Journal of Neuroscience Methods 219 (2013) 1–9

Contents lists available at ScienceDirect

Journal of Neuroscience Methods

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

Basic Neuroscience

In vitro and in vivo testing of a novel recessed-step catheter for reflux-free convection-enhanced drug delivery to the brain

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HIGHLIGHTS

- The optimisation of convection-enhanced drug delivery (CED) to the brain is fundamentally reliant on minimising drug reflux.
- We describe the in vitro and in vivo testing of a novel stepped catheter for CED incorporating a "recessed-step".
- The recessed step demonstrated superior volumes of distribution compared to conventional one- and two-stepped catheters.
- Preliminary in vivo testing of the recessed-step catheter in pigs demonstrates the facility to perform high volume infusions without reflux.

ARTICLE INFO

Article history:
Received 11 January 2013
Received in revised form 24 June 2013
Accepted 28 June 2013

Keywords:
Convection-enhanced delivery
Reflux
Drug delivery

ABSTRACT

Introduction: The optimisation of convection-enhanced drug delivery (CED) to the brain is fundamentally reliant on minimising drug reflux. The aim of this study was to evaluate the performance of a novel reflux-resistant CED catheter incorporating a recessed-step and to compare its performance to previously described stepped catheters.
Methods: The in vitro performance of the recessed-step catheter was compared to a conventional "one-step" catheter with a single transition in outer diameter (OD) at the catheter tip, and a "two-step" design comprising two distal transitions in OD. The volumes of distribution and reflux were compared by performing infusions of Trypan blue into agarose gels. The in vivo performance of the recessed-step catheter was then analysed in a large animal model by performing infusions of 0.2% Gadolinium-DTPA in Large White/Landrace pigs.
Results: The recessed-step catheter demonstrated significantly higher volumes of distribution than the one-step and two-step catheters ($p = 0.0001$, one-way ANOVA). No reflux was detected until more than 100 ul had been delivered via the recessed-step catheter, whilst reflux was detected after infusion of only 25 ul via the 2 non-recessed catheters. The recessed-step design also showed superior reflux resistance to a conventational one-step catheter in vivo. Reflux-free infusions were achieved in the thalamus, putamen and white matter at a maximum infusion rate of 5 ul/min using the recessed-step design.
Conclusion: The novel recessed-step catheter described in this study shows significant potential for the achievement of predictable high volume, high flow rate infusions whilst minimising the risk of reflux.

1. Introduction

Convection enhanced delivery (CED) describes a method of targeted drug delivery to the brain parenchyma using micro-catheters and controlled infusion rates to distribute drugs homogenously through the extracellular space, carried by bulk flow (Bobo et al., 1994). This method has considerable potential for the delivery of a wide range of therapeutics for neurological disease that can be targeted to specific brain areas, bypassing the blood brain barrier, and limiting side effects.

Drug distribution by CED is achieved by establishing a pressure gradient at the tip of the catheter that is sufficient to drive infusate through the extracellular space, in preference to it refluxing back along the catheter–tissue interface. To distribute therapeutic agents homogenously through large and clinically relevant volumes, the flow rate needs to be as high as the brain can safely tolerate. This is because the pressure gradient drops according to

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http://dx.doi.org/10.1016/j.jneumeth.2013.06.008

the inverse of the distance from the catheter tip squared, and so to achieve bulk flow one has to establish a sufficient pressure gradient up to the boundary of the desired brain volume whilst competing against dynamic extracellular fluid clearance, particularly through the perivascular spaces, which act as peristaltic pumps (Barua et al., 2012; Krauze et al., 2005). Excessive flow rates at the catheter tip will however result in tissue fracturing, and once this has occurred, the fracture will tend to be propagated in preference to distribution through the extracellular space (White et al., 2011a,b). In addition, high flow rates are associated with increased reflux along the catheter–tissue interface, and the magnitude of this appears to be related to the extent of tissue trauma produced by catheter insertion and to the catheter's external diameter. The optimisation of CED is critically dependent upon minimising reflux of the infusate and this in turn is dependent upon catheter design, implantation technique and the infusion protocol.

Reflux can be minimised when infusing into grey matter at flow rates of up to 5 μl/min, by using catheters that have an outside diameter of approximately 0.4 mm or less (Chen et al., 1999; Morrison et al., 1999), and preferably with a rounded tip, which causes less trauma on insertion (White et al., 2011a,b). When catheters of larger diameter are employed, they cause greater tissue trauma upon insertion in the annular space around them and through this low resistance pathway the infusate will reflux. However, Bienemann et al. (2012) have also shown that if a catheter of larger diameter (0.6 mm) is left in situ for sufficient time to allow the tissue to heal, then its tendency to reflux is substantially reduced.

