



Chronic, intermittent convection-enhanced delivery devices



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HIGHLIGHTS

- State of the art review of catheter designs for convection-enhanced delivery.
- Analysis of the design features, materials and methods of use which could be applied to chronic intermittent drug delivery systems and clinical trials to minimise risk of trial failure and opportunities to optimise intraparenchymal distributions.

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ABSTRACT

Background: Intraparenchymal convection-enhanced delivery (CED) of therapeutics directly into the brain has long been endorsed as a medium through which meaningful concentrations of drug can be administered to patients, bypassing the blood brain barrier. The translation of the technology to clinic has been hindered by poor distribution not previously observed in smaller pre-clinical models. In part this was due to the larger volumes of target structures found in humans but principally the poor outcome was linked to reflux (backflow) of infusate proximally along the catheter track. Over the past 10 years, improvements have been made to the technology in the field which has led to a small number of commercially available devices containing reflux inhibiting features.

New method: While these devices are currently suitable for acute or short term use, several indications would benefit from longer term repeated, intermittent administration of therapeutics (Parkinson's, Alzheimer's, Amyotrophic lateral sclerosis, Brain tumours such as Glioblastoma Multiforme (GBM) and Diffuse intrinsic Pontine Glioma (DIPG), etc.).

Results: Despite the need for a chronically accessible platform for such indications, limited experience exists in this part of the field.

Comparison with existing method(s): At the time of writing no commercially available clinical platform, indicated for chronic, intermittent or continuous delivery to the brain exists.

Conclusions: Here we review the improvements that have been made to CED devices over recent years and current state of the art for chronic infusion systems.

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1. Introduction

With global population and predicted lifespan increasing, the prevalence of neurological disease is set to rise. At present over 4.6 million patients have been identified with Parkinson disease (PD) in the top 10 populated countries of the west (*with an undefined global population*) while there are in excess of 20 million patients globally who suffer with Alzheimer disease (Dorsey et al., 2007; Kowal et al., 2013). Forecast burden models show predicted volumes of PD cases doubling within 15–25 years, while Alzheimer disease is predicted to triple (81.1 million) by 2040 (Lopez, 2011; WHO, 2006). This will place a very high demand on healthcare resources all over the world.

As has previously been reported, oral and intravascular medication are ineffective against these types of pathologies given that <1% of systemically administered drugs reach the brain (Stockwell et al., 2014). A series of tight junctions in the endothelial layer of the vascular system provides a highly effective filtration system that prevents the transport of therapeutic molecules to the tissues and fluids of the brain. This filtration system is called the Blood Brain Barrier (BBB) (Bauer et al., 2014).

Bypassing the BBB and delivering therapeutics directly to the parenchyma, offers the user the ability to introduce therapeutics locally, at doses and concentrations that would otherwise have to be delivered at toxic levels systemically. Bolus injection and the reliance on natural diffusion from the point of delivery, is not a valid administration paradigm as the spread of the therapeutic is limited to a few millimetres from the cannula. Delivery of infusate via a pressure driven regime amplifies the distances permeated by macromolecules and produces a more continuous concentration distribution (Bobo et al., 1994; Morrison et al., 1994). This technique, convection-enhanced delivery (CED), replicates the bulk flow of fluid through the interstitial spaces observed in natural processes, such as vasogenic oedema, by increasing the pressure local to a point source. Therapeutic is driven homogeneously into tissues beyond the infusion boundary that would be achieved by diffusion alone (Fig. 1). Intuitively, smaller molecules were associated with larger dispersions than bigger molecules however receptor binding, charge and other molecular properties also impact on the distribution of an infusate (Saito et al., 2006).

Despite positive results pre-clinically (Gash et al., 1996) and in phase I clinician led studies (Gill et al., 2003; Patel et al., 2013; Slevin et al., 2005) clinical translation of CED has been hampered by high profile failed studies (Kunwar et al., 2010; Lang et al., 2006). Retrospective investigations have found that overly ambitious study design, catheter target accuracy and predictability of distribution were major factors failing to achieve successful outcomes (Mueller et al., 2011; Sampson et al., 2010).

Recent improvements, notably to the delivery platform, has reinvigorated the application of clinical CED with eight active studies registered (ClinicalTrials.gov, 2015). More studies that do not require registration may also be active.

A small number of devices have been commercialised which display good acute performance when used with the principles of CED (Brady et al., 2014; Richardson et al., 2011). Progress in this field has therefore focused on acute or short term infusions. These devices are suited to the delivery of small volume payloads for the delivery

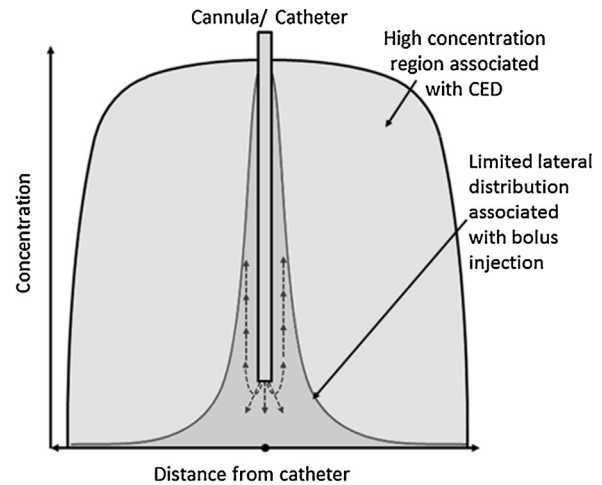


Fig. 1. Graphic depiction comparing the distribution associated with convection-enhanced delivery (CED) and bolus injection (reproduced and modified from Lam et al. (2011)). Note that the region of high concentration has spread laterally a much larger distance from the catheter than simply injecting a bolus which is the signature of CED.

of viral vectors and stem cells, but little exists in the experience of chronic CED applications.

