general analgesia, or hypnosis may be used.

Ester type local anaesthetics	Amide type local anaesthetics
Benzocaine	Bupivacaine
Chloroprocaine	Dibucaine
Cocaine	Etidocaine
Procaine	Lidocaine
Propoxycaine	Mepivacaine
Tetracaine	Prilocaine

TABLE 1. *Ester- and amide type local anaesthetics.*

Allergic reactions to local anaesthetics may be caused by a metabolite of ester type local anaesthetics, the amide type local anaesthetics, or a constituent of the preparation. The most likely source of allergic reactions to local anaesthetics is PABA, a metabolite of ester type local anaesthetics. The preservative agent methylparaben is also metabolised to PABA. Methylparaben is found in ester and amide type local anaesthetics. So patients who are allergic to PABA may show cross-reactivity with ester and amide type local anaesthetics which contain methylparaben.
Anti-oxidants rarely produce allergic reactions. However, allergic reactions to sodium bisulfite and metabisulfite have been reported. Hypersensitivity reactions to preservative-free amide type local anaesthetics are rare, but have been reported [21].

Many so-called 'allergic' reactions to local anaesthetics are autonomic or toxic effects rather than a true immunologic response.

AUTONOMIC REACTIONS

Autonomic and immediate allergic reactions are similar in primary presentation so that these reactions may be difficult to discern. In patients who are afraid of receiving injections and patients with anticipatory problems concerning medical and dental procedures, autonomic related symptoms might occur.

These include tachycardia, sweating, and perhaps syncope. Autonomic adverse effects show a resolution of symptoms within several minutes and require minimal supportive treatment compared with type I allergic reactions.

TOXIC REACTIONS

Toxic reactions occur when an excessive dose of the local anaesthetic is given, an inadvertent intravascular injection is given, the metabolism of the local anaesthetic in the patient is abnormal, or if there is a slow elimination of the agent. Toxic manifestations first appear at a serum lidocaine concentration of 5 mg/l and worsen progressively at higher levels [12]. Toxic concentrations of local anaesthetics give rise to adverse central nervous system effects like diplopia, dizziness, muscle twitching, numbness and at higher doses tremors and seizures. The toxic effect leads to a negative inotropic effect on cardiac muscle and vasodilatation. Hypotension and rapid breathing resembling an allergic reaction may occur with cardiovascular collapse.
Lidocaine intoxication has been reported after various routes of administration. Severe and even lethal intoxications have been described after local application to mucous membranes or after ingestion and also from cutaneous absorption [12].

IMMUNOLOGICAL RESPONSES (ALLERGIC REACTIONS)

Allergic reactions are classified into four categories based on the immune system's antigen-antibody response. Types I, II and III are immediate-type reactions. Type IV is a delayed-type reaction [21].

TYPE I ALLERGIC REACTION

Type I reactions may be limited to the skin surrounding the site of administration with a mild rash, erythema, or urticaria. Severe localised reactions like angioedema may also occur. Severe generalised reactions (anaphylaxis) may occur. Hypotension, bronchospasm and cardiac arrest may lead to life-threatening situations. A 27-year-old woman was reported with acute bronchospasm following administration of lidocaine. The dentist treating her used lidocaine with epinephrine as a local anaesthetic. There were no

reactions. Three months later she was treated again. Within 2 minutes after administration of the same local anaesthetic, the patient experienced extreme respiratory distress. A subcutaneous test with the local anaesthetic resulted in acute bronchospasm [22].

TYPE IV ALLERGIC REACTIONS

Type IV reactions are the most prominent with local anaesthetics. Cellular immunity is involved where T cells are sensitised to the local anaesthetic on first exposure but no antibodies are produced. On secondary exposure with the same local anaesthetic, the memory T cells release lymphokines that induce inflammatory reactions and activate macrophages to release mediators of inflammation. Recently the cellular immune response to lidocaine was investigated in 4 patients with a proven allergy to lidocaine. The patients had contact dermatitis after topical application of lidocaine and local swelling or generalised erythema exudativum multiforme after submucosal/subcutaneous injection of lidocaine. T cell lines and clones were generated from the peripheral blood of these patients. Two of three lidocaine-specific T cell lines were oligoclonal and one even became monoclonal. The simultaneously analysed immune response to tetanus toxoid was polyclonal. The lidocaine-specific T cell lines cross-reacted with mepivacaine, but not with other local anaesthetics. A heterogeneous T cell response was found. The majority of reactive T cells belonged to the CD_4 cell lineage (MHC class II restricted), but cloning also revealed some MHC class I restricted $CD8^+$ clones. Few clones were $CD_4^-CD8^-$ and expressed gamma-delta T cell receptor (TCR). A rather polarised cytokine pattern was produced by the majority of the CD_4 clones. A dominance of Th2-like cytokines showed a high IL-5 production. Some CD_4^+ and all $CD8^+$ clones secreted high IFN-gamma and low levels of IL-4 and IL-5 (Th1-like) [23].

Allergological investigations were performed in a recent study in 177 patients with 197 reported episodes of adverse reactions to local anaesthetics. Standard procedures were conducted routinely beginning with prick testing, followed by intracutaneous testing and finally by challenge testing. The skin prick tests and the intracutaneous tests were evaluated after 20 minutes and 24 hours. In a total of 54 selected cases, specific circulating IgE was detected using radioimmunoassay.
Prick tests and intracutaneous tests with the causative agent and unrelated substances were negative at early and late readings. Prick tests for preservatives were positive with sodium metabisulfite in 3 of 120 cases and with parahydroxybenzoic acid ester in 2 of 164 cases at the first reading. Challenges with causative agents showed objective symptoms in 3 of 143 patients. One patient showed local itching, erythema, and papules at the test site one day after subcutaneous injection of mepivacaine. Histological investigation showed an eczematous reaction. Additional patch tests were positive with 1% mepivacaine solution and with 1% lidocaine solution. Two other patients had itchy wheals and erythema at the test sites and on the trunk shortly after exposure to lidocaine or

articaine. This resolved spontaneously after 2 hours. The results of radioimmunoassay, including the 2 patients with the positive challenge tests were negative in all patients. It can be assumed that direct histamine release induced by local anaesthetics is most likely to be the major mechanism causing wheal and flare reactions in these patients [24].

In a 43-year-old woman suffering from recurrent localised swellings and an eczematous dermatitis starting 1 day after an injection of lidocaine was evaluated by intradermal patch and lymphocyte transformation tests. Delayed-type hypersensitivity was proven by these in vivo and in vitro tests [25].

Delayed-type allergy to injected local anaesthetics is best proven by patch testing. Immediate-type hypersensitivity to local anaesthetics or preservatives is rare, especially IgE-mediated allergic reactions. In clinical practice, however, various adverse reactions after injection of local anaesthetics are frequently observed. Dose-related toxic events, psychomotor reactions and reactions caused by hidden allergens such as latex-containing gloves must contribute in most cases [24].

Despite a widespread and frequent use of EMLA® cream as a local anaesthetic, we found only 2 cases of allergic contact dermatitis caused by EMLA® in the literature (TABLE 2). The first patient was a 78-year-old man treated with EMLA® because of a painful arterial ulcer and reported by Van den Hove et al. EMLA® was applied 2 x daily and covered by a chloramine cream. It was applied during 3 months. The patient then suddenly developed a dermatitis all over the back of the treated foot. EMLA® was discontinued. The rash subsided within a few days [26]. Thakur et al. described the second patient who was treated with EMLA® because of intractable post-herpetic neuralgia. After 4 weeks of EMLA® therapy a pruritic, persistent, 'prickly heat'-type rash developed at the site of the EMLA® application. Examination revealed erythematous, warm, indurated, vesiculated and excoriated lesions. After discontinuation of EMLA® and treatment with both systemic and topical steroids, the dermatitis remitted within a week [27]. In both patients patch tests for EMLA® and prilocaine were positive.

Indication EMLA®	Application period	Side effects	Patch tests
Arterial leg ulcer	3 months, 2X daily	Dermatitis treated foot	EMLA® and prilocaine positive
Post-herpetic neuralgia	4 weeks	Rash over application site	EMLA® and prilocaine positive

TABLE 2. *Allergic contact dermatitis caused by* EMLA®: 2 *cases.*

We only observed 1 patient with an eczematous reaction after EMLA®. We could not perform patch tests because of the parent's refusal. However, the mother informed us that the child had been treated with EMLA® several times following this reaction without suffering any adverse reaction.

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Part 2
Pain-prevention

Chapter 8

Skin Application Food Test (SAFT) based on Contact Urticaria Syndrome (CUS): a painless alternative for prick tests

based on:

Oranje AP, Waard-van der Spek FB de, Oostende L van, Aarsen RSR, Toorenenbergen AW van and Dieges PH. Food-induced contact urticaria syndrome (CUS) in young children with atopic dermatitis: practical consequences. J Eur Acad Derm Venereol 1994; 3: 295-301

Chapter 8

Skin Application Food Test (SAFT) based on Contact Urticaria Syndrome (CUS): a painless alternative for prick tests

Introduction to and examples of diagnostic problems

INTRODUCTION

Common symptoms of food allergy (FA) with the skin as the most prominent target are refusal of foods, vomiting and urticaria around the mouth and on the hands. These symptoms belong to the 'Contact Urticaria Syndrome' (CUS). Contact urticaria syndrome can be defined as a direct urticarial reaction after contact with an allergen (for example food or animal products). The term CUS was introduced by Maibach and co-workers in 1975 [1]. Other terms are 'immediate contact reactions' [2,3], and 'immediate contact hypersensitivity' (only immune-mediated) [4,5]. The most accepted and widely used term is CUS. The mechanisms underlying contact reactions are divided into two main types, namely immunological (IgE-mediated) and non-immunological immediate contact reactions. However, there are substances causing immediate contact reactions whose mechanism (immunological or not) remains unknown. The unique aspect of the immunological variety which distinguishes it from the non-immunological form is its ability to involve other organ systems. Another feature which distinguishes immunological contact urticaria from the non-immunological variety is the relative prevalence of the two types among atopic patients. Immunological contact urticaria is considered to be more prevalent in atopic patients compared with non-atopic patients. The non-immunological contact urticaria affects the two groups with equal frequency [6].

Urticarial reactions can be induced by food consumption and by direct food-skin contact [1]. Contact urticaria is a wheal and flare response to agents rapidly absorbed via intact skin. Urticaria often develops within a few minutes after cutaneous exposure to inducing agents. Delayed onset contact urticaria (up to 4-6 hours) has been reported. The mechanism for the delay may be slower percutaneous penetration [1].

