

Comparison of ibuprofen, cyclobenzaprine or both in patients with acute cervical strain: a randomized controlled trial

S. Mustafah Khwaja, DO; Max Minnerop, MD; Adam J. Singer, MD

ABSTRACT

Objective: We compared pain severity and time to resumption of activities in patients with cervical strains treated with a nonsteroidal anti-inflammatory drug (NSAID), a centrally acting muscle relaxant or both.

Methods: We performed a double-blinded, randomized controlled trial of adults with cervical strains from motor vehicle collisions or from falls who presented to a suburban academic emergency department (ED). Patients were randomly assigned to receive ibuprofen 800 mg, cyclobenzaprine 5 mg or both, 3 times daily as needed for up to 7 days. Outcome measures included a pain score on a 100-mm visual analog scale, pain relief scores, the time to resumption of normal activities, the use of rescue medications, and adverse outcomes. We used repeated-measures analysis of variance to compare pain relief over time. Our sample size of 20 patients in each group had a power of 80% to detect a difference of 15 mm in pain relief scores between the highest and lowest groups.

Results: We randomly assigned 61 patients to receive ibuprofen ($n = 20$), cyclobenzaprine ($n = 21$) or both ($n = 20$). Mean (standard deviation) age was 34 (11) years; 58% were women and 72% were white. Although pain scores improved over time in all groups, there were no significant differences between the groups in any of the outcome measures. The rate of adverse events was also similar between groups.

Conclusion: Our study suggests that there is little benefit to routinely using or adding cyclobenzaprine to NSAIDs for ED patients with acute cervical strain.

Keywords: cervical strain, ibuprofen, cyclobenzaprine

RÉSUMÉ

Objectif : Nous avons comparé la gravité de la douleur et le temps de reprise des activités chez les patients présentant une entorse du rachis cervical et ayant été traités avec un anti-inflammatoire non stéroïdien (AINS) ou un relaxant musculaire à action centrale, ou les deux.

Méthodes : Nous avons réalisé un essai contrôlé randomisé à double insu auprès d'adultes qui ont consulté le service d'urgence d'un centre hospitalier universitaire de banlieue pour une entorse du rachis cervical liée à un accident de véhicule automobile ou à une chute. Les participants ont été répartis de façon aléatoire pour recevoir 800 mg d'ibuprofène, 5 mg de cyclobenzaprine, ou les deux, 3 fois par jour, au besoin, pour un maximum de 7 jours. Les principales mesures des résultats comprenaient le score de douleur sur une échelle visuelle analogique de 100 mm, les scores de soulagement de la douleur, le délai de reprise des activités normales, l'utilisation de médicaments de secours et les événements indésirables. Nous avons utilisé une analyse de variance à mesures répétées pour comparer le soulagement de la douleur dans le temps. Chaque groupe de 20 patients était capable à 80 % de détecter une différence de 15 mm quant au score de gravité de la douleur entre le groupe le plus élevé et le groupe le plus bas.

Résultats : Soixante et un patients ont été répartis de façon aléatoire pour recevoir de l'ibuprofène ($n = 20$), de la cyclobenzaprine ($n = 21$) ou les deux ($n = 20$). L'âge moyen était de 34 ans (écart-type, 11); 58 % étaient des femmes et 72 % étaient Blancs. Bien que les scores de douleur se soient améliorés au fil du temps pour tous les groupes, il n'y avait pas de différences significatives entre les groupes pour aucune des mesures de résultats. Le taux d'événements indésirables était également similaire pour tous les groupes.

Conclusion : Notre étude indique qu'il y a peu d'avantages à prescrire la cyclobenzaprine ou à l'ajouter de façon routinière aux AINS chez les patients se présentant à l'urgence pour une entorse du rachis cervical.

INTRODUCTION

In each year there are 13 million motor vehicle collisions (MVCs) in the United States and an estimated 500 000 to 1 million result in cervical strains.¹ The diagnosis, treatment and insurance payments directly related to cervical

From the Department of Emergency Medicine, Stony Brook University, Stony Brook, NY

Submitted Aug. 30, 2008; Revised Mar. 17, 2009; Accepted Aug. 10, 2009

This article has been peer reviewed.

