PHARMACOLOGICAL STUDIES ABOUT THE INTERACTIONS BETWEEN ETORICOXIB RESPECTIVELY TRAMADOL ASSOCIATED WITH ENALAPRIL

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Keywords: *Etoricoxib, Tramadol, Enalapril, interactions, pharmacological studies*

Abstract: *The purpose of this study was to verify the influence of antinociceptiv effect by associating an opioid drog respectively a NSAID with an angiotensin converting enzyme inhibitor . We also tested the analgesic effect of each drug used and we compared the results. Material and method: We used 5 groups of 10 mice Swiss breed and device Tail Flick Unit, standardized assessment to analgesics activities in animal experiments. The 5 groups were treated as follows: Group I: Tramadol; Group II: Etoricoxib; Group III: Enalapril; Group IV: Tramadol and Enalapril; Group V: Etoricoxib and Enalapril. Subsequently each animal from the lots above were exposed to pain stimulus 0, 15, 30, 60 and 90 minutes after treatment. Results: The mice from each lots had the maximum analgesic point at 30 minutes after the treatment administration. Among the 5 groups at the same time (T 30) animals in group I had the lowest sensitivity to pain stimulus (p <0.0001) followed by the animals in group II, III respectively group V. Conclusions: Among all the treatments done, the most effective was for the group treated with tramadol, although the measurements done at T 60 and T 90, its analgesic effect was matched by Etoricoxib. We observed a decrease in analgesic effect when we associated tramadol respectively Etoricoxib with Enalapril. Between the two was the more effective combinations that I used along with Enalapril Tramadol to all measurements (p <0.05), although the group treated with enalapril had a mild analgesic effect measurements made at 15 ', 30' , 60 'and 90' compared with the time T0 (p <0.05).*

Cuvinte cheie: *Etoricoxib, Tramadol, Enalapril, interacţiuni, studii farmacologice*

Rezumat: *Scopul studiului a fost verificarea influentei efectului antinociceptiv prin asocierea unor analgezice opioide respectiv non-opioide cu un inhibitor al enzimei de conversie a angiotensinei. Deasemeni am testat efectul analgezic al fiecarui preparat folosit si am comparat rezultatele obtinute. Material şi metodă: am folosit 5 loturi de cate 10 soareci rasa Swiss si aparatul Tail Flick Unit, standardizat pentru evaluarea activitatatii analgezice in experimentele pe animale. Cele 5 loturi au fost tratate dupa cum urmeaza: Lotul I: Tramadol (1 mg/kgc/soarece)-ip; Lotul II: Etoricoxib (2 mg/kgc/soarece)-po;Lotul III: Enalapril (0,5 mg/kgc/soarece)-po;Lotul IV: Tramadol (1 mg/kgc/soarece)-ip si Enalapril (0,5 mg/kgc/soarece)-po;Lotul V: Etoricoxib (2 mg/kgc/soarece)-po si Enalapril (0,5 mg/kgc/soarece)-po; Ulterior fiecare animal din loturile enumeratele mai sus au fost expuse stimulului algic la 0, 15, 30, 60 si 90 de minute de la administrarea tratamentului. Rezultate: Soarecii din fiecare din cele 5 loturi au avut punctul analgezic maxim, la 30 minute de la administrarea fiecaruia din regimurile de tratament administrate. Intre cele 5 loturi, la acelasi timp (T 30') animalele din lotul I a avut sensibilitatea cea mai scazuta la stimulul algic (p<0.0001) urmate fiind de animalele din lotul II , III respectiv lotul V . Concluzii: Regimul de tratament cu tramadol a avut cel mai eficient efect analgezic pentru toate măsurătorile efectuate, deşi pentru măsuratorile de la T 60 şi T 90, efectul său analgezic a fost egalat de Etoricoxib. Am observat o diminuare a efectului analgezic atunci cand am asociat tramadolul respectiv Etoricoxibul cu Enalapril. Între cele doua asocieri mai eficienta a fost cea în care am administrat împreună Tramadol cu Enalapril la toate măsurătorile efectuate (p<0,05), deşi şi lotul tratat cu Enalapril a avut un uşor efect analgezic pentru măsurătorile făcute la 15', 30', 60' şi 90' comparativ cu timpul T0 (p<0,05).*

