CLINICAL ASSESSMENT OF TRAMADOL ANALGESIC EFFECT IN COMPARISON TO COMBINATION OF PARACETAMOL AND CHLORZOXAZONE IN ACUTE NEUROPATHIC PAIN IN IRAQI PATIENTS

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Key words : chlorzoxazone, paracetamol, tramadol, neuropathic pain
Received(October) Accepted(December)

ABSTRACT
Neuropathic pain (NP) is pain initiated or caused by a primary lesion or dysfunction in the nervous system. Many common diseases, injuries, and interventions cause NP by producing lesions in somatosensory pathways in the peripheral or central nervous system. Its treatment is complex with often inadequate response to treatment. Tramadol has been considered as the analgesic of choice for patients in moderate to severe pain and used as a control treatment. Combination of the skeletal muscle relaxant chlorzoxazone and the non-opioid analgesic paracetamol was investigated for their efficacy of blocking NP in comparison with the control treatment. Forty eight patients with age range 20-40 years old (27 males and 21 females) who were treated for acute neuropathic pain in Dijlah rehabilitation hospital were involved. The efficacy of treatment was assessed using 0-10 numeric pain scale. The safety issue of drugs was assessed by investigating liver function test, serum creatinine and hematological parameters. The results revealed that there is no statistical difference ($p \geq 0.05$) in pain treatment efficacy between the investigated treatment and the control group. The safety issue showed that there is no statistical difference ($p \geq 0.05$) between the measurement of laboratory data before and after time schedule of the treatment. It is concluded that chlorzoxazone / paracetamol combination therapy is an effective and safe treatment for neuropathic pain comparable to tramadol.

التقييم ألسريري للتأثير المسكن للألم للترامادول بالمقارنة مع توليفة من الباراسيتامول والكلورزوكسازون لمرضى الم الاعتلال العصبي الحاد للعراقيين

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الخلاصة
الم الاعتلال العصبي هو الألم الناشئ أو المتسبب من آفة أولية أو خلل وظيفي في الجهاز العصبي. عدد من الأمراض الشائعة والإصابات والتداخلات تؤدي إلى الم الاعتلال العصبي عن طريق حدوث آفات في المسلك الحسي الجسدي للجهاز العصبي المركزي أو المحيطي وعلاجه معقد مع استجابة غير كاملة للعلاج أحيانا. يعتبر الترامادول من المسكنات المختارة للمرضى المصابين بالألم متوسط إلى شديد وتم استخدامه كعلاج للسيطرة. تم اختيار توليفة من مرخي العضلات الهيكلية الكلورزوكسازون والمسكن غير افيوني المفعول البراسيتامول لدراسة نجاعته في إيقاف الم الاعتلال العصبي بالمقارنة مع مجموعة السيطرة. ثمان واربعون مريضا تتدرج أعمارهم من 20-40 سنة (27 ذكر و 21 أنثى) والذين كانوا يعالجون من الم الاعتلال العصبي في مستشفى دجلة للتأهيل الطبي شملوا بالدراسة. تم تقييم نجاعة العلاج باستخدام مقياس الألم العددي (0-10). وتقييم مأمونية العلاج بفحص وظائف الكبد والكرياتينين في مصل الدم والفحوصات الدمائية. أظهرت النتائج عدم وجود فرق إحصائي في نجاعة علاج الألم بين العلاج المستخدم في الدراسة

وعلاج السيطرة. كما ظهر عدم وجود فرق إحصائي في القياسات المخبرية قبل وبعد العلاج المجدول زمنيا. تستنتج الدراسة أن توليفة الكلورزوكسازون مع الباراسيتامول علاج ناجع وآمن لألم الاعتلال العصبي مقارنة مع الترامادول.

1. INTRODUCTION

The International Association for the Study of Pain (IASP) defines neuropathic pain (NP) as pain ‘‘initiated or caused by a primary lesion or dysfunction in the nervous system’’. It is estimated to afflict millions of people worldwide, although precise figures are not available. Many common diseases, injuries, and interventions cause NP by producing lesions in somatosensory pathways in the peripheral or central nervous system [(1)] .