Immunological contact urticaria is a common manifestation of food allergy in children with atopic dermatitis (AD) [2,4,7]. The frequency with which contact urticaria occurs in patients with AD and FA is unknown [7]. The role of IgE is important in AD, but was underestimated for a long time. Most of the IgE responses occur together and often a direct reaction is followed by a late one. The mechanism of immunological contact urti-

caria is a type I hypersensitivity immunological reaction mediated by specific IgE antibodies in the patient's serum against the causative agent. This mechanism requires that the individual has previously been exposed to the causative agent and has become 'sensitised' (specific IgE antibodies have been produced). The route of sensitisation may be via the skin, mucous membranes, or via other organs such as the respiratory and gastrointestinal tracts. Absorbed antigen binds to specific IgE molecules on the surface of basophils and mast cells. The cutaneous symptoms of wheal and flare result from the release of cell-bound mediators, the most important of which is histamine. Individuals must first become sensitised and subsequent production of specific IgE is needed before a clinical manifestation is elicited.

Not only do mast cells and circulating basophils have Fc-receptors for IgE molecules, but eosinophils, peripheral B and T lymphocytes, platelets, monocytes and alveolar macrophages can also bind IgE. Patients with atopic dermatitis, but not other atopics or normal controls have IgE on their epidermal Langerhans cells [8,9]. An important function of epidermal Langerhans cells is antigen presentation in delayed-type contact allergic reaction. It can be hypothesised that protein allergen (e.g. food, inhalant) for type I immediate contact reactions binds to specific IgE molecules present on epidermal Langerhans cells and is presented to mononuclear cells and induce a delayed-type hypersensitivity reaction resulting in eczematous skin lesions. This may be the mechanism whereby repeated immediate contact reactions lead to more persistent eczematous lesions [10].

Foods are the most common causes of immediate allergic contact reactions.

Non-immunological contact urticaria appear within minutes to an hour after contact with the eliciting substance and usually disappear within a few hours in most exposed individuals without previous sensitisation. The symptoms usually appear and remain in the contact area. Although the exact mechanism of non-immunological contact urticaria remains elusive, antibody or cell-mediated immunological processes do not appear to be involved. H1 antihistamines do not inhibit these reactions. The response can be inhibited with oral or topical therapeutics that interfere with the production of prostaglandins and leucotrienes indicating a mechanistic role for these inflammatory mediators [6,11].

CONTACT URTICARIA SYNDROME: DIAGNOSIS

Based on the mechanism of CUS, imitating provocation tests have been described [12-14]. These tests are specially performed in young children with AD suspected of food allergy. Tests available, among others, are the open application test, the RUB test, the prick-prick test and the Skin Application Food Test (SAFT) developed by Oranje [12-14]. The SAFT is a very child-friendly painless test. The children are less anxious because no needles are used.

Skin Application Food Test (SAFT)

The Skin Application Food Test (SAFT) is performed as follows: 2 square cm areas are marked. Finn Chambers (big size, 1 cm^2 containing food (allergen) or control fluid (0.9% Sodium chloride) on filters are applied to the skin area cleansed of fat using 96% alcohol. The foods (0.1 ml or a slice) are fixed to the skin with Finn Chamber Scanlon^R plasters (Norgeplaster, A/S Oslo, Norway) (FIGURE 2, chapter 2). Additionally, the patch sites are examined at intervals of 10 minutes. Maximum time of application is 30 minutes. Scores of 0 and 1+ (only redness) are regarded as negative. The reactions 2+ (redness & oedema) and 3+ (redness & oedema covering 4 cm^2) are regarded as positive. Positive tests correlate well with RAST scores and oral provocation (chapter 10). If the SAFT is negative on normal skin and the suspicion of CUS is high, the SAFT test can be repeated on eczematous skin [4]. The last-mentioned method is not used anymore. In small children aged less than 3 years, the SAFT is considered as adequate in clinical practice. The possible value of the SAFT in clinical use was investigated in 8 patients with atopic dermatitis and suspected CUS. These 8 patients serve to illustrate the problems encountered in the diagnostics. Patients in whom there were discrepancies in history and test results, an oral challenge was performed. Allergen-specific IgE antibodies were determined with the CAP Radioimmunoassay system, according to the manufacturer's instructions (Kabi-Pharmacia, Uppsala, Sweden). Results were expressed as RAST (CAP) classes.

CASE REPORTS (EXAMPLES OF DIAGNOSTIC PROBLEMS)

Case 1

A 2-year-old girl had atopic dermatitis (AD) since the age of 3 weeks. After consuming eggs, her lips became swollen and her breathing was impaired. One day later, AD exacerbated. She refused to eat peanuts. She was hospitalised because of serious generalised AD. Treatment was started with oral erythromycin, local tar ointments and oral hydroxizine.

During her stay in the hospital, she was tested using SAFT and CAP RAST. The SAFT and CAP RAST results were positive for egg and peanut. An immune response to cow's milk (CAP RAST class 2) was not clinically relevant. At the hospital she ate a piece of pie containing egg with distressing results; her face became swollen (lips, ears and eyes) and within a few days AD exacerbated.

Case 2

A 10-month-old boy had AD since early age. Generalised urticaria or redness after consuming eggs was observed by his mother. She also thought that the child was allergic to cow's milk. Later the boy refused to eat eggs. After bathing in water with bath oil containing peanut oil, he cried and the skin showed generalised erythema. SAFT and CAP RAST results for egg and peanuts were positive. SAFT and CAP RAST were negative for

cow's milk. There was an extreme flare-up of AD during and after the SAFT. An open oral challenge with cow's milk was negative. Diet without egg and peanut was highly beneficial. AD was thus controlled more effectively.

Case 3

A 1-year-old girl had very mild AD. After she vomited cow's milk formula, her mother changed her diet to soy milk. However, in the first year, she had been fed with a cow's milk-based formula. The dietician discovered that the food was not completely free from cow's milk products. SAFT and CAP RAST tests were negative for cow's milk, egg and soy. The CAP RAST for peanut was class 1, however without clinical consequences. After the tests, and upon our advice, cow's milk products (in bulk) were re-introduced without any problem.

Case 4

A 1-year-old boy with AD was admitted to our clinic for test after FA. The mother could not remember having seen any direct skin/oral reaction to foods. She still (!) breast-fed her child. AD was resistant to therapy. SAFT and CAP RAST results to cow's milk and egg were positive. During the test, a serious flare-up of AD occurred.

Case 5

A 1-year-old girl suffered from therapy-resistant AD. After her mother had restricted all cow's milk products, her dermatitis almost disappeared within a few weeks. SAFT and CAP RAST results for egg and peanut were strongly positive. The SAFT for cow's milk was positive, though the CAP RAST score was negative. After institution of a cow's milk-, egg- and peanut-free diet, AD cleared completely.

Case 6

A 6-month-old girl was hospitalised because of intense itching and severe AD. The dermatitis had existed since the age of 3 months. As AD was therapy-resistant, SAFT testing was performed. Within 15 minutes, the SAFT for cow's milk was positive (2+), followed by a flare-up of dermatitis. SAFT with egg, soy, cow's milk hydrolysate and peanut were completely negative. During her stay at the hospital, one of the nurses accidentally gave the child cow's milk. This was directly followed by generalised urticaria. After institution of the diet, AD improved remarkably.

Case 7

A 6-month-old boy with AD was breast-fed. The mother consumed a lot of cow's milk. After direct skin contact with cow's milk and bread, urticaria developed. The mother bathed the child in wheat containing bath oil upon which the child quickly became red and developed urticaria over the whole body. SAFT results of cow's milk, wheat and the bath oil (WOLO®, Gouda, The Netherlands) were positive. Specific IgE to cow's milk and wheat were strongly positive. During the SAFT testing a generalised urticarial rash and swelling of the arms and the feet developed. His AD improved after diet restriction.

Case 8

A girl, almost 1-year-old, suffered from serious AD. She developed urticaria after drinking cow's milk. She refused to eat eggs and peanut butter. After being kissed by her brother who had cow's milk on his lips, she developed contact urticaria. SAFT results were positive for peanut and for cow's milk, but only on eczematous skin. The suspected egg allergy could not be confirmed by SAFT. CAP RAST results for cow's milk, egg and peanut were all strongly positive.

The results of SAFT and CAP RAST for all tested foods (cow's milk, egg, peanut, soy, wheat) are compared in TABLE 1. Strong positive SAFT scores corresponded well with high CAP RAST classes against the same food allergen. RAST tests were also often positive without clinical symptoms, and thus were not relevant.

	SAFT positive ≥2	SAFT negative
RAST classes 0-2	10	1
RAST classes ≥2	7	13

TABLE 1. SAFT *and* CAP RAST *scores in eight children with atopic dermatitis and suspected contact urticaria syndrome.*

DISCUSSION

The clinician should be aware of the different mechanisms by which foods can induce urticaria. Contact urticaria, in particular, was overlooked until 10 years ago. Seven children with AD also suffering from contact urticaria were evaluated (case no. 3 had no CUS). Common symptoms such as (contact) urticaria, Quincke's oedema and food refusal indicating FA were present in some of these patients. These symptoms belong to CUS. In cases 1, 2, 4 and 6 immediate contact reaction led to more persistant eczematous lesions. Although the number of patients was rather limited, SAFT as imitating provocation test correlated well with symptoms of FA. We focused on the practical consequences of food-induced CUS, illustrating the importance of this symptom in young children with AD.

Atopic dermatitis (AD) is a multi-factorial inflammatory disease with a variety of triggering factors such as aero-allergens, foods and pathological stress. Dietary restrictions are indicated in selected cases of AD and especially useful in children aged 0-4 years with AD. Next to clear-cut cases of AD combined with FA, one should also consider dietary intervention in the above mentioned 'local therapy'-resistant AD. Cases 5 and 6 illu-

strate therapy-resistant AD, which was successfully controlled by dietary intervention. Screening with the mixed-food RAST is a useful tool to identify children with atopic immune response to six common allergenic foods (cow's milk, eggs, peanuts, soy, cod fish and wheat). Only a few cases are missed using this method [15].

Case 5 illustrates another problem. The SAFT to cow's milk was positive, but IgE antibodies could not be detected. This child was in fact suffering from contact urticaria induced by cow's milk. It is possible that in this case a non-immunological mechanism is responsible for complaints induced by cow's milk. We are aware that this phenomenon sometimes occurs from a large scale series [4]. Another possibility is that all the IgE has been bound to the tissue so that no specific IgE antibodies could be detected in the serum. In children with therapy-resistant AD, one should look for food allergy and food-induced CUS.

