British Journal of Anaesthesia **90 (3)**: 377–9 (2003)
DOI: 10.1093/bja/aeg054

Comparison of four strategies to reduce the pain associated with intravenous administration of rocuronium

A. B. Chiarella[1]*, D. T. Jolly[1]*, C. M. Huston[1] and A. S. Clanachan[2]

[1]Department of Anesthesiology and Pain Medicine, 3B2.32 Walter C. Mackenzie Health Sciences Centre, University of Alberta Hospitals, 8440-112 Street, Edmonton, Alberta, Canada T6G 2B7. [2]Faculty of Pharmacy and Pharmaceutical Science, 3118 Dentistry-Pharmacy Centre, University of Alberta, Edmonton, Alberta, Canada T6G 2N8

**Corresponding authors: E-mail: dtjolly@compusmart.ab.ca and achiarel@ualberta.ca*

Background. I.V. rocuronium produces intense discomfort at the site of injection in conscious patients. Four strategies to reduce or prevent this discomfort were studied.

Methods. Two hundred and fifty adult patients, ASA I–III, were randomized into five groups of 50 patients in a blinded, prospective study. The control group received rocuronium 10 mg alone. For the remaining four groups, rocuronium 10 mg was mixed with sodium bicarbonate 8.4% 2 ml, fentanyl 100 μg, lidocaine 2% or normal saline. The pH and osmolality of all mixtures were measured. Patient data were analysed using ordinal logistic regression. Osmolality and pH data were analysed using the Kruskal–Wallis test with Dunn's multiple comparison test.

Results. When compared with rocuronium alone, only the addition of saline failed to significantly reduce the pain reported by patients. The addition of fentanyl reduced the complaint of pain by 1.9 times ($P<0.049$) and the addition of lidocaine 2% reduced it by 3.6 times ($P<0.0001$). Sodium bicarbonate 8.4% reduced the reporting of pain by 18.4 times ($P<0.0001$).

Conclusions. Sodium bicarbonate 8.4%, when added to rocuronium, markedly reduces the experience of pain during the i.v. administration of a small dose of rocuronium.

Br J Anaesth 2003; **90**: 377–9

Keywords: anaesthetics, rocuronium; injection, pain; osmolality; pH

Accepted for publication: October 21, 2002

A variety of i.v. anaesthetic agents cause pain when injected.[1] Rocuronium, in particular, causes intense discomfort at the site of injection in conscious patients.[1–3] When administered in a subparalysing dose, 50–100% of patients report discomfort.[2 4] Attempts to reduce this adverse effect have used premedication with i.v. midazolam, fentanyl or lidocaine.[5–7] Even after induction of anaesthesia with propofol or pentothal, rocuronium causes

Table 1 Patient's assessment of pain or discomfort during i.v. injection of rocuronium mixtures

Pain score	Severity of pain	Patient's response
0	None	No pain or discomfort reported when questioned
1	Mild	Pain or discomfort reported by the patient to be mild when questioned
2	Moderate	Pain or discomfort reported by the patient to be moderate when questioned
3	Severe	Pain or discomfort reported spontaneously by the patient and stated to be severe
4	Very severe	Pain or discomfort associated with a strong vocal response, hand or arm withdrawal, facial grimacing or crying, and reported to be very severe

hand or limb withdrawal or generalized movements in 85% of patients, suggesting the presence of intense nociception even under anaesthesia.[3 6]

The purpose of this study was to determine the effectiveness of four strategies to reduce the pain associated with the i.v. administration of rocuronium 10 mg. The pH and osmolality of all study solutions were measured.

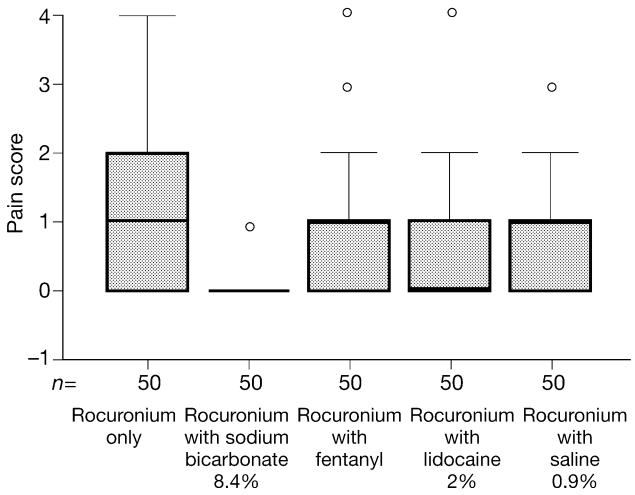

Fig 1 Boxplot of pain scores and rocuronium study solutions. Thick horizontal bars represent the median pain score. The histogram represents the first quartile above or below the median pain score. The whiskers represent the second quartile above the median pain score. Open circles denote the presence of outlier(s).