It may be associated with abnormal sensations called dysesthesia, and pain from normally non-painful stimuli (allodynia). Neuropathic pain may have continuous and/or episodic (paroxysmal) components. The latter resemble electric shocks. Common qualities include burning or coldness, "pins and needles" sensations, numbness and itching. Nociceptive pain, by contrast, is more commonly described as aching [(2)] .

Up to 7-8 % of the European population is affected, and in 5% of persons it may be severe. Neuropathic pain may result from disorders of the peripheral nervous system or the central nervous system (brain and spinal cord). Thus, neuropathic pain may be divided into peripheral neuropathic pain, central neuropathic pain, or mixed (peripheral and central) neuropathic pain [(3,4)].

Causes of central neuropathic pain is found in spinal cord injury, multiple sclerosis and some strokes[(5)]. Aside from diabetes and other metabolic conditions, the common causes of painful peripheral neuropathies are herpes zoster infection, HIV-related neuropathies, nutritional deficiencies, toxins, remote manifestations of malignancies, immune mediated disorders and physical trauma to a nerve trunk [(6,7)]. Neuropathic pain is common in cancer as a direct effect of cancer on peripheral nerves (e.g., compression by a tumor), or as a side effect of chemotherapy (chemotherapy-induced peripheral neuropathy**)**, radiation injury or surgery[(8,9)] .

Tramadol is a non-opioid derived synthetic opiod which has the additional property of inhibiting intersynaptic reuptake of noradrenaline and serotonin, thus giving it a dual mode of analgesic action. This gives tramadol a unique place in the pain relieving armamentarium in that not only does it provide analgesia over a wide range of pathologies, but it also has significant advantages over other opioids. These include its lack of significant respiratory depressant effects, unlikely development of tolerance and dependence, and a low adverse event profile.

Tramadol has proved to be a valuable addition to the range of effective analgesic drugs, and as further aspects of its use are revealed, may well become the analgesic of choice for patients in moderate to severe pain[(10)].

Paracetamol is an analgesic, antipyretic derivative of acetanilide. It has weak anti-inflammatory properties and is used as an analgesic and antipyretic. Paracetamol is classified as a mild analgesic. It is commonly used for the relief of headaches and other minor aches and pains and is a major ingredient in numerous cold and flu remedies. In combination with opioid analgesics, paracetamol can also be used in the management of more severe pain such as post-surgical pain and providing palliative care in advanced cancer patients[(11)]. Though paracetamol is used to treat inflammatory pain [(12)].

Chlorzoxazone is a centrally acting muscle relaxant used to treat muscle spasm and the resulting pain. It acts on the spinal cord by depressing reflexes. It is used for the relief of pain and inflammation in rheumatoid arthritis, osteoarthritis and other musculoskeletal disorders. It works by blocking the action of cyclo-oxygenase [(13)].

Skeletal muscle relaxants have been studied as adjunctive therapy to analgesics in treating acute low back pain [(14)].

2. MATERIALS AND METHODS

The present study was carried out at Dijlah rehabilitation center, Salah-Aldeen governorate, from January until May 2014. The study was designed as an open labeled study in which forty eight patients with age range 20-40 years old (27 males and 21 females) who were treated for acute neuropathic pain were chosen.

Inclusion criteria

Patients attending Dijlah rehabilitation center complaining of acute neuropathic pain for the last six months.

Exclusion criteria

1. Chronic neuropathic pain (neuropathic pain lasting more than six months).
2. Patients with constitutional symptoms suggestive of inflammatory origin of the pain.
3. Patients with chronic systemic diseases and other co-morbidities including liver and renal illnesses.

Study protocol

The diagnosis of acute neuropathic pain was made by neurologist on the basis of history and clinical examination of the patients with acute neuropathic pain of less than six months duration. Laboratory investigations involving complete blood count and erythrocyte sedimentation rate (CBC& ESR), liver function test (Alanine amino transferase"ALT" ,

Aspartate aminotransferase "AST" and Alkaline phosphatase "ALP") and renal function test (Serum creatinine "S.Cr"), were done to exclude the cases that have significant changes in the laboratory findings suggesting other medical problems or an underlying systemic pathology .