CJEM 2010;12(1):39-44

strains cost an estimated US\$4.5 billion to \$29 billion annually.² The injury is caused by sudden acceleration or deceleration of the head relative to the trunk.³ The cause of pain associated with cervical strains is poorly understood. Studies using human cadavers suggest that the occipital pain is caused by the stretch of dorsal root ganglia of C1 and C2, and that the characteristic lower cervical pain is caused by compression of the cervical facet joints.⁴ Symptoms of cervical strain include pain in the neck, shoulder, arm, head or jaw, dizziness, tinnitus, and difficulties with memory or concentration.⁵

Pain and muscle spasm are closely related in musculoskeletal pain syndromes. The initial injury is believed to cause reflex spasm of the affected muscles. This muscle spasm results in further pain propagating a vicious cycle of increased pain and discomfort.⁶ As a result, many physicians prescribe muscle relaxants in addition to analgesics and anti-inflammatory agents.^{7,8} Previous studies of muscle relaxants in combination with non-steroidal anti-inflammatory drugs (NSAIDs) for lower back pain have demonstrated minor advantages of the combination therapy over single-agent therapy.^{9–12} However, most of these studies recruited non-emergency patients, were industry funded and took place more than 20 years ago, when bed rest was recommended rather than early mobility. Other treatment modalities such as physiotherapy and exercise programs have not been studied in the emergency department (ED) setting.

The objective of the current study was to determine whether a centrally acting muscle relaxant (cyclobenzaprine) reduces pain and speeds recovery when compared with NSAIDs alone or in combination for ED patients with acute cervical strains.

METHODS

Study design

We used a prospective, double-blinded, randomized clinical trial (no. NCT00790270) to test the study hypothesis. All patients provided written informed consent. Our institutional review board approved the study.

Setting

We conducted the study in the ED of a suburban teaching hospital with an accredited emergency medicine residency program and an annual census of 75 000. The study site is a regional level-1 trauma centre.

Participants

A convenience sample of patients was enrolled Monday through Saturday from 8:00 am to 10:00 pm when a trained research assistant was on site.¹³ Patients were eligible for enrolment if they presented to the ED within 24 hours of an MVC or fall, were 18 years of age or older, and answered the question “Do you have any neck pain?” in the affirmative. The question was initially asked by the triage nurse and treating physician, and repeated by a trained research assistant immediately before enrolment. The location, quality or severity of the injury did not otherwise affect eligibility for enrolment. Plain radiographs of the cervical spine were obtained in selected patients based on the criteria of the National Emergency X-Radiography Utilization Study.¹⁴ We excluded patients for the following reasons: they were not available for telephone follow-up; they were pregnant; they had an allergy or intolerance to any of the study drugs; they had used a monoamine oxidase inhibitor within 14 days; they had a history of arrhythmias, heart failure, recent myocardial infarction, hyperthyroidism, cervical spine fractures or dislocations, or focal neurologic findings (either central or peripheral); they were admitted to hospital; they experienced impaired cognitive function that would preclude informed consent and pain assessment. We also excluded patients with a history of gastrointestinal bleeding or substance abuse.

Interventions

After giving informed consent, all participants were administered 800 mg of ibuprofen by mouth and were then randomly assigned in equal proportion to 1 of 3 treatment groups. This initial dose of ibuprofen was given to ensure that even patients randomly assigned to cyclobenzaprine alone received at least 1 dose of analgesic. We determined assignment of therapy by opening the next consecutively numbered opaque envelope. The study assignments were based on a computerized random numbers table and were prepared by personnel who were not involved in the study. Both physicians and patients were blinded to treatment allocation. Patients assigned to the first study group were treated with ibuprofen 800 mg and an inactive placebo tablet, 3 times daily by mouth. Patients assigned to the second study group were treated with a similarly appearing inactive placebo tablet and cyclobenzaprine 5 mg, 3 times daily. Patients assigned to the third group were treated with both ibuprofen 800 mg and cyclobenzaprine

5 mg, 3 times daily. All treatments were to be taken as needed for up to 7 days or until pain relief was considered adequate by the patient. There were no dose adjustments based on weights of participants.