Chronic, intermittent delivery could be useful to treat a range of neurological diseases such as Alzheimer's, Parkinson's (Gill et al., 2003), Gaucher disease (Lonser et al., 2005) among others where repeated infusions could maintain elevated levels of therapeutic within a target tissue, where it is quickly cleared or metabolised (e.g., chemotherapy). While the application of chronic CED may be useful in the treatment of brain tumours such as Glioblastoma Multiforme (GBM) and Diffuse Intrinsic Pontine Glioma (DIPG) tumours, targeting strategies will be key to place long term catheters in areas of likely recurrence. While direct targeting of a tumour will deplete its core of dividing cells, the resulting necrotic core may act as a sump for further therapeutic delivered, preventing convection into the surrounding tissues. Catheters will need to be placed around the periphery of a tumour in areas of likely recurrence.

Broadening the knowledge of this niche has been hindered in part by the lack of commercially available chronic CED systems to undertake clinical research. Given the predicted volume of demand for intraparenchymal delivery options, including chronic administration systems, a new appreciation of the field must be generated. Novel, chronic systems will provide clinicians 'enabling technology' to treat patients and provide the pharmaceutical industry a new platform to develop therapeutics.

As highlighted in the following review, a large range of catheter profiles have been reported following use in CED infusions. Debinski and Tatter previously highlighted five categories of catheter design category (Fig. 2); End Port Cannula (EPC), Stepped Profiles Catheters (SPC), Multi-Port Catheters (MPC), Porous tipped catheters (PTC) and Balloon Tipped Catheters (BTC) (Debinski and Tatter, 2009). Designs are not limited to these categories however and numerous variations and overlaps exist.

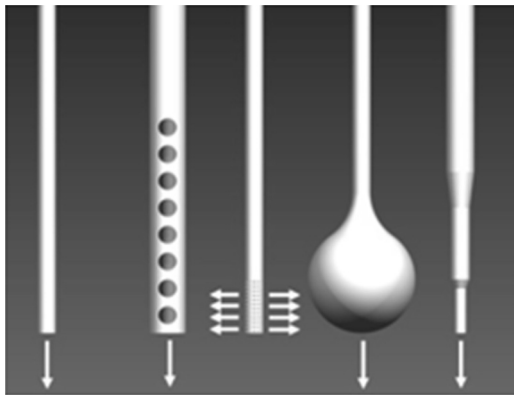


Fig. 2. Device design groups used in CED studies (left to right); End Port Cannula, Multi-Port Cannula, Porous Tipped Catheters, Balloon Tipped Catheters and Stepped Profile Catheters—image reproduced and modified from [Debinski and Tatter \(2009\)](#).

Here we review and consolidate information on catheter design, experience and materials which have been published when performing CED infusions in pre-clinical and clinical studies over the past 20 years. This review of the state of the art will guide the design and optimisation of new chronic intraparenchymal catheters and their use.

2. Intracranial CED devices

2.1. End port cannula (EPC)

Much of the earliest work which categorised the basic knowledge of CED was performed with EPC. While EPC are defined as having a singular external profile, no restriction is made to the material, devices can be rigid (e.g., fused silica, PEEK or steel hypotube) or flexible (e.g., polyurethane, silicone).

[Bobo et al. \(1994\)](#) first defined the V_d/V_i ratio, a multiplication ratio used to describe the proportional increase in volume distributed in the brain (V_d) from the volume infused (V_i). Bobo observed that the V_d/V_i ratio was not constant for all infusions. Smaller molecules displayed larger distributions ([Bobo et al., 1994](#)). Later studies highlighted that the ratio was also linked to the tissue type, as the interstitial fraction is lower in grey matter than white matter ([Lieberman et al., 1995](#)). Larger volumes and faster infusion rates developed to infuse clinically relevant volumes in an acceptable timeframe. Increases in flow rates were however linked to increases in the amount of reflux (leakback/backflow) along the catheter track ([Chen et al., 1999](#)). Reflux is detrimental to CED as the loss of fluid around the point of distribution drops the local pressure, limiting further distribution. Leakages into unintended regions can lead to unwanted side effects ([Nutt et al., 2003](#); [Tanner et al., 2007](#)). Investigation of infusion parameters affecting distribution identified that increases in cannula diameter strongly correlated to increases in the volume and distance of reflux ([Chen et al., 1999](#); [Fig. 3](#)) which was also predicted mathematically ([Morrison et al., 1999](#)). Increasing the concentration of the infusate or delaying the start of an infusion (tissue-to-catheter sealing time) were discounted experimentally as having little to no effect on reflux. However, it was later shown that increases in tissue trauma (common with larger bore devices) positively correlated to volume and extent of reflux ([White et al., 2011](#)). The sealing times described by Chen would not have been long enough for healing mechanisms to reduce oedema associated with local trauma allowing the tissue to seal around the device.

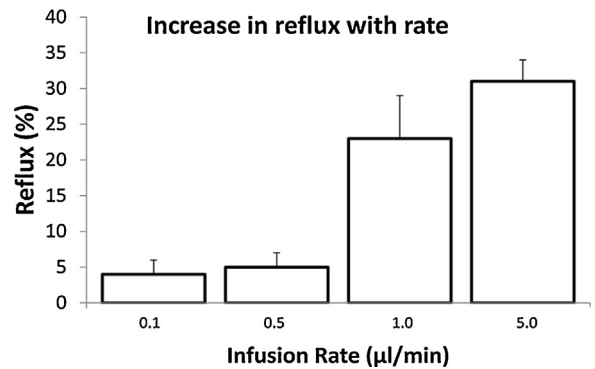


Fig. 3. Increases in flow rate have been shown empirically to generate increases in reflux along the catheter track—graph reproduced and modified from [Chen et al. \(1999\)](#).

