Case Report

Intracerebroventricular Pain Treatment with Analgesic Mixtures including Ziconotide for Intractable Pain

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Intracerebroventricular (ICV) administration of opioids for control of intractable cancer pain has been used since 1982. We present here our experience of intracerebroventricular administration of pain treatments including ziconotide associated with morphine and ropivacaine for patients resistant to a conventional approach, with nociceptive, neuropathic, or mixed pain.

These clinical cases were conducted with patients suffering from refractory pain, more than 6/10 on a numerical pain rating scale (NPRS) while on high-dose medical treatment and/or intolerance with significant side effects from oral medication. The baseline study visit included a physical examination and an assessment of pain intensity on a NPRS. Under general anesthesia, a neuronavigation device was used to place the catheter on the floor of the third ventricle, supported by an endoscope. Then, drugs were injected in the cerebroventricular system, through a pump (external or subcutaneous). The primary objective was to measure pain evaluation with ICV treatment after a complete withdrawal of other medications.

Four patients were enrolled: 3 with intractable cancer pain and one with central neuropathic pain. The median NPRS at baseline was 9.5 [8.5; 19]. The mean NPRS after one month was 3.5 [3; 4.5]. Ziconotide was initiated at 0.48 µg/dy and up to a median of 1.2 µg/dy [1.0; 1.56]. The median dose of morphine and ropivacaine used initially was respectively 0.36 mg/dy [0.24; 0.66] up to 0.6 mg/dy [0.45; 4.63] and 1.2 mg/dy [0; 2.4] up to 2.23 mg/dy [1.2; 3.35]. Minor side effects were initially observed but transiently. One psychiatric agitation required discontinuation of ziconotide infusion.

For intractable pain, using ziconotide by intracerebroventricular infusion seems safe and efficient, specifically for chronic neoplastic pain of cervicocephalic, thoracic, or diffuse origin and also for pain arising from a central neuropathic mechanism.

Key words: Intracerebroventricular infusion, ziconotide, intractable pain, nociceptive and neuropathic pain

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In 1963, Ommaya published about a new device: a subcutaneous reservoir for sterile access to ventricular cerebrospinal fluid (1). Its first use was only for managing patients with meningitis. In 1973, the identification of opiate receptors in the brain (2,3) and then in the spinal cord (4) had opened up a new way for pain treatment.

Intracerebroventricular (ICV) drug delivery is a direct administration of drugs, especially morphine, into the intraventricular cerebrospinal fluid (CSF). This targeted drug delivery provides deep and sustained analgesia with very small doses. Some case reports and studies have been published since 1982, after the initial study of Leavens et al (5). All of them showed great pain relief with few side effects (5-32). At the same time as the ICV route emerged, intrathecal was

developed with the same results (for the same type of patients) (18,25). Less invasive and easier to apply, intrathecal therapy has grown quickly to the detriment of the ICV route. Moreover during the 90s, with the development of long-acting opioids and the emergence of breakthrough pain treatment, it became increasingly possible to treat intractable pain with a single therapy be it oral, transcutaneous, or transmucosis administration.

Nevertheless, 10 to 20% of patients present with refractory cancer pain (33), and in Europe in 2007, EPIC reported that 31% of patients with cancer pain (moderate to severe) don't have therapy for pain; 82% with a therapy reported they had breakthrough pain even so (34). With regards to neuropathic pain, a systematic review published in 2014 found that the prevalence rates of neuropathic pain as a global clinical entity ranged from 1 to 17.9% (35). Especially for central post-stroke pain, in a population-based study published in 2011, 34% of the population studied report a pain increased with no pain relief whatsoever (36).

In 2000 in order to control intractable pain, a new step was proposed to the 3-step ladder established in 1986 by the World Health Organization (37,38). This fourth step includes all interventional therapies like surgery, radiotherapy, interventional radiology, and targeted drug delivery. In this context, a new drug was introduced in 2004, in order to improve pain relief: ziconotide (39). Ziconotide, a highly basic peptide of about 25-residues, exerts a physiological effect, blocking N calcium voltage dependent channels (40). In fact, N calcium channels are expressed at high density on the central terminals of primary afferent neurons that terminate in the dorsal horn of the spinal cord (41). This area is important for processing pain. That's why after binding of ziconotide on N calcium channels in the dorsal horn, calcium influx into the nerve terminal is blocked, thereby reducing release of pain-relevant neurotransmitters from the primary afferent nerve terminals into the synaptic cleft. Ziconotide was introduced as a first line therapy, using an intrathecal route, for the management of pain (42), be it nociceptive or neuropathic.

Intrathecal therapy is not an option for patients with cephalic or diffuse refractory pain, as diffusion of intrathecal treatment is limited to the tip of the catheter (43-45). So, for them, ICV treatment seems the only suitable option.

Ziconotide was never used for ICV therapy but N type calcium channel receptors distribution is certainly ubiquitous. Studies in vivo on mice show a larger amount around the third ventricle (46,47). Moreover morphine and ziconotide have a synergic effect when they are used intrathecally (48,49) with lower rate of adverse effects (50).

We present here our experience of ziconotide ICV therapy associated with other drugs for patients resistant to a conventional approach.

Methods

These clinical cases were conducted from February 2011 through July 2015 in the neurosurgery department of Angers university Hospital in cooperation with the anesthesiology and pain department of the Institut de Cancérologie de l'Ouest-Paul Papin (ICO-PP), France. The primary objective was to measure pain relief of ICV therapy by a numerical pain rating scale (NPRS). The secondary objectives were to evaluate the adverse effects and consumption of analgesic drugs with ICV therapy. All patients gave informed written consent prior to implantation for use of off-label drugs. The local institutional review board approved the study.

Patient Selection

ICV therapy selection of patients was based on strict clinical criteria: intractable pain rated above 6/10 on a NPRS while on high-dose medical treatment and/or significant side effects from using oral medication. Pain could be either central neuropathic pain, cancer pain from head or neck, or diffuse malignant pain. Exclusion criteria consisted of coagulation disturbances, cutaneous infection, and septicemia. A multidisciplinary meeting was held to select eligible patients and all available interventional techniques like neurolytic blocks, radiofrequency, vertebra cementoplasty, and surgical interruption of the nociceptive pathways were considered. Selected patients attended an information consultation.