All the individuals included in the study were well informed about the study methodology and also about the (0–10) Numeric Pain Rating Scale[15] prior to their inclusion. The individuals were unaware of the analgesic which they had taken during the study.

Response and safety measures were assessed after 1, 2 and 3 weeks for both groups.

The drugs chlorzoxazone 375mg/paracetamol 500 mg (relaxone) capsule were procured from Jamjoom pharmaceuticals, batch No. PG0024/ exp. date July 2015, and tramadol 50 mg capsule (trabilin-50) were procured from mepha pharmaceuticals, batch No. 1351504/ exp. date April 2016, and they have been assigned a code. Patients were randomly assigned in either treatment groups with an assigned code.

The laboratory hematological investigations were done using Mindray Auto Hematology Analyzer BC-2800 (China) to assess complete blood count, and biochemistry investigations were performed using Reflotron Plus Haematology Analyzer (United Kingdom) to measure renal and liver function tests. ESR was measured using Westergren method.

All investigations were done before treatment, after 1, 2 and 3 weeks of continuous treatment.

Patients groups

Forty eight patients were included in the study and divided into two groups containing 24 patients (14 males and 10 females) in the 1st group and 24 patients (13 males and 11 females) in the 2nd group. The mean age was 29.7 year for the 1st and 32.2 year for the 2nd group :

Group 1 : taking tramadol 50mg capsule twice daily oral dose for three consecutive weeks.

Group 2 : taking chlorzoxazone 375mg/paracetamol 500 mg (relaxone) . single daily oral dose at bed time for three consecutive weeks.

All the codes of administered drugs were disclosed only after the pain assessment. The group '1' received tramadol 50mg twice daily oral dose at bed time for three consecutive weeks. The group '2' received chlorzoxazone (relaxone) single daily oral dose at bed time for three consecutive weeks.

Pain assessment was done by (0–10) Numeric Pain Rating Scale [15] (0 : no pain, 5 : moderate pain and 10 : worst possible pain). The pain assessment was started immediately before treatment and then assessed after treatment at time points of 1, 2 and 3, weeks.

Statistical analysis of data

The statistical analysis was performed by Graph Pad Prism (Version 5.01) which includes:

1. Mean ± Standard error of mean (mean ±SEM).
2. Two way analysis of variance (ANOVA) was used to examine the difference of the mean of data between the study groups. The results of analysis with P values < 0.05 was considered significant. If there are significant differences, unpaired T-test was used to determine the difference between the two variables, one before management and the second after 1, 2 or 3 weeks of management. The results of analysis with P values < 0.05 was considered significant.

3. RESULTS

Effect of treatment on the 0-10 numeric pain scale

Table 1 and Figure 1 show the effect of treatments for group1 (tramadol 50mg capsule twice daily oral dose) and group 2 (chlorzoxazone 375mg/paracetamol 500) on the 0-10 numeric pain scale after 1,2 and 3 weeks. It is obvious that there is differences in the pain scale value depending on the type of the studied drugs as compare to the control one, and also regarding to the investigated time intervals as compared to base line.

Table 1: Effect of treatments on group 1 (tramadol 50mg capsule twice daily oral dose) as a control group, and group 2 (chlorzoxazone 375mg/paracetamol 500 mg single daily oral dose at bed time) for five consecutive days, after 1,2 and 3 weeks of treatment.

Group no.	Before treatment	After 1 week	After 2 weeks	After 3 weeks
1 (N=24)	8.08±0.28	6.83±0.27 **a b**	4.83±0.24 **a b**	2.75±0.21 **a b**
2 (N=24)	8.16±0.24	6.41±0.28 **a b**	4.58±0.19 **a b**	2.66±0.18 **a b**

values are presented as mean ± standard error of the mean(SEM).

a Significant difference ($P<0.05$) as compared with baseline (before treatment) values (analyzed by unpaired T-test).

b No significant difference ($P\geq0.05$) as compared with control group values (analyzed by unpaired T-test).