Measures and outcomes

Research assistants recorded patient demographics, medical history, medications prescribed and initial pain scores onto standardized forms. We obtained pain scores from patients using a previously validated unhatched 100-mm visual analog scale (VAS) marked “no pain” and “most pain” at the low and high ends, respectively.¹⁵ Patients were asked to record in a daily log neck pain severity and return to work, school or other normal activities after discharge. The pain severity was to be recorded using a 100-mm VAS 30–60 minutes after taking the morning dose of the assigned treatment. A previous study¹⁶ demonstrated a high correlation between pain scores recorded at home and in the ED. Treatment was continued for 7 days or until pain relief was considered satisfactory by the patients. Patients also recorded the use of ice packs and rescue with acetaminophen 1 g every 6 hours. Use of ice packs or other nonpharmacological therapies were not considered rescue therapies. Patients were also asked to record the occurrence of nausea, vomiting and dizziness, as well as any other adverse events. The study protocol did not specify how physicians should instruct patients with regard to the use of physiotherapy or exercise programs. After 7 days, patients were to return the diaries by mail using self-addressed envelopes. We conducted telephone reminders when the diaries were not received within 2 weeks.

The main outcome measure was the change in pain scores over time as measured by the pain intensity differences (PIDs), which were the differences between the baseline pain VAS and the VAS at each follow-up measurement point in time; positive values of the PIDs indicate decreases in pain. Secondary outcomes were the time-weighted summed pain intensity difference (SPID) score, the number of days until resumption of normal daily activities, the use of rescue medications, and adverse events. We calculated the SPID score by weighting the PIDs by the number of days since the previous observation and summing these weighted differences.

Data analysis

Continuous data are presented as means and confidence intervals (CIs) and compared with analysis of variance

(ANOVA) and repeated-measures ANOVA as appropriate; data were tested for normality to justify the necessary assumptions for using these tests. We present binomial data as percent frequency of occurrence with 95% CIs and we compared the data with χ^2 or Fisher exact tests. We compared the primary outcome among groups using repeated-measures ANOVA. A sample size of 20 patients in each group had greater than 80% power to detect a difference of 15 mm in PID scores between the highest and lowest groups assuming a common standard deviation of 15, further assuming that the mean PID of the ibuprofen alone and cyclobenzaprine alone groups were more similar than that of the combined group. Data analysis was on an intention-to-treat basis using SPSS 15.0 for Windows (SPSS Inc.).

RESULTS

During the study period 61 patients were enrolled. Their mean age (standard deviation [SD]) was 34 (11) years; 58% were women and 72% were white. Most (87%) cervical strains were the result of an MVC. The mean initial pain using VAS pain scoring was 52.8 mm (95% CI 48.2–57.5 mm). No patients were lost to follow-up.

The patients were randomly assigned to receive ibuprofen ($n = 20$), cyclobenzaprine ($n = 21$) or both ($n = 20$). The 3 study groups were similar in baseline characteristics such as age, sex, race, initial pain scores and mechanism of injury (Table 1).

The changes in pain scores over time were similar among the 3 treatment groups (Fig. 1). There was a slight increase in pain in all groups the day after baseline (mean PID on day 1 -4.5 , -8.5 and -5.1 for the ibuprofen, cyclobenzaprine and combination groups, respectively), and the most pain relief was measured on day 7 (mean PID on day 7 was 26.0, 35.0 and 43.3). In the ibuprofen group there was a tendency toward a slower rate of pain relief over time as indicated by the repeated-measures ANOVA interaction term ($p = 0.06$). Individually, only the PID on day 6 was significantly different among the 3 groups ($p = 0.05$, unadjusted for multiple testing). In all 3 study groups there was a significant reduction in pain scores over time ($p < 0.001$). The SPID was not significantly different across groups (Table 2). Patients who received ibuprofen, with or without cyclobenzaprine, tended to require fewer rescue medications, but this difference was not statistically significant ($p = 0.17$). Similarly, patients assigned to receive ibuprofen, with or without cyclobenzaprine, tended to be more likely to resume normal activities the

following day, but this difference was also not significant ($p = 0.11$).

Four patients receiving cyclobenzaprine alone or in combination reported dizziness, and 1 patient treated with ibuprofen alone reported nausea.

DISCUSSION

The results of our study demonstrate that the addition of cyclobenzaprine to ibuprofen does not result in better pain relief or earlier resumption of normal daily activities than ibuprofen alone. Moreover, the number of adverse events in the combined therapy group was slightly greater than either study group alone. Because the addition of cyclobenzaprine increases the costs and has the potential to also increase the risks of adverse events, our study suggests that there is little, if any, benefit to routinely adding cyclobenzaprine to NSAIDs in the management of ED patients with acute cervical strain.