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Chapter 9

Contact Urticaria Syndrome and childhood atopic dermatitis

based on:

Waard-van der Spek FB de, Oranje AP. Contact urticaria syndrome and childhood atopic dermatitis. In: Amin S, Lahti A, Maibach HI (eds). Contact Urticaria Syndrome. CRC Press, New York 1997

Waard-van der Spek FB de, Oranje AP. Contact Urticaria Syndrome by milk and milk products. In: Amin S, Lahti A, Maibach HI (eds). Contact Urticaria Syndrome. CRC Press, New York 1997

Chapter 9

Contact Urticaria Syndrome and childhood atopic dermatitis

DEFINITION AND CLINICAL PICTURE

Atopic dermatitis is a multi-factorial, genetically determined skin disorder, which mainly arises during childhood. Asthma and/or atopic rhinitis may accompany atopic dermatitis. Criteria for establishing the diagnosis have been proposed by Hanifin & Rajka [1]. These were modified by Oranje [2] and by Williams [3] for the practice.
Atopic dermatitis usually starts at the age of about three months. Below the age of 2 years, erythema, squamae, papules, vesicles and crusts are mostly located on the cheeks and forehead, on the trunk and extremities, particularly on the ventral sides of the legs. Lichenification occurs after the age of two years. Eczema appears on the flexures of the extremities, on the wrists, on the ankles and on the neck. In addition to the typical lesions, there are unusual variants, for example nummular eczema and inverse atopic dermatitis.
Atopic dermatitis follows a course with exacerbations and remissions. Different factors may play a role. One of them is food allergy, mainly in the young child. Others are inhalant allergies and contact allergy. Diagnostic investigations are necessary for establishing food allergy in children. The prick-prick test is painful and makes the children anxious. A painless skin test (Skin Application Food Test: SAFT) was developed for use in young children with atopic dermatitis and evaluated here.

PATHOGENESIS OF ATOPIC DERMATITIS

The histology of acute or sub-acute atopic dermatitis (AD) is comparable with that of allergic contact dermatitis. Most investigators feel that although AD is an immunological type IV skin reaction, IgE-mediated mechanisms play a primary role [4]. In the early development of AD an imbalance in Th2 and Th1 cells is postulated. Production of IgE antibody is dysregulated in atopic diseases. AD is often associated with high levels of IgE and eosinophilia. Cytokines produced by T lymphocytes regulate the switch of B lymphocytes to antibody-secreting plasma cells. The close interaction between Th2 cells and B cells through several receptors is called 'cognate interaction'. This process together with interleukin [IL]-4 and IL-13 is the signal for B cells to switch to IgE production

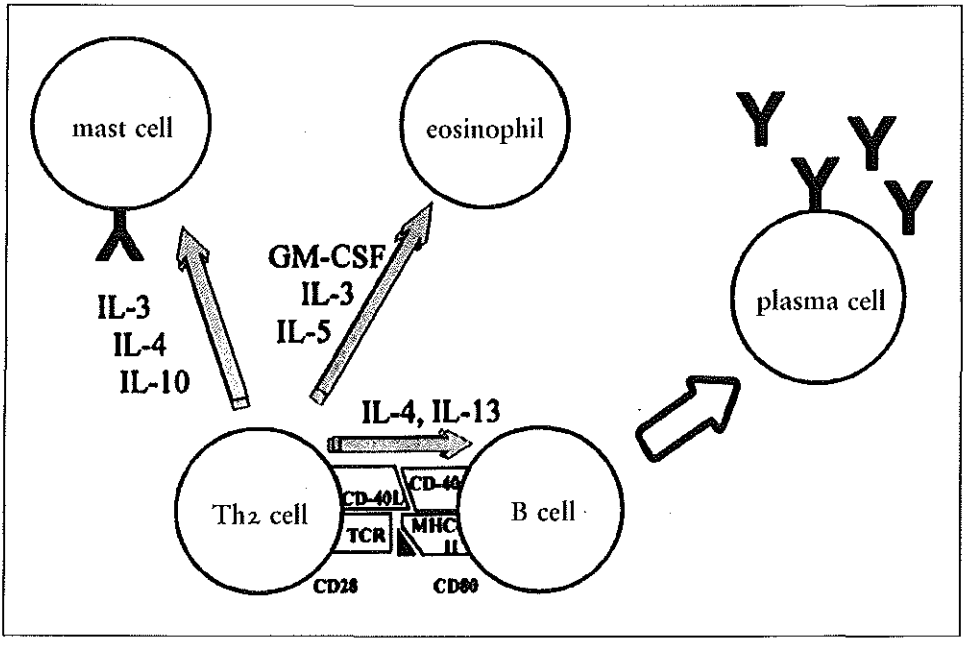

FIGURE 1. *Pathogenetic model in atopic dermatitis.* IL=*interleukin;* GM-CSF=*granulocyte monocyte colony stimulating factor;* TCR=*T cell receptor;* MHC II=*major histocompatibility complex class* II.

(FIGURE 1). Eosinophils are attracted by IL-3, IL-5 and platelet activating factor (PAF). Eosinophils have several membrane receptors including that for the Fc part of IgE. Eosinophils contain granules, encompassing major basic protein (MBP) and eosinophilic cationic protein (ECP) as the main proteins [5,6]. After activation, eosinophils degranulate rapidly producing mediators such as prostaglandins, leucotrienes and PAF. Eosinophilic cationic protein is probably a marker of disease activity and its levels are significantly increased in AD [6].

Cellular immunity is diminished in AD [4]. IgE-bearing Langerhans cells play an important role in triggering AD [7,8]. The patho-mechanism is comparable with that of contact allergic dermatitis. In contrast to that observed in contact allergic dermatitis, Th2 cells are predominantly observed in AD.

The mast cell is also important in the pathogenesis of AD. The mast cell is loaded with IgE. Allergens may reach cutaneous mast cells and Langerhans cells via the skin or via the blood circulation after entering the mucosal surfaces [4]. The mast cells degranulate after contact with allergens (FIGURE 2). Several mediators such as histamine, prostaglandins, serotonin, leucotrienes, cytokines (IL-3, IL-5) and PAF are released. The direct response results in urticaria. Both IL-3 and IL-5 in combination are a strong signal for inducing maturation of the mast cell and for recruiting eosinophils. Eosinophils play an

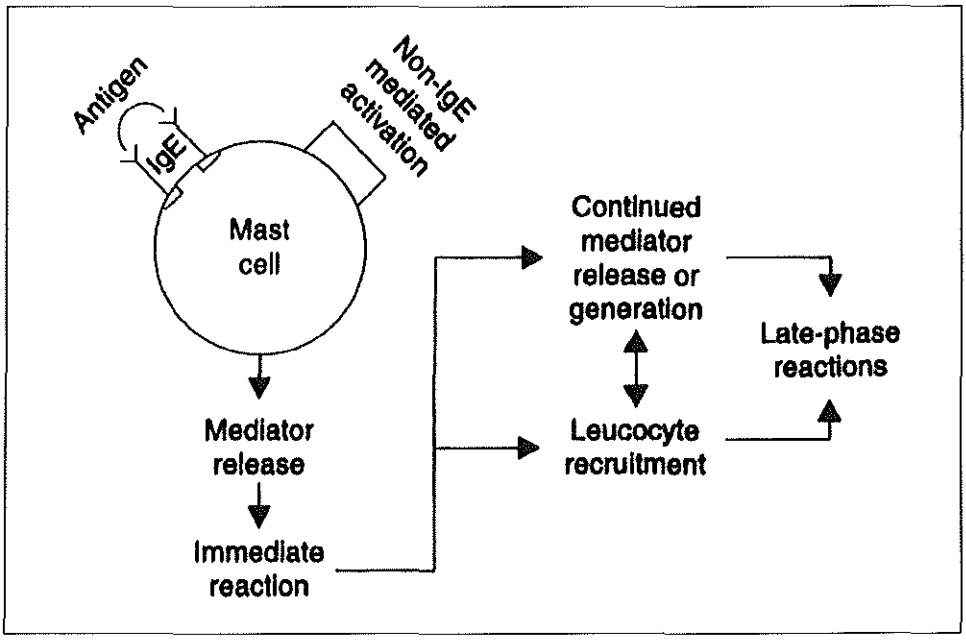

FIGURE 2. *Mast cell, direct and late reaction. (adapted from: Oranje AP. Development of childhood eczema and its classification. Pediatr Allergy Immunol 1995; 6 (57): 31-35).*

important role in the initiation of the early and late phase skin reactions. Th2 cells also produce both IL-3 and IL-5.

The resulting mononuclear infiltrate consists of T cells. The majority of the T cells belong to the Th2 subset. A minority belongs to the Th1 subset. Cells of the Th2 subset have a high, whereas Th1 cells have a low IL-4/IFN-gamma ratio. IL-4 stimulates IgE production, whereas IFN-gamma inhibits it [9].

CONTACT URTICARIA SYNDROME

Food-induced contact urticaria syndrome (CUS) occurs in more than one-half of the infants and toddlers with AD [10]. Contact urticaria induced by foods is of immunological or non-immunological origin [11-13]. Non-immunological contact urticaria is an inflammatory reaction that appears within minutes to an hour after contact with the eliciting substance and usually disappears within a few hours. These reactions have also been called immediate-type irritancy which occur in most exposed individuals without previous sensitisation. A unique and serious clinical feature of immunological contact urticaria is the ability of the reaction to spread beyond the site of contact and progress to generalised urticaria, involvement of internal organs, and/or anaphylaxis. Immunological contact urticaria is considered to be more prevalent in atopic patients

compared with non-atopic patients. The non-immunological contact urticaria affects the two groups with equal frequency. The contact urticaria syndrome is usually allergic. Contact urticaria is often observed in young children with AD, but also in adults with AD or contact dermatitis. Urticaria occurs preferably in the eczematous areas because antigens penetrate the skin more easily. The clinical presentation in older children and in adults differs somewhat and is more restricted to and around the mouth. Then it is called oral allergy syndrome. IgE responses are divided into early, late and delayed reactions [13]. Most of the IgE responses occur together and often an early reaction is followed by a late one. This means that an urticarial reaction may be followed by an eczematous eruption.

FOOD-INDUCED CUS

Many foods can provoke food-induced contact urticaria (TABLE 1). Overall, the most common allergen is egg, followed by cow's milk and others such as wheat, fish and peanut. Different other foods may induce CUS. It depends on early exposure to the allergen.

Foods inducing contact urticaria in infants and toddlers with atopic dermatitis according to our own experiences

Almond	Fish (especially cod)	Pork
Banana *	Hazelnut	Raw potato
Chicken meat	Kiwi *	Sesame
Beef	Nuts (various)	Tomato
Cow's milk	Paprika	Wheat
Egg	Peanut	

* These are also natural histamine liberators.

TABLE 1.

For differential diagnostic reasons, one should realise that animal products (saliva, hair) may also induce CUS. Atopic dermatitis is a complicated disease often strongly influenced by flare factors such as contact urticaria, allergic contact dermatitis and late phase reactions. Contact urticaria may induce eczema not only by basic immunological mechanisms but also by scratching [13,14].

CLINICAL SYMPTOMS

Common symptoms of food allergy (FA) are refusal of foods, vomiting and urticaria on the hands and around the mouth. These symptoms belong to CUS [10]. Food allergy is variable in presentation depending on the organ involved [13]. Symptoms on the skin and the mucous membranes may be the sole manifestations of FA (TABLE 2).

