Literature review

Comparative Pharmacology and Toxicology of Tramadol & Tapentadol

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https://doi.org/eiki/xxxxx

Abstract: Pain is a common symptom in various health conditions and can significantly impact a person's quality of life if not managed properly. Although non-steroidal anti-inflammatory drugs (NSAIDs) like ibuprofen are widely used for mild to moderate pain, they may not suffice for moderate to severe pain requiring combination therapy. In such cases, synthetic drugs like Tramadol and Tapentadol offer effective pain relief with improved safety profiles. This article aims to compare the pharmacokinetics, pharmacodynamics, and safety profiles of Tapentadol and Tramadol.

Tapentadol, a direct-acting synthetic opioid, demonstrates a reliable mode of action as it starts working upon reaching the bloodstream. In contrast, Tramadol requires metabolic conversion into active metabolites, resulting in a delayed onset of action. Furthermore, Tramadol's effectiveness is dependent on the presence of the CYP2D6 enzyme, with approximately 6% of Caucasians being deficient in this enzyme. Dosage adjustments may be required for individuals with impaired liver or kidney function.

Both Tapentadol and Tramadol primarily affect mu-opioid receptors (MOR), providing potent pain relief. However, Tramadol also inhibits the reuptake of noradrenaline and serotonin, while Tapentadol lacks an effect on serotonin. Tapentadol exhibits a higher affinity for MOR receptors, making it a more potent central acting painkiller compared to Tramadol. Nevertheless, Tapentadol's increased opioid activity increases the likelihood of mild and transient opioid-like side effects, such as drowsiness, constipation, and respiratory depression.

In terms of toxicology, both Tapentadol and Tramadol offer a safer alternative to morphine with reduced side effects. Tapentadol's greater opioid activity translates into a higher potential for opioid-related side effects, whereas Tramadol's serotonergic activity is associated with a higher incidence of vomiting and nausea. The absence of significant effects on CYP450 enzymes distinguishes Tapentadol from Tramadol, reducing the likelihood of drug interactions.

Overall, Tapentadol demonstrates several advantages over Tramadol, including faster onset of action, greater pain relief, and fewer side effects related to serotonergic activity. However, it is essential to consider that Tapentadol, although more effective, carries a higher probability of side effects associated with its increased opioid activity. Clinicians should carefully evaluate individual patient characteristics and requirements when selecting between these two medications for pain management.

Keywords: pain management, Tapentadol, Tramadol, opioids, pharmacokinetics, pharmacodynamics, safety profile.

Received: 07 June 2023

Accepted: 20 June 2023

Published: 25 June 2023

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Introduction

Pain is the primary symptom in a range of health conditions. Poorly managed acute or chronic pain may negatively influence numerous aspects of a person's life. However, managing pain adequately remains a challenge in many conditions[1].

For mild to moderate pains, NSAIDs (non-steroidal anti-inflammatory drugs) remain the mainstay of treatment. NSAIDs like ibuprofen have some distinct benefits like they are readily available. In addition, they do not cause dependence. However, they might often fail in moderate to severe pain requiring combination drug therapy[2].

In moderate to severe pain, synthetic drugs like Tramadol and Tapentadol may provide excellent relief. These are synthetic analogues of morphine with a considerably improved safety profile. It means that they can be readily prescribed for various painful conditions, infrequently cause side effects, and rarely cause any dependence.

However, it is worth knowing that sometimes these medications may work better when combined with NSAIDs. It is because, unlike NSAIDs, they do not have anti-inflammatory properties. These drugs are primarily painkillers.

Although Tapentadol and Tramadol share many traits, with quite a similar mode of action, they differ considerably in pharmacokinetics (how the body processes drugs) and pharmacodynamics (mechanism of action).

Tapentadol vs Tramadol – Pharmacokinetics

Although they may have similar effective dosages in many conditions, and both are commonly available as 50 mg tablets. Still, there are many differences between the two.

First and foremost, tramadol works mainly through active metabolites, and tapentadol is directly active. It means that tapentadol starts working as soon as it reaches the bloodstream, with a reliable mode of action. However, tramadol is first metabolized into active metabolites, with different modes of action. These metabolites of tramadol are more potent than the parent molecule. Since tramadol needs to be metabolized, it generally has a delayed onset of action and less reliable effect in some individuals[3].

The second significant difference between the two is that tramadol is dependent on the enzyme CYP2D6 for conversion into active metabolites. Its two major active metabolites are (+) and (-) enantiomers. These two enantiomers have a different modes of action4. In practice, it means that those deficient in these enzymes may not get sufficient benefit from the drug. Studies show that about 6% of Caucasians may be deficient in this enzyme[5].

