AstraZeneca

DRUG PRODUCT	Naropin®	**Synopsis**	(FOR NATIONAL AUTHORITY USE ONLY)
DRUG SUBSTANCE(S)	Ropivacaine	REFERRING TO PART	
DOCUMENT NO.	802-550-LC-0520	OF THE DOSSIER	
VERSION NO.	01		
STUDY CODE	CF-ROP-0005		
DATE	March 30, 2001		

Femoral infusion of ropivacaine 2 mg/mL for the management of postoperative pain after major knee surgery. A comparison of three strategies: patient-controlled femoral analgesia (PCFA), continuous infusion, and PCFA + continuous infusion.

STUDY CENTRES

Multicenter study conducted in 13 centers in France

PUBLICATION

None

STUDY PERIOD

- **DATE OF FIRST PATIENT ENROLLED** June 1999
- **DATE OF LAST PATIENT COMPLETED** March 2000

PHASE OF DEVELOPMENT

Therapeutic confirmatory

OBJECTIVES

Efficacy objectives: to assess the efficacy of ropivacaine 2 mg/mL administered as patient-controlled femoral infusion analgesia (PCFA), compared to a continuous femoral infusion (Inf), or both Inf and PCFA for postoperative (48 hours) pain relief on mobilization (*primary objective*), at rest and after daily physiotherapy, in patients who had undergone major knee surgery under general anesthesia.
Secondary objectives: to compare in the three groups

- The total dose of ropivacaine and additional analgesics

- Overall patient satisfaction
- Tolerability

STUDY DESIGN

Multicenter, randomized, open-label study with three parallel groups, designed to compare the efficacy of the various treatments.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION/EXCLUSION

Patients included in this study fulfilled the following criteria

- Major unilateral knee surgery under general anesthesia,
- Age > 18 years,
- Weight ≥ 50 kg,
- ASA status I to III,
- Written informed consent.

Patients presenting with any one of the following criteria were excluded from the study:

- previous history of allergy to local anesthetics of the amide type,
- patients on anticoagulants,
- contraindications to either ketoprofen or propacetamol,
- severe liver or renal insufficiency,
- gastric ulcer,
- women of childbearing age,
- concomitant drugs that inhibit the P1A cytochrome pathway,
- patients unlikely to be fully cooperative during the study such as those with neurological or psychiatric disorders or alcohol or drug abuse,
- participation in another study within the previous thirty days,
- patients who had already been included in the study.

TEST PRODUCTS, BATCH NUMBERS, DOSAGE AND MODE OF ADMINISTRATION

Ropivacaine hydrochloride, 7.5 mg/mL for a combined sciatic/fascia iliac compartment nerve block, batch no. AA 134, expiry date: February 01, 2002.

Ropivacaine hydrochloride, 2 mg/mL, patient-controlled dosage by femoral infusion, each bolus injection: up to 20 mg/hour, or by continuous femoral infusion of either 20 mg/h (alone) or 10 mg/h (plus patient-controlled dosage by femoral infusion, 10 mg per administration) batch no. ZA 216, expiry date February 01, 2000 and batch no. AH 350, expiry date September 01, 2001.

DURATION OF TREATMENT

Treatment in the three arms of the study was given for 48 hours in the immediate postoperative period.

MAIN VARIABLES

- **EFFICACY**

- Pain assessed by the patient on a visual analogue scale (VAS 0 to 100 mm: 0 = no pain, 100 = worst pain) during the first postoperative 48 hours, on mobilization (primary efficacy variable), at rest, and after the daily physiotherapy session.
- Amount of ropivacaine administered during this period,
- Amount of additional analgesics consumed during this period,
- Overall patient satisfaction regarding pain relief.

- **SAFETY**

- Adverse events both reported by the patient and/or observed by the investigational team.