2.2. Shunts and peritoneal catheters used for CED (including multi-port catheters (MPC))

Hydrocephalus shunts, designed for long term implantation in the brain are routinely used to deliver and aspirate liquids to and from the ventricles in the brain. They are made from flexible materials such as silicones or polyurethanes. Shunts typically come with an end port, fish mouth or multiport design and usually have a large bore (>1 mm) to aid the rapid clearance of excess cerebrospinal fluid (CSF). Shunts however may not be optimal for CED as they lack functional features (i.e., small diameters, reflux inhibiting profiles, etc.; discussed later) which are critical to effectively distribute infusates into the interstitial fluids of the brain through pressure driven means.

Large calibre, flexible end port style ventricular catheters (2–3 mm outer diameter) that have been implanted in clinical trials to treat glioma have failed to distribute effectively and have been linked to poor distributions ([Kunwar et al., 2010](#); [Tanner et al., 2007](#)). Cases treating Diffuse Intrinsic Pontine Glioma (DIPG), assumed spherical distribution but required a low flow rate, ~1 µl/min to delivery (~6ml in 100h), to minimise the risk of reflux. As no diagnostic tracer was used to confirm the distribution (as acknowledged by the author) it is not possible to evaluate the infusion effectively, however, T2 weighted MRI scans indicated some elevated signal around the catheter tip ([Anderson et al., 2013](#)).

In other phase I clinical trials, multi-port catheters were implanted into the striatum of patients with promising results ([Slevin et al., 2005](#)). It was suggested that the increased number of holes may have aided delivery of therapeutics to the parenchymal tissues but as no post infusion imaging was performed on the distribution of these infusions it is impossible to fully qualify this assertion.

Subsequent investigations of MPC for CED in gel showed that they performed poorly ([Raghavan et al., 2006](#); [Salvatore et al., 2006](#)) with preferential flow occurring from the proximal holes.

Investigations of multiport hydrocephalus shunts ([Lin et al., 2003](#)) demonstrated that of the available eight holes along the device, 80% of the flow escaped from the most proximal three holes ([Fig. 4](#)). This was proven empirically and then supported through a Computational model.

Preferential flow seen in hydrocephalus devices might help explain the patterns of distribution seen in CED studies using these devices in the opposite flow direction.

2.3. Micro porous tipped cannula (PTC)

PTC are similar to MPC in that they have a number of holes along their outer wall but PTC have a much larger number of

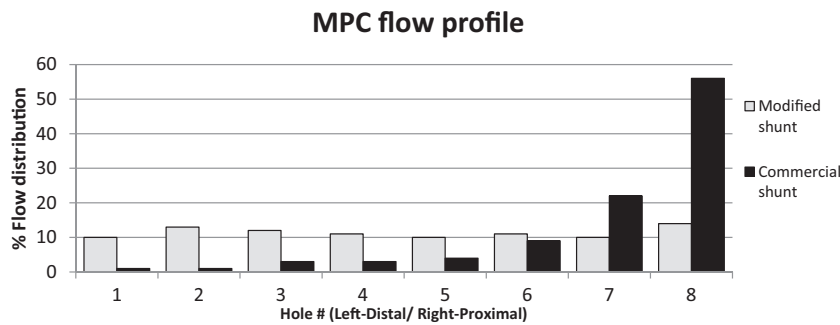


Fig. 4. Graphical representation of uneven flow distribution within multiport hydrocephalus catheters (black) and a more even flow which could be achieved through modifications to the hole profiles and arrangement (white). The distal end is shown on the left of the graph—image reproduced and modified from Lin et al. (2003).

much smaller holes ($\leq 0.45 \mu\text{m}$ diameter). These holes make up the porous, ceramic walls in the tips of these devices. During an infusion, each pore experiences a very small volumetric flow which will drop the pressure within the core of the device by an equally small amount. By maintaining a high internal pressure more distal pores also experience a modest flow which contributes to the overall distribution along the length of the porous tip (Fig. 5).

When compared to EPC the PTC was shown to increase the distribution of infusate into the surrounding gel substrate and murine brain tissue (Oh et al., 2007). A later study found that PTC cannula produced a comparable infusion profile to 3 mm step profile cannula in vivo (Brady et al., 2013). PTC are being commercialised for drug delivery by Twin Star Medical.

2.4. Balloon tipped catheters (BTC)

While not commonly used in CED trials, a small number of studies have shown that BTC may have use in treating oncology subjects who have undergone resection of their tumour mass. As the penumbra of a resection cavity is most at risk of metastasis, it has been argued that infusions targeting dividing cells should be administered preferentially into these areas. Intra-ventricular infusions have shown little diffusion of infusate beyond the ependymal layer of the ventricles (Nutt et al., 2003) while catheters placed too close to a resection cavity have been linked to losses into these CSF spaces, dramatically stagnating further distribution into surrounding tissues (Sampson et al., 2011).