Cyclobenzaprine is a tricyclic amine similar in structure and pharmacology to amitriptyline, and a weak inhibitor of presynaptic norepinephrine and serotonin reuptake. It has strong anticholinergic, antihistaminic

and sedative properties but weak antidepressant effects. Based on animal studies, cyclobenzaprine is believed to relieve muscle spasm by acting centrally in the brainstem to reduce descending tonic discharges on γ - and

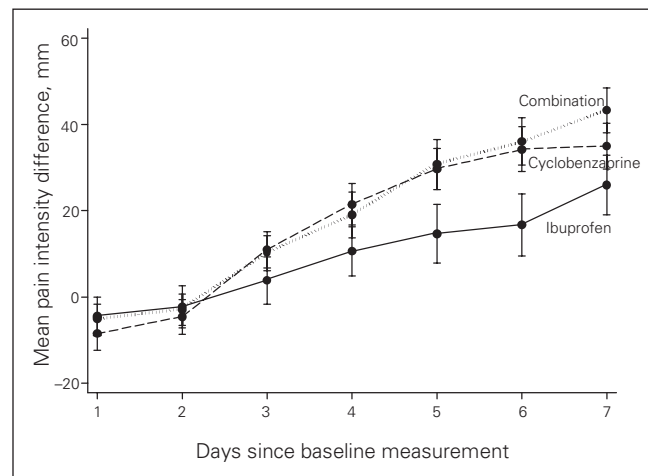


Fig. 1. Mean change in pain (pain intensity difference) over time (d). A positive value represents a decrease in pain score, by self-report on a 100-mm visual analog scale 30 to 60 minutes after morning dose of study medication. Bars represent standard errors.

Table 1. Baseline characteristics of 61 patients included in the study, by treatment group

Characteristic	No. (%) of patients*			p value
	Ibuprofen, n = 20	Cyclobenzaprine, n = 21	Ibuprofen + cyclobenzaprine, n = 20	
Mean (SD) age, yr	32 (11)	37 (13)	34 (10)	0.33
Female	11/18 (61)†	14/21 (67)	9/20 (45)	0.35
White	14/20 (70)	16/21 (76)	14/20 (70)	0.84
Mean (SD) initial pain score, mm†	52 (18)	50 (8)	57 (19)	0.41
MVC	15/19 (79)§	20/21 (95)	18/19 (95)§	0.12

MVC = motor vehicle collision; SD = standard deviation.

*Unless otherwise indicated.

†Measured on a 100-mm visual analog pain scale.

‡2 patients with unspecified sex.

§1 patient with unspecified cause of injury.

Table 2. Secondary outcomes of 61 patients included in the study, by treatment group

Outcome	No. (%) of patients*			p value
	Ibuprofen, n = 20	Cyclobenzaprine, n = 21	Ibuprofen + cyclobenzaprine, n = 20	
Mean (95% CI) SPID score	65 (13–143)	118 (61–175)	131 (75–188)	0.29
Used rescue medications	9 (45)	13 (62)	9 (45)	0.17
Resumed activities next day	14 (70)	8 (38)	13 (65)	0.11
Adverse events	1 (5)	1 (5)	3 (15)	0.40
Dizziness	0	1	3	—
Nausea	1	0	0	—

CI = confidence interval; SPID = summed pain intensity difference.

*Unless otherwise indicated.

α -motoneurons. Cyclobenzaprine may also have direct activity on spinal motoneurons.⁹

Other studies have also evaluated centrally acting muscle relaxants, such as cyclobenzaprine, with or without NSAIDs, for musculotendinous injuries. A previous meta-analysis performed by Browning and colleagues⁹ demonstrated that cyclobenzaprine was significantly better than placebo for the treatment of lower back pain. This meta-analysis included 14 clinical studies, most of which were poorly randomized, unblinded and industry sponsored. Additionally, the beneficial effect of cyclobenzaprine was modest and limited to the first few days after injury. A double-blind trial of diflunisal, with or without cyclobenzaprine,¹⁰ demonstrated a significant advantage of the combination therapy limited to the fourth day of treatment only. A nonblinded comparative study of naproxen, with or without cyclobenzaprine using nonvalidated outcomes,¹¹ reported a non-significant improvement in function and pain in the combined therapy group. The minimal effects of muscle relaxants on pain may be explained by the suggestion that muscle spasm does not increase pain as previously believed.¹⁷