Common symptoms of food allergy in children with atopic dermatitis, with the skin as the main target

Urticaria	Pruritus or pain in the mouth (and swelling) *
Contact urticaria	Perleche, aphthae
Quincke's oedema	
Flare-ups of AD	Food refusal, vomiting, diarrhoea #

* Oral allergy syndrome / # common, though instead of other listed symptoms, not of skin and mouth.

TABLE 2.

GUIDELINES FOR EXAMINATION

Very often, the parents notice contact urticaria. However, its exact origin and the history are often not completely clear. The parents do not know exactly which food(s) or other substance is responsible. We observe CUS rarely in our patients at the out-patient clinic. CUS has disappeared before the patient visits us. Tests for CUS are performed if the history is suspect, in therapy-resistant atopic dermatitis and in doubtful cases with vomiting, diarrhoea or refusal of food(s).

MANAGEMENT

Atopic dermatitis (AD) is a multi-factorial inflammatory disease with a variety of triggering factors such as aero-allergens, foods and pathological stress. Dietary restrictions are indicated in selected cases and especially useful in children aged 0-5 years with AD. The younger the child, the higher are the chances that a diet would be helpful in the management of AD. The diagnosis of FA relies on the combined interpretation of 'weighted' history and on the results of serological and skin tests. Final and ideal proof of FA is achieved by (double-blind) oral provocation. From the age 3 years, we perform

the double-blind placebo-controlled oral challenge (DBPCOC). An open challenge is conducted in children younger than 3 years.
Food allergy is not only based on direct IgE-mediated reactions, but also delayed-type reactions are common. Late IgE reactions can be observed by later reading of SAFT [15]. Patch tests for delayed-type reactions (atopy patch tests) read after 1 and 2 days or (preferably) after 2 and 3 days detect approximately another 10% of the patients with FA. We observed positive reactions with several foods, e.g. cow's milk, egg and wheat [own observations, 15].

CUS BY MILK AND MILK PRODUCTS

Cow's milk allergy affects 2-8% of infants [16]. It is the most common food allergen together with egg white. The clinical presentation is very variable. One distinguishes milk-induced pulmonary disease, allergic gastro-enteropathy, iron-losing enteropathy, neonatal thrombocytopenia and milk-induced colitis in infancy. Hill [16] mentioned urticaria, angioedema, circumoral lesions, morbilliform eruptions, eczema and perianal eruptions as dermatological symptoms, but did not include milk-induced contact urticaria. Contact urticaria is common in infants and toddlers with AD and FA. The reason(s) for the variations in the symptoms of FA is not yet clear.

Milk-induced contact urticaria is a wheal and flare reaction elicited after cutaneous exposure to cow's milk or cow's milk products such as cheese, yoghurt and others. Children with AD and milk allergy may present with immune-mediated contact urticaria [10,17].

INCIDENCE AND COURSE OF CUS BY MILK AND MILK PRODUCTS

The real prevalence of CUS caused by cow's milk is unknown. About one-half of the children with AD and FA also suffer from CUS. Allergens such as milk may penetrate the skin easily and cause urticarial reactions in sensitised individuals. A 12-month-old boy who had a strong history of cow's milk allergy, had developed two episodes of anaphylaxis following cutaneous application of a casein containing ointment to an inflamed diaper area was reported [18]. At our out-patient clinic, a manifest FA was observed in 20% of the children with atopic dermatitis [19]. The most common allergens were cow's milk, egg and peanut. After the age of 2 years, CUS caused by cow's milk decreased. At the age of 4 years, 75% of all the cases had cleared. A possible explanation is the role of the inadequate immune system in young allergic children [20]. It concerns, especially, the immaturity of the gastro-intestinal tract. In the first 3 years of life, cow's milk allergy has an estimated prevalence of 2.3-2.8%. Adult onset of IgE-mediated allergy to cow's milk has only been described in several case reports and in a synopsis of 34 patients [21].

ALLERGENS IN MILK

Cow's milk contains more than 25 proteins. The major protein in cow's milk is casein, but is not as important in allergy as beta-lactoglobulin which makes up only 10% of the total protein content [22]. Allergens in cow's milk are beta-lactoglobulin, casein, lactalbumin and bovine serum albumin [22]. Human milk contains mainly beta-lactoglobulin [23].

Cutaneous antigen-positive lymphocytes from children with milk-induced AD can be expanded in vitro with casein [24]. Casein-specific T cell clones were generated from the blood of patients with milk-responsive AD. These findings point to a possible significance of food-specific T cell responses in the pathogenic process of AD in these patients. Casein is composed of several protein fractions. A pronounced cellular immune response to the κ-casein fraction in milk-responsive patients with AD was observed underlining the patho-physiological importance of the bovine κ-casein sub-fraction in patients with milk-responsive AD [25].

DIETARY INTERVENTIONS

Children with cow's milk allergy need intensive nutritional counselling and regular monitoring of growth. A 4-year-old boy who had rickets, thought to be the result of dietary calcium deficiency caused by the prolonged elimination of cow's milk and milk products from his diet because of allergy was reported. Adequate intake of calcium resulted in rapid improvement [26]. Milk substitutes are largely used in children with cow's milk allergy. Protein hydrolysates are also used. There are reports that some children develop intolerance to protein hydrolysates. Polypeptides of protein hydrolysates may induce an IgE antibody response or cross-react with IgE antibodies against determinants of cow's milk proteins [27]. Sensitisation or cross-reactivity to protein hydrolysates may occur and may be associated with poor response to an exclusion diet based on protein hydrolysates [28].

PRACTICAL CONSEQUENCES

Often, contact urticaria syndrome is not difficult to recognise. The most important symptoms of FA with the skin as the most prominent target are refusal of food(s) and redness on hands and around the mouth. In infancy, cow's milk especially is the most common allergen. In case of cow's milk allergy, one has to evaluate the allergy again after the age of two years, because in most children the cow's milk allergy disappears by then. Children with cow's milk allergy need intensive nutritional counselling and regular monitoring of growth. Sensitisation or cross-reactivity to protein hydrolysates may occur and should be kept in mind. Contact urticaria to large particulated hydrolysates has been described and also observed by us.

There are two important questions in practice:

- Does FA play a role in all or a certain proportion of children with AD? Are these mainly young children?
- To what extent does diet restrictions influence AD?

The frequency with which FA plays a role in AD was investigated in a retrospective study of all patients undergoing treatment for atopic dermatitis in 1989 at the out-patient clinic of the Paediatric Dermatology Unit of the Sophia Children's Hospital in Rotterdam. The study involved 375 patients. Their age at first visit to the out-patient clinic varied from 0 to 15 years.

A restrictive diet had been prescribed to 77 (21%) of the 375 patients prior to their first visit because of suspected rash caused by foods. Further analysis of the investigations for a suspected FA using skin tests and blood tests showed the following:

- Fourteen (18%) of these 77 patients were in fact allergic to the foods which had been omitted from the diet.
- Twelve (16%) patients had additional allergy to one or more foods so that further diet restrictions were warranted.
- Four (5%) patients appeared to have allergy to foods other than those mentioned in their medical records.
- Thirty-five (45%) of these 77 patients appeared not to have food allergy. Normal diet was re-introduced in these patients without any further problems.
- In the remaining 12 patients, it was not known whether the restrictive diet had been justified because these patients failed to keep their appointment.

From the 298 patients who were not on a restrictive diet, only 15 appeared to have FA. A restrictive diet was advised in these children. One patient was already on a diet because of intestinal problems. Skin test was conducted in this patient.

Finally, it appeared that only 46 (12%) out of the 375 patients with atopic dermatitis had food allergy. The incidence of FA was different at different ages. Food allergy occurred particularly at very young age. Fifty-four percent of the patients with a FA were younger than 1 year, 17% were 1 year old, 15% were 2 years old and 4% were 3 years old. It appeared from this that 90% of the children with FA were younger than 4 years. Children younger than 2 years were mostly allergic to cow's milk.

Food allergy related to AD thus appeared to occur mainly in children younger than 4 years. Diet intervention had a beneficial effect on the course of AD in about 40% of these children. Food allergy was not correlated with AD beyond the age of 4 years.

CONTACT URTICARIA SYNDROME: PROGNOSIS AND COMPLICATIONS

Contact urticaria syndrome to cow's milk normally disappears in most cases within a

period of 3 years. Allergy to egg shows lower regression. Allergy to peanut persists lifelong in 99% of the cases. The most severe presentations of CUS are a generalised reaction and anaphylaxis. Generalised reactions occurred after local application of milk or egg containing products [18,29]. Anaphylaxis after cutaneous exposure has also been described [18].

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Chapter 10

Diagnostic tests in children with atopic dermatitis: pain-preventing approaches

based on:

Waard-van der Spek FB de, Elst EF, Mulder PGH, Munte K, Devillers ACA, Oranje AP. Diagnostic tests in children with atopic dermatitis and food allergy. Allergy 1998; 53: 1-5

Chapter 10

Diagnostic tests in children with atopic dermatitis: pain-preventing approaches.

INTRODUCTION

In food allergy, one can speak of a hypersensitivity reaction to foods in which the immune system is involved. The prevalence of food allergy is estimated at about 2-8% [1]. Patients with atopic disorders appear to have a higher prevalence of food allergy. The more severe the atopic dermatitis in young children, the more likely they are to have food allergy [1,2]. Allergic reactions to foods may show symptoms of various organ systems. The skin, the gastro-intestinal system and the respiratory system are the most affected [1,3]. It is very important to use appropriate procedures to evaluate food hypersensitivity. Mis-diagnosis of food allergy and implementation of highly restrictive diets can lead to severe malnutrition. It may also lead to a delay in the diagnosis and the treatment of serious underlying organic disorders [1].

The IgE-mediated allergic reaction in the skin is dependent on mast cells that are rapidly degranulated after allergen challenge. It consists of an immediate wheal and flare reaction. It is consistently followed by a late-phase reaction, which is due to IgE antibodies. The late-phase reaction involves an inflammatory infiltrate predominantly consisting of mononuclear cells. Eosinophils, basophils, neutrophils, and an extensive deposition of fibrin are also observed. The same cellular pattern, however, can also be found after an immediate wheal and flare reaction that does not lead to a macroscopic late-phase reaction [4,5]. Urticarial exacerbations, developing mainly after consuming food, may be observed in young children with atopic dermatitis. Direct contact with the food concerned frequently leads to (contact)-urticarial reactions around the mouth and on the hands. Such reactions which develop within several minutes are most probably immunologically mediated (IgE). Several procedures can be used to test IgE-mediated food allergy.

Skin testing is a common diagnostic procedure in food allergy. The skin prick(-prick) test is the test of first choice for investigating this type of immediate reaction [4,5]. Oranje [6,7] developed the Skin Application Food Test (SAFT) on the basis of the mechanism of the Contact Urticaria Syndrome (CUS). Today, intracutaneous skin testing with food extracts is seldom used in the diagnosis of immediate-type, IgE-mediated, allergy [8].