A team at Emory University performed resections in canine subjects with the aim of investigating whether CED could be effectively used to distribute infusate into a tumour penumbra by first filling

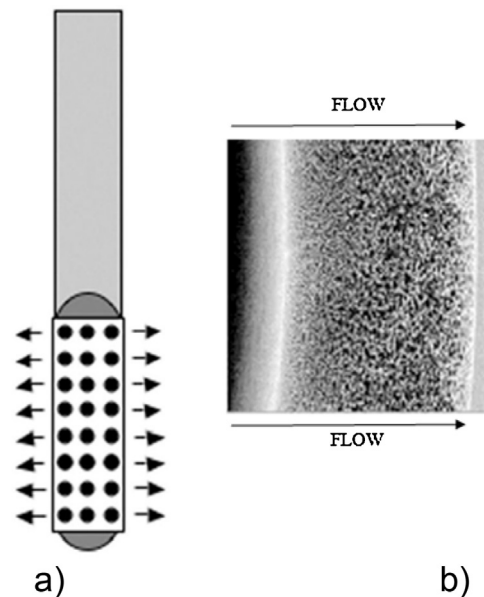


Fig. 5. Microporous tipped cannula (a) illustration of even flow possible over elongated portions of the device (note blocked tip), (b) radial view of the cannula wall showing tortuous pathway for infusate through the porous wall—images reproduced from Oh et al. (2007).

the resection cavity with a balloon (Olson et al., 2008). The study infused continuously for 4 days at a rate of $83 \mu\text{l/h}$ and stated that in 2 of 3 cases 97–99% of the brain achieved coverage. The images of coverage (Fig. 6), however, do not appear to display the

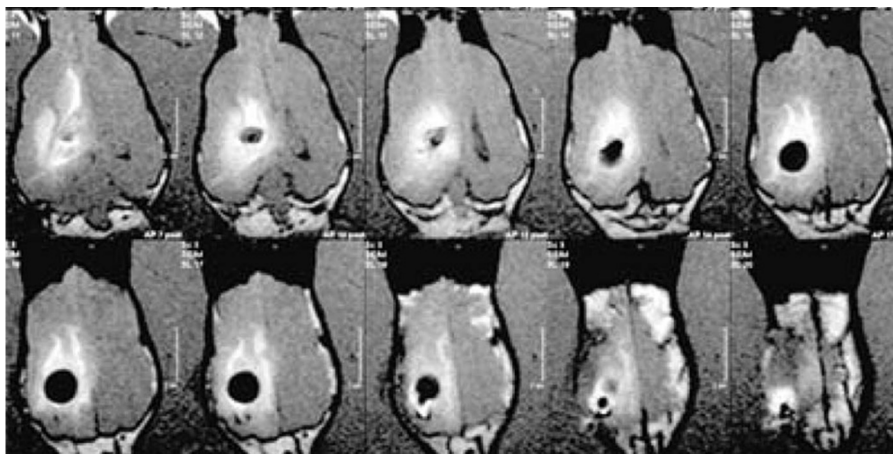


Fig. 6. Infusions into the penumbra of a resection cavity using a 2 channel Gliasite® brachytherapy catheter, infusing 75% saline/25% Gd-DTPA Magnevist—image reproduced from Olson et al. (2008).

homogenous distribution profile associated with CED. The large coverage may be attributed to the large concentration of the MRI visible tracer—75% saline/25% Gd-DTPA (Magnevist, Berlex; [Olson et al., 2008](#)) and prolonged period of infusion, with gadolinium being carried along with natural parenchymal CSF turnover. Further work is required to expand the knowledge for this application.

2.5. Stepped profile cannula (SPC) assemblies

Several designs of SPC have been used to perform CED infusions in clinical and pre-clinical studies. Stepped profiles can be produced through the assembly of tubes at the time of implantation or within a monolithic assembly that is implanted as a single unit, although it can be argued that the later exhibits much less traumatic delivery characteristics for acute delivery.

Monolithic stepped profiles were pioneered by a team at the University of California, San Francisco (UCSF) showing that where end port cannula alone would have refluxed, the addition of stepped features would inhibit the progression of backflow ([Krauze et al., 2005](#); [Sanftner et al., 2005](#); [Fig. 7](#)).

The distribution of the stepped profile was evaluated first in agarose gel containers and later histologically following infusions in the rat and primate model. Agarose gel is a standard phantom material for brain tissue which has been validated against the porcine brain model ([Chen et al., 2004](#)). A monolithic SPC is being commercialised by MRI interventions Inc. which contains a ceramic, fused silica liner and a polymer sheath, though it is currently approved for intra-ventricular use only.

Research conducted at Cornell University utilised silicon industry technology to manufacture printed cannula tips containing dual lumen. These can be independently coupled to proximal tubing away from a delivery site enabling the delivery of a multitude of infusates in addition to the integration of sensor technology. This could be used during delivery to monitor the local environment or to actively monitor the infusate itself (flow rate, temperature, air in line, etc.; [Olbricht et al., 2010](#)). The tip design is being incorporated into a stepped profile cannula and commercialised by Alcyone Inc. though again, this design is only approved for intra-ventricular use.

Investigations using the dual channel tip were conducted in the porcine model at varying flow rates with a number of infusates. When combined with a stepped profile design comparable distributions to other SPC were achieved. Infusion rates as high as 20 $\mu\text{l}/\text{min}$ were published for white (internal capsule) and grey (thalamus,

putamen) matter targets but no investigation of tissue damage was conducted ([Brady et al., 2014](#)). Earlier studies noted tissue damage at infusion rates in excess of 10 $\mu\text{l}/\text{min}$ when delivered from a cannula with a 102 μm diameter bore. The authors speculated that the tissue damage may be attributed to the delivery of excessive volume however subsequent studies have successfully infused larger volumes ([Chittiboina et al., 2014](#)) discounting the theory that volume alone is the cause of the observed tissue damage. It is therefore possible that the tissue damage found by the UCSF team may be linked to the fluid velocity at the tip of the catheter. At 10 $\mu\text{l}/\text{min}$, a cannula with a 102 μm internal diameter would eject a fluid stream at 5.1 mm/s. Evaluating the smaller cannula outlet produced by the micro-fabricated dual channel tips (30 \times 53 μm^2), a comparable flow rate may have produced a fluid jet travelling at over 10 times this rate. It is therefore essential that new cannula and catheter designs are tested not only for performance with diagnostic imaging but the infusion regimes must be validated at a cellular level to provide future users a set of safe operational parameters. Further investigation of this and other designs is therefore warranted.