A study of 77 ED patients with diverse acute myofascial strains by Turturro and coworkers¹² did not find any benefit of adding cyclobenzaprine to ibuprofen. The cyclobenzaprine did not reduce pain, and it was associated with an increased rate of central nervous system side effects (42% v. 18%). However, in that study there was no group treated with cyclobenzaprine alone and the dose of cyclobenzaprine used was 10 mg. For our study we chose to use a 5-mg dose of cyclobenzaprine, since updated recommendations by the manufacturer suggest that this lower dose is as effective yet has fewer adverse events. Another difference is that our study population was more homogenous including only patients with cervical strains.

Our findings are consistent with the clinical practice guideline on acute lower back pain problems in adults published by the Agency for Health Care Policy and Research, which concluded that skeletal muscle relaxants have not been shown to be more effective than NSAIDs, and that no additional benefit was gained by using muscle relaxants in combination with NSAIDs over use of NSAIDs alone.¹⁸

Limitations

Our study has several notable limitations. This was a convenience sample of patients who were enrolled

when research assistants were present, and we cannot exclude a selection bias. We also did not collect data on those patients who were not enrolled in the study for comparison. The small sample size limited our ability to detect smaller differences in outcomes (a type II error). We also did not measure the presence and the severity of any associated muscle spasm. However, this is likely to be subjective and subject to interrater variability and we could not identify validated measures of muscular spasm. Potential confounders may have been overlooked. For example, we did not measure the use of physiotherapy and exercising during the study period. We also did not assess function other than resumption of daily activities. Finally, we chose a fixed-dose design, and cannot comment on the safety or effectiveness of other doses.

CONCLUSION

The addition of cyclobenzaprine to ibuprofen in the treatment of ED patients with acute cervical strains resulting from MVCs or falls does not appear to result in more effective pain relief or faster resumption of normal daily activities. Thus we do not recommend routinely adding cyclobenzaprine to ibuprofen in patients presenting to the ED with cervical strains.

Competing interests: None declared.

REFERENCES

1. Dreyer SJ, Boden SD. Nonoperative treatment of neck and arm pain. *Spine* 1998;23:2746-54.
2. Freeman MD, Croft AC, Rossignol AM, et al. A review and methodologic critique of the literature refuting the whiplash syndrome. *Spine* 1999;24:86-98.
3. Sturzenegger M, DiStefano G, Radanov BP, et al. Presenting symptoms and signs after whiplash injury: the influence of accident mechanisms. *Neurology* 1994;44:688-93.
4. Cusick JF, Pintar FA, Yoganadan N. Whiplash syndrome: kinematic factors influencing pain patterns. *Spine* 2001;26:1252-8.
5. Spitzer WO, Skovron ML, Salmi LR, et al. Scientific monograph of the Quebec Task Force on Whiplash-Associated Disorders: redefining "whiplash" and its management. [Erratum, *Spine* 1995; 20:2372.]. *Spine* 1995;20(Suppl):1S-73S.
6. Roland M. A critical review of the evidence for a pain-spasm-pain cycle in spinal disorders. *Clin Biomech (Bristol, Avon)* 1986;1:102-9.
7. Chang D, Bosco JA. Cervical spine injuries in the athlete. *Bull NYU Hosp Jt Dis* 2006;64:119-29.
8. Zmurko MG, Tannoury TY, Tannoury CA, et al. Cervical sprains, disc herniations, minor fractures, and other cervical injuries in the athlete. *Clin Sports Med* 2003;22:513-21.
9. Browning R, Jackson JL, O'Malley PG. Cyclobenzaprine and back pain. A Meta-analysis. *Arch Intern Med* 2001;161:1613-20.
10. Basmajian JV. Cyclobenzaprine hydrochloride effect on