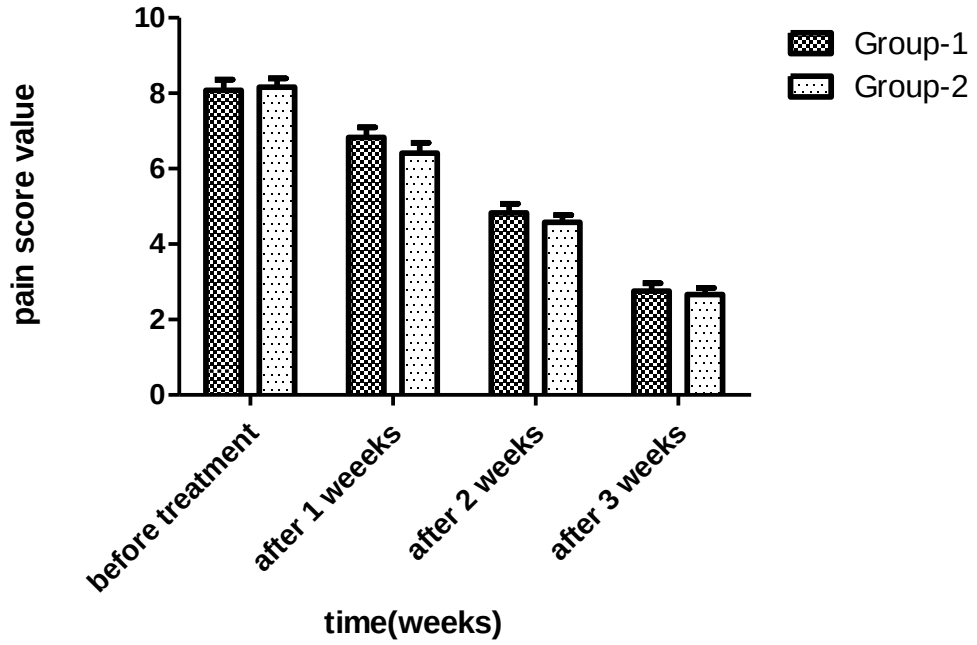

Figure 1: 0-10 numeric pain scale : mean values for groups 1 and 2 versus time (1,2 and 3 weeks of treatment).

Effect of studied drugs on the laboratory parameters

- **Effect of studied drugs on the liver function tests**

The baseline mean values of liver function enzymes (AST, ALT and ALP) before treatment for group 1 were 21.59 , 34.18 and 50.62 U/L respectively . The enzymes level after 1 week treatment were 21.52, 34.22 and 50.45 U/L respectively . And the enzymes level after 2 weeks of treatment were 21.55, 34.24 and 50.65 respectively. The enzymes level after 3 weeks of treatment were 21.64, 34.28 and 50.61 respectively.

The baseline mean values of liver function enzymes (AST, ALT and ALP) before treatment for group 2 were 22.25 , 35.08 and 50.92 U/L respectively . The enzymes level after 1 week treatment were 22.65, 34.95 and 50.77 U/L respectively. And the enzymes level after 2 weeks of treatment were 22.48, 34.88 and 50.82 respectively. The enzymes level after 3 weeks of treatment were 22.51, 34.97 and 50.89 respectively.

Analyzing the mentioned results statistically showed that there is no significant difference ($p \geq 0.05$) in liver function test when comparing the baseline values with the values after 1,2 and 3 weeks of treatment for both groups for all the three investigated enzymes.

Effect of studied drugs on serum creatinine

The baseline mean values of serum creatinine before treatment for group 1 was 0.98 mg/dl . The level after 1 week treatment was 0.92, mg/dl . The level after 2 weeks of treatment was 0.96 mg/dl. The level after 3 weeks of treatment was 0.94 mg/dl.

The baseline mean values of serum creatinine before treatment for group 2 was 0.96 mg/dl . The level after 1 week treatment was 0.95, mg/dl . The level after 2 weeks of treatment was 0.98 mg/dl. The level after 3 weeks of treatment was 0.92 mg/dl.