Prior to the release of commercial alternatives, other groups treating DIPG clinically have pre-clinically investigated the use of FS components from Plastics one, a supplier of pre-clinical infusion systems, before implanting a similar device in humans. A large bore guide tube (16–18 Gauge) is implanted into the brain stereotactically and is bonded into a burr hole formed in the cranium, with the distal tip 15–35 mm short of the target. A primed silica catheter is then inserted to depth in the guide tube, with the tip located in the brainstem ([Lonser et al., 2002, 2007a,b](#)).

Monolithic SPC usually combine steel or ceramic tubing with fused silica (FS) liners. This rigid construction is advantageous for acute infusions as devices can be implanted with a stereotactic guide system which helps minimise macro-motion during insertion and infusion which is critical to reducing reflux ([Chen et al., 2004](#)). Long term implantation of these monolithic assemblies is not feasible due to the rigidity of the cannula. The relative movement between the brain and the device will promote reflux but may also accelerate natural healing processes. We postulate that as the brain encases the device in a sheath of glial tissue the permeability around the cannula will drop which may further increase reflux.

A modified hybrid of the monolithic SPC ([Fig. 7](#)) made from flexible tubing and a rigid, FS tip was investigated by the same team at UCSF, Medgenesis Therapeutics and Brainlab AG. This enabled the device to be implanted in a rigid state (to aid stereotactic delivery),

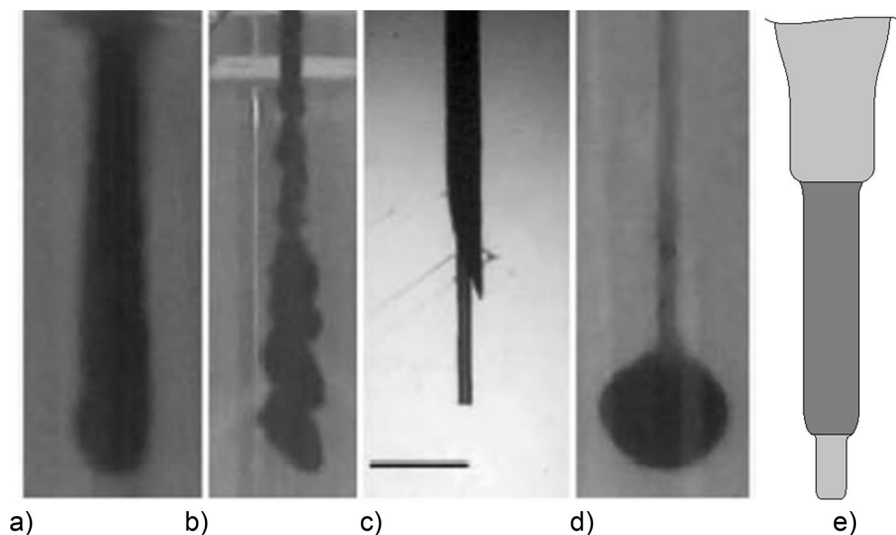


Fig. 7. Infusion profiles of end port cannula (a, b) and improvement possible through introduction of a reflux inhibiting feature (c, d)—images reproduced and modified from [Krauze et al. \(2005\)](#). (e) MRI interventions – SmartFlow cannula – commercial embodiment of the stepped profile cannula.

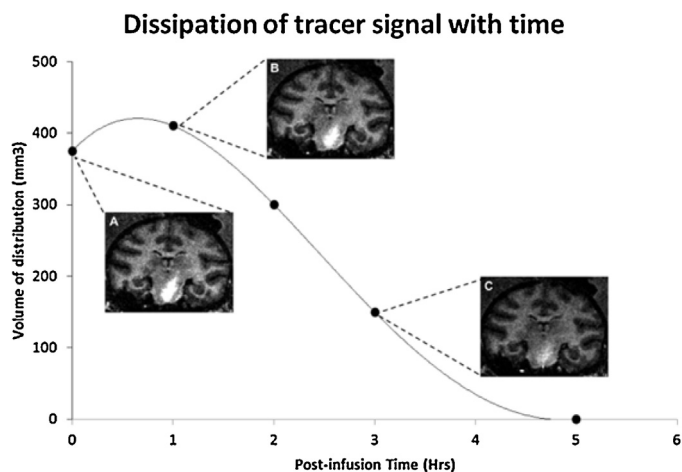


Fig. 8. Decrease in the intensity of a gadolinium tracer in the brainstem following the end of an infusion (A) immediately after completion of the infusion, (B) after 1 h, (C) after 3 h. Note the initial increase in the distribution due to diffusion and clearance processes but the large drop by 3 h post infusion (39% of the V_d at infusion end)—images reproduced and modified from [Lonser et al. \(2007a\)](#).

before a delivery rod was removed leaving the flexible, indwelling device (with rigid tip) in situ. The flexible tubing outside the skull could then be routed beneath the skin to a distal exit point. Evidence of acute but not chronic intermittent infusions, in addition to images of the device were published ([Rosenbluth et al., 2011](#)).

Similar, stepped catheter designs were fabricated in Medtronic sponsored studies. Needle tip catheters were used in a 10 day study in the porcine model, coupled to an implantable pump ([Kim et al., 2014](#)) and later a 28 day study in adult primates ([Fan et al., 2015](#)). Following a 3 or 7 day infusion (flow rate; $0.3 \mu\text{l}/\text{min}$) of a Gd-DTPA solution into the brain, distribution volumes of $1.544 \text{ ml} \pm 0.420 \text{ ml}$ ($V_d/V_i = 1.2$) were recorded in the pig and $1.936 \pm 0.660 \text{ ml}$ ($V_d/V_i = 1.68$) were recorded in the primate. The low distribution volumes may be accounted for by a high clearance rate of Gd-DTPA seen in other studies ([Lonser et al., 2007a](#); [Fig. 8](#)). Acute infusions in the primates showed much higher V_d/V_i ratios (5.56 ± 1.6) indicating clearance may be a major factor in low flow, continuous infusion.