THE AIM OF THE STUDY

The purpose of this study was to verify the influence of antinociceptiv effect by associating an opioid drog respectively a NSAID with an angiotensin converting enzyme inhibitor . We found frequently in the medical literature the association between Etoricoxib and Enalapril or other antihypertensive agents in studies for patients with rheumatologic disease who had the associated hypertension pathology [1,2,3]. These studies have shown that this combination will produce an increase in blood pressure. Because COX inhibition is associated with antinatriuretic and vasoconstrictor effects mediated through the inhibition of the actions of prostaglandin E_2 and prostacylin [4,5]. The first 2 studies that evaluated the effects of NSAIDs on BP demonstrated that mean arterial pressure could rise by as much as 5 to 6 mm Hg in a population of patients with hypertension [6]. The

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greatest effects of NSAIDs on BP control were observed in patients on monotherapeutic regimens of ß-adrenergic blocking drugs, diuretics, or angiotensin-converting enzyme (ACE) inhibitors [7,8,9].

MATERIAL AND METHOD

We used 5 groups of 10 mice Swiss breed and device Tail Flick Unit, standardized assessment to analgesics activities in animal experiments.

The 5 groups were treated as follows:

- Lot I: Tramadol (1 mg/kg of bodyweight/mouse)-ip;
- Lot II: Etoricoxib (2 mg/kg of bodyweight/mouse)-po;
- Lot III: Enalapril (0,5 mg/kg of bodyweight/mouse)-po;
- Lot IV: Tramadol (1 mg/kg of bodyweight/mouse)-ip and Enalapril (0,5 mg/kg of bodyweight/mouse)-po;
- Lot V: Etoricoxib (2 mg/ kg of bodyweight/mouse)-po and Enalapril (0,5 mg/kg of bodyweight/mouse)-po.

Subsequently each animal from the lots above were exposed to pain stimulus 0, 15, 30, 60 and 90 minutes after treatment.

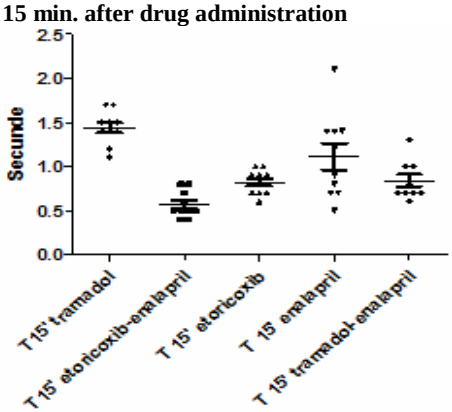
RESULTS AND DISCUSSIONS

We followed the variation of analgesic point depending on the time elapsed from administration of therapy for each lot. Thus all groups had an analgesic point within 30 minutes after treatment and the other times we got this effect antinociceptiv for each group:

For a properly statistical analysis to compare the studied groups, we calculated the difference in seconds between the times measured at times T 15, T 30, T60 and T 90 to T 0 (which represents for each animal its own control) after treatment administration. Thus we got the real growth to the nociceptive stimulus.

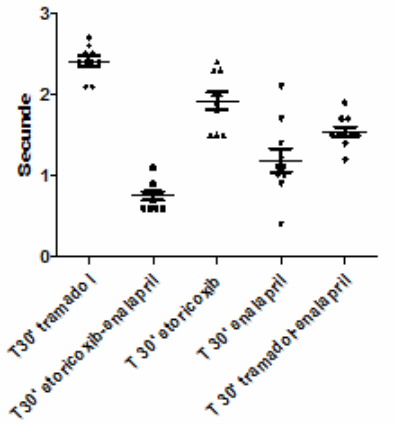
At 15 minutes after the all the treatments, the more effective analgesic effect appeared at the animals treated with Tramadol. Between this group and the others studied wasn't statistical difference ($p < 0.05$) except the group treated with Enalapril. The effect of this 2 substances (Enalapril and Tramadol) wasn't additive, on the contrary the association had a noticeable decrease in analgesic effect. Observation is emphasized by the statistical calculation. Between the groups treated with Etoricoxib, Enalapril and Enalapril - Tramadol wasn't statistical difference ($p > 0.05$). Again, Etoricoxib with Enalapril combination had a lower analgesic effect. The minimum antinociceptiv effect was at this association (Fig.1).

