International Journal of Pharmaceutics 416 (2011) 1–11

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Review

Needle-free and microneedle drug delivery in children: A case for disease-modifying antirheumatic drugs (DMARDs)

Utpal U. Shah[a,b,*], Matthew Roberts[b], Mine Orlu Gul[c,d], Catherine Tuleu[c], Michael W. Beresford[e], on behalf of the NIHR MCRN/Arthritis Research UK Paediatric Rheumatology Clinical Studies Group

[a] Cheshire, Merseyside and N. Wales NIHR Medicines for Children Research Network, Alder Hey Children's NHS Foundation Trust Hospital, Eaton Road, Liverpool, L12 2AP, United Kingdom
[b] School of Pharmacy and Biomolecular Sciences, Liverpool John Moores University, Byrom Street, Liverpool, L3 3AF, United Kingdom
[c] Department of Pharmaceutics & Centre for Paediatric Pharmacy Research, The School of Pharmacy, University of London, 29-39 Brunswick Square, London, WC1N 1AX, United Kingdom
[d] London & South East NIHR Medicines for Children Local Research Network, Somers Clinical Research Facility, Level 1 Frontage Building, Great Ormond Street Hospital for Children NHS Trust, Great Ormond Street, London, WC1N 3JH, United Kingdom
[e] Department of Women's and Children's Health, Institute of Translational Medicine (Child Health), University of Liverpool, Alder Hey Children's NHS Foundation Trust Hospital, Eaton Road, Liverpool, L12 2AP, United Kingdom

ARTICLE INFO

Article history:
Received 8 March 2011
Received in revised form 30 June 2011
Accepted 2 July 2011
Available online 8 July 2011

Keywords:
Transdermal
Jet injector
Needle-free
Microneedle
DMARD
Biologic

ABSTRACT

Parenteral routes of drug administration have poor acceptability and tolerability in children. Advances in transdermal drug delivery provide a potential alternative for improving drug administration in this patient group. Issues with parenteral delivery in children are highlighted and thus illustrate the scope for the application of needle-free and microneedle technologies. This mini-review discusses the opportunities and challenges for providing disease-modifying antirheumatic drugs (DMARDs) currently prescribed to paediatric rheumatology patients using such technologies. The aim is to raise further awareness of the need for age-appropriate formulations and drug delivery systems and stimulate exploration of these options for DMARDs, and in particular, rapidly emerging biologics on the market. The ability of needle-free and microneedle technologies to deliver monoclonal antibodies and fusion proteins still remains largely untested. Such an understanding is crucial for future drug design opportunities. The bioavailability, safety and tolerance of delivering biologics into the viable epidermis also need to be studied.

Contents

Abbreviations: CINCA, chronic infantile neurologic cutaneous and articular; CIVAS, central intravenous additive services; DMARD, disease-modifying antirheumatic drug; i/v, intravenous; i/m, intramuscular; JIA, juvenile idiopathic arthritis; NSAID, non-steroidal anti-inflammatory drug; PK, pharmacokinetic; s/c, subcutaneous; SC, stratum corneum; TDD, transdermal drug delivery; TEWL, transepidermal water loss.

* Corresponding author at: Cheshire, Merseyside and N. Wales NIHR Medicines for Children Research Network, Alder Hey Children's NHS Foundation Trust Hospital, Eaton Road, Liverpool, L12 2AP, United Kingdom. Tel.: +44 151 252 5570; fax: +44 151 282 4759.
E-mail addresses: utpal.shah@alderhey.nhs.uk (U.U. Shah), M.Roberts1@ljmu.ac.uk (M. Roberts), mine.orlu.gul@pharmacy.ac.uk (M. Orlu Gul), catherine.tuleu@pharmacy.ac.uk (C. Tuleu), M.W.Beresford@liverpool.ac.uk (M.W. Beresford).

0378-5173/$ – see front matter © 2011 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2011.07.002

1. Introduction

Recent European paediatric drug legislation (Anon, 2006) underlined the need to develop age-appropriate formulations. This need extends to 'easy to administer' and minimally invasive/painless drug delivery methods and devices. The parenteral route is particularly problematic in children and thus transdermal drug delivery (TDD) provides a potential alternative. As such, paediatric rheumatology patients are a pertinent population often subjected to intravenous (i/v), intramuscular (i/m) and subcutaneous (s/c) routes of drug administration and often on a long term basis. Children present with juvenile idiopathic arthritis (JIA) from 1 to 2 years of age exemplifying the need for drug delivery systems that are less painful and have less impact on daily activities. The focus of this paper is to highlight the administration related issues of parenteral (i/v, i/m and s/c) drug therapy in children and to discuss the opportunities and challenges for developing needle-free and microneedle TDD technologies to deliver disease-modifying antirheumatic drugs (DMARDs) used in paediatric rheumatology.