The baseline study visit included a physical examination and an assessment of pain intensity on an 11-level NPRS (0, no pain; 10, worst pain imaginable).

Before implantation, a computed tomography (CT) brain scan was carried out to determine the cerebral ventricle's size, and for neuronavigation device use.

Implantation Technique

In the operating room, the patient was under general anesthesia, with Mayfiel headrest. Patient position: supine, head midline, neck flexed 5°. A neuronavigation device (BrainLab ® Vector Vision 2) was used for

accurate third ventricle localization. A classic ventricular catheterization was made with Kocher's point (preferably placed in the right frontal region). A rigid endoscope was inserted perpendicular to brain surface to a depth of 5 – 7 cm. The interventricular foramen was viewed and the catheter (Medtronic ® model 8731 SC, 8780 or 8781) was introduced along the endoscope and its tip placed on the floor of the third ventricle (Fig. 1). Then, the catheter was tunneled subcutaneously from the bur hole to a subcutaneous pump using a connector if necessary. After verification of CSF flow, the catheter was linked up. When life expectancy was superior to 3 months, an internal pump (SynchroMed II, by Medtronic ® USA) was implanted, usually under the right abdominal skin. Both 20 mL (ref 8637) and 40 mL (ref 8637) versions of the pump were used according to the patient morphology and dosage. When life expectancy was less than 3 months, an external pump was linked up to a thoracic subcutaneous port (BardPort, Bard France, Ref.060224CE). A systematic x-ray control was realized (Fig. 2) at the end of the procedure.

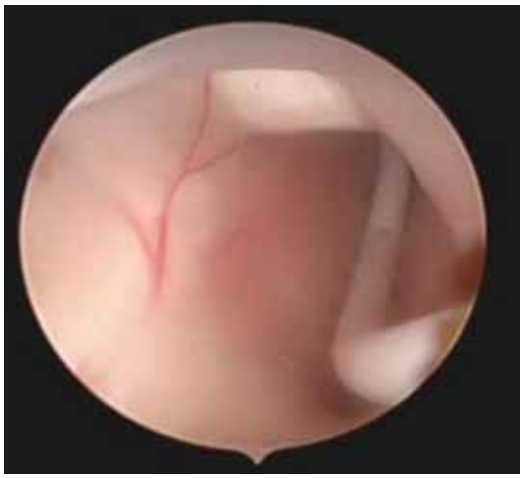

Fig. 1. *Catheter positioning in the third ventricle by endoscopic device.*

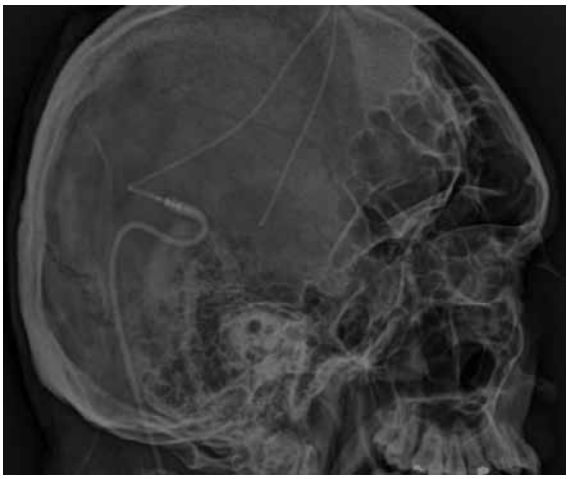

Fig. 2. *Systematic x-ray control.*

Drugs

Armed with past studies about synergic efficiency, we chose ziconotide and morphine in combination for the intrathecal route (50,51). Ziconotide also antagonizes N-type calcium channels of the cerebral cortex and the neurohypophysis, but not the neuromuscular junction (52,53). Local anesthetics have already been used with success by an intracisternal route to manage intractable cancer pain (54), even though there is no data on ICV use.

Studies show that local anesthetics metabolites produce central analgesia due to a dual action: agonist at inhibitory glycine receptor (whose blocking induces pain) and co-agonist at excitatory N-methyl-D-aspartate (NMDA) receptors (whose stimulation have an analgesic effect) (55).

Bupivacaine is generally preferred because of its long duration of action but is not available in France in the high concentrations required for intrathecal or ICV administration, and we consequently use ropivacaine instead.

Given the literature data and safety concerns, we decided to use a conversion ratio of 1/1000 for morphine and, without any previous reference, we started at a dose of 0.5 µg/d for ziconotide and 2.5 mg/d for ropivacaine.

The prescription was established with the help of software (anathec®). Then, the prescribed drug mixtures were prepared under a laminar flow hood at the centralized hospital pharmacy of the ICO-PP with a systematic prospective dosage of each drug since 2013 (51) and was then packaged in a sterile sachet.

Analgesic ICV Titration

After surgery, patients remained 24 hours in the intensive care unit of the neurosurgery department, and then, they were monitored for 48 hours in the intensive care unit at ICO-PP in order to start ICV therapy titration and to withdraw other treatments (oral, subcutaneous, intravenous).

Slow administration was carried out with a 1 mL/d flow rate for internal pumps and 4.8 mL/d for external pumps, in order to test the efficiency, the first dose was respectively 1/1000 of oral morphine equivalent for morphine. Despite the lack of data in the literature, for ziconotide we chose to initiate treatment at 0.5 µg/d or less and for ropivacaine 2.4 mg/d. Boluses were authorized during the titration phase under medical control. The level of bolus was 1/10 of daily dose, just to 10 times per day with a refractory period of one hour. After the titration phase, patients were discharged to home.

Evaluations

During the titration phase, evaluations were performed daily, and then we visited the patient at each pump refill. The same numerical pain scale was used as at baseline to assess pain intensity based on the most severe pain experienced within the last 24 hours. We also recorded the complications related to the ICV therapy such as meningitis, ventriculitis, shift in pump orientation, cutaneous infection, and catheter migration. In addition, we checked side effects due to treatment (drowsiness, confusion, mood disorders, visual disorders, vertigo, nausea, Creatine Kinase elevation, urinary retention, hypotension, memory impairment, dizziness, respiratory depression, miosis), according to the Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0.