Statistical analysis of the results showed that there is no significant difference ($p \geq 0.05$) in serum creatinine when comparing the baseline values with the values after 1,2 and 3 weeks of treatment for both groups
for serum creatinine levels.

Effect of studied drugs on hematological parameters

- **Effect of studied drugs on WBC count :**

The baseline mean values of WBC count before treatment for group 1 was 7.62 $\times 10^9$ cell/L . The level after 1 week treatment was 7.43 $\times 10^9$ cell/L, mg/dl . The level after 2 weeks of treatment was 7.24 $\times 10^9$ cell/L. The level after 3 weeks of treatment was 7.62 $\times 10^9$ cell/L.

The baseline mean values of WBC count before treatment for group 2 was 7.56 $\times 10^9$ cell/L. The level after 1 week treatment was 7.45, $\times 10^9$ cell/L. The level after 2 weeks of treatment was 7.61 $\times 10^9$ cell/L. The level after 3 weeks of treatment was 7.52 $\times 10^9$ cell/L.

Assessment of the mentioned results statistically showed that there is no significant difference ($p \geq 0.05$) in WBC count when comparing the baseline values with the values after 1,2 and 3 weeks of treatment for both groups for WBC count levels.

- **Effect of studied drugs on platelets count :**

The baseline mean values of platelets count before treatment for group 1 was 245.82 $\times 10^9$ cell/L . The level after 1 week treatment was 238.96 $\times 10^9$ cell/L. The level after 2 weeks of treatment was 243.55 $\times 10^9$ cell/L. The level after 3 weeks of treatment was 237.99 $\times 10^9$ cell/L.

The baseline mean values of platelets count before treatment for group 2 was 252.12 $\times 10^9$ cell/L. The level after 1 week treatment was 247.32 $\times 10^9$ cell/L. The level after 2

weeks of treatment was 249.11 $\times 10^9$ cell/L. The level after 3 weeks of treatment was 246.98 $\times 10^9$ cell/L.

Analyzing the mentioned results statistically showed that there is no significant difference ($p \geq 0.05$) in platelets count when comparing the baseline values with the values after 1,2 and 3 weeks of treatment for both groups for platelets count levels.

- **Effect of studied drugs on Hb level :**

The baseline mean values of Hb levels before treatment for group 1 was 14.95 g/dl . The level after 1 week treatment was 14.21 g/dl . The level after 2 weeks of treatment was 14.64 g/dl. The level after 3 weeks of treatment was 14.58 g/dl.

The baseline mean values of Hb level before treatment for group 2 was 15.21 g/dl . The level after 1 week treatment was 14.92 g/dl . The level after 2 weeks of treatment was 14.66 g/dl. The level after 3 weeks of treatment was 14.82 g/dl.

The mentioned results statistically showed that there is no significant difference ($p \geq 0.05$) in Hb count when comparing the baseline values with the values after 1,2 and 3 weeks of treatment for both groups for Hb count levels.

- **Effect of studied drugs on ESR level**

The baseline mean values of ESR levels before treatment for group 1 was 16 mm/hr . The level after 1 week treatment was 18 mm/hr . The level after 2 weeks of treatment was 14 mm/hr. The level after 3 weeks of treatment was 17 mm/hr.

The baseline mean values of ESR before treatment for group 2 was 19 mm/hr . The level after 1 week treatment was 16 mm/hr. The level after 2 weeks of treatment was 15 mm/hr. The level after 3 weeks of treatment was 17 mm/hr.

Evaluation of the mentioned results statistically showed that there is no significant difference ($p \geq 0.05$) in ESR values when comparing the baseline values with the values after 1,2 and 3 weeks of treatment for both groups for ESR values.

4. DISSCUSION

Neuropathic pain (NP) management is complex with often inadequate response to treatment. Even with well-established NP medications, effectiveness is unpredictable, dosing can be complicated, analgesic onset is delayed, and side effects are common. Evidence-based consensus treatment recommendations exist[16], but additional medications have become available since their publication. Because of gaps and controversies in the literature, considerable interpretation of available evidence, judgment, and experience is required to develop treatment approaches that can be used in clinical practice [17].

