AstraZeneca

DRUG PRODUCT	Ropivacaine for injection	**Synopsis**	(FOR NATIONAL AUTHORITY USE ONLY)
DRUG SUBSTANCE	Ropivacaine		
DOCUMENT NO.	802-550-LC-0401-01	THE DOSSIER	
VERSION NO.	01		
STUDY CODE	SP-ROA-0013		
DATE	04 June, 1999		

Efficacy and tolerability of 1, 2 and 3mg/kg ropivacaine administered as a single caudal block for pain management after inguinal surgery in children aged 4-12 years with a body weight of up to 25kg: a comparative, randomized and double-blind study.

STUDY CENTER(S)

Multicenter study. Two centers.

PUBLICATION (REFERENCE)

N.A.

STUDY PERIOD

- **DATE OF FIRST ENROLLMENT** March, 1998
- **DATE OF LAST COMPLETED** November, 1998

PHASE OF DEVELOPMENT

IV

OBJECTIVES

The primary objective was to compare the efficacy and tolerability of the three different doses (1, 2 and 3mg/kg) of ropivacaine administered as 1, 2 and 3mg/mL in patients aged 4-12 years with a body weight of up to 25kg, as a single caudal injection for pain management after inguinal surgery.

The primary efficacy variable was the time to the first administration of analgesics.

The secondary objective was to evaluate the systemic absorption of ropivacaine following caudal injection in patients aged 4-12 years with a body weight of up to 25kg, by means of an estimate of the peak plasma concentration (Cmax).

STUDY DESIGN

Randomized, double-blind and parallel group study.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION/EXCLUSION

Pediatric/Per and postoperative pain management after caudal block.

Inclusion criteria:

1. Patients scheduled for inguinal surgery, performed during caudal epidural block and general anesthesia or sedation.
2. ASA risk category: I or II.
3. Age: 4-12 years.
4. Body weight ≤ 25kg.

Exclusion criteria:

1. Contraindications to caudal epidural block, general anesthesia or sedatives, paracetamol or opioids, as judged by the investigator.
2. A known history of allergy, sensitivity or any other form of reaction to local anesthetics of the amide type, paracetamol or opioids.
3. Medical history and/or concomitant disease which could lead to unreliability of clinical assessments, as judged by the investigator.
4. Significant neurological disease, as judged by the investigator.
5. Surgery expected to cause significant blood loss, as judged by the investigator.
6. Parenteral administration of a local anesthetic of the amide type in the week prior to surgery.
7. Analgesics administered within 24 hours prior to surgery, except for EMLA® cream.

TEST PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

Ropivacaine 1, 2 and 3mg/mL solution for injection was supplied in
1 x 50mL vials. Batch no: 1mg/mL - 1201-3-2, 2mg/mL - 1202-80-8, 3mg/mL - 1203-3-2.
Dose: 1mL/kg of the different concentrations 1, 2 or 3mg/mL (corresponding to 1, 2 or 3mg/kg) administered as a caudal epidural block.

COMPARATOR PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

N.A.

DURATION OF TREATMENT

Single-dose.

- **EFFICACY**

- Time from start of injection of ropivacaine to the first administration of analgesics

- Proportion of patients receiving analgesics in the first 8 hours after the start of injection of ropivacaine
- Postoperative pain assessments over time by study nurse/investigator
- AUCM of postoperative pain assessments by study nurse/investigator during different time periods
- Postoperative pain assessments over time by patient
- AUCM of postoperative pain assessments by patient during different time periods
- Maximum sensory block postoperatively
- Postoperative sensory block over time
- Postoperative motor block assessments by segmental evaluation over time
- Time from the start of injection of ropivacaine to the first measurement with no motor block (score=0)
- Total dose of paracetamol from the start of injection of ropivacaine divided by different time periods
- Total dose of Valoron® (opioid, generic name= tilidine) from the start of injection of ropivacaine divided by different time periods

- **PHARMACOKINETICS**

- Peak plasma level (C_{max})
- Time to reach C_{max} (t_{max})
- Free plasma concentration of ropivacaine (Cu) at 30 minutes
- α-1-acid glycoprotein (AAG) at 30 minutes
- Free fraction of ropivacaine (fu) at 30 minutes
- Calculated free plasma concentration of ropivacaine at t_{max} ($Cu_{max, calc}$)

- **SAFETY**

- Systolic and diastolic blood pressure and pulse rate over time
- ECG
- Blood loss
- Adverse events
- Time from the start of injection of ropivacaine to the first micturition
- Time from the start of injection of ropivacaine to the first intake of food/fluid

STATISTICAL METHODS

The data sets analyzed were based on different populations of patients according to evaluability. These sets of patients are referred to as the per protocol for efficacy (PP_E), per protocol for pharmacokinetics (PP_K) and the intention to treat (ITT) data sets.

The statistical analysis for all variables consists of descriptive statistics and graphs. Stratified Wilcoxon (mid) rank sum test and survival analysis, e.g. the logrank test were used for

pairwise comparisons. All tests and estimates, except the log rank test, were adjusted for centers and a p-value < 0.05 was regarded as statistically significant.

The dose proportionality in Cmax and Cu was evaluated with a power function.