STATISTICAL METHODS

This study was designed to compare the efficacy of the various treatments. Statistical analysis was performed by AstraZeneca R&D Södertälje, Sweden. The statistical analysis for all variables consisted of individual listings, descriptive statistics, and graphs. A stratified Wilcoxon (mid)rank-sum test was used for pairwise comparisons between the three treatment groups. All tests and estimates were adjusted for centers. The Bonnferroni-Holm method was used for the primary efficacy variable to correct for multiplicity and reach an overall alpha level of 0.05.The efficacy variables were analyzed in the intention-to-treat (ITT) set of subjects and in the per-protocol (PP) set of subjects.

PATIENTS

The distribution of the patients is displayed in the following table:

	Group 1 (PCFA)	**Group 2 (Inf)**	**Group 3 (Inf +PCFA)**	**Not randomized**	**Total**
No. planned	45	45	45		135
No. Enrolled	44	46	47	3	140
No. with ≥ 1 dose of ropivacaine	44	46	47	2	139
No. randomized and treated	44	46	47	0	137
Males/Females	18/26	24/22	27/19		
Mean age (range)	49.5 (19.5–82.4)	52.2 (19.9–80.8)	49.7 (19.4–86.5)		
No. analyzed for efficacy	44	46	46		136
No. analyzed for safety	44	46	47	2	139
No. completed	41	41	39		121

SUMMARY

Patients scheduled for open major knee surgery under general anesthesia participated in the study.

Prior to surgery and the induction of general anesthesia, a combined sciatic/fascia iliac compartment nerve block was performed in all patients with ropivacaine 7.5 mg/mL (20 + 20 mL), after which a 20-gauge catheter was threaded 10–15 cm below the iliac fascia. Following surgery, patients were randomized in the recovery room to receive during the first 48 postoperative hours:

- Group 1: Patient-controlled femoral analgesia (PCFA) with ropivacaine 2 mg/mL, boluses up to 10 mL (20 mg/h), lockout time: 60 min.
- Group 2: Continuous femoral infusion of ropivacaine 2 mg/mL at 10 mL/h.
- Group 3: Continuous femoral infusion of ropivacaine 2 mg/mL at 5 mL/h and PCFA boluses up to 5 mL (10 mg), lockout time 60 min.

Additional analgesics: propacetamol 2 g x 4/24 hours was administered IV to all patients. In the event of insufficient pain relief, IV ketoprofen 100 mg x 3/24 hours maximum was administered. Postoperative pain was assessed by the patient on a visual analogue scale (VAS) at rest, and on mobilization: every two hours during the first twelve hours, thereafter every six hours up to 48 hours.
The primary efficacy variable was pain experienced on mobilization assessed by VAS. The VAS ruler was presented to the patient at each evaluation by the investigational team with the cursor at the level “No pain.” The patient indicated the intensity of pain by moving the cursor of the ruler from “No pain” up to the level of pain experienced. Pain during physiotherapy was assessed at the end of each daily physiotherapy session. The overall quality of pain relief was evaluated by the patient at 48 hours.
Adverse events were recorded from the start of injection of ropivacaine 7.5 mg/mL in the sciatic/iliac fascia compartment nerve block up to discharge from hospital.

- **EFFICACY RESULTS**

  Primary objective: PCFA provided effective postoperative pain relief on mobilization reflected in the low VAS score rated by patients in this painful type of surgery. There was no statistically significant difference compared to the other treatment groups.
  Secondary objective: PCFA showed the same results when the secondary criteria were evaluated: pain relief at rest and after physiotherapy, additional prescription of analgesics, and overall patient satisfaction (excellent or good in 80% of cases). The results were comparable to those observed in the other groups. However, these results were obtained with a two to threefold lower total amount of ropivacaine in the PCFA group in relation to the other groups.

- **SAFETY RESULTS**

All the three therapeutic strategies were well tolerated. The most frequent adverse events reported were hypotension, nausea, vomiting, bradycardia, and insomnia. These were mild or

moderate in the majority of cases, in no case leading to withdrawal of treatment. Hypotension and bradycardia were recorded mainly in the peroperative period and were resolved immediately using ephedrine and atropine respectively.
All the adverse events resolved at the end of the study. There were four serious adverse events affecting four patients during the study, none of which were considered to be related to the study drugs. No death occurred during the study period.