DEVELOPMENT OF A PRACTICAL GUIDE TO DRUG THERAPY OF REFRACTORY PAIN IN ADVANCED PALLIATIVE SITUATION.

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BACKGROUND & OBJECTIVE

Complex situations of medical management of refractory pain in patients in advanced or terminal phase of a serious and incurable disease and development of home care have led the French Agency for Sanitary Safety of Health Products to develop recommendations on how to use eight classes of drugs outside their Marketing Authorization.

Our work is to provide a guide to regulate off-label use of these drugs often reserved for hospital use or restricted prescription as unknown by the –hospital health professionals or non-specialist who often called for assistance.

MATERIAL & METHOD

A multidisciplinary working group (specialists in palliative care, pharmacists and paramedics) was established to develop practical guide for using these drugs. This booklet is a tool for the prescribing, dispensing and administration of these products. After validation by the Committee against Pain and the Committee of Drug, this guide will be disseminated to doctors and nurses at the Hospital of Pau, but also to non-hospital doctors, paramedics and pharmacists through the local network of palliative care and various continuing education sessions.

RESULTS

	Context	Administration	Brand Name	Availability	Prescriber	Dosage	Side effects	Surveillance
Local anesthetics	**Pain refractory to morphine** used alone by epidural and/or in case of intolerance to opioids	Epidural	**Bupivacaïne®** 2,5mg/ml - flacons of 20ml 5mg/ml - flacons of 20ml **Lévobupivacaïne (Chirocaïne®)** 0,625 - 1,25mg/ml - solution 100-200ml 2,5 - 5mg/ml - amp 10ml	**Hospital**	Initiation by hospital staff trained in pain. Continued at home after 72 hours if stable via the doctor.	12,5 to 18,5 mg/h (400mg max a day) 12,5 to 18,75mg/h continuous flow	Hypotension, nausea, headache, paresthesias.	Regularly to prevent an engine block, sympathetic blockade
		Intrathecal	**Ropivacaïne (Naropéine®)** 2mg/ml - amp 10-20ml - solution 100-200ml 7,5 - 10mg/ml - amp 10-20ml			12 to 25 mg/24h continuous flow		
	In the final intention in refractory pain after treatment failure and adjuvants suitable opioids (antidepressants, anticonvulsants, ketamine)	Parenteral (IV)	**Lidocaïne injectable (Xylocaine®)** 5-10-20mg/ml - amp 10-20ml	**City**	Agreement cardiologist	5 mg/kg/d in continuous intravenous infusion max dose = 8 mg/kg/d	Nervousness, agitation, nystagmus, logorrhea	Mouth numb, headache
	wounds ulcers - skin pain (nodules or necrotic metastases cut) **Neuropathic pain focused**	Topical	**Lidocaïne-prilocaïne cream (Emla®)** **Lidocaïne plaster (Versatis®)**	**City**		1 to 2 g/10 cm2 (<10g) Maximum 3 by 12h/24h on healthy skin	Erythema, pallor at the application point	Risk of resorption faster and more important if lesion
Fentanyl, sufentanil	**Intractable pain, in case of failure or intolerance to morphine and oxycodone parenteral**	Parenteral (IV or SC)	**Fentanyl®** 50µg/ml - amp 2-10ml **Sufentanil (Sufenta®)** 5µg/ml - amp 2-10ml 50µg/ml - amp 5ml	**Hospital**	Initiation by hospital staff trained in pain and continued home via the doctor with PCA. Prescription limited to 7 days.	PCA: hourly dose in one time + reRespiratory rateactory period of 10min in IV and 15-20min in SC	respiratory depression, apnea, bradycardia, hypotension	Vigilance, Respiratory rate (risk: respiratory depression)