Skin tests may be performed with commercially available extracts of foods or fresh

foods [1,8]. Rancé et al. reported that fresh food extracts were more effective than commercial extracts in detecting sensitisation. Results of skin prick tests with fresh food extracts were also better correlated with positive challenges than commercial extracts [9].
Ideal and final proof of the diagnosis of food allergy is obtained only by (double-blind and placebo-controlled) oral challenge.

AIM OF THE STUDY

Investigations into the relevance of the SAFT in young children with atopic dermatitis and (suspected) food allergy was compared with another skin test (prick-prick test) and the radioallergosorbent test (RAST) (Pharmacia, Uppsala, Sweden). The relationship between the SAFT test and oral challenge was also examined.

MATERIALS AND METHODS

STUDY GROUP

Children younger than 4 years who attended the out-patient clinic of the Paediatric Dermatology Unit of the Sophia Children's Hospital in Rotterdam because of atopic dermatitis and suspected food allergy in 1994-1996 were recruited into this study. Children with reactions to foods without atopic dermatitis were not included.

METHODS

Fifty-two young children (2-4 years of age) with atopic dermatitis and (suspected) food allergy were tested with two different skin tests. Skin tests with cow's milk, egg and peanuts were included in the investigations. All the children were tested with the SAFT and the prick-prick test.
In the SAFT test, the food, in the same state as it was consumed, was applied on the back of the patients using large 'Finn chambers'. The test was read after 10, 20 and 30 minutes. The results were scored as follows: 0 = no reaction; 1+ = erythema; 2+ = erythema and oedema within the area of the patch test; 3+ = erythema and oedema up to the outer area of the patch test. Reactions with a score of 2+ or 3+ were regarded as positive.
A microlancet with a 1-mm needle with shoulders (ALK, Benelux) was used in the prick-prick test. The needle was first pricked in the food and then vertically into the lower arm. A drop of histamine dihydrochloride solution (10 mg/ml, ALK, Benelux) was used as the positive control. The negative control consisted of a drop of physiologic saline. The test was read after 15 and 30 minutes. The reaction to the food was evaluated by comparing it with the reaction to histamine. A positive reaction to food had an average diameter of the wheal that was at least 3 mm above the negative control.
A serological test (specific IgE-RAST; Pharmacia, Uppsala, Sweden) was compared with the SAFT in 82, 87 and 81 children, respectively, for cow's milk, egg and peanuts, and

with the prick-prick test in 48, 44 and 48 children, respectively, for cow's milk, egg and peanuts. We studied the relevance of the SAFT in children younger than 4 years, so we compared the SAFT with the oral provocation test (challenge) in 64 children younger than 4 years.

For the oral provocation test, the children were admitted to the day-care unit, where the standardised procedure was performed. Before starting the procedure, the emergency set was prepared and made ready for use. The child was examined and the blood pressure and pulse rates were noted. Then a small amount of the food was given. All observed reactions were noted.

Positive reactions may be an urticarial rash, peri-oral redness, flare up of the eczema, itching, increasing pulse rate, depression of the blood pressure, respiratory or gastrointestinal complaints. If no reactions were observed after 1 hour, a double amount of the food was given, and after 2 hours the amount was doubled again. After 3 hours the food was given without restrictions. The total amount given correlated to age-related average 'daily intake'. If a positive reaction was observed, the test was stopped. If no reaction was observed, the child was discharged after 8 hours. The parents were urged to contact the dermatologist if a (possible) late reaction was observed so that this reaction could be evaluated.

STATISTICAL ANALYSIS

In order to compare the different tests with each other, kappa [κ] was calculated and used as a measure of agreement between the different tests. Kappa has a maximum of 1.00 when agreement is perfect, whereas a value of zero indicates agreement as expected purely by chance. Values between 0 and 1 are interpreted as follows: < 0.20 = poor agreement, 0.21-0.40 = fair agreement, 0.41-0.60 = moderate agreement, 0.61-0.80 = good agreement and 0.81-1.00 = very good agreement [10].

The McNemar test was used for testing differences between the marginal distributions of the RAST, the prick-prick test and the SAFT [11].

RESULTS

The results of the comparison between the SAFT and the prick-prick test are shown in TABLE 1. The number of patients in the various groups was 52. There was a good agreement between the different skin tests in the group of 2-4 year-old children that was investigated. The calculated value of kappa [κ] was 0.50 for cow's milk, 0.70 for egg, and 0.84 for peanuts.

The standard errors for kappa (SE [κ]) were 0.14, 0.10 and 0.07 respectively. The p values for κ showed highly significant differences from zero ($p<0.001$). The results of the McNemar test are also shown in TABLE 1.

There was no significant difference between the percentages of positive scores of both skin tests. The p values in the McNemar test were 0.110, 0.126 and 1.000 respectively.

	n	κ	SE(κ)	p(κ)	% pos. pr.pr.	% pos. SAFT	pMcNemar
SAFT-pr.pr. Cow's milk	52	0.50	0.14	<0.001	31	19	0.110
SAFT-pr.pr. Egg	52	0.70	0.10	<0.001	38	29	0.126
SAFT-pr.pr. Peanuts	52	0.84	0.07	<0.001	58	54	1.000

n = number of patients, κ = kappa, SE (κ) = standard error for kappa, p = p value,
SAFT = Skin Application Food Test, pr.pr. = prick-prick test, pos. = positive

TABLE 1. *Comparison between skin test (SAFT, prick-prick [pr.pr.]) in children aged 2-4 years.*

The results of the comparison between the SAFT and the prick-prick tests and the serological test (RAST) in children aged 2-4 years are shown in TABLE 2.
The numbers of patients in the SAFT versus RAST group were 82, 87 and 81, respectively for cow's milk, egg and peanuts. There was a slight difference in the numbers because all three foods were not tested in certain cases. A moderate agreement (κ ranging from 0.41 to 0.58) was observed between the SAFT and the serological test (RAST).

	n	κ	SE(κ)	p(κ)	% pos. skin test	% pos. RAST	pMcNemar
SAFT-RAST Cow's milk	82	0.41	0.10	<0.001	24	49	<0.001 RAST>SAFT
SAFT-RAST Egg	87	0.47	0.09	<0.001	39	60	<0.001 RAST>SAFT
SAFT-RAST Peanuts	81	0.58	0.09	<0.001	52	63	0.049 RAST>SAFT
pr.pr.-RAST Cow's milk	48	0.59	0.12	<0.001	29	40	0.180
pr.pr.-RAST Egg	44	0.68	0.11	<0.001	36	48	0.126
pr.pr.-RAST Peanuts	48	0.66	0.11	<0.001	56	60	0.726

n = number of patients, κ = kappa, SE (κ) = standard error for kappa, p = p value,
SAFT = Skin Application Food Test, pr.pr. = prick-prick test, pos. = positive

TABLE 2. *Comparison between skin test (SAFT and prick-prick [pr.pr.]) and RAST in children aged 2-4 years.*

Significantly more positive results in the RAST test were observed than in the SAFT (McNemar: for cow's milk and egg, $p<0.001$; for peanuts, $p=0.049$).
The numbers of patients in the prick-prick test versus RAST group were 48, 44 and 48, respectively, for cow's milk, egg and peanuts. A moderate to good agreement was observed between the prick-prick tests and the RAST (κ of 0.59, 0.68 and 0.66, respectively, for cow's milk, egg and peanuts). The McNemar test showed no significant difference between the percentages of positive scores of the prick-prick test and the RAST (for McNemar, $p=0.180$, 0.126 and 0.726, respectively).

The SAFT test was compared with the oral provocation test with cow's milk, egg or peanuts in 64 children younger than 4 years. The results are shown in TABLE 3. Nineteen children had a positive SAFT and a positive oral provocation. Both tests were negative in 41 children. In 4 children, there was a discrepancy in one direction only: a negative SAFT was followed by a positive oral challenge. It concerned 2 girls and 2 boys. One girl was aged 3 years during the challenge. She was known to be allergic to cow's milk and had a positive SAFT in the past. The SAFT had become negative, but the RAST was still positive (class 3). She developed an urticarial reaction peri-orally upon oral challenge. The second child was a boy aged 3 years and 4 months. He was known to be allergic to cow's milk and the earlier positive SAFT had become negative. The RAST was positive (class 2). The oral challenge was positive. A prick-prick test was also performed in his case. This test was positive for cow's milk. The 3rd and 4th cases had positive oral challenges for egg. In the boy aged 2 years and 8 months, the SAFT was negative and the RAST positive (class 2). A girl aged 2 years and 9 months had a negative SAFT and a positive RAST (class 3). The challenge was negative during the day-care hospitalisation. On her way home, she developed a skin reaction which was examined by the general practitioner. He informed the parents that this reaction was a late reaction to the oral challenge. We later considered the test to have been positive, but on questionable grounds. There was a very good agreement between the SAFT and the oral challenge ($\kappa=0.86$). There was no significant difference between the positive results in the McNemar test ($p=0.125$).

	Challenge positive	Challenge negative	κ	SE(κ)	$p(\kappa)$	% pos. SAFT	% pos. Challenge	pMcNemar
SAFT positive	19	0	0.86	0.07	<0.001	30	36	0.125
SAFT negative	4	41						

TABLE 3. *Comparison between the results of* SAFT *and oral challenges (cow's milk, egg and peanuts) in* 64 *children younger than* 4 *years.*

DISCUSSION

The following points are important for establishing the diagnosis of food allergy: symptomatology directed history, an accurate anamnesis of nutrition, a family history of allergic disorders, physical examination including weight, length and growth; and supplementary investigations, among others, of specific IgE, total IgE and skin tests, and elimination and provocation tests. The (double-blind and placebo-controlled) oral challenge is regarded as the reference standard for the diagnosis of food allergy. However, this test is very time-consuming and brings with it a certain risk that the challenge may result in a reaction that may be more severe than anticipated from the medical history [12,13].

Several skin tests such as the open application test [14], the 'Reibtest' [15], the scratch test, and the prick(-prick) test [4,5] have been developed. Skin prick tests were reported as the method of first choice [4,5]. In practice, the prick test in small children may pose problems because the children are frightened when they see a needle being used and the superficial prick is still felt. This test then may become a traumatic experience for the child. Most physicians neglect this aspect.

The SAFT test was developed by Oranje and is based on the mechanism of contact urticaria [6]. The SAFT test can be performed without any problems in small children because it does not have the disadvantage of using a needle and superficial pain. Contact urticaria syndrome is an important skin condition in infants and toddlers with atopic dermatitis and food allergy, with the skin as the target organ. IgE-bearing mast cells play a central role in the pathogenesis of type I allergic skin reactions and in acute urticarial flare-ups of atopic dermatitis [6,7].