Medications that have demonstrated efficacy in several different NP conditions may have the greatest probability of being efficacious in additional, as yet unstudied, conditions. However, it is possible that some types of NP respond differently to treatment [18,19] .

Unfortunately, there is insufficient evidence to rank first-line medications for NP by their degree of efficacy or safety and little is known regarding the treatment response of patients with mild to-moderate NP because randomized clinical trials (RCTs) have typically evaluated chronic NP of moderate to severe intensity, whereas the current study investigate cases of acute NP of less than six weeks duration [20] .

Individual variation in the response to the medications used to treat NP is substantial and unpredictable. Although evidence-based recommendations encourage the use of specific medications, the overall approach should be recognized as a stepwise process intended to identify the medication, or medication combination, that provides the greatest pain relief and fewest side effects for a given patient [20] .

Regarding effect of investigated drugs on neuropathic pain, the results of the present study denotes that the treatment with chlorzoxazone 375 mg/ paracetamol 500 mg for three consecutive weeks for patients with acute neuropathic pain have comparable efficacy to the established treatment with tramadol 50 mg for the same duration (three weeks) since there is no statistical difference ($p \geq 0.05$) between the investigated drug and the control one during the same management time profile.

Where previous studies evoked that Paracetamol is used in the symptomatic management of pain due to its activity by peripheral blockage of pain impulse generation[21,22], and Chlorzoxazone is a skeletal muscle relaxant principally used for relieving painful muscle spasms occurring in musculoskeletal and neuromuscular disorders, due to its activity in blocking interneuronal conduction in spinal cord and sub-cortical brain area by depressing polysynaptic reflexes[23-25]. These facts suggest that there might be a potential effective analgesia due to the synergistic action performed by combination of different mechanisms of pain suppression that was comparable to tramadol analgesia.

Regarding effect of investigated drugs on the laboratory parameters, the results of present study showed that after treatment of the two groups of patients enrolled in the study that there is no significant difference in the investigated parameters (AST, ALT, ALP, S.Cr, WBC count, Plt. count, Hb and ESR) levels after 1, 2 and 3 weeks of treatment as compared with the baseline levels. This indicates that the studied drugs did not affect the level of these parameters significantly ($p \geq 0.05$) and the safety of these drugs regarding this point of view can be considered. This result is compatible with the previous studies that showed the safety profile of the investigated drugs [26- 28].

5. CONCLUSION

The results of this study revealed that chlorzoxazone 375mg/ paracetamol 500 mg combination therapy is an effective treatment for the management of neuropathic pain. The efficacy of the studied combination is comparable to that obtained by tramadol 50mg twice

daily. The safety profile of combination therapy was approved for the study time. It is recommended that further studies are suggested to establish strategies of prediction of optimum combinations, including methods to assess the interactions of multiple concurrent analgesic drugs and adverse effects. Further trials must evaluate the components of the combination with each of the constituent drugs on their own, to best show the value added by the combination. Furthermore, careful attention is needed to define the optimum dose ratio between components used in pain treatment.

REFERENCES

1. Dworkin R H , O'Connor A B , Backonja M, et al (2007). Pharmacologic management of neuropathic pain: Evidence-based recommendations. Pain: 132; 237–251.

2. Merskey H, Bogduk N (1994). Classification of Chronic Pain: Descriptions of Chronic Pain Syndromes and Definitions of Pain Terms. 2nd edn. Seattle: IASP Press; 209–14.

3. Torrance N, Smith BH, Bennett MI, Lee AJ (April 2006). The epidemiology of chronic pain of predominantly neuropathic origin. Results from a general population survey. J Pain 7 (4): 281–9.

4. Bouhassira D, Lantéri-Minet M, Attal N, Laurent B, Touboul C (June 2008). Prevalence of chronic pain with neuropathic characteristics in the general population. Pain 136 (3): 380–7.

