

### IS THE FUTURE AS ROSY AS IT SEEMS?

In the 21<sup>st</sup>. century, we are becoming accustomed to highly sophisticated medical technology which allows us to perform intricate invasive techniques which would have been unthinkable 100 years ago.

Furthermore, we judge ourselves completely competent in the use of these skills, without necessarily questioning too closely (or, rather, closely enough) the wisdom of their use.

In fact, we have learnt little since Eric Oldberg's plea in 1940( [\[1\]](#) ), that the highly vulnerable central nervous system not be subjected to chemical insult unless there were overwhelming evidence that benefit outweighs risk.

Much more recently, Hetherington and Dooley ( [\[2\]](#) ) have written about the efficacy of the intrathecal route of administration vis-?-vis reducing systemic effects, but have also cautioned that it

"can increase the risk of local adverse effects such as arachnoiditis."

They point out that

"It is accepted practice that any spinal injection should not contain preservatives."

Nowadays, we see the spread of intraspinal chemotherapy from its initial use, in the terminally ill

patient, to those with chronic conditions (such as Multiple Sclerosis or Spinal Cord Injury), who may require this treatment, or indeed, suffer the ill effects of it, for their remaining, often long, lifespan.

Moreover, we no longer confine what could be seen as experimental techniques to use in adults: children are also being treated not only for potentially fatal conditions such as leukaemia, but also chronic, albeit highly debilitating conditions such as spasticity due to cerebral palsy. (see Table 1 for list of intraspinal drugs)

Clinicians have argued and will continue to contend that the severe nature of the problems confers an undoubted benefit that is well worth the risk of later complications.

However, it must be noted that, for instance, intrathecal injection of baclofen (Lioresal) is clearly denoted as 'Not recommended' for use in children in the British National Formulary ([\[3\]](#)).

Yet this treatment is now being administered routinely for spasticity in children with cerebral palsy.

Baclofen was approved by the United States FDA, in 1996 for the use in Medtronic pumps, to treat 'cerebral spasticity'.

Previously trials of up to 41 months had been undertaken and reported efficacy and safety in adults with spinal spasticity (Nance et al [\[4\]](#)).

However, more than one study noted frequent complications: Ordia et al ([\[5\]](#)) reporting catheter-related problems occurring 19 times in 15 patients (out of 59 in the study), whilst Levin and Sperling ([\[6\]](#)) cited an 'overall incidence of total complications' of 62% (24% with Infusaid pumps, 167% in Medtronic pumps).

However, these studies were both in the mid 90s, and the pump techniques and technology have improved somewhat since then.

Of greater concern is the effect of chemical insult on the vulnerable subarachnoid space, into which the drug is directly delivered.

Whilst intrathecal preparations of baclofen must be completely devoid of neurotoxic preservatives in order to comply with regulations, there remains some concern as to the direct effects of the drug itself as well as the mechanical insult of the constantly present catheter, which has been recognised as causing fibrosis (scarring) and indeed, Medtronic admit that arachnoiditis is a known sequela.

In 1996, Albright( [\[7\]](#) ) reported complications in around 20% of patients and infection necessitating pump removal in 5%.

In 1997, Armstrong et al ( [\[8\]](#) ) studied 12 children with a follow-up of 1-5 years.

There were "favourable" results, although some central side effects.

There were 10 mechanical complications, local infections in 3 children and meningitis in 2.

The authors concluded:

"Results demonstrate the potential value of continuous intrathecal baclofen infusion for the treatment of severe spasticity of cerebral origin. However, this treatment can result in significant complications and more experience is required before the long-term benefits can be determined."

More recent studies have reported that baclofen administered intrathecally is effective in managing the spasticity associated with cerebral palsy.

In 2000, Gilmartin and colleagues( [\[9\]](#) ) studied this in 44 patients who were followed up for up to 43 months.

Adverse events occurred in 42 patients, although procedural/system problems were also reported as 59 events occurring in 30 patients.

Adverse effects included hypotonia, seizures, somnolence and nausea/vomiting.

A study published in February of this year ( [\[10\]](#) ) evaluated the baclofen pump in treating spasticity in adolescents and adults with cerebral palsy.

After one year, all the patients had some improvement.

The authors noted that the side effects common after an oral dose (drowsiness and confusion) were reduced by the spinal delivery of the drug.

The Cochrane review (2000 [\[11\]](#) ), cited 2 studies that had demonstrated a significant effect of intrathecal baclofen(ITB) in reducing spasticity due to spinal cord injury, but concluded, having reviewed several studies on the various antispastic agents, that

“There is insufficient evidence to assist clinicians in a rational approach to antispastic treatment for SCI. Further research is urgently needed to improve the scientific basis of patient care.”

The Hyman-Newman Institute for Neurology and Neurosurgery at the Beth Israel Medical

Center in New York, categorise complications associated with the use of intrathecal baclofen into those associated with the pump and those due to the drug.