The properties of skin tests in the diagnosis of food allergy depend highly on the potency of the allergen used. Many food extracts do not contain all the relevant allergens [8]. It was reported that skin tests were negative with commercially available extracts, but were positive in the same patients with fresh food [12]. A possible explanation for this may be that certain allergens were lost during the preparation of such extracts. Fresh food represents the naturally occurring allergen to which the patient has been sensitised and thus reacts [8,12]. Rosen et al. [12] also suggested that the patients should be tested with the food in the form that caused the reaction, i.e. in the form it was consumed. Rancé et al. studied correlations between skin prick tests using commercial extracts and fresh foods, specific IgE, and food challenges in 430 children (average age 4.2 years, range 2 months to 20 years). The overall concordance between a positive prick test and a positive challenge was 58.8% with commercial extracts and 91.7% with fresh foods. The results indicated that fresh foods are more effective in detecting sensitisation to food allergens. They concluded that fresh food should be used for primary testing for suspected allergy to egg, peanut and cow's milk [9].

We compared the SAFT in young children with the prick-prick test using fresh foods in the same state as it was consumed, with the serological RAST test and with the reference standard (the oral challenge). A comparison between the SAFT and the prick-prick test has, to our knowledge, never been done before. We observed that the SAFT appeared to

be a reliable skin test for evaluating food allergy in the investigated group of children younger than 4 years with atopic dermatitis. There was a good agreement between the SAFT and the prick-prick test. From the discrepancies between the results of the SAFT and the RAST test, it appeared that in the serological test one exclusively measures an atopic immune response that may not always be clinically relevant. An explanation may be that, in some children, the food protein allergen may not reach the sensitised cells. Another explanation may be that other cells, cell products, or cellular interactions may be necessary to elicit symptoms that may not occur in some children [16].

We studied the relevance of the SAFT in children younger than 4 years. We compared the SAFT with the oral provocation test (challenge) in 64 children younger than 4 years. The relevance of the skin prick test and the RAST has been widely evaluated. We did not compare these tests with the oral challenge in this study. In particular, there was a very good agreement between the SAFT and the oral provocation test. In the group of 64 children in which the SAFT was compared with the oral challenge, there were only 4 discrepancies. One of the subjects had a possible reaction on her way home. We were not able to confirm this reaction ourselves because the parents did not contact us. So probably the number of discrepancies was only 3. We always stress to the parents that they should contact us in case of a possible late reaction in order to classify objectively such reactions ourselves. In the case mentioned, we chose to consider the test positive, although questionable.

It is wise to bear in mind that the interpretation of a positive oral challenge is food intolerance, because a positive result does not automatically allow the use of the term 'immunologically' or even 'IgE-mediated' reaction. The proof from immunological tests, such as specific IgE or lymphocyte responses is necessary together with positive clinical reactions to assess a positive challenge as 'food allergy' [17].

In conclusion, it can be stated that the SAFT test is a reliable and child-friendly skin test for evaluating (suspected) food allergy in children younger than 4 years with atopic dermatitis. In practice, we perform SAFT test in children younger than 3 years, whereas the prick-prick test is performed above this age. We recommend the use of this child-friendly test in young children for evaluating food allergy. The very good correlation with the oral challenge indicates that one may probably consider the SAFT a 'skin provocation' in children younger than 4 years.

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Part 3
Discussion and summary

Chapter 11

Discussion

Pain is an impressive adverse event experienced by children which is no less than that by adults. For many decades, various scientists misconstrued that very young children and neonates felt no pain and did not have a memory of pain [1]. Early pain experience is one of the most relevant factors in the ontogeny of pain perception [2]. Children's previous experiences with pain will affect how they react to subsequent painful events. One essential feature of a Pavlovian or classical conditioning paradigm is that an organism learns by associating neutral with non-neutral stimuli. One may learn to associate a previous neutral stimulus like visiting a physician or a dentist with non-neutral stimuli such as pain, fear and anxiety. Such a person may then develop a phobic reaction to physicians or dentists because of their association with unpleasant stimuli [3].
Children learn to be afraid of all kinds of injections at a very early age. Health professionals not always seem to realise fully the anxiety and the dread that the needle provokes in their patients. Pain-prevention, or at least pain-reduction, is most important to reduce children's distress.

The first part of the thesis consists of investigations into pain-reducing measures for superficial (dermatological) interventions. A local anaesthetic only was used in all investigations. EMLA® is a topical anaesthetic cream developed by Broberg and Evers for use on intact skin [4]. The acronym EMLA® stands for Eutectic Mixture of Local Anaesthetics. EMLA® is a mixture of lidocaine 25 mg/g and prilocaine 25 mg/g. The base that is used in EMLA® makes it possible to achieve high concentrations of lidocaine and prilocaine in an aqueous solution allowing a good absorption through intact skin. A high concentration of the drug is also necessary for optimal penetration through diffusion barriers. The emulsion droplets of EMLA® contain a high concentration of the local anaesthetics, although the total concentration in the emulsion is relatively low (5%).
EMLA® produced effective analgesia in the skin prior to a variety of superficial skin interventions. The duration of application of EMLA® is very important. The main factor on which the application time depends is the structure of the skin to which it is applied. This is because the local anaesthetics must penetrate through the epidermis, diffuse down into the dermis and permeate the nerve cell membranes before any analgesic effect is produced. In intact skin, the duration of application required may vary according to the local blood flow and the epidermal and dermal thickness of the skin, but is generally

60 minutes. In our double-blind, placebo-controlled time response study in which we evaluated the efficacy and minimal effective application time of EMLA® cream for removing mollusca contagiosa in children, an application time of less than 60 minutes was satisfactory. EMLA® cream effectively prevented the pain of curettage of mollusca contagiosa after 15, 30 and 60 minutes application in children aged 4 to 12 years. We observed no significant difference among the 15-, 30- and 60-minute EMLA®-treated groups.

Shorter application times are required in areas of skin lesions where the epidermis is not an effective barrier or on mucous membranes which do not possess a keratinised layer of cells.

There are local differences in the onset and duration of action of EMLA®. Variations occur according to the site of the body to which it is applied. Local epidermal and dermal thickness mainly influence the onset of action of EMLA®. The duration of action depends on the rate of diffusion of the anaesthetics into the surrounding tissues and the systemic circulation and is thus influenced by local blood flow [5-8].

In atopic skin and on psoriatic plaques, an application time of 15 minutes appeared to produce effective analgesia, but the effect persisted for only 15 to 30 minutes. This was in contrast to normal adult skin, where as a rule an application time of 60 minutes was needed for complete anaesthesia. This rapid but shorter analgesia is probably explained by an enhanced penetration of the anaesthetics into the dermis and a higher cutaneous blood flow resulting in a faster vascular uptake of the analgesics [9,10].

In contrast to the skin, mucous membranes offer less protection to the nerve endings and allow faster penetration of local anaesthetics resulting in a faster onset of action. Higher vascular flow allows faster clearance resulting in a more rapid decline of the analgesia. Application of EMLA® (1 g) for 2 minutes on the gingiva produced effective analgesia for 10 minutes. The maximum pain threshold was reached immediately after removal of the cream [11].

In our randomised, double-blind and placebo-controlled study on the analgesic effect of the EMLA® patch as a local pre-medication for obtaining a skin biopsy in children, we observed that the anaesthetic patch was significantly more effective than the placebo patch in decreasing the pain at the injection site of the lidocaine infiltration. There was no significant difference in pain scores of the biopsy, confirming that infiltration with lidocaine, although painful, provided adequate anaesthesia [12].

EMLA® cream significantly relieved pain at the MMR vaccination in the group of girls that were investigated in a randomised, double-blind and placebo-controlled study. The difference in VAS score in the whole group almost reached statistical significance [13]. Probably the pain at MMR vaccination is not due to skin penetration, but due to the injection of the liquid vehicle in the subcutaneous space. In this study, EMLA® seemed not to provide adequate analgesia.

The most commonly observed side effects of EMLA® are not serious and consist of blanching or erythema. These side effects may be due to effects of the anaesthetics on vascular smooth muscle and may be concentration dependent. At very low concentrations (e.g. short application times), they may produce vascular contraction, whereas at

higher concentrations which would be achieved after long application times, the anaesthetics relax vascular and bronchial smooth muscles and could thus induce erythema. Side effects that are more serious are only reported incidentally. Methaemoglobinemia and toxic purpura have been described because of a high level of absorption. Other side effects are allergic reactions.
We observed purpura after application of EMLA® in 5 patients: in 4 patients with molluscum contagiosum 30 minutes after the application of EMLA® cream and in one patient 60 minutes after application of EMLA® in whom it was used as a local anaesthetic for taking a lip biopsy. This purpura reaction could not be reproduced upon patch testing. We concluded that the reaction was not of an allergic nature. It may be possible that the purpura were caused by a toxic effect on the capillary endothelium inducing the extravasation of the erythrocytes [14].

Taken together, the results of these investigations showed that EMLA® was an effective and child-friendly local anaesthetic which provides adequate pain-reduction for various indications in paediatric and general dermatology.

The second part of the thesis deals with studies into child-friendly painless diagnostic investigations in children with atopic dermatitis. Different factors may play a role in atopic dermatitis. One of them is food allergy mainly in the young child. Skin testing is a common diagnostic procedure in food allergy. The skin prick test is the test of first choice for investigating the immediate IgE-mediated reaction [15,16]. In practice, the prick test in small children may pose problems because such children are frightened when they see a needle being used and the superficial prick is still felt. This test may become a traumatic experience for the child. Most physicians neglect this aspect. A painless skin test (SAFT: skin application food test) was developed for establishing food allergy in children. The SAFT is based on the mechanism of the contact urticaria syndrome (CUS) [17]. This test is very child-friendly and painless. The children are less anxious because no needles are used. We studied the relevance of the SAFT in children younger than 4 years with atopic dermatitis and (suspected) food allergy as compared with the prick-prick test, the radioallergosorbent test (RAST) and the oral challenge [18]. A comparison between the SAFT and the prick-prick test has, to our knowledge, never been done before. In the skin tests, we used fresh food in the same state as it was consumed. Fresh foods were found to be more effective in detecting sensitisation to food allergens as compared with commercial extracts [19]. There was a good agreement between the SAFT and the prick-prick test. A moderate agreement was observed between the SAFT and the serological test (RAST). Significantly more positive results in the RAST were observed as compared with those in the SAFT. From the discrepancies between the results of the SAFT and the RAST, it appeared that in the serological test, one exclusively measures atopic immune response that may not always be clinically relevant. An explanation may be that, in some children, the food protein allergen may not reach the sensitised cells. Another explanation may be that other cells, cell products, or cellular interactions may be necessary to elicit symptoms which may not occur in some children [20].