In order to cover the larger human putamen ($3.98 \pm 0.15 \text{ ml}$; [Yin et al., 2009](#)) using this system it may be necessary to implant multiple catheters with each attached to a pump. Alternatively, higher coverage ratios might be achieved by running the pump at a higher rate for a short period of time before natural clearance removes the infusate from the local area. Continuous infusions were shown to achieve larger overall infusions. A recent study of prolonged CED in the rat brainstem ([Ho et al., 2015](#)) produced no neurological behavioural changes or signs of local toxicity. The relatively short period of the study (10 days) may not have provided sufficient time for the onset of local toxicity due to point source accumulation identified in other studies ([Barua et al., 2013b](#)).

Flexible guide tube and catheter assemblies, suitable for long term implantation, were manufactured specifically for a phase I investigational study of Glial cell-line Derived Neurotrophic Factor (GDNF) at Frenchay hospital, Bristol, UK ([Gill et al., 2003](#)). Sub 1 mm diameter catheters and guide tubes were used to minimise the risk of reflux which had been shown to occur in larger diameter cannula ([Chen et al., 1999](#)). The catheter was manufactured in Carbothane™, an aliphatic polyurethane which was later shown to be critical in achieving low blockage rates ([Bienemann et al., 2012](#)). Despite promising clinical outcomes in a small number of cases, it was not possible to measure infusion performance of this system as MRI tracers such as gadolinium (Gd-DTPA) were not routinely used.

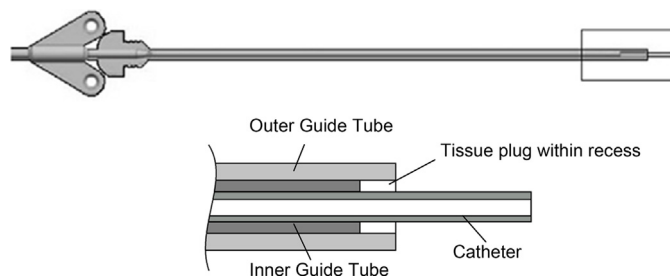


Fig. 9. Assembled catheter design with a reflux inhibiting feature: a recessed step—images reproduced and modified from [Gill et al. \(2013\)](#).

Successful intermittent infusions performed over 163 days in the porcine model were demonstrated by the University of Bristol, utilising a similar system to that described by Gill in 2003. Novel infusion regimes were used to deliver intermittently which differed from previous, longer term studies in which fluids were supplied continuously from an implanted reservoir pump ([Bienemann et al., 2012](#)). The flexible guide tube assembly was further developed with the incorporation of a third cannula. Instead of a dual step design the central cannula is cut shorter than the outer tube, producing a recessed design ([Fig. 9](#)).

We have identified that contrary to the initial description of CED as a point source event ([Bobo et al., 1994](#)), infusions naturally involve a degree of reflux which can be incorporated into the infusion distribution model ([Woolley et al., 2013](#)). Immediately following the start of an infusion, fluid passes into the interstitial spaces of the surrounding tissue as expected from the standard model. As the pressure continues to build however the contact forces between the outer wall of the catheter and the tissue surrounding it will reach a state of equilibrium. At this point fluid will pass into this space, passing up the outside of the catheter as reflux. As fluid escapes from the tip area the local pressure drops the contact forces high up the catheter track remain high which combined, stem the flow of fluid.

By embracing and this inevitable reflux, we have demonstrated it is possible to exert a degree of control over it. We have previously published evidence on the indwelling performance of the recessed step catheter ([Gill et al., 2013](#)) over a month in the porcine model and subsequently within clinical glioblastoma cases ([Barua et al., 2013a, 2015](#)). While monolithic SPC utilise progressively larger diameters to inhibit and retard this flow acutely, no chronic infusion data is available therefore their efficacy cannot be stated. A chronic, pre-clinical infusion system and a similar chronic, clinical platform are being commercialised by Renishaw PLC.

A novel aspect of the assembled guide tube platform is the ability to modify the length of the step between the smallest diameter tube (catheter) and the outer guide tube specific to each target site. Together with the recessed step feature, it has been demonstrated that increasing the protruding step length has the effect of minimising the volume of reflux which travels beyond the flow inhibiting step feature, achieving a controlled form of reflux ([Woolley et al., 2013](#)).

We have identified, and will subsequently present data ([Lewis, 2015](#)), that it is possible to manipulate infusion morphology through modifications to the step length and the infusion regime of a recessed step catheter. The ability to modify infusion parameters permits non-surgically invasive optimisation of infusion distributions following implantation and potentially longer term.

For chronically implanted devices, attributes such as a 90° bend in the tube at the skull surface, and access via a distal port, facilitate real time monitoring to make informed decisions on the progress of the infusion.

A novel accessory described by a team at the University of Wisconsin creates a ‘valve tip’ and prevents blockage by occluding the inner bore of the cannula with a solid rod during insertion. Following insertion the rod is retracted a short distance (~3 to 5 mm) within the catheter where the inner bore opens slightly leaving room for fluid to pass around the rod (Sillay et al., 2012). This design has the additional benefit of reducing the dead volume within implanted systems but will increase the pressure required to infuse. Comparisons to monolithic stepped cannula designs and also microporous tipped cannula showed that the ‘valve tip’ design produced comparable infusion profiles but no marked improvement in distribution (Brady et al., 2013; Sillay et al., 2012). This design would therefore only offer improved robustness and possibly reduced tissue trauma on entry.