Statistical Analysis

Results were collated in an Access 2013 database (Microsoft Corporation, Redmond, WA) and were analyzed using the statistical software Winstat 7.0 (R.Fitch Software, Chicago, IL). All data are presented as median and interquartile ranges.

Results

Four patients with intractable pain were recruited. Two men and 3 women, all Caucasians. Mean age was 61 (± 10) years. Cancer was the diagnosis for 3 patients and neuropathic pain for the other one (Table 1). The time of intractable pain before ICV therapy ranged from 8 to 12 months. The intractable pain was due to mouth cancer, breast cancer with extensive cutaneous metastasis, skull base meningioma (WHO grade III, anaplastic meningioma) for cancer patients, and cerebral vascular stroke (left thalamic nuclei) for the other one.

The topography and type of pain were different for each patient. The patient with mouth cancer suffered from neck, upper limb, and thorax mixed pain; diffuse mixed pain for the patient with extensive breast cancer. Pain for the patient with meningioma was localized in the head, nociceptive behind the right eye and neuropathic pain in the homolateral trigeminal area. The patient with a cerebral vascular stroke suffered from central neuropathic pain situated in the whole contralateral hemi body.

Median oral equivalent morphine (OEM) daily level at baseline, before surgery, was 1200 mg/d [720; 2400] for the 3 patients with cancer (details in Table 1). For the fourth one (neuropathic pain), his treatment before surgery is described in Table 1.

The average length of surgery was less than 60 minutes. The average follow-up was 10 months (2 to 18 months).

Efficacy

The pain intensity score on the NPRS significantly decreased from baseline at one, 2, 3, 6, and 18 months after ICV therapy initiation (Table 2). The median NPRS at baseline was 9.5 [8.5; 10]. The median NPRS after one month was 3.5 [3; 4.5]. At the third month and at the last follow-up, for each patient, the NPRS was 3/10.

All patients could be discharged.

Dosages Used

Table 1. *Baseline characteristics of the patients.*

Patient	Age	Sex	Type of pathology	Pain localization	Treatment
1	65	M	Cancer (mouth) (nociceptive and neuropathic pain)	head	EMO: 1200 mg/d
2	51	F	Cancer (breast) (nociceptive and neuropathic pain)	diffuse	EMO: 3600 mg/d
3	60	F	Meningioma (skull base) (neuropathic pain)	head	EMO: 240 mg/d Pregabaline 300 mg/d
4	71	M	Cerebral Vascular Stroke (neuropathic pain)	Diffuse	Gabapentine: 2400 mg/d Lamaline: 6 cap/d

Table 2. *NPRS for each patient.*

Patient	D0	D10	D30	M2	M3	M4	M5	M6	M12	M18
1	10	3	4	5	dead	dead	dead	dead	dead	dead
2	10	8	6	2	3	3	dead	dead	dead	dead
3	9	4	3	3	3	3	dead	dead	dead	dead
4	7	5	3	3	3	3	2	3	3	3
median	9.5	4.5	3.5	3	3					

Table 3. *Dosages of each medication.*

MORPHINE (mg/dy)		**10 days**	**30 days**	**2 months**	**3 months**	**4 months**	**5 months**	**6 months**	**12 months**	**18 months**
Patient 1		1.2	4.5	5	-	-	-	-	-	-
Patient 2		0.48	6.24	6	8.64	8.64	-	-	-	-
Patient 3		0.24	0.08	0.1	0.15	0.35	-	-	-	-
Patient 4		0.24	0.48	0.5	0.5	0.6	0.6	0.6	0.9	1
	median	0.36	2.49	2.75	0.5	0.6	0.6	0.6	0.9	1
	quartile 1	0.24	0.38	0.4	0.325	0.475				
	quartile 3	0.66	4.935	5.25	4.57	4.62				
ZICONOTIDE (µg/dy)		**10 days**	**30 days**	**2 months**	**3 months**	**4 months**	**5 months**	**6 months**	**12 months**	**18 months**
Patient 1		0.48	0.5	0	0	-	-	-	-	-
Patient 2		0.48	1.68	1.44	1.8	1.92	-	-	-	-
Patient 3		0.48	0.5	0.24	0.35	0.7	-	-	-	-
Patient 4		0.48	0.96	1	1	1.2	1.2	1.3	1.9	2
	median	0.48	0.73	0.62	0.675	1.2	1.2	1.3	1.9	2
	quartile 1	0.48	0.5	0.18	0.2625	0.95				
	quartile 3	0.48	1.14	1.11	1.2	1.56				
ROPIVACAINE (mg/dy)		**10 days**	**30 days**	**2 months**	**3 months**	**4 months**	**5 months**	**6 months**	**12 months**	**18 months**
Patient 1		0	1.92	2.2	2.2	-	-	-	-	-
Patient 2		2.4	8.16	6	4.8	4.3	-	-	-	-
Patient 3		0	0	0	0	0	-	-	-	-
Patient 4		2.4	2.4	2.4	2.4	2.4	2.4	2.4	1.8	1.8
	median	1.2	3.12	2.65	2.35	2.233333	2.4	2.4	1.8	1.8
	quartile 1	0	1.44	1.65	1.65	1.2				
	quartile 3	2.4	3.84	3.3	3	3.35				

For ICV administration: ziconotide was always used in combination. The introduction dose was at median 0.48 µg/d [0; 0] up to 1.2 µg/d [1.0; 1.56].

Median initial morphine dose was 0.36 mg/d [0.24; 0.66] up to 0.6 mg/d [0.45; 4.63], based upon 1/1000 of median OEM daily level at baseline. In fact, the median initial ratio between OEM and ICV doses was 0.001 [0.0005; 0.001] and up to 0.002 [0.001; 0.003].

Ropivacaine was used for only 3 patients. Median initial dose was 1.2 mg/d [0; 2.4], and at the end of the follow-up 2.23 mg/d [1.2; 3.35].

The dosages for every medication used are listed in Table 3.

Only ICV therapy was used for all patients, no more oral, transcutaneous, or transmucosis drugs.