Both drugs are effective from 50 mg onwards. However, unlike Tapentadol, Tramadol may need a loading dosage (starting dose) of 100 mg, followed by 50 mg every 6 hours, or as required. These differences are mainly due to differences between the two in pharmacokinetics[5,6].

Ultimately, both the drugs are metabolized in the liver, and their inactive metabolites are excreted via kidneys. Generally, mild to moderate kidney or liver disease does not affect their metabolism. However, those living with severe kidney or liver disease may need dosage correction.

Tapentadol vs Tramadol – Pharmacodynamics

Both these medications share numerous traits with morphine. However, these drugs were created as effective and yet much safer analogues of morphine. Although both the drugs work by influencing opioid receptors (especially mu-opioid receptors or MOR), there is a difference[3]. Activation of MOR receptors results in the potent painkilling effect of opioids.

Tramadol

It is a MOR activator and powerful Noradrenaline (NA) and 5HT (serotonin) reuptake inhibition. As it is metabolized to (+) and (-) enantiomers, it is worth knowing that its (+) enantiomer has more potent action on MOR receptors, causing higher pain relief. Unfortunately, it also means that tramadol has poor efficacy in those deficient in CYP2D6 enzyme, which may be close to 6% of the European population[7].

Studies show that most of its actions are due to its effects on MOR receptors and inhibition of NA uptake, with 5HT inhibition playing a minor role[7].

Tapentadol

Quite like tramadol, it affects MOR receptors and inhibits NA receptors. However, unlike tramadol, it does not influence 5HT. Moreover, tapentadol is not a prodrug. Thus, it starts acting soon after absorption by the body. It is not dependent on liver enzymes for conversion to active forms[8].

As tapentadol's affinity to MOR receptors differs from tramadol, further lack of action on 5HT means it differs in efficacy and safety.

Studies show that tapentadol has a more significant influence on MOR (that is, opioid) receptors than NA inhibition. Therefore, it appears to be a more potent central acting pain killer than tramadol. Some experts think it is 2-3 times more potent than tramadol, though it is less potent and safer than morphine[9].

Tapentadol vs Tramadol – toxicology

Both Tapentadol and Tramadol were created as a safer alternative to morphine. Morphine is more potent than both these drugs, but it causes numerous side effects characteristic of opioids like dry mouth, constipation, vomiting, nausea, sedation, respiratory depression, addiction10. Tapentadol and tramadol are much safer alternatives.

Tapentadol is much more potent than tramadol. It is because it has a greater influence on opioid receptors than tramadol. However, it also means greater chances of opioid-like side effects (but much milder and transient) like drowsiness, constipation, respiratory depression. But it also means that tapentadol has fewer chances of side effects associated with the serotonergic activity of tramadol like vomiting and nausea[9,11].

How does tapentadol compare to tramadol?

To conclude, it appears that tapentadol has the edge over tramadol. It is more effective in many ways[12].

Feature	Tapentadol	Tramadol	Advantage
Opioid activity	Higher opioid activity	Moderate action	Greater painkilling effect
Other actions	NA reuptake inhibition, no action on 5HT	NA and 5HT reuptake inhibitor	Fewer side effects related to serotonergic activity
Role of metabolites	Active drug	Mainly prodrug	Faster onset and reliable effect of tapentadol
Onset of action	32 min	Within 60 min	Faster action
Drug interactions	No effect on CYP450 enzymes	Metabolized by CYP450 enzymes	Greater chances of tramadol's interaction with other drugs

Variation of action	Not dependent on CYP pathway	Dependent of activity of CYP pathway	Less effective in individuals who are genetically deficient in these enzymes

Table 1 Adapted from; Singh DR, Nag K, Shetti AN, Krishnaveni N. Tapentadol hydrochloride: A novel analgesic. Saudi J Anaesth. 2013;7(3):322-326. doi:10.4103/1658-354X.115319)

As is evident from Table 1 that, tapentadol is better than tramadol in some ways. Nonetheless, it is worth noticing that tapentadol, though more effective than tramadol, is not essentially safer as it is more probable to cause side effects related to its higher opioid activity.

Conclusion

In conclusion, the comparative analysis between Tapentadol and Tramadol reveals distinct differences in their pharmacokinetics, pharmacodynamics, and safety profiles. Tapentadol emerges as a more effective painkiller, offering faster onset of action and greater affinity for mu-opioid receptors. Its unique properties make it a valuable option for moderate to severe pain management. However, it is important to note that Tapentadol's increased opioid activity also poses a higher risk of opioid-related side effects. Clinicians must carefully consider individual patient characteristics and balance the benefits and risks when selecting between these medications. Further research and clinical studies are warranted to gain a deeper understanding of their optimal use in specific patient populations.

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