- skeletal muscle spasm in the lumbar region and neck: two double-blind controlled clinical and laboratory studies. *Arch Phys Med Rehabil* 1978;59:58-63.
11. Borenstein DG, Lacks S, Wiesel SW. Cyclobenzaprine and naproxen versus naproxen alone in the treatment of acute low back pain and muscle spasm. *Clin Ther* 1990;12:125-31.
 12. Turturro MA, Frater CR, D'Amico FJ. Cyclobenzaprine with ibuprofen versus ibuprofen alone in acute myofascial strain: a randomized, double-blind clinical trial. *Ann Emerg Med* 2003;41:818-26.
 13. Hollander JE, Singer AJ. An innovative strategy for conducting clinical research: the Academic Associate Program. *Acad Emerg Med* 2002;9:134-7.
 14. Hoffman JR, Wolfson AB, Todd K, et al. Selective cervical spine radiography in blunt trauma: methodology of the National Emergency X-Radiography Utilization Study (NEXUS). *Ann Emerg Med* 1998;32:461-9.
 15. Scott J, Huskisson EC. Graphic representation of pain. *Pain* 1976;2:175-84.
 16. Singer AJ, Kowalska A, Thode HC. Ability of patients to accurately recall the severity of acute painful events. *Acad Emerg Med* 2001;8:292-5.
 17. Hirayama J, Yamagata M, Ogata S, et al. Relationship between low-back pain, muscle spasm and pressure pain thresholds in patients with lumbar disc herniation. *Eur Spine J* 2006;15:41-7.
 18. Bigos S, Bowyer O, Braen G, et al. *Acute low back problems in adults. Clinical practice guideline, quick reference guide number 14*. Rockville (MD): US Department of Health and Human Services, Public Health Service, Agency for Health Care Policy and Research; 1994.

Correspondence to: Dr. Adam Singer, Department of Emergency Medicine, HSC-L4-080, 8350 SUNY, Stony Brook NY 11794-8350; adam.singer@stonybrook.edu

SERVICE INFORMATION

Subscription and sales

The *Canadian Journal of Emergency Medicine (CJEM)* is supplied to paid-up members of the Canadian Association of Emergency Physicians (CAEP) as a requisite of membership; others may subscribe yearly. Rates for 2010 (6 issues): Canada (personal), \$225; Canadian institutions, \$399; outside Canada (personal), US\$254; US institutions, US\$449. Contact the CAEP office (800 463-1158). Single copies of current year issues \$50; back issues \$50 (subject to availability). Payment should be made to CAEP in funds specified drawn on a Canadian or US bank. VISA and MasterCard are also accepted.

Change of address

We require 6-8 weeks' notice to ensure uninterrupted service. Please fax your current mailing label, new address and effective date to 613 523-0190 or email: cjem@caep.ca.

Reprints

Bulk reprints of *CJEM* articles are available in minimum quantities of 50. For information or orders, please contact the reprint coordinator, Janis Murrey, 800 663-7336 or 613 731-8610 x2110, fax 613 565-7704, janis.murrey@cma.ca.

Electronic availability

CJEM is available on the CAEP website (cjem-online.ca).

Indexing

CJEM is indexed by MEDLINE/PubMed, EMBASE,

CINAHL, International Pharmaceutical Abstracts (IPA), BIOME/OMNI, Scirus, Cochrane Prehospital and Emergency Health Field, and PubsHub.com

Copyright and permissions

Copyright for all material is held by *CJEM* or its licensors unless otherwise indicated. You may reproduce or otherwise use material from this Journal only in accordance with Canadian copyright law and provided that credit is given to the original source. In the case of photocopying or other reprographic copying, please contact the Canadian Copyright Licensing Agency (Access Copyright): 800 893-5777; accesscopyright.ca. For any other use, including republishing, redistribution, storage in a retrieval system or transmission, in any form or by any means, please contact the *CJEM* Editorial Office, Andrea Schaffeler, Interim Managing Editor, *Canadian Journal of Emergency Medicine*, 628 Cowan Circle, Pickering ON L1W 3K7, cjem@rogers.com

Instructions for authors

Published in the January issue of each volume. The most recent version is available online at cjem-online.ca.

Advertising

Classified ads: Contact Bev Kirkpatrick or Deborah Rodd, *CJEM*, 1867 Alta Vista Dr., Ottawa ON K1G 5W8; 800 663-7336 or 613 731-8610 x2127/2314, fax 613 565-7488, advertising@cma.ca. See Classified Advertising section of the Journal for information on rates. **Display ads:** Contact Deborah Woodman (see preceding information); x2159.