The former seem to comprise the majority of the more serious, short-term events, but recent developments in pump technology have reduced some of the early problems.

Of the latter, there are 2 types of problem: first, those seen with a therapeutic dose (adverse reactions) and secondly, those due to overdose.

No mention is made of longer-term problems, of which arachnoiditis could well be one.

Internet information on the use of intrathecal baclofen in children, aimed at medical professionals and on other sites, at parents of sick children, fails to address the issue of long term use.

Indeed, whilst details of the procedure and logistics of the planned admission are available, with some brief mention of possible short-term problems and those relating to too high a dose of baclofen, there is absolutely not mention of the possibility of serious long-term adverse effects. Hence, one surely cannot claim that the parents are able to give INFORMED CONSENT to the implementation of this treatment?

Remembering that arachnoiditis secondary to myelogram dyes may have a substantially delayed onset (up to 20 years), one must surely sound a note of caution, if not of alarm, at the now quite widespread clinical use of ITB in children.

The ARIF (Aggressive Research Intelligence Facility) based in the Midlands, cited a SchARR (Trent Institute for Health Services Research) review on ITB in management of patients with severe spasticity, published in January 2000.

The review addressed the use of ITB in both adults and children and noted that although the

therapy did appear promising as regards efficacy, that there remain questions as to the incidence of adverse effects, particularly in children.

ARIF comment on their website ( [\[12\]](#) ) that they feel the review &quot;does not deal adequately with the important issue of adverse effects and complications.&quot;

Moving on to chemotherapy: patients with breast cancer that has metastasised to the meninges may now be treated with DepoCyt, a slow-release formulation of the cytotoxic drug, cytarabine.

This treatment has been reported in studies published in October 2000( [\[13\]](#) ) and January 2001( [\[14\]](#) ).

Both report encouraging therapeutic benefit in combating neoplastic meningitis in breast cancer, but cite arachnoiditis as one of the major adverse effects: 19% in one study, of which 88% were Grade 1 or 2 and &quot;chemical arachnoiditis (i.e. headaches, fever, nausea, vomiting) was common&quot;.

Despite a probably low survival (1 year survival projected as 19%) and the need for fewer injections (about a quarter the number needed in 'conventional' therapy) one must register concern as to the high incidence of arachnoiditis and the potential longer-term effects for those survivors.

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[\[1\]](#) Oldberg E *Surgery Gynecology & Obstetrics* 1940 Vol 10:724-5 A Plea For Respect for the Tissues of the Central Nervous System

[\[2\]](#) Hetherington NJ, Dooley MJ *Med J Aust* 2000 Aug 7; 173 (3): 141-3 Potential for patient harm from intrathecal administration of preserved solutions.

[3] BNF 40 September 2000 p.473

[4] Nance P, Schryvers O, Schmidt B, Dubo H, Loveridge B, Fewer D *Can J Neurol Sci* 1995 Feb; 22(1):22-9 Intrathecal baclofen therapy for adults with spinal spasticity: therapeutic efficacy and effect on hospital admissions

[5] Ordia JI, Fischer E, Adamski E, Spatz EL *J Neurosurg* 1996 Sep; 85(3):452-7 Chronic intrathecal delivery of baclofen by a programmable pump for the treatment of severe spasticity.

[6] Levin AB, Sperling KB, *Stereotact Funct Neurosurg* 1995;65(1-4):147-51 Complications associated with infusion pumps implanted for spasticity.

[7] Albright AL *J Child Neurol* 1996 Mar; 11(2) : 77-83 Baclofen in the treatment of cerebral palsy.

[8] Armstrong RW, Steinbok P, Cochrane DD, Kube SD, Fife SE, Farrell K *J Neurosurg* 1997 Sep; 87 (3) :409-14 Intrathecally administered baclofen for treatment of children with spasticity of cerebral origin.

[9] Gilmartin R *J Child Neurol* 2000; 15:71-77 Westport Newsroom 203 319 2700

[10] Meythaler et al *Archives of Physical Medicine and Rehabilitation* 2001; 82:155-161

[11] Taricco M, Adone R, Pagliacci C, Telaro E *Cochrane Database Syst Rev* 2000; (2): CD001131 Pharmacological interventions for spasticity following spinal cord injury.

[12] [www.hrsc.org.uk/links/arif/baclofen.htm](http://www.hrsc.org.uk/links/arif/baclofen.htm) Intrathecal baclofen cerebral palsy/spasticity.

[13] Murray DJ, Blaney SM *Ann Pharmacother* 2000 Oct; 34(10):1173-8 Clinical pharmacology of encapsulated sustained-release cytarabine.

[14] Jaeckle KA et al *Br J Cancer* 2001 Jan; 84 (2): 157-63 Intrathecal treatment of neoplastic meningitis due to breast cancer with a slow-release formulation of cytarabine.