Method and results

After institutional ethics approval and informed patient consent, 250 patients were recruited for a prospective, randomized and blinded study. Exclusion criteria included age <18 yr, allergy to any of the anaesthetic medications being administered, ASA class IV or V, and inability to provide informed consent. Patients were assigned to one of five study groups using a restricted randomization procedure. The control group received only rocuronium 10 mg. For the remaining four groups, rocuronium 10 mg was mixed with sodium bicarbonate 8.4% 2 ml, fentanyl 100 μg, lidocaine 2% or normal saline. The patient's age, sex, height, weight and body mass index (BMI) were recorded. The gauge of the i.v. cannula was recorded.

All patients received midazolam 1 mg followed by fentanyl 100 μg. Thirty seconds later the study mixture was administered. After another 30 s, the patient was asked if they experienced any pain or discomfort from the injection. Patients who responded positively were asked to rank their discomfort (Table 1). Patients were observed for signs of limb withdrawal, grimacing or crying. Immediately thereafter, propofol 2.0 mg kg^{-1} was given.

The pH and osmolality of the solutions used were measured. Triplicate measurements were performed on five samples of each solution using the Fischer Accumet pH meter™ (Fisher Scientific, Pittsburgh, PA, USA) and the Advanced Micro-Osmometer Model 3MO™ (Advanced Instruments, Norwood, MA, USA).

Patient data were analysed using ordinal logistic regression. The response variable evaluated was the reported amount of injection pain. The controlled explanatory variables were the study solutions administered. Data were analysed for observational associations between pain scores and age, sex, height, weight, BMI and i.v. cannula gauge. The appropriateness of the ordinal logistic regression for the data analysed was confirmed by the Pearson and deviance of goodness-of-fit tests. The pH and osmolality data were analysed using the Kruskal–Wallis test with Dunn's multiple comparison test. The level of statistical significance selected was a P-value <0.05.

The age, weight, height and sex distribution were comparable in all groups. Despite i.v. premedication with midazolam 1 mg and fentanyl 100 μg, patients continued to report a substantial amount of pain with the i.v. injection of rocuronium. Rocuronium alone produced the highest reported pain response (Fig. 1). Sixty-six per cent of patients reported pain. Although the median pain score was 1 (mild), 30% reported the pain to be moderate to very severe. The addition of saline 0.9% or fentanyl 100 μg to rocuronium produced identical pain score distributions, with median pain scores of 1. In both these groups, 64% of patients reported pain and 14% reported the pain to be moderate to very severe. The odds ratio for reducing pain was 1.5 for saline and 1.9 for fentanyl. The addition of saline failed to significantly reduce the pain reported by patients. Although the addition of fentanyl achieved a P-value <0.05, this result is attributable to the influence of the outliers identified by the analysis. The addition of lidocaine 2% to rocuronium significantly reduced the pain and discomfort reported by patients (P<0.0001). The odds ratio was a 3.6 times reduction in reported pain. The median pain score for this group was 0. Forty-eight per cent of patients reported pain or discomfort with the administration of this mixture. However, only 8% reported the discomfort to be moderate to very severe. The addition of sodium bicarbonate 8.4% to rocuronium reduced the patients' reported pain experience

by 18.4 times ($P<0.0001$). The median pain score for the bicarbonate group was 0; 86% reported no discomfort on injection of this mixture. The remaining 14% reported only mild discomfort.

Men reported pain 2.8 times less frequently than women ($P<0.0003$). Younger and taller patients were more likely to report pain ($P<0.002$ and $P<0.04$ respectively). Pain scores were independent of the size of the i.v. cannula, body weight and BMI.