5. Foley P, Vesterinen H, Laird B, et al (2013). Prevalence and natural history of pain in adults with multiple sclerosis: Systematic review and meta-analysis. Pain 154 (5): 632–42.

6. Portenoy RK (1989). Painful polyneuropathy. Neurol Clin 7 (2): 265–88.

7. Vaillancourt PD, Langevin HM (1999). Painful peripheral neuropathies. Med. Clin. North Am. 83 (3): 627–42.

8. Oncologypt.org. Chemotherapy-induced Peripheral Neuropathy Fact Sheet, Retrieved on 29 December 2008.

9. Cancerbackup, Macmillan Cancer Support. Peripheral neuropathy, Retrieved on 29 December 2008.

10. Budd K (December 1999). The role of tramadol in acute pain management. Acute Pain; 2: 189–196.

11. Shaikh KA, Devkhile AB (2008 Aug). Simultaneous determination of aceclofenac, paracetamol and chlorzoxazone by RP-HPLC in pharmaceutical dosage form. Journal of Chromatographic Science, 46: 649-2.

12. Hazlewood G, van der Heijde DM, Bombardier C (2012). Paracetamol for the management of pain in inflammatory arthritis: a systematic literature review. J Rheumatol Suppl. Sep;90:11-6.

13. Manasa P, Srilatha S (2014). Design and evaluation of bilayer tablets of paracetamol and chlorzoxazone. World journal of pharmacy and pharmaceutical sciences; 3: 1057-1072.

14. See S, Ginzburg R (2008 Aug). Choosing a skeletal muscle relaxant. Am fam physician. 1;78(3): 365-370..

15. McCaffery M, Pasero C (1999). Pain: Clinical Manual. St. Louis; P. 16. Copyrighted by Mosby, Inc.

16. Dworkin RH, Backonja M, Rowbotham MC, Allen RR, Argoff CR, Bennett GJ, et al (2003). Advances in neuropathic pain: diagnosis, mechanisms, and treatment recommendations. Arch Neurol; 60:1524–34.

17. Finnerup NB, Otto M, Jensen TS, Sindrup SH (2005). Algorithm for neuropathic pain treatment: an evidence based proposal. Pain;118:289–305.

18. Hansson PT, Dickenson AH (2005). Pharmacological treatment of peripheral neuropathic conditions based on shared commonalities despite multiple etiologies. Pain;113:251–4.

19. Attal N, Cruccu G, Haanpa¨a¨ M, Hansson P, Jensen TS, Nurmikko T, et al (2006). EFNS guidelines on pharmacological treatment of neuropathic pain. Eur J Neurol;13:1153–69.

20. Cruccu G, Anand P, Attal N, Garcia-Larrea L, Haanpa¨a¨ M, Jorum E, et al (2004). EFNS guidelines on neuropathic pain assessment. Eur J Neurol;11:153–62.

21. Stricker BHC, et al (1985). Acute hypersensitivity reactions to paracetamol. Br Med J, 291:938- 9.

22. Van Diem L, Grilliat JP (1990). Anaphylactic shock induced by paracetamol. Eur J Clin Pharmacol; 38:389-90.

23. Rosin MA (1981). Chlorzoxazone induced spasmodic torticollis. JAMA, 246:2575.

24. Powers BJ, et al (1986). Chlorzoxazone hepatotoxic reaction: an analysis of 21 identified or presumed cases. Arch Intern Med, 146:1183-6.

25. Moore MR, Mccollkel (1991). Porphyria Research Unit, University of Glasgow.

26. Rose JB1, Finkel JC, Arquedas-Mohs A, Himelstein BP, Schreiner M, Medve RA (2003 Jan). Oral tramadol for the treatment of pain of 7-30 days' duration in children. Anesth Analg ;96(1):78-81.

27. Hughes, John (2008). Pain Management: From Basics to Clinical Practice. Elsevier Health Sciences.

28. Chou R1, Peterson K, Helfand M (2004 Aug). Comparative efficacy and safety of skeletal muscle relaxants for spasticity and musculoskeletal conditions: a systematic review. J Pain Symptom Manage ;28(2):140-75.