3. A systems based approach

While this review has focused on catheter design for chronic intraparenchymal delivery, previous experience from clinical trials indicates that dealing with problem areas in isolation is the root cause of failures to tackle the clinical translation of CED.

Novel delivery platforms for chronic infusions should therefore be founded on the successes pioneered in the acute setting while incorporating lessons from previous, failed trials to consider new approaches. While a detailed review of other aspects of CED is beyond the scope of this review, here we acknowledge the inter-relationship between the catheter design and other variables. Chronic, repeated delivery is a complex problem with a number of interdependent elements that require consideration if optimised, reliable and repeatable intraparenchymal drug delivery is to be achieved (Woolley et al., 2013).

This multi factorial approach to successful infusions, depicted as the pinnacle of the CED pyramid (Fig. 10), relies on expertise and knowledge across several disciplines. Here it is believed that optimal CED can be attained if based on a solid foundation of effective stereotaxy, sophisticated surgical planning software, ridged stereotactic delivery instruments and appropriate, responsive infusion pumps.

It seems likely that only once a solid platform is achieved can reflux resistant chronic drug delivery systems be implanted with the required accuracy to ensure that critical catheter features are positioned within target structures. The CED pyramid also illustrates the need to consider contributing factors that affect

particular therapeutics, such as; molecular size, weight, charge, tissue affinity together with receptor binding, deactivation and potency levels to material and geometry used in the design of the implantable device.

Natural variations in the population as well as a changing internal environment over time due to healing processes present further complicating factors which demand individual attention and will require ongoing evaluation to optimise the infusion regimes to ensure the patient receives treatment where it is required.

4. Discussion

Following years of basic research which characterised the performance issues associated with CED systems, there is now a growing community which actively use the principles of CED in pre-clinical and clinical investigations of new and existing drugs.

Despite the immaturity of the knowledge surrounding successful implementation of CED systems and the ability to achieve acceptable coverage of target structures, CED continues to be practiced within a small number of research centres who accept the current limitations, enabling the implantation of infusion devices based on empirical, historic knowledge and experience of each device’s prior performance.

A limited number of acute devices have received market approval, and fewer still have received authorisation for marketisation as CED devices, but no commercially available system is currently indicated for chronic intraparenchymal delivery.

Drug device combination programmes developing pharmaceuticals and improving catheter designs are likely to benefit from development within a systematic, lab to clinic process where first principles and empirical evidence combine to optimise the delivery. Translation of device design should start with distribution characterisation in an isotropic, homogenous substrate such as agarose gel to baseline performance. Distribution properties should then be confirmed pre-clinically within *in vivo* models before finally being translated to clinical indications.

While only an indicator of infusion morphology, we have found, and will subsequently be publishing, that agarose gel infusions offer baseline infusion morphology data which is specific to each device. Reflux inhibiting features can be trialled and gain a degree of supporting empirical evidence before it is trialled in the complex *in vivo* environment. Users must appreciate that gel data presents an excellent starting point which can inform clinical decisions but this is only a starting point and knowledge of the infusion distribution properties of the local structures (and more preferably, prior clinical experience) should be incorporated into the planning and implementation process. Published evidence of safe, achievable distributions in the *in vivo* pre-clinical model should also form the basis of a CED practitioner’s planning arsenal, specifically whilst this technique is being adopted and experience gained.

In order to enable optimisation of infusion systems following implantation, it is beneficial for flexibility to be built in to study or treatment protocols. It is now obvious that CED infusions must be visualised following the implantation of chronic infusion systems to confirm target acquisition and characterise the distribution achieved. Where poor target structure coverage or other undesirable distributions are observed, clinicians must be given the knowledge of how best to intervene and optimise the distribution. It is unacceptable to permit treatments or trials to fail where the technology exists, and can be easily implemented, to modify the input infusion regimes and improve outcomes for patients. Such a controllable infusion system will maximise clinical benefits and reduce the risk of adverse events while accelerating the development of new drugs to clinic. Pre-clinical correlation mapping of a pharmaceutical agent to imaging tracers should precede clinical use to ensure representative diagnostic imaging interpretations.

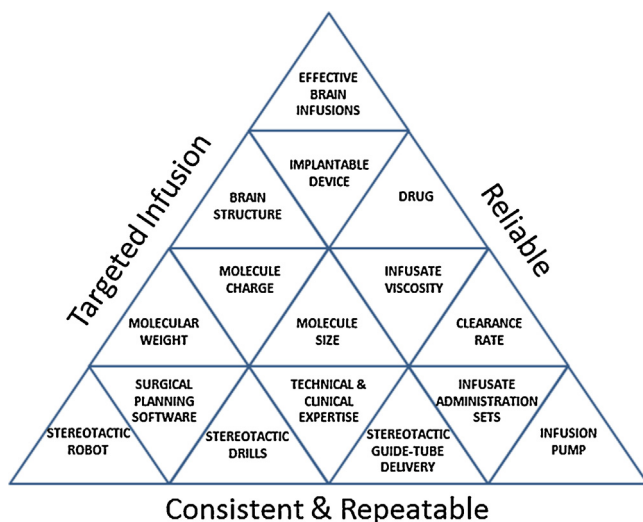


Fig. 10. Pyramid of effective drug delivery to the brain—image reproduced and modified from Woolley et al. (2013).

For chronic infusions, periodic mapping of the distribution, using diagnostic imaging tracers, will help characterise ongoing distribution of therapeutics within target tissues and permit intervention to optimise coverage.