Ketamine	**Refractory pain in combination with a mixed opioid therapy** when it is inadequate or poorly tolerated (the addition of ketamine to reduce opioid doses). The use of ketamine for **pain treatment** may be considered after failure of standard therapy (opioids, nitrous oxide), and if general anesthesia in an operating room can be organized	Parenteral (IV or SC)	**Ketamine®** 10mg/ml - amp 5ml 50mg/ml - amp 5ml	**Hospital**	Initiation by hospital staff trained in pain and continued home via the doctor with PCA.	IV: 0,5 mg/kg/d in continuous titrated every 24h with dosage increments of 0,25 mg /kg/d or discontinuous SC: same doses (if no IV access) PO: dilute IV ampoules in a glass of water (same doses)	doses dependents : Mind-altering disorders, respiratory depression, HTA	For 2 hours at each dose change and then every 4 hours. Effectiveness, intolerance, Drowsiness, Respiratory rate ? Mind-altering effects
		Per os	Magistral preparation: oral solution					
MEOPA	**Analgesia care painful** when administered repeatedly, may be beyond the 15 days, depending on the efficacy observed and the condition of the patient	Inhalation	Shell white + blue stripes horizontal and vertical	**City**	Professional use	Do not exceed 15 days if prolonged administration (beyond possible depending on the effectiveness and the patient's condition)	Nausea, vomiting, headache, agitation and sedation	Dependence, regular airing of local and mobile bottle. Only during a treatment.
Methadone	**Last resort after opioid rotation** and adjuvant therapy well conducted	Per os	**Methadone®** Syrup : 5 mg/3,75 ml - 10 mg/7,5 ml - 20 mg/15 ml - 40 mg/15 ml - 60 mg/15 ml capsules : 1-5-10-20-40mg	**City**	Initiation by hospital staff trained in pain. Continued from home via the doctor. Renewed by general practitioner if retrocession hospital. Prescription limited to 7 or 14 days.	Protocol conversion of opioids to methadone. Dosage based on side effects Child : 1mg/kg potential lethality if not dependent on opioids	Drowsiness and Respiratory rate	Assessment of pain, cardiovascular monitoring (ECG), clinic, electrolytic. Caution, releasing between 4th and 6th day
Midazolam	**Terminal sedation for distress in first-line**, given its rapid onset of action and its short duration of action. Analgesic treatment should be maintained and adapted, **midazolam with no analgesic**	Parenteral (IV or SC) Per os	**Midazolam (Hypnovel®)** 1mg/ml - amp 5ml 5mg/ml - amp 1-10ml	**Hospital**	Initiation by hospital staff trained in pain. Continued from home via the doctor.	SC: 0,01 to 0,05 mg/kg according to weight and effect wanted IV: same dose VO: ampoule IV (same doses)	Drowsiness, rash, urticaria, pruritus	respiratory depression: deep or apnea (Antidote: flumazenil possible in IV, IM, SC). For a care: Surveillance every 15' for 1st hour then 2 times/day
Morphine	**Pain rebels to high doses of opioids** administered by other routes of administration (oral, parenteral, transdermal) or therapeutic rapid escalation **Uncontrolled side effects of opioids** administered by other routes of administration (oral, parenteral, transdermal)	Perimedullar Intracerebro-ventricular	**Morphine®** 1mg/ml - amp 1ml 10mg/ml - amp 1-5ml 20mg/ml - amp 1-5ml 40mg/ml - amp 10ml 50mg/ml - amp 5-10-20ml	**City**	Initiation by hospital staff trained in pain. Continued from home via the doctor. Prescription limited to 7 or 28 days.	IV: 10 mg Epidural: 1 mg Intathecal: 0,1 to 0,5 mg Intracerebroventricular: 0,01 to 0,05 mg	Drowsiness, nausea, vomiting, constipation, sedation, dependence	Puncture point, skin (risk of infection), vigilance, Respiratory rate
Propofol	**Last resort in the terminal sedation, on failure of midazolam**	Parenteral (IV)	**Propofol (Diprivan®)** 10mg/ml - amp 20-50ml 20mg/ml - amp 50ml	**Hospital**	Reserved for hospital use on the advice of an anesthetist. No use at home. Drug of last resort.	IV: 0,5 mg/kg/h, dosage increments of 0,5 mg/kg/h	Systemic effects, bradycardia, hypotension, apnea, nausea, vomiting	Regular clinic assessment.

CONCLUSION

We hope this tool will provide assistance to every professional affected y palliative situations in hospital and at the patient's home. We will conduct a satisfaction survey of the different users in order to make improvements if necessary.

-Poster n°CPC085 – 17th EAHP Congress – Milan, 21-23 March 2012, Italy.