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ORIGINAL ARTICLE

Validated chromatographic method for the simultaneous determination of eight drugs (morphine, ropivacaine, bupivacaine, baclofen, clonidine, sufentanil, fentanyl and ziconotide) for intrathecal analgesia

Validation d'une méthode chromatographique pour le contrôle des préparations intrathécales à base de 8 molécules (morphine, ropivacaïne, bupivacaïne, baclofène, clonidine, sufentanil, fentanyl et ziconotide)

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KEYWORDS
Intrathecal analgesia;
Morphine;
Ropivacaine;
Bupivacaine

Summary Intrathecal analgesia has increased over the past two decades in various indications: chronic refractory pain from cancerous or non-cancerous origins, spasticity. These different indications involve the use of different molecules alone or in combination such as morphine, ropivacaine, bupivacaine, fentanyl, sufentanil, clonidine, baclofen and ziconotide. Pump refills are prepared at the pharmacy under a laminar flow hood. An analytical control

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Baclofen;
Clonidine;
Sufentanil;
Fentanyl;
Ziconotide;
UPLC-UV

should be carried out before release of the preparation. A new method of analytical control by chromatography has been developed and validated according to the International Conference on Harmonization guideline in order to secure the production process.

MOTS CLÉS
Analgésie intrathécale ;
Morphine ;
Ropivacaïne ;
Bupivacaïne ;
Baclofène ;
Clonidine ;
Sufentanil ;
Fentanyl ;
Ziconotide ;
UPLC-UV

Résumé L'analgésie intrathécale a considérablement augmenté au cours des 20 dernières années dans diverses indications : douleur chronique réfractaire d'origine cancéreuse ou non cancéreuse, spasticité. Ces différentes indications impliquent l'utilisation de molécules diverses et variées telle que la morphine, ropivacaïne, bupivacaïne, fentanyl, sufentanil, clonidine, baclofène et ziconotide. Les recharges de pompes intrathécales sont préparées à la pharmacie sous une hotte à flux laminaire. Un contrôle analytique de ces préparations doit être réalisé avant la libération. Une nouvelle méthode de contrôle analytique par chromatographie liquide a été développée et validée selon les recommandations internationales dans le but de garantir une préparation conforme.

Introduction

For 30 years, the treatment of pain in cancer remains a major and unresolved challenge. French studies find a prevalence of 53 to 57% of painful patients in oncology [1,2]. These data are consistent with the international literature. Among these painful patients, 10 to 15% have pain that is refractory to World Health Organization (WHO) standard treatments, due to excessive pain intensity or adverse effects [3–6].

In these cases, intrathecal analgesia should be considered for better pain control as well as for improving the quality of life [7]. The administration of drugs in the central nervous system can achieve better analgesic results and can be easier to use for clinicians.

Bottros and Christo evaluated the efficacy of intrathecal analgesia by a randomized controlled trial that shows the rate of intrathecal analgesia success of 85% against 71% for traditional routes of administration [8]. In addition, a randomized controlled trial showed that patients receiving intrathecal morphine showed increased survival with fewer side effects and months of pain [9,10].

Other studies published since then find comparable results with a level of pain reduction of more than 50% [11–17].

In France, the indication of intrathecal analgesia exists according to the French Society of Anesthesy Reanimation (SFAR) in the case of refractory chronic cancer pain despite a well conducted treatment according to the WHO recommendations, as well as in patients with adverse effects related to the invalid analgesic treatment the quality of life of patient [7,18].

It can also be used in the case of severe spasticity or chronic refractory pain caused by a non-cancerous origin.

The 2017 Polyanalgesic Consensus Conference (PACC) has established an algorithm for nociceptive pain and neuropathic pain [19]. Various molecules can be used alone or mixed together: morphine, ropivacaine, bupivacaine, fentanyl, sufentanil, clonidine, baclofen, ziconotide.

To secure the preparation, a systematic analytical control should be performed before release. Prospective assay of Dupoiron et al. show the benefits of an analytical control to secure preparations and limits dosage errors [20].

The aim of this study was to develop and validate a new method of analytical control of morphine, ropivacaine, bupivacaine, fentanyl, sufentanil, clonidine, baclofen and ziconotide using ultra-performance liquid chromatography (UPLC) combined with an ultraviolet detector (UV).

Materials and methods

Analytes and reagents

For development and validation of the method, the commercial pharmaceutical products were used.

Morphine 50 mg/mL vials were bought to CDM Lavoisier (La Chaussée Saint-Victor, France). It was an intravenous and intrathecal formulation including the excipients water for injection, hydrochloric acid and sodium chloride.

Ropivacaine (Fresenius Kabi, Sèvres, France) bottles are supplied in 10 mg/mL bottles and the excipients were hydrochloric acid, sodium hydroxide, and water for injection.

Bupivacaine sintetica (Sintetica SA, Mendrisio, Italy) 40 mg/mL contains sodium chloride and water for injection.

Baclofen 2 mg/mL (Novartis Pharma, Rueil-Malmaison, France) is available under a ready-to-use intravenous and

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