The pH of the rocuronium injectable was 4.0. When the pH of rocuronium alone was compared with the pH of the study mixtures, only rocuronium and sodium bicarbonate 8.4%, with a pH of 7.39, differed significantly ($P<0.01$). The osmolality of rocuronium was 280. The osmolalities of the mixtures of rocuronium and sodium bicarbonate 8.4% (osmolality 1200) and of rocuronium and fentanyl (osmolality 95) differed significantly from the osmolality of rocuronium ($P<0.05$).

Comment

Pain associated with the administration of rocuronium is common and distressing for patients. This study demonstrates that the pain associated with administration of a 10 mg dose of rocuronium bromide can be almost eliminated by combining it with sodium bicarbonate 8.4% in a 1:2 volume ratio. Clinically, the effect of fentanyl was identical to that of saline. The explanation for the ability of fentanyl to reduce injection pain is simply dilution. Like previous investigators, we found that lidocaine was effective in alleviating the pain accompanying rocuronium injection.[4 6] Although lidocaine 2% significantly reduced the complaint of injection pain with rocuronium by 3.6 times, it was not as effective as the 18.4 times reduction accomplished by sodium bicarbonate.

The aetiology of the discomfort caused by the i.v. administration of rocuronium is unknown. Peripheral veins are innervated with polymodal nociceptors that mediate the pain response to the injection of certain anaesthetic agents.[8] Rocuronium is an isotonic solution with a pH of 4.0.[2] Pain on injection has been associated with solutions with a pH of 4 or less.[8] Consequently, it has been suggested that the injection pain produced by rocuronium is related to its low pH.[2 4] Others have reported that the acid pH of rocuronium is not the cause of such pain.[7] Because the preparation is isotonic, this physiochemical attribute probably does not contribute to the pain rocuronium produces. The addition of sodium bicarbonate 8.4% to rocuronium altered the pH and osmolality of the resulting mixture significantly. Whether the resulting changes in pH and osmolality were responsible for the marked reduction in pain reported by patients requires elucidation.

The purpose of this study was to evaluate strategies to reduce the pain associated with the administration of rocuronium. Rocuronium has been evaluated previously as a precurarization agent; it demonstrates superior effectiveness compared with d-tubocurarine, vecuronium, atracurium and mivacurium in preventing fasciculations and post-succinylcholine myalgias.[9] The intense pain produced by rocuronium in patients has restricted its use as a precurarization agent. The addition of sodium bicarbonate 8.4% to a precurarization dose of rocuronium will resolve this problem.

Acknowledgement

The authors would like to thank Dr William Colmers, Department of Pharmacology, University of Alberta, for technical assistance with the laboratory portion of this study.

References

1 Dalgleish DJ. Drugs which cause pain on intravenous injection. *Anaesthesia* 2000; **55**: 828–9
2 Lockey D, Coleman P. Pain during injection of rocuronium bromide. *Anaesthesia* 1995; **50**: 474
3 Borgeat A, Kwiatkowski D. Spontaneous movements associated with rocuronium: is pain on injection the cause? *Br J Anaesth* 1997; **79**: 382–3
4 Cheong KF, Wong WH. Pain on injection of rocuronium: influence of two doses of lidocaine pretreatment. *Br J Anaesth* 2000; **84**: 106–7
5 Joshi GP, Whitten CW. Pain on injection of rocuronium bromide. *Anesth Analg* 1997; **84**: 228
6 Shevchenko Y, Jocson JC, McRae VA, *et al.* The use of lidocaine for preventing the withdrawal associated with the injection of rocuronium in children and adolescents. *Anesth Analg* 1999; **88**: 746–8
7 Borgeat A, Kwiatkowski D, Ruetsch Y. Spontaneous movements associated with rocuronium injection: the effects of prior administration of fentanyl. *J Clin Anesth* 1997; **9**: 650–2
8 Klement W, Arndt JO. Pain on i.v. injection of some anaesthetic agents is evoked by the unphysiological osmolality or pH of their formulations. *Br J Anaesth* 1991; **66**: 189–95
9 Marten R, Carrier J, Pirlet M, *et al.* Rocuronium is the best non-depolarizing relaxant to prevent succinylcholine fasciculations and myalgia. *Can J Anaesth* 1998; **45**: 521–5