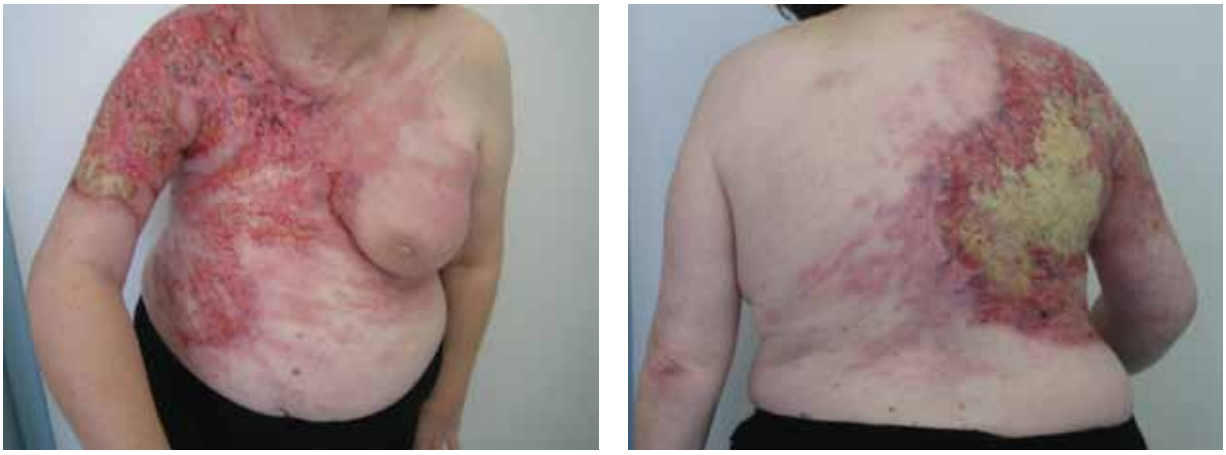

Fig. 3. *Extensive cutaneous metastases, patient 3.*

Safety

Nausea and vomiting (grade 2 according to the CTCAE) were initially reported but always transiently. Drowsiness and respiratory depression were observed (grade 1 CTCAE) only for patient 3, at the fifteenth day, 48 hours after the last dose increase, completely resolved after decreasing ICV dosage (for a good pain relief). No miosis, no urinary retention, and CK elevation were reported. One ziconotide side effect was observed (psychiatric agitation) at a level of 0.96 µg/d. This behavior disorder happened at the final stage of patient's illness and can therefore not be attributed with certainty to ziconotide. However ziconotide was discontinued. Morphine and ropivacaine remained. The patient died 3 days later of cataclysmic hemorrhage.

No infection (local or ventriculitis), no hematoma (cerebral or subcutaneous), and no CSF fistula were observed.

Follow-up

For patient 1 with mouth cancer, life expectancy was superior to 3 months, so an internal pump was implanted. But, he died due to a carotid tumor invasion, which lead to a cataclysmic hemorrhage, 2 months after the surgery.

For patient 2 with breast cancer and extensive cutaneous metastases, life expectancy was estimated at less than 3 months (Fig. 3). Lumbar percutaneous access was not available due to cancer progression. She was discharged with good pain relief (NPRS < 3), 5 days after surgery. She remained at home for 3 months and died in a palliative care unit 4 months after implantation.

For patient 3 with anaplastic meningioma, life expectancy was more than 3 months, so an internal pump was also implanted. She died due to the tumor evolution, 4 months later.

Patient 4 with central neuropathic pain is still alive after 18 months. At the last follow-up evaluation, NPRS was 3 without any oral treatment.

Dosages of ICV drugs used for patients are summarized in Table 3.

Discussion

ICV therapy provides significant pain relief in patients with severe, refractory head, upper limb, thorax, or diffuse pain when other medical and surgical therapies have failed. Moreover, sometimes, spinal intrathecal administration via a lumbar access is contraindicated due to skin evolution of the disease (patient 2). This observational study adds to the existing literature on the successful use of ICV therapy for management of intractable pain 56).

In these 4 patients suffering from intractable chronic pain despite systemic treatment with high level of opioids (median OME 1200 mg/d) we obtained good pain relief with low doses of morphine (0.35 to 8.64 mg), ziconotide (0.5 to 1.92 µg), and ropivacaine (1.8 to 4.3 mg) using ICV administration. The pain relief was effective regardless of the pain location (NPRS ≤ 3), as is perfectly illustrated by patient 2. All authors have reported this efficiency; our results are consistent with previous studies (Table 4).

Clinical practice of ICV therapy is spotty, although some reviews have highlighted great efficiency (22,56,57). Our observational study shows that ICV

therapy is a credible option for patients suffering from neuropathic central pain or intractable cancer pain. Most past studies used a daily bolus by the Ommaya device. The internal pump and continuous infusion used here probably allow more stable pain relief with fewer adverse events due to high ICV concentration and less risk of infection than with daily boluses.

Ziconotide

Our study shows that ICV ziconotide administration is feasible and can be used for long-term therapy. This is the first ICV utilization. Although ziconotide is authorized for intrathecal use only, it should be logical to use it for ICV therapy owing to the N-type high-voltage calcium channels brain distribution. Cav2.2, subunit specific for the N-type calcium was primarily described with a main location in dendritic shafts and in presynaptic terminals making synapses on the dendrites (58), then in astrocytes (cortical white and grey mater) playing an important role in glia–neurone communications (59,60).

The association of morphine and ziconotide probably provides a synergic effect, with lower doses of each drug preventing side effects. (48,51,61-63).

The molecule moves rostral up the neuraxis and reaches the brain. Neurological side effects, such as dizziness, confusion, ataxia, abnormal gait, memory impairment, nystagmus, or hallucinations are a consequence of the central effect of ziconotide (64). But there is no evidence on central ziconotide effect on pain relief.

The computer assisted prescription, the preparation by pharmacy technicians under laminar flow hood, and prospective drugs dosage help to produce accurate mixtures and so, probably decrease the rate of side effects, because of the low dose of ziconotide required for this technique.