PATIENTS

	Ropivacaine 1mg/kg	Ropivacaine 2mg/kg	Ropivacaine 3mg/kg	**Total**
No. planned PPE patients	35	35	35	105
No. randomized and treated patients	36	38	36	110
Males/Females	34/2	34/4	32/4	100/10
Mean age (range)	6.3 (3.4 - 8.8)	6.8 (4.0 - 12.4)	6.4 (4.1 - 12.0)	
No. analyzed for efficacy (ITT)	36	38	36	110
No. analyzed for safety	36	38	36	110
No. analyzed for pharmacokinetics (PPK)	13	14	16	43

SUMMARY

- **EFFICACY RESULTS**

The time to administration of the first dose of analgesics, after the start of administration of ropivacaine, did not show any statistically significant difference between any of the dose groups, however the median time of the first dose occurred slightly later in the 2 and 3mg/kg dose groups, compared to the lowest dose group (3.3, 4.5 and 4.2 hours in the 1, 2 and 3mg/kg dose groups respectively).

The proportion of patients receiving analgesics in the first eight hours (about 75% in all dose groups), after the start of administration of ropivacaine, did not show any statistically significant difference between any of the dose groups.

The 1mg/kg dose group showed statistically significantly higher AUCM values for postoperative pain assessments by the study nurse/investigator (simplified pain scale), compared to the other dose groups, between 0 and 4 hours after the start of administration of ropivacaine (p= 0.010 and 0.011).

No statistically significant difference was found between any of the dose groups for the AUCM values of postoperative pain assessments by the study nurse/investigator

(simplified pain scale), between 4 and 8 hours after the start of administration of ropivacaine.

The 1mg/kg dose group showed statistically significantly higher AUCM values for postoperative pain assessments by the patient (faces scale), compared to the 3mg/kg dose group, between 0 and 4 hours after the start of administration of ropivacaine (p= 0.011).

No statistically significant difference was found between any of the dose groups for the AUCM values of postoperative pain assessments by the patient (faces scale), between 4 and 8 hours after the start of administration of ropivacaine.

In awake patients the median sensory block reached T12 in all dose groups one hour after the start of administration of ropivacaine.

The median upper sensory block over time showed that the 1mg/kg dose group had no block at L3, two hours after the start of administration of ropivacaine. The 2 and 3mg/kg dose groups showed that the median upper sensory block disappeared at L3, three and four hours after the start of administration of ropivacaine respectively.

The motor block was completely regressed earlier in the 1mg/kg dose group (one hour after the start of administration of ropivacaine), compared to the 2 and 3mg/kg dose groups (four and five hours after the start of administration of ropivacaine).

The incidence of motorblock at any time was 0, 13 and 28% in the 1, 2 and 3 mg/kg dose groups respectively.

The total dose of paracetamol was higher in the 1mg/kg dose group (median 138mg), compared to the other dose groups (median 0mg), between 0 and 4 hours after the start of administration of ropivacaine.

The total dose of Valoron® (opioid, generic name is tilidine) was higher in the 1mg/kg dose group (median 1.3mg), compared to the other dose groups (median 0mg), between 0 and 4 hours after the start of administration of ropivacaine.

No obvious differences were found in efficacy between the dose groups, between 4 and 8 hours after the start of administration of ropivacaine.

- **PHARMACOKINETIC RESULTS**

Following a caudal block of ropivacaine 1, 2 or 3mg/mL in a dose of 1, 2 or 3mg/kg in pediatric patients aged 4-12 years C_{max} increased in proportion to dose with C_{max}-values at 0.27 (0.08), 0.64 (0.25) and 0.90 (0.31) mg/L following 1, 2 and 3 mg/kg respectively. Median (range) t_{max} was 60 (16-241) minutes, 53 (30-240) minutes and 31(15-61) minutes in the 1, 2

and 3mg/kg dose groups respectively. The mean free fraction of ropivacaine was 5.0, 5.4 and 5.1% in the 1, 2 and 3mg/kg dose group respectively. The free concentration of ropivacaine 30 minutes after the injection increased in proportion to dose with values at 0.012 (0.006), 0.027 (0.009) and 0.040 (0.010) mg/L for 1, 2 and 3mg/kg respectively.

Plasma levels of unbound ropivacaine were well below threshold levels for toxicity in adults.

- **SAFETY RESULTS**

The most common adverse event was vomiting. This adverse event is commonly seen during the postoperative period and may be associated with opioid treatment or early feeding.

In the table below all adverse events are shown ordered in decreasing order of frequency.

Number of patients in each treatment group
1 mg/kg=36 2 mg/kg=38 3 mg/kg=36

Grand total	Preferred term	Treatment group (ROPI)	Time period - No.(%) of patients. No time recorded	Before End of surgery	Between End of surgery and Discharge	After Discharge
29	VOMITING	1 mg/kg			10(28)	
		2 mg/kg			13(34)	
		3 mg/kg			6(17)	
2	NAUSEA	1 mg/kg				
		2 mg/kg			2(5)	
		3 mg/kg				
1	ABDOMINAL PAIN	1 mg/kg				
		2 mg/kg				
		3 mg/kg			1(3)	
	DIARRHOEA	1 mg/kg				
		2 mg/kg			1(3)	
		3 mg/kg				
	INTRAOPERATIVE AE, IATROGENIC	1 mg/kg				
		2 mg/kg				
		3 mg/kg			1(3)	

One serious adverse event occurred. The patient suffered from an iatrogenic bladder injury due to the surgery. This event was not considered to be related to ropivacaine.

No clinically significant deterioration relative to the baseline was found in ECG, pulse and blood pressure.

The median time to first intake of food was similar in all dose groups (about 2.5 hours).

The median time to first micturition occurred slightly later in the 3mg/kg dose group, compared to the other dose groups (3.9, 4.2 and 4.6 hours in the 1, 2 and 3mg/kg dose groups respectively).