There was a very good agreement between the SAFT and the oral challenge (κ=0.86). The results showed that the SAFT was a reliable and child-friendly skin test for evaluating (suspected) food allergy in children younger than 4 years with atopic dermatitis [18]. The very good correlation with the oral challenge indicated that one may probably consider the SAFT a 'skin provocation' in children younger than 4 years.
It was concluded that the SAFT was a painless, effective and child-friendly skin test for evaluating direct IgE-mediated allergic reactions to foods in young children with atopic dermatitis.

Methods for reducing pain in diagnostic and therapeutic procedures in paediatric dermatology were evaluated in the investigations described in this thesis. The initial investigations that were pursued focused on the evaluation of pain-reducing measures at the paediatric dermatological clinic whereby the diagnostic interventions and treatment may be approached in a child-friendly manner. This has several advantages. The dermatologist can conduct the examinations more thoroughly which contributes towards better diagnostics. If certain interventions can be carried out easily then these would be more efficient. Moreover, the child will have less traumatic memories of the visit to the physician whereby examinations and therapy at subsequent visits would be easier.

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Chapter 12

Summary

Fear and pain can make relatively simple investigations and treatments in children a traumatic experience. There is an increasing focus on the recognition, assessment, and management of pain in children.

In chapter 1, various aspects of pain in medical care in children are discussed. There is an interaction between neuro-physiological, developmental, behavioural and psychological factors. Clinical pain can neither be seen primarily as a biological phenomenon or as only a psychological event, nor can pain be divorced from the social contact. An appropriate assessment of pain in clinical settings is important for the management of pain in children. Pain can be measured by behaviour, biological markers and self-report. A number of instruments for measuring pain in children are discussed. There was a misconception that very young children and neonates do not feel pain and do not have a memory of pain. Early pain experience is one of the many relevant factors in the ontogeny of pain expression. One essential feature of a Pavlovian or classical conditioning paradigm is that an organism learns by associating neutral with non-neutral stimuli. One may learn to associate a previous neutral stimulus like visiting a doctor or dentist with non-neutral stimuli such as pain, fear and anxiety. Such a person may then develop a phobic reaction to doctors and dentists because of their association with unpleasant stimuli. Extreme fear can make minor procedures very traumatic for the child and time-consuming for the personnel involved. It is preferable to avoid this.

Chapter 2 describes the aims of the studies presented in this thesis. The studies described in the first part of the thesis (chapters 3-7) consist of the investigations into pain-reducing measures for superficial (dermatological) interventions. A local anaesthetic only was used in all investigations. It was investigated whether the application of an emulsion provided adequate pain reduction for various indications. Adverse side effects of this emulsion were also investigated. The second part of the thesis (chapters 8-10) deals with studies into painless diagnostic tests in young children with atopic dermatitis. Prick tests, standard tools for investigating IgE-mediated allergic reactions, are painful. A painless skin test (SAFT: skin application food test) was developed for establishing food allergy in children. This test was used to investigate food allergy in children. The test was investigated further and compared with prick-prick test, RAST and oral challenge.

In chapter 3, the general principles and classification of topical anaesthetics in dermatology are described. An overview of indications of a eutectic mixture of lidocaine and prilocaine (EMLA®) is given.

In chapter 4, the treatment of molluscum contagiosum using a lidocaine/prilocaine cream (EMLA®) is presented. Eighty-three 4- to 12-year-old children, scheduled for curettage of at least five molluscum contagiosum lesions, participated in a double-blind study. The children were randomly allocated to receive lidocaine/prilocaine (EMLA®) cream (n=58) or placebo cream (n=25), applied 15, 30, or 60 minutes before treatment. The pain was assessed by the children and the physician as none, slight, moderate, or severe. In addition, the children rated the pain on a visual analogue scale. EMLA® cream effectively prevented the pain after all three application times ($p<0.01$). No significant difference in pain was observed among the 15-, 30-, and 60 minute EMLA®-treated groups, but the proportion of children reporting no pain on the verbal scale increased from 36% in the 15-minute group to 61% in the 60-minute group. In the placebo group, only one (4%) of 24 children reported no pain. Transient local redness was the only side effect noted. We concluded that an application time of EMLA® cream of less than 60 minutes was satisfactory for the curettage of molluscum contagiosum in children. In our practice we use an application time of 30 minutes.

Chapter 5 presents the study in which a lidocaine/prilocaine patch (EMLA®) was used as a pre-medication for taking skin biopsy in children. The study was randomised, double-blind and placebo-controlled. Sixty-three children were randomly recruited into the study. Sixty children were evaluated. The remaining three were withdrawn from the study.
The anaesthetic patch was significantly more effective than the placebo patch in decreasing the pain at injection site. There was no significant difference in pain scores of the biopsy between the study groups.
Serious side effects were not observed. We concluded that the anaesthetic EMLA® patch reduced pain in children undergoing skin biopsy.

In chapter 6, the value of EMLA® cream as a local anaesthetic in Mumps/Measles/Rubella (MMR) vaccination is presented. The study was randomised, double-blind and placebo-controlled. Ninety-six children aged about 9 years were randomly assigned into the study. There was a significant ($p=0.017$) difference in VAS (Visual Analogue Scale) pain scores between the EMLA® and the placebo groups in girls. This difference in boys was clearly not significant ($p=0.514$). In the whole group, the difference in VAS scores between the EMLA® and the placebo groups was not significant, but almost reached significance ($p=0.052$). In this study EMLA® did not significantly reduce the pain of MMR vaccination. None of the children showed serious side effects.

In chapter 7, the side effects of EMLA® are described. The most commonly observed side effects are not serious and consist of blanching or erythema. We have used EMLA®

during the past 10 years in at least 4000 patients. We observed purpura in 4 patients with molluscum contagiosum and in 1 patient in whom it was used as a local anaesthetic for taking a lip biopsy. We investigated whether the purpura we observed was of an allergic nature using patch tests. The results of patch tests were negative in all the 5 patients at the early reading after 30 minutes as well as after 48 and 72 hours. We concluded that the purpura reaction was not of an allergic nature.

In chapter 8, the Skin Application Food Test [SAFT] as painless test is described. This test is based on the mechanism of the Contact Urticaria Syndrome [CUS]. In atopic dermatitis urticarial reactions can be induced by food consumption and by direct food-skin contact. Skin tests were performed in children with atopic dermatitis who were suspected to have food allergy.

In chapter 9, the Contact Urticaria Syndrome and childhood atopic dermatitis are discussed. Atopic dermatitis follows a course with exacerbations and remissions. Different factors may play a role. One of them is food allergy, mainly in the young child. About one-half of the children with atopic dermatitis and food allergy also suffer from CUS. Many foods can provoke food-induced contact urticaria.

The relevance of the SAFT as diagnostic test in young children with atopic dermatitis and (suspected) food allergy is described in chapter 10. Skin testing is a common diagnostic procedure in food allergy. The skin prick test is the test of first choice for investigating the immediate IgE-mediated reaction, but can be experienced as very painful. We studied the relevance of the painless SAFT in children younger than 4 years with atopic dermatitis and (suspected) food allergy as compared with the prick-prick test, the radio-allergosorbent test (RAST) and the oral challenge. In the skin tests, we used fresh food in the same state as it was consumed. There was a good agreement between the SAFT and the prick-prick test. A moderate agreement was observed between the SAFT and the serological test (RAST). Significantly more positive results in the RAST were observed as compared with those in the SAFT. There was a very good agreement between the SAFT and the oral challenge (κ=0.86). It could be stated that the SAFT is a reliable and child-friendly skin test for evaluating (suspected) food allergy in children younger than 4 years with atopic dermatitis. At least the painless SAFT is equivalent to the painful prick-prick test. The very good correlation with the oral challenge indicates that one may probably consider the SAFT a 'skin provocation' in children younger than 4 years.

Pain-prevention, if possible or at least pain-reduction is very important to reduce children's distress. This is also true for diagnostic and therapeutic procedures in paediatric dermatology.

Samenvatting

Angst en pijn kunnen ertoe leiden dat relatief eenvoudige onderzoeken en behandelingen bij kinderen als traumatisch door hen ervaren worden. Er is toenemende aandacht voor de herkenning van, de beoordeling van, het omgaan met, het voorkomen en de behandeling van pijn bij kinderen.

In hoofdstuk 1 worden verschillende aspecten van pijn bij medische zorg van kinderen besproken. Er is een interactie tussen neurofysiologische, ontwikkelings-, gedrags- en psychologische factoren. Pijn die ervaren wordt in het ziekenhuis kan nooit gezien worden als een biologisch fenomeen op zich of als een zuiver psychologische gebeurtenis, en kan ook niet los gezien worden van de sociale context. Om de pijn, die kinderen ervaren, te kunnen beheersen is een betrouwbare beoordeling ervan tijdens het onderzoek of de behandeling in de kliniek van belang. Pijn kan gemeten worden met behulp van gedragskenmerken, biologische maten en rapportage van het kind zelf. Een aantal instrumenten om de pijn die kinderen ervaren te meten wordt besproken. Ten onrechte bestond de opvatting dat neonaten en zeer jonge kinderen geen pijn zouden voelen en zich de geleden pijn later niet zouden herinneren. Vroege ervaring met pijn is één van de belangrijkste factoren bij de ontwikkeling van het uiten van pijn. Een belangrijk kenmerk van klassieke conditionering volgens Pavlov is dat een organisme leert door neutrale met niet-neutrale stimuli te associëren. Zo kan men een eerdere neutrale stimulus, zoals het bezoek aan een dokter of tandarts, leren te associëren met niet-neutrale stimuli zoals pijn, vrees en angst. Zo'n persoon kan dan een fobische reactie ontwikkelen ten aanzien van dokters of tandartsen ten gevolge van zijn associatie met onplezierige stimuli. Door extreme vrees kunnen eenvoudige procedures als zeer traumatisch door het kind ervaren worden, en zeer tijdrovend worden voor het betrokken personeel. Het verdient de voorkeur dit te voorkomen.

Hoofdstuk 2 beschrijft het doel van de studies die in dit proefschrift worden gepresenteerd. De studies, die in het eerste deel van het proefschrift (hoofdstukken 3 - 7) worden beschreven bestaan uit onderzoeken naar pijn-reducerende maatregelen bij oppervlakkige (dermatologische) ingrepen. Bij alle onderzoeken hebben we gebruik gemaakt van een lokaal anaestheticum (EMLA®). We onderzochten of het aanbrengen van de emulsie voldoende vermindering van pijn tot stand kon brengen voor verschillende indicaties. Tevens hebben we onderzoek gedaan naar bijwerkingen van deze emulsie.
Het tweede deel van het proefschrift (hoofdstukken 8 - 10) gaat over pijnloze diagnostische onderzoeken bij jonge kinderen met atopisch eczeem. Prik tests, standaard onderzoeken naar directe IgE-gemedieerde allergische reacties, zijn pijnlijk. Een pijnloze huidtest (SAFT: Skin Application Food Test) werd ontwikkeld voor het aantonen van

voedselallergie bij kinderen. Met behulp van deze test werd voedselallergie bij kinderen bestudeerd. De test werd ook nader bestudeerd en vergeleken met de prik-prik test, een serologische test (RAST) en de orale belastingtest.