Table 4. *Literature review.*

Publications		*number of patients*	efficiency			
			excellent	good	partial	poor
Lee DJ	2014	***6***	100%			
Adolph MD	2010	***1***		comfortable		
Smith MT	1999	***14***	nd	nd	nd	nd
Karavelis A	1996	***90***	68%	14%	13%	5%
Seiwald M	1996	***20***	70%		15%	15%
Lazorthes YR	1995	***82***	80%		18%	2%
Loriferne JF	1995	***1***	nd	nd	nd	nd
Cramond T	1993	***52***	100%			
Candrina R	1992	***5***	100%			
Lajat Y	1992	***63***	75%		20%	5%
Sandouk P	1991	***7***		60%	40%	
Lu S	1991	***28***	74%	22%	4%	
Houdek M	1990	***5***	100%			
Reeve WG	1990	***2***	100%			
Lee TL	1990	***1***	100%			
Dennis GC	1990	***7***		83%	17%	
Blond S	1989	***79***	75%	20%		5%
Carlisle SW	1989	***1***		100%		
Lazorthes Y	1988	***55***		94%		
Lazorthes Y	1988	***51***	94%			
Weigl K	1987	***8***	nd	nd	nd	nd
Madrazo I	1987	***1***	90%			
Obbens EA	1987	***20***	65%			35%
Kock-Jensen C	1987	***nr***	nd	nd	nd	nd
Su C.F	1987	***8***	87%	13%		
Caputi CA	1986	***nr***	nd	nd	nd	nd
García-March G	1986	***nr***	nd	nd	nd	nd
Lazorthes Y	1985	***18***	89%			
Thiebaut JB	1985	***nr***	nd	nd	nd	nd
Lenzi A	1985	***38***	63%	32%	3%	2%
Nurchi G	1984	***6***	100%			
Roquefeuil B	1984	***8***	80%	20%		
Lobato RD	1983	***11***	73%	27%		
Roquefeuil B	1983	***8***	75%	13%	12%	
Leavens ME	1982	***4***	75%	25%		

nd : not describe

Morphine and Ropivacaine

Before, in most studies, only morphine was used for ICV infusion (6-16,18-21,23-32,65-71). Some anecdotal case reports were published with octreotide, somatostatine, ocytocine, vasopressine, and angiotensine (72,73). Contrary to well-founded fears, the risk of central drug side effects, especially respiratory depression, is low. We observed it only for one patient related to increasing dosage, completely resolved after decreasing it, still with pain relief. Drowsiness, sedation, and digestive disturbance are also rare, like in the literature 22,56). High-dose oral or parenteral morphine is often complicated by high plasma concentrations of metabolites, producing side effects. By contrast, ICV bypasses this metabolism, and decreases central effects.

Regarding to ropivacaine, we chose to use it, like for intrathecal and cisternal therapy (49,54,74,75). In addition, local anesthetics can induce global anesthesia after systemic administration of rather low doses. So, we chose it for the analgesic mixture, wishing to potentiate the global analgesic effect, already described for morphine and ziconotide. But further studies are required to evaluate the efficiency of the twosome, morphine/ziconotide, and compare this combination with ropivacaine.

Catheter Position

We decided to place the tip of the catheter on the floor of the third ventricle for several reasons. First, ziconotide is a selective blocker of N-type voltage sensitive calcium channels, and their distribution is certainly ubiquitous but studies in vivo on mice show a larger amount around the third ventricle (46,47). Moreover, the highest density of opiate receptors has been described close to the mesencephalic aqueduct and periaqueductal gray (76-80). In 1988, Lazorthes et al (19), in his series of 51 patients, described a significant correlation between the exact position of the catheter and feeling effective analgesia. Due to the small size of the ventricle in those patients, neuronavigation was helpful in combination with ventriculoscopy for catheter positioning.

It's worth to point that a new intrathecal catheter (ascenda® MEDTRONIC) allows a percutaneous placement of the tip just to the cisterna magna 54) and could be an alternative to the ICV therapy due to an easier procedure. Lumbar percutaneous placement is obviously less invasive but needs to be evaluated, particularly if the placement in the cisterna magna is as effective as in the third ventricle. But, this implies there are no CSF flow obstacles along the spinal cord.

Technologically, ICV therapy requires a medical team, available 24 hours a day, 7 days a week, for the filling and managing the potential concerns linked to the pump and/or side effects. ICV therapy can't be used routinely and calls for a hospital background with physicians and pharmacists to avoid mistakes.

Obviously, 4 cases are not enough to demonstrate the superiority of the ICV therapy using ziconotide in combination with other drugs like morphine and ropivacaine, but results are promising and require further researches.

Limitations

The limitations of this study include the observational type and a very small sample of patients not statistically powerful. The study is mono-centric. Our results do not produce a reliable efficiency of those drugs but aim to prepare for a wider multi-centric study.

Furthermore all tests to detect side effects were not achieved (no cognitive evaluation before and during the therapy). They should be made in order to authorize ziconotide ICV use.

In studies about ziconotide side effects, the central nervous system can be evaluated with clinical examinations (64) (agitation, hallucination, nystagmus, dysmetria, ataxia, nausea, vomiting) but memory impairment or cognitive deficits can never be objectively assessed (64,81,82).

Conclusion

According to these 4 cases, ICV administration with analgesic mixtures seems efficient for intractable pain (nociceptive, neuropathic, or mixed pain). To our knowledge, it is the first utilization of ziconotide. Moreover, we describe no more side effects than by intrathecal infusion.

Then, association with morphine probably decreases the mixture drugs' dosages for the same pain relief, and so, restricts both side effects.

At last, ICV therapy by continuous injection acts as a security feature due to the decreasing mixtures' concentration whose high dosages can produce important central outcomes.

Nevertheless, this analgesic mixture ICV injection needs to be evaluated by a prospective clinical trial in order to establish the real efficiency, in particular versus placebo. And, it will be probably interesting to compare this ventricular direct access to a percutaneous lumbar one getting to the cisterna magna.