Figure no. 1. Variation of the analgezic effect of different drugs at 15 min. after drug administration



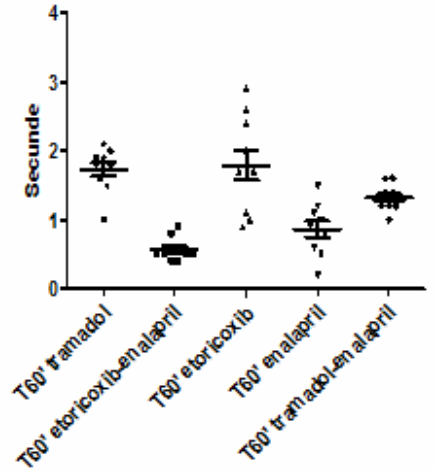
At 30 minutes after the medication administration also the group treated with Tramadol had the longest exposure to pain stimulus. Mice treated with Etoricoxib had a higher pain threshold than 15 minutes. There was no statistical difference between these and the mice treated with the combination of Tramadol and Enalapril ($p > 0.005$). The group of animals treated with Enalapril had a lower analgesic effect than all the lots. Again, groups treated with two drugs combinations had a lower analgesic effect than monotherapic treated groups. Note again that the best analgesic effect has the group trated with Tramadol (Fig.2).

Figure no. 2. Variation of the analgezic effect of different drugs at 30 min.after drug administration



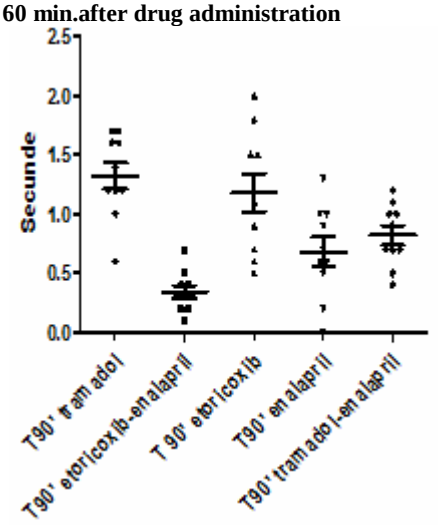
At 60 minutes after medication administration the groups treated with Tramadol and Etoricoxib have resisted the longest time after exposure to pain stimulus. However it should be noted that animals treated with Tramadol had an effect antinociceptiv lower than the measurement did at the time T 30. The group treated with Etoricoxib instead has maintained constant the analgesic effect at the measurement made at time T 60 ($p > 0.05$). Unlike the first time, respectively time T 90 when we made the measurements, when the combination of Tramadol and Enalapril were statistically lower in terms of analgesic effect compared with the group treated with Tramadol, when we made the measurements at time T 60 there wasn't statistical differences between the 2 groups. On the other hand the association between Etoricoxib and Enalapril compared with the group treated only with Enalapril, it was maintained a better antinociceptiv effect for the monotherapic treated group. The groups with the lowest analgesic effect were those which were treated with Enalapril respectively the combination between Enalapril and Etoricoxib, between this two groups there was no difference in statistical terms ($p < 0.05$) (Fig.3)

Figure no. 3. Variation of the analgezic effect of different drugs at 60 min.after drug administration



At 90 minutes after administration of medication were kept the same algesimetric values that we presented for time T 90, with the exception mentioned above related to the analgesic differences between Tramadol and Tramadol associated with Enalapril-treated group. It should be emphasized that at the time T 90, the group treated with Enalapril associated with Etoricoxib was the only one which hasn't a statistical difference with their control T 0 in terms of antinociceptive effect (Fig.4).

Figure no. 4. Variation of the analgezic effect of different drugs at 60 min.after drug administration



CONCLUSIONS

Among all the treatments done, the most effective was for the group treated with tramadol, although the measurements done at T 60 and T 90, its analgesic effect was matched by Etoricoxib. We observed a decrease in analgesic effect when we associated tramadol respectively Etoricoxib with enalapril. Between this two, the more effective combinations was for the group treated with Tramadol and Enalapril at all measurements we did ($p<0.05$), although the group treated with Enalapril had a slight analgesic effect on measurements made at T 15', T 30', T 60', and T 90' versus time T 0 ($p<0.05$).

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