In hoofdstuk 3 worden de algemene principes en de classificatie van lokale anaesthetica in de dermatologie beschreven. Een overzicht van indicaties voor een eutectisch mengsel van lidocaïne en prilocaïne (EMLA®) wordt gegeven.

In hoofdstuk 4 wordt de behandeling van mollusca contagiosa met gebruik making van lidocaïne/prilocaïne crème (EMLA®) gepresenteerd. Drieëntachtig kinderen in de leeftijd van 4 tot 12 jaar met tenminste 5 mollusca contagiosa die gecuretteerd moesten worden, namen deel aan deze dubbelblinde studie. De kinderen werden gerandomiseerd verdeeld over een groep die lidocaïne/prilocaïne crème (EMLA®) kreeg (n=58) en een groep die placebo crème kreeg (n=25) gedurende 15, 30 of 60 minuten voor de behandeling. De pijn werd aangegeven door de kinderen en de behandelend arts als 'geen, lichte, matige of ernstige pijn'. De kinderen gaven de pijn ook aan op een visuele analoge schaal (VAS). EMLA® crème verminderde de pijn effectief na alle 3 applicatie tijden ($p<0.01$). Er werd geen significant verschil in pijn gevonden tussen de EMLA® groepen die 15, 30 of 60 minuten applicatie kregen. In de placebo groep gaf slechts 1 van de 24 kinderen (4%) 'geen pijn' aan. Kortdurende plaatselijke roodheid van de huid was de enige bijwerking die gezien werd. We concludeerden dat een applicatietijd van minder dan 60 minuten met EMLA® crème voldoende is voor curettage van mollusca contagiosa bij kinderen. In de praktijk gebruiken wij een applicatietijd van 30 minuten.

In hoofdstuk 5 wordt de studie naar de werking van een lidocaïne/prilocaïne 'patch' (EMLA®) als pre-medicatie voor het nemen van een huidbiopsie bij kinderen beschreven. De studie was gerandomiseerd, dubbelblind en placebo gecontroleerd. Drieënzestig kinderen werden ingesloten. Zestig kinderen werden geëvalueerd. De overige 3 kinderen vielen uit de studie. De lidocaïne/prilocaïne 'patch' was significant meer effectief in het verminderen van de pijn van de injectieplaats dan de placebo 'patch'. Er was geen significant verschil in pijn scores van de biopsie tussen beide studie groepen. Ernstige bijwerkingen werden niet gezien. We concludeerden dat de EMLA® 'patch' de pijn van het nemen van een huidbiopsie bij kinderen verminderde.

In hoofdstuk 6 wordt de waarde van EMLA® crème als locaal anaestheticum bij Bof/Mazelen/Rubelle (BMR) vaccinatie gepresenteerd. De studie was gerandomiseerd, dubbelblind en placebo gecontroleerd. Zesennegentig kinderen van omstreeks 9 jaar oud werden gerandomiseerd ingesloten in de studie. Er was een significant verschil ($p=0.017$) in VAS pijn scores tussen de EMLA® en de placebo groep bij meisjes. Het verschil was bij de jongens duidelijk niet significant ($p=0.514$). In de gehele groep was het verschil in VAS scores niet, maar wel bijna, significant ($p=0.052$). In deze studie verminderde EMLA® niet significant de pijn ten gevolge van een BMR vaccinatie. Er werden geen ernstige bijwerkingen gezien.

In hoofdstuk 7 worden de bijwerkingen van EMLA® beschreven. De bijwerkingen, die het meest gezien worden zijn niet ernstig en bestaan uit bleekheid of erytheem. We hebben EMLA® in de afgelopen 10 jaar toegepast bij tenminste 4000 patiënten. Wij zagen purpura bij 4 patiënten met mollusca contagiosa en bij 1 patiënt bij wie het werd gebruikt als een lokaal anaestheticum voor het nemen van een lip biopsie. We onderzochten of de purpura, die we gezien hadden, allergisch van aard waren met behulp van epicutaan allergologisch onderzoek. Deze plakproeven waren bij alle 5 patiënten negatief, zowel bij de eerste aflezing na 30 minuten, als bij de aflezingen na 48 en 72 uur. We concludeerden dat de purpura reactie niet allergisch van aard was.

In hoofdstuk 8 wordt de 'Skin Application Food Test' (SAFT) beschreven. Deze test is gebaseerd op het mechanisme van het Contact Urticaria Syndroom (CUS). Bij atopisch eczeem kunnen urticariële reacties geïnduceerd worden door het nuttigen van voedingsmiddelen en door direct contact van voeding met de huid. Huidtests werden verricht bij kinderen met atopisch eczeem die werden verdacht van het hebben van een voedselallergie.

In hoofdstuk 9 worden het Contact Urticaria Syndroom en atopisch eczeem bij kinderen besproken. Atopisch eczeem verloopt met exacerbaties en remissies. Verschillende factoren spelen een rol. Eén van deze factoren is voedselallergie, voornamelijk bij het jonge kind. Ongeveer de helft van de kinderen met atopisch eczeem en voedselallergie lijdt ook aan CUS. Vele voedingsmiddelen kunnen voedsel-geïnduceerde contact urticaria veroorzaken.

De relevantie van de SAFT als diagnostische test bij jonge kinderen met atopisch eczeem en (verdenking op) voedselallergie is beschreven in hoofdstuk 10. Het verrichten van huidtests is een gebruikelijke diagnostische procedure bij voedselallergie. De prik test is de methode van eerste keuze voor het onderzoeken van de directe IgE-gemedieerde reactie, maar kan als erg pijnlijk ervaren worden. Wij onderzochten de relevantie van de pijnloze SAFT bij kinderen jonger dan 4 jaar met atopisch eczeem en (verdenking op) voedselallergie. Deze test vergeleken we met de prik-prik test, de 'radioallergosorbent test' (RAST) en de orale belastingtest. We gebruikten voor de huidtests verse voedingsmiddelen, in de vorm waarin ze geconsumeerd werden. Er was een goede overeenkomst tussen de SAFT en de prik-prik test. Een matige overeenkomst werd gezien tussen de SAFT en de serologische test (RAST). Bij de RAST werden significant meer positieve resultaten gevonden dan bij de SAFT. Er was een zeer goede overeenkomst tussen de SAFT en de orale belastingtest (κ= 0.86). De SAFT bleek een betrouwbare en kind-vriendelijke huidtest te zijn voor de evaluatie van (verdenking op) voedselallergie bij kinderen jonger dan 4 jaar met atopisch eczeem. De pijnloze SAFT was tenminste gelijkwaardig met de pijnlijke prik-prik test. De zeer goede correlatie met de orale belastingtest geeft aan dat men de SAFT mogelijk kan beschouwen als een 'huidprovocatie' bij kinderen jonger dan 4 jaar.

Pijn-preventie, indien mogelijk, of tenminste pijn-reductie is zeer belangrijk om leed bij kinderen te verminderen. Dit geldt ook voor diagnostische en therapeutische procedures in de kinderdermatologie.

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List of publications

Publications related to this thesis

1. Waard-van der Spek FB de, Oranje AP, Lillieborg S, Hop WCJ and Stolz E. Treatment of molluscum contagiosum using a lidocaine/prilocaine cream (EMLA®) for analgesia. Journal of the American Academy of Dermatology 1990; 23: 685-688.

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2. Oranje AP, Waard-van der Spek FB de (eds). Handboek Kinderdermatologie. Derde editie, De Tijdstroom, Utrecht 1996. ISBN 90-352-1508-7.

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1. Oranje AP, Bilo RAC, Waard-van der Spek FB de (eds). Paediatric Dermatology. Intermedics, Doesburg 1997.

Curriculum Vitae

The author was born in 1962 in Rotterdam. She obtained high school diploma (VWO) in 1980 and commenced medical studies at the Faculty of Medicine, Erasmus University Rotterdam in the same year. She received her medical degree (MD) with honours in 1987.

From 1987 to 1993, she worked as a resident not in training (AGNIO) at the Paediatric Dermatology Unit of the Department of Dermatology and Venereology of the University Hospital Rotterdam. Her duties involved research and in- and out-patient care. She also worked at the out-patient Venereology clinic for 2 years. In addition to her duties at the Department of Dermatology and Venereology, she also followed a course on infant welfare and child health care in 1987. She was awarded certification in 1988. From 1987 to 1993 she worked as a physician at various infant welfare and child health care centres.

From 1993 to 1996, she was a resident in training at the Department of Dermatology and Venereology of the University Hospital Rotterdam and was registered as a Dermato-Venereologist in 1996. She was appointed as staff member and head of in-patient Dermatology clinic in the same year, and is also substitute consultant in Paediatric Dermatology.

Curriculum Vitae

De schrijfster van dit proefschrift werd in 1962 in Rotterdam geboren.
Op 31 mei 1980 behaalde zij het VWO-diploma. In september 1980 begon zij de studie geneeskunde aan de faculteit der Geneeskunde van de Erasmus Universiteit te Rotterdam. Op 16 januari 1987 studeerde zij met lof af.
In december 1986-januari 1987 deed zij het keuze-coschap kinderdermatologie. Van 1 februari 1987 tot 1 januari 1993 was zij werkzaam in het Academisch Ziekenhuis te Rotterdam op de afdeling Dermatologie en Venereologie, subafdeling Kinderdermatologie als assistent geneeskundige niet in opleiding (AGNIO). Ze deed wetenschappelijk onderzoek en verrichtte poliklinische en klinische werkzaamheden in de patiëntenzorg. Ze deed tevens gedurende 2 jaar poliklinische spreekuren op de polikliniek Venereologie. Naast de werkzaamheden in het Academisch Ziekenhuis te Rotterdam op de afdeling Dermatologie en Venereologie, volgde zij in het najaar van 1987 de applicatiecursus voor consultatiebureau-artsen te Rotterdam. In mei 1988 ontving zij het certificaat. Zij was van februari 1987 tot januari 1993 tevens als consultatiebureau-arts werkzaam op consultatiebureaus voor zuigelingen en kleuters in Zuid-Holland.

Van 1 januari 1993 tot 1 juli 1996 was zij in het Academisch Ziekenhuis te Rotterdam op de afdeling Dermatologie en Venereologie werkzaam als arts-assistent in opleiding tot arts-specialist voor het specialisme Dermatologie en Venereologie.
Per 1 juli 1996 is zij ingeschreven in het register van erkende specialisten voor het specialisme Dermatologie en Venerologie. Sinds 1 juli 1996 is zij als staflid-chef de clinique en plaatsvervangend consulent Kinderdermatologie werkzaam op de afdeling Dermatologie en Venereologie in het Academisch Ziekenhuis te Rotterdam.