References

1. Ommaya A. Subcutaneous reservoir and pump for sterile access to ventricular cerebrospinal fluid. *The Lancet* 1963; 282:983-984.
2. Atweh SF, Kuhar MJ. Autoradiographic localization of opiate receptors in rat brain. II. The brain stem. *Brain Res* 1977; 129:1-12.
3. Kuhar MJ, Pert CB, Snyder SH. Regional distribution of opiate receptor binding in monkey and human brain. *Nature* 1973; 245:447-450.
4. Atweh SF, Kuhar MJ. Autoradiographic localization of opiate receptors in rat brain. I. Spinal cord and lower medulla. *Brain Res* 1977; 124:53-67.
5. Leavens ME, Hill CS, Cech DA, Weyland JB, Weston JS. Intrathecal and intraventricular morphine for pain in cancer patients: initial study. *J Neurosurg* 1982; 56:241-245.
6. Adolph MD, Stretanski MF, McGregor JM, Rawn BL, Ross PM, Benedetti C. Intracerebroventricular Morphine for Refractory Cancer Pain: Transitioning to the Home Setting. *Am J Hosp Palliat Med* 2010; 27:326-332.
7. Blond S, Guieu JD, Meynadier J, Le Bars D, Wilier JC. Intracerebroventricular morphine, analgesia, and nociceptive spinal reflexes. *The Lancet* 1994; 343:857-858.
8. Blond S, Meynadier J, Dupard T, Assaker R, Brichard C, Christiaens JL, Demaille A. Intracerebroventricular morphine therapy. Apropos of 79 patients. *Neurochirurgie* 1989; 35:52-57.
9. Caputi CA, Busca G, Fogliardi A, Rychlicki F, Basili P. Epidural and intraventricular morphine therapy in the treatment of cancer pain. *Minerva Anestesiol* 1986; 52:351-355.
10. Carlisle DW, Smith KA, Frank E, Meyers FJ. Intraventricular morphine administered by hospice nurses to a patient with intractable pain. *Am J Hosp Care* 1989; 6:36-39.
11. Cramond T, Stuart G. Intraventricular morphine for intractable pain of advanced cancer. *J Pain Symptom Manage* 1993; 8:465-473.
12. Dennis GC, DeWitty RL. Long-term intraventricular infusion of morphine for intractable pain in cancer of the head and neck. *Neurosurgery* 1990; 26:404-407; discussion 407-408.
13. García-March G, Robaina F, Piquer J, Briz E, del Barrio E, Muriel C, Rodríguez-Hernández JL, Barberá M, Badenes R, de Vera JA, Intraventricular administration of morphine in the treatment of pain of neoplastic origin. Cooperative study. *Rev Esp Anestesiol Reanim* 1986; 33:68-72.
14. Houdek M, Opavský J, Ostrizek J. Intracerebroventricular application of morphine in the treatment of intractable malignant pain. *Acta Univ Palacki Olomuc Fac Med* 1990; 128:101-106.
15. Karavelis A, Foroglou G, Selviaridis P, Fountzilas G. Intraventricular administration of morphine for control of intractable cancer pain in 90 patients. *Neurosurgery* 1996; 39:57-61; discussion 61-62.
16. Lazorthes Y. Intracerebroventricular administration of morphine for control of irreducible cancer pain. *Ann N Y Acad Sci* 1988; 531:123-132.
17. Lazorthes YR, Sallerin BA, Verdié JC. Intracerebroventricular administration of morphine for control of irreducible cancer pain. *Neurosurgery* 1995; 37:422-428; discussion 428-429.
18. Lazorthes Y, Verdie JC, Bastide R, Lavados A, Descouens D. Spinal versus intraventricular chronic opiate administration with implantable drug delivery devices for cancer pain. *Appl Neurophysiol* 1985; 48:234-241.
19. Lazorthes Y, Verdié JC, Caute B, Maranhao R, Tafani M. Intracerebroventricular morphinotherapy for control of chronic cancer pain. *Prog Brain Res* 1988; 77:395-405.
20. Lee DJ, Gurkoff GG, Goodarzi A, Muizelaar JP, Boggan JE, Shahlaie K. Intracerebroventricular opiate infusion for refractory head and facial pain. *World J Clin Cases* 2014; 2:351-356.
21. Lee TL, Kumar A, Baratham G. Intraventricular morphine for intractable craniofacial pain. *Singapore Med J* 1990; 31:273-276.
22. Lobato RD, Madrid JL, Fatela LV, Sarabia R, Rivas JJ, Gozalo A. Intraventricular morphine for intractable cancer pain: rationale, methods, clinical results. *Acta Anaesthesiol Scand* 1987; 31:68-74.
23. Lobato RD, Madrid JL, Fatela LV, Rivas JJ, Reig E, Lamas E. Intraventricular morphine for control of pain in terminal cancer patients. *J Neurosurg* 1983; 59:627-633.
24. Lu SL, Wang JL, Weng RZ, Wang QA. Clinical application of a patient-controlled apparatus for ventricular administration of morphine in intractable pain: Report of 28 cases. *Neurosurgery* 1991; 29:73-75.
25. Nurchi G. Use of intraventricular and intrathecal morphine in intractable pain associated with cancer. *Neurosurgery* 1984; 15:801-803.
26. Obbens EA, Hill CS, Leavens ME, Ruthenbeck SS, Otis F. Intraventricular morphine administration for control of chronic cancer pain. *Pain* 1987; 28:61-68.
27. Reeve WG, Todd JG. Intraventricular diamorphine via an Ommaya shunt for intractable cancer pain. *Br J Anaesth* 1990; 65:544-547.
28. Roquefeuil B, Benezech J, Batier C, Blanchet P, Gros C, Mathieu-Daude JC. Value of intraventricular morphine analgesia in intractable neoplasm pain. Apropos of 8 cases with self-administration in 4. *Neurochirurgie* 1983; 29:135-141.
29. Roquefeuil B, Benezech J, Blanchet P, Batier C, Frerebeau P, Gros C. Intraventricular administration of morphine in patients with neoplastic intractable pain. *Surg Neurol* 1984; 21:155-158.
30. Sandouk P, Serrie A, Urtizberea M, Debray M, Got P, Scherrmann JM. Morphine pharmacokinetics and pain assessment after intracerebroventricular administration in patients with terminal cancer. *Clin Pharmacol Ther* 1991; 49:442-448.
31. Seiwald M, Alesch F, Kofler A. Intraventricular morphine administration as a treatment possibility for patients with intractable pain. *Wien Klin Wochenschr* 1996; 108:5-8.
32. Weigl K, Mundinger F, Chrubasik J. Continuous intraventricular morphine- or peptide-infusion for intractable cancer pain. *Acta Neurochir Suppl (Wien)* 1987; 39:163-165.
33. Meuser T, Pietruck C, Radbruch L, Stute P, Lehmann KA, Grond S. Symptoms during cancer pain treatment following WHO-guidelines: A longitudinal follow-up study of symptom prevalence, severity and etiology. *Pain* 2001; 93:247-257.
34. Breivik H, Cherny N, Collett B, *et al.* Cancer-related pain: A pan-European survey of prevalence, treatment, and patient attitudes. *Ann Oncol Off J Eur Soc Med Oncol ESMO* 2009; 20:1420-1433.
35. Van Hecke O, Austin SK, Khan RA, Smith BH, Torrance N. Neuropathic pain in the general population: A systematic review of epidemiological studies. *Pain* 2014; 155:654-662.
36. Klit H, Finnerup NB, Andersen G, Jensen TS. Central poststroke pain: A population-based study. *Pain* 2011; 152:818-824.