Minimising reflux may also be achieved by employing a cannula with a stepped outer diameter with the diameter of the step or steps decreasing from the proximal to the distal end, as described by Krauze et al. (2005). This stepped design has been validated in small and large animal studies and will be used in forthcoming clinical trials of adeno-associated viral vector-mediated gene therapy for Parkinson's disease (Richardson et al., 2011; Yin et al., 2010a,b). The methods by which a catheter step acts to control reflux are not fully understood, and are likely to be multifactorial. One contributing factor may be that the step may prevent or limit reflux along the catheter/tissue interface by focally compressing the tissue to create a seal. For the step to be efficient, the tissue sealing pressure achieved by tissue compression needs to exceed the hydraulic pressure from the refluxing fluid.

One of the major barriers to effective clinical translation is reflux (or "backflow") of infusate along the catheter–brain interface. In this study we have evaluated the performance of a novel reflux resistant CED catheter incorporating a recessed-step that has been designed to create a more effective tissue seal than the previously described stepped catheters. The catheter has been tested in vitro and in vivo, by performing CED infusions in agarose gels and in the brains of Large White/Landrace pigs.

2. Materials and methods

2.1. The recessed-step catheter design

The recessed-step catheter comprised 2 elements – a guide tube and an indwelling catheter with adjustable winged stop (Fig. 1). The guide tube was formed from carbothane and had a 1 mm outer diameter (OD), and a 0.6 mm internal diameter (ID). It had a proximal hub, with a threaded distal section and a proximal section of larger diameter in the form of a slotted dome, which was in continuity with the lumen of the tube. The catheter was manufactured from polyether ether ketone (PEEK, OD 0.6 mm, ID 0.25 mm), which was bonded onto a fused silica cannula with a laser-cut tip (OD 0.23 mm, ID 0.15 mm). These catheter dimensions were

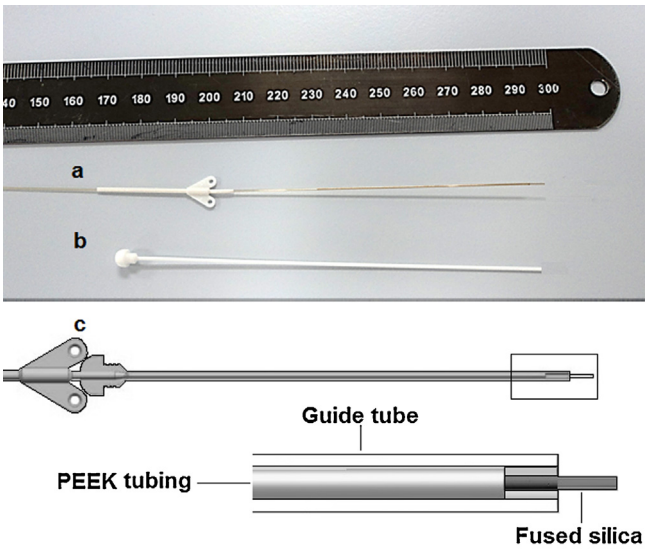

Fig. 1. Recessed-step catheter design. The recessed-step catheter comprised of an adjustable length of polyether ether ketone (PEEK) tube (a), which is bonded onto a fused silica cannula with a laser-cut tip (OD 0.23, ID 0.15). The winged stop of the catheter engaged with the domed hub of the guide tube (b). The fully assembled catheter turned 90° at the skull surface allowing the scalp flap to be closed during infusion. The recessed-step (c) was formed by ensuring that the transition from PEEK tubing (OD 0.6 mm) to fused silica (0.23 mm) lay within the guide tube on completion of implantation.

selected following extensive in vivo testing which demonstrated optimum performance following acute implantation (White et al., 2011a,b).

The fused silica cannula may extend beyond the distal end of the PEEK tube by variable lengths (e.g. 6–30 mm or more) depending on the required volume of distribution. For this study the fused silica extended 6 mm beyond the distal end of the PEEK tube. An over-moulded sleeve on the proximal end of the catheter allowed attachment to an infusion line via a bayonet. The adjustable winged stop, which engaged with the domed hub of the guide tube, was bonded at a measured distance along the PEEK tube with UV light curing adhesive (Triad Gel, Dentsply DeTrey, Germany), thus defining the depth of catheter insertion through the guide tube. The recessed-step was formed by ensuring that the point of transition from PEEK tubing (OD 0.6 mm) to fused silica (OD 0.23 mm) lay within the guide tube on completion of implantation (Fig. 1c).

In vitro performance of the recessed-step catheter was compared with two "control" catheters, which were chosen to reflect the design of previously validated CED catheters (Krauze et al., 2005; White et al., 2011a,b):

1. A carbothane catheter with a step transition from 1 mm OD carbothane to 0.23 mm OD fused silica resulting in the same external profile as the recessed-step catheter – subsequently referred to as the "one-step catheter" (Fig. 2a).
2. A ceramic catheter with a two-step design comprising an initial transition from 1.3 mm to 0.6 mm OD, and a second transition positioned 10 mm distally from 0.6 mm ceramic to 0.23 mm OD fused silica – subsequently referred to as the "two-step catheter" (Fig. 2b).

The design of all 3 catheters was similar in that they each had a 3 mm length of fused silica (0.23 mm OD, 0.15 mm ID) extending beyond their distal stepped outer diameter (Fig. 2).