2. Difficulties with parenteral drug delivery in children

Some drugs need to be given parenterally due to instability and enzymatic degradation in the gut (e.g. proteins and peptides), variable oral absorption, the need for rapid onset of action or to avoid first-pass metabolism and gastrointestinal side effects (e.g. methotrexate). Consequently, i/v, i/m and s/c injections are commonly used administration routes.

The difficulty with injections is that they usually have to be administered by professionally trained staff and cause pain (Cummings et al., 1996; Gill and Prausnitz, 2007c). Patients or carers can be taught to self administer s/c injections at home, but anxiety associated with needle phobia (Broome et al., 1990) in the paediatric population can be significant. The i/v route usually involves frequent infusions requiring preparation under sterile conditions. Some of the excipients used in the formulation may also be unsuitable for younger children (Breitkreutz and Boos, 2007) as metabolic pathways are still developing. The infection risk is also higher with the i/v route compared to other routes. Furthermore, intravenous access in young children may be challenging. For example, peripheral venous access can be very difficult due to smaller veins in children. It can lead to tissue damage or extravasation and repeated cannulations for regular, repeated treatments can be a major challenge to the child, their family and healthcare professionals. Central venous access may address some of these issues, but requires general anaesthesia for insertion and removal and is associated with specific complication risks including infection. Compatibility of i/v medications with typical diluents, syringes, tubing and infusion bags also needs to be considered.

For s/c injections, in addition to needle pain and phobia, the volume administered needs to be small to avoid pain. Whilst the volume in adults should be $\leq$2 mL (Ansel et al., 2004), for children it is usually restricted to $\leq$1 mL. The s/c route is also limited to formulations that are non-irritating to the tissue and do not cause necrosis and sloughing at the injection site.

For i/m injections, children have smaller muscle mass that can affect drug delivery and absorption. Again, the volume administered will affect the pain felt and is usually restricted to 2–3 mL. Adverse effects of the i/m route commonly include persistent pain which may affect mobility, erythema and hematoma, and rarely include muscle contracture, nerve damage, abscess formation, bleeding, tissue necrosis, cellulitis and gangrene (Bergeson et al., 1982; Dewit, 2001) and thus this route is avoided in children wherever possible.

Thannhauser et al. (2009) investigated non-adherence to s/c glatiramer acetate, interferon b1a, interferon b1b and i/m interferon b1 in adolescents with multiple sclerosis. Reasons for discontinuation included intolerance to injections, side effects and the medication-peer tug-of-war, described as the psychological and social conflicts experienced by these patients in integrating the medication administration into their daily routines. For example, adolescents felt it a struggle to decide between interacting with peers or staying home to do their injections, felt unsafe to do injections in public places and felt isolated and 'not normal' due to a negative reaction of peers to injections, e.g., needle phobia. These psychosocial effects in children apply generally across disease areas where chronic medication regimes impact on daily routines.

Anecdotal evidence suggests infants as young as 5 months will react to the sight of an injection if they have had it before. Negative early experiences may lead to persistent challenges of engagement with healthcare. If children struggle, there is a risk of injury to themselves and/or their carers. In addition, the impact of hidden parental distress should be taken into consideration as needle procedures are stressful events for parents during their child's treatment (Caty et al., 1989). In severe cases of non-compliance there may be a need for play specialists or restraints.

Where parenteral products are marketed in inappropriate strengths or dose-volumes for use in children, the requirement for dose calculation, measurement of very small volumes, part-usage of vials and multiple dilutions increase the risk of medication errors (Beaney, 2010). Other safety concerns include the risk of needlestick injuries, cross-contamination and safe disposal of sharps.

There are also facility and staff resource issues to consider. The preparation of infusions of immunosuppressants and biologics require appropriate protective and contained environments as offered by central intravenous additive services (CIVAS) in hospitals, which increases workload. Even prefilled syringes for s/c or i/m injection that are not of the appropriate strength for children require decanting in such facilities to obtain the appropriate dose.

3. Challenges with current drug administration in paediatric rheumatology

Paediatric rheumatic diseases comprise a complex group of autoimmune, auto-inflammatory and musculoskeletal conditions characterised by pain, inflammation and loss of function that can lead to tissue damage and significant associated morbidity and/or mortality. Symptomatic treatment includes use of non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids to treat pain, inflammation and stiffness. NSAIDs are usually administered orally whereas corticosteroids may be given orally, intravenously or locally by i/m or more commonly by intra-articular injection. DMARDs are aimed at suppressing disease activity, inducing and maintaining remission and so change the natural history of the disease in question.