37. Miguel R. Interventional treatment of cancer pain: The fourth step in the World Health Organization analgesic ladder? *Cancer Control J Moffitt Cancer Cent* 2000; 7:149-156.
38. Ventafridda V, Tamburini M, Caraceni A, De Conno F, Naldi F. A validation study of the WHO method for cancer pain relief. *Cancer* 1987; 59:850-856.
39. Wallace MS. Ziconotide: A new nonopioid intrathecal analgesic for the treatment of chronic pain. *Expert Rev Neurother* 2006; 6:1423-1428.
40. Wermeling DP. Ziconotide, an intrathecally administered N-Type calcium channel antagonist for the treatment of chronic pain. *Pharmacother J Hum Pharmacol Drug Ther* 2005; 25:1084-1094.
41. Schmidtko A, Lötsch J, Freynhagen R, Geisslinger G. Ziconotide for treatment of severe chronic pain. *The Lancet* 2010; 375:1569-1577.
42. Deer TR, Prager J, Levy R, Rathmell J, Buchser E, Burton A, Caraway D, Cousins M, De Andrés J, Diwan S, Erdek M, Grigsby E, Huntoon M, Jacobs MS, Kim P, Kumar K, Leong M, Liem L, McDowell GC 2nd, Panchal S, Rauck R, Saulino M, Sitzman BT, Staats P, Stanton-Hicks M, Stearns L, Wallace M, Willis KD, Witt W, Yaksh T, Mekhail N. Polyanalgesic Consensus Conference 2012: Recommendations for the Management of Pain by Intrathecal (Intraspinal) Drug Delivery: Report of an Interdisciplinary Expert Panel: INTRATHECAL THERAPY CONSENSUS. *Neuromodulation Technol Neural Interface* 2012; 15:436-466.
43. Yaksh TL, de Kater A, Dean R, Best BM, Miljanich GP. Pharmacokinetic analysis of ziconotide (SNX-111), an intrathecal N-Type calcium channel blocking analgesic, delivered by bolus and infusion in the dog: Kinetics of intrathecal ziconotide in dog. *Neuromodulation Technol Neural Interface* 2012; 15:508-519.
44. Bernards CM. Cerebrospinal fluid and spinal cord distribution of baclofen and bupivacaine during slow intrathecal infusion in pigs. *Anesthesiology* 2006; 105:169-178.
45. Flack SH, Bernards CM. Cerebrospinal fluid and spinal cord distribution of hyperbaric bupivacaine and baclofen during slow intrathecal infusion in pigs. *Anesthesiology* 2010; 112:165-173.
46. Saegusa H, Matsuda Y, Tanabe T. Effects of ablation of N-and R-type Ca 2+ channels on pain transmission. *Neurosci Res* 2002; 43:1-7.
47. Xu JH, Long L, Wang J, Tang YC, Hu HT, Soong W and Tang FR. Nuclear localization of Ca v 2.2 and its distribution in the mouse central nervous system, and changes in the hippocampus during and after pilocarpine-induced status epilepticus. *Neuropathol Appl Neurobiol* 2010; 36:71-85.
48. Wallace MS, Kosek PS, Staats P, Fisher R, Schultz DM, Leong M. Phase II, open-label, multicenter study of combined intrathecal morphine and ziconotide: Addition of ziconotide in patients receiving intrathecal morphine for severe chronic pain. *Pain Med* 2008; 9:271-281.
49. Wallace MS, Rauck RL, Deer T. Ziconotide combination intrathecal therapy: rationale and evidence. *Clin J Pain* 2010; 26:635-644.
50. Dupoiron D, Bore F, Lefebvre-Kuntz D, , Brenet O, Debourmont S, Dixmerias F, Buisset N, Lebrec N, Monnin D. Ziconotide adverse events in patients with cancer pain: A multicenter observational study of a slow titration, multidrug protocol. *Pain Physician* 2012; 15:395-403.
51. Dupoiron D, Devys C, Bazin C,Folliard C, Lebrec N, Boré F, Dubois PY, Kieffer H. Rationale for prospective assays of intrathecal mixtures including morphine, ropivacaine and ziconotide: Prevention of adverse events and feasibility in clinical practice. *Pain Physician* 2015; 18:349-357.
52. Pope JE, Deer TR. Ziconotide: A clinical update and pharmacologic review. *Expert Opin Pharmacother* 2013; 14:957-966.
53. Wermeling DP. Ziconotide, an intrathecally administered N-type calcium channel antagonist for the treatment of chronic pain. *Pharmacotherapy* 2005; 25:1084-1094.
54. Appelgren L, Janson M, Nitescu P, Curelaru I. Continuous intracisternal and high cervical intrathecal bupivacaine analgesia in refractory head and neck pain. *Anesthesiology* 1996; 84:256-272.
55. Zeilhofer HU, Schmelz M. Local anesthetics take a central action in analgesia. *Pain* 2015; 156:1579-1580.
56. Ballantyne JC, Carwood CM. Comparative efficacy of epidural, subarachnoid, and intracerebroventricular opioids in patients with pain due to cancer. *Cochrane Database Syst Rev* 2005; CD005178.
57. Raffa RB, Pergolizzi JV. Intracerebroventricular opioids for intractable pain. *Br J Clin Pharmacol* 2012; 74:34-41.
58. Westenbroek RE, Hell JW, Warner C, Dubel SJ, Snutch TP, Catterall WA. Biochemical properties and subcellular distribution of an N-type calcium channel alpha 1 subunit. *Neuron* 1992; 9:1099-1115.
59. Day NC, Shaw PJ, McCormack AL, Craig PJ, Smith W, Beattie R, Williams TL, Ellis SB, Ince PG, Harpold MM, Lodge D, Volsen SG. Distribution of alpha 1A, alpha 1B and alpha 1E voltage-dependent calcium channel subunits in the human hippocampus and parahippocampal gyrus. *Neuroscience* 1996; 71:1013-1024.
60. D'Ascenzo M, Vairano M, Andreassi C, Navarra P, Azzena GB, Grassi C. Electrophysiological and molecular evidence of L-(Cav1), N- (Cav2.2), and R- (Cav2.3) type Ca2+ channels in rat cortical astrocytes. *Glia* 2004; 45:354-363.
61. Alicino I, Giglio M, Manca F, Bruno F, Puntillo F. Intrathecal combination of ziconotide and morphine for refractory cancer pain: A rapidly acting and effective choice. *Pain* 2012; 153:245-249.
62. Webster LR, Fakata KL, Charapata S, Fisher R, MineHart M. Open-label, multicenter study of combined intrathecal morphine and ziconotide: Addition of morphine in patients receiving ziconotide for severe chronic pain. *Pain Med* 2008; 9:282-290.
63. Deer TR, Kim C, Bowman R, Tolentino D, Stewart C, Tolentino W. Intrathecal ziconotide and opioid combination therapy for noncancer pain: An observational study. *Pain Physician* 2009; 12:E291-E296.
64. Penn RD, Paice JA. Adverse effects associated with the intrathecal administration of ziconotide. *Pain* 2000; 85:291-296.
65. Smith MT, Wright AW, Williams BE, Stuart G, Cramond T. Cerebrospinal fluid and plasma concentrations of morphine, morphine-3-glucuronide, and morphine-6-glucuronide in patients before and after initiation of intracerebroventricular morphine for cancer pain management. *Anesth Analg* 1999; 88:109-116.
66. Loriferne JF, Souchal Delacour I, Rostaing S, N'Guyen JP, Bonnet F. Cephalic cancer pain controlled by intraventricular administration of morphine and clonidine. *Ann Fr Anesthèsie Rèanimation* 1995; 14:233-236.
67. Kock-Jensen C, Hole P, Tange M. [Management of pain in cancer patients by intraventricular administra-