Following the initial description of CED which used simple cannula, development of infusion parameters (flow rate, ramping regimes, etc.) have preceded device development. Numerous infusion cannula and catheter systems have since been trialled for CED with varying degrees of success. Published distribution data indicates that each device performs differently and infusion parameters should be developed for each device to optimise distributions. All systems will benefit from further investigation and clinical use to generate a better understanding of their performance attributes. A small number of physical attributes appear critical across all designs which can be translated to that of a chronically implanted catheter system.

Larger diameters are linked to increased distance of undesirable reflux along the catheter track. Large diameter tubing is therefore undesirable for intraparenchymal delivery. Increases in infusion rates raise the local pressure around the infusion site and also increases the extent of reflux if the pressure surpasses that required to achieve bulk flow of the interstitial fluid. If reflux is observed then further distribution is limited as the additional infusate follows the path of least resistance around the catheter. Actively dropping an infusion rate may decrease the pressure local to the site of reflux and halt further progression.

From this review and from our own work, we have found that a reflux inhibiting feature is required to halt backflow along the catheter entry track. Simultaneously this maximises local interstitial pressure and achieves bulk flow of the therapeutic into the tissue volume.

For prolonged chronic indications it is essential that the catheter systems are made from a flexible material which can move with the brain during every day activities. All devices must be placed accurately without lateral macro motion as this can increase trauma and have a detrimental effect on the distribution.

In addition to physical features, certain practical and transferable attributes are essential for CED devices to facilitate this novel treatment regime.

If we accept that the local environment surrounding each catheter site is unique and each patient specific, then it is unlikely that a standard infusion regime will produce comparable distributions between patients. Catheter specific optimisation may be required to achieve acceptable coverage of the target structure. Therefore catheter designs need to be flexible so that specific features that inhibit reflux can be optimally placed in the intended target structure.

Devices must be compatible with imaging modalities such as MRI (or nuclear imaging in the cases of radio-labelled markers) to enable real time visualisation of distributions to verify acceptable coverage or intervene and implement a modified infusion regime to optimise the distribution. Until a standard model of repeatable delivery is achieved patient specific infusion regimes provide a practical method of providing patients with optimal coverage of targeted tissues (Healy and Vogelbaum, 2015). As an emerging field, CED will require specialist clinical infusion pumps and software that are capable of running at low infusion rates (0.1–10 $\mu\text{l}/\text{min}$). Pump or pump software should have the functionality to house patient specific infusion regimes which can be categorised at test infusion milestones (e.g., first infusion).

There are a range of pre-clinical and clinical options for accessing intracranial catheter systems. Active, implantable osmotic pumps (Alzet[®]) are routinely used to continuously deliver infusate pre-clinically. More recently Primetech Corp. have manufactured a programmable, micro infusion pump containing a 900 μl reservoir which can be programmed to run intermittently using an on board

micro-processor (iPrecio[®]) and a radial peristaltic pump. This micro pump has a maximum flow rate of 0.5 $\mu\text{l}/\text{min}$. While not indicated for it, the low peak rate would be of limited clinic use to achieve CED.

Passive subcutaneous access ports (e.g., PinPorts/Soloports-Instech Solomon, Portacath- Smiths Medical, Porthales- Tricumed Medizintechnik GmbH, etc.) provide a means of periodically accessing implanted catheter systems injecting into or cutting down to make the connection immediately prior to an infusion. While subcutaneous ports, osmotic and reservoir pumps can be connected to intracranial catheters, chronic infusion systems may benefit from having an externally accessible port to facilitate easy connection and prolonged attachment during infusions (several hours) with minimal implanted hardware (Barua et al., 2013b, 2015).

Despite a small number of commercially available reflux resistant catheter designs, and some stiff tipped indwelling catheters, no evidence of their chronic efficacy is available. Further work is required to develop knowledge of how to implant, optimise and maintain chronically implanted convection-enhanced delivery infusion systems.

5. Conclusions

Forecast burden models indicate that the growing and ageing global population will cause a steep rise in the prevalence of neuro-oncology and neurodegenerative disease which will place a high demand on palliative healthcare resources.

Convection-enhanced delivery provides a paradigm for pharmaceutical and academic institutions to provide not only acute infusions of gene therapy but also chronic, intermittent infusions of proteins, neurotrophic factors, chemotherapeutics or other quickly metabolised molecules.

A small number of dedicated CED devices are starting to enter the marketplace but are targeted at acute, stereotactic delivery and indicated for intra-ventricular use. No devices are commercially available which are indicated for chronic, intermittent CED to the brain parenchyma.

Targeted chronic catheter and study design should be developed to enable development of novel treatment regimes which can be based upon the principles developed within acute delivery systems.

All catheter designs have unique attributes which must be characterised to be used effectively. It should not be assumed that infusions parameters can be utilised uniformly across all commercially available catheter platforms.

Chronic infusion catheter systems will benefit from small diameters and the inclusion of reflux inhibiting features. To remain in the brain long term, catheters will need to be made from soft materials but still need to achieve excellent target accuracy which is likely to require a 'systems based approach' which tackles peripheral issues around the design of the catheter to ensure effective delivery.

Following implantation, and initial characterisation of the distribution, further periodic test infusions will be required to assess changes to the distribution pattern which may be caused by healing mechanisms and natural changes to the internal environment. In order to do this, device design must facilitate real-time imaging, enable alterations to infusion distribution and be minimally invasive whilst maximising the patient's quality of life.

Further work is required to generate understanding of infusion distributions which can be achieved by utilising chronically implanted CED systems.

Disclosures

While undertaking the research for this review, O. Lewis, M. Woolley and D. Johnson were employees of Renishaw PLC.

S.S. Gill, N.U. Barua and A.S. Bienemann were consultants to Renishaw PLC.

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