tion of morphine]. *Ugeskr Laeger* 1987; 149:2080-2081.

68. Su CF, Liu MY, Lin MT. Intraventricular morphine produces pain relief, hypothermia, hyperglycaemia and increased prolactin and growth hormone levels in patients with cancer pain. *J Neurol* 1987; 235:105-108.
69. Lenzi A, Galli G, Gandolfini M, Marini G. Intraventricular morphine in paraneoplastic painful syndrome of the cervicofacial region: Experience in thirty-eight cases. *Neurosurgery* 1985; 17:6-11.
70. Leavens ME, Hill CS, Cech DA, Weyland JB, Weston JS. Intrathecal and intraventricular morphine for pain in cancer patients: Initial study. *J Neurosurg* 1982; 56:241-245.
71. Choi CR, Ha YS, Ahn MS, Lee JS, Song JU. Intraventricular or epidural injection of morphine for severe pain. *Neurochirurgia (Stuttg)* 1989; 32:180-183.
72. Madrazo I, Franco-Bourland RE, León-Meza VM, Mena I. Intraventricular somatostatin-14, arginine vasopressin, and oxytocin: analgesic effect in a patient with intractable cancer pain. *Appl Neurophysiol* 1987; 50:427-431.
73. Candrina R, Galli G. Intraventricular octreotide for cancer pain. *J Neurosurg* 1992; 76:336-337.
74. Dougherty PM, Staats PS. Intrathecal drug therapy for chronic pain: From basic science to clinical practice. *Anesthesiology* 1999; 91:1891-1918.
75. Kress HG, Simpson KH, Marchettini P, Ver Donck A, Varrassi G. Intrathecal therapy: What has changed with the introduction of ziconotide. *Pain Pract* 2009; 9:338-347.
76. Baumgärtner U, Buchholz H-G, Bellosevich A, Magerl W, Siessmeier T, Rolke R, Höhnemann S, Piel M, Rösch F, Wester HJ, Henriksen G, Stoeter P, Bartenstein P, Treede RD, Schreckenberger M. High opiate receptor binding potential in the human lateral pain system. *NeuroImage* 2006; 30:692-699.
77. Jones AK, Luthra SK, Maziere B, Pike VW, Loc'h C, Crouzel C, Syrota A, Jones T. Regional cerebral opioid receptor studies with [11C]diprenorphine in normal volunteers. *J Neurosci Methods* 1988; 23:121-129.
78. Maarrawi J, Garcia-Larrea L. Imagerie des réecepteurs opioïdes chez l'homme. *Douleur Analgésie* 2009; 22:248-260.
79. Willoch F, Schindler F, Wester HJ,Empl M, Straube A, Schwaiger M, Conrad B, Tölle TR. Central poststroke pain and reduced opioid receptor binding within pain processing circuitries: A [11C] diprenorphine PET study. *Pain* 2004; 108:213-220.
80. Willoch F, Tölle TR, Wester HJ, Munz F, Petzold A, Schwaiger M, Conrad B, Bartenstein P. Central pain after pontine infarction is associated with changes in opioid receptor binding: A PET study with 11C-diprenorphine. *AJNR Am J Neuroradiol* 1999; 20:686-690.
81. Rauck RL, Wallace MS, Burton AW, Kapural L, North JM. Intrathecal ziconotide for neuropathic pain: A review. *Pain Pract* 2009; 9:327-337.
82. Rauck RL, Wallace MS, Leong MS, Minehart M, Webster LR, Charapata SG, Abraham JE, Buffington DE, Ellis D, Kartzinel R; Ziconotide 301 Study Group. A randomized, double-blind, placebo-controlled study of intrathecal ziconotide in adults with severe chronic pain. *J Pain Symptom Manage* 2006; 31:393-406.