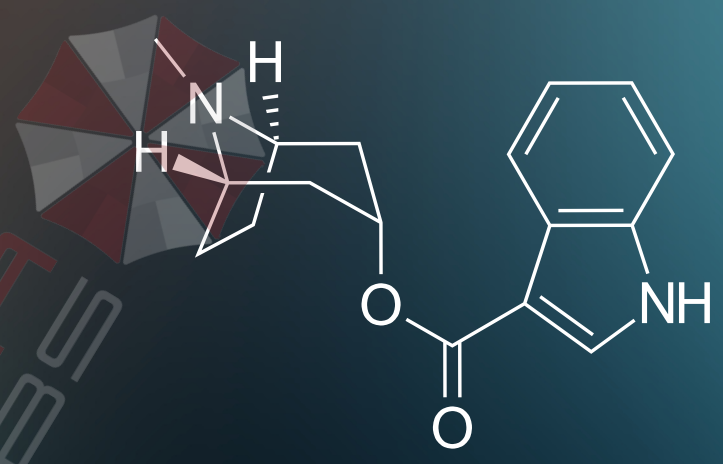


Tropisetron - A Multifaceted Approach to Neuroprotection and Pain

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History

Tropisetron is a substance originally developed to counter vomiting and nausea (antiemetic compound). It was originally referred to as ICS 205-930. Tropisetron was first patented in 1982, the first studies on the pharmacological profile and human trials appeared soon after. It is a part of a wider pharmacological group which names end in -setron, including ondansetron, dolasetron, granisetron, Tropisetron and palonosetron and more. The oldest of this group is ondansetron, which is also the most widely applied setron to this day, with Tropisetron being the second oldest. Tropisetron is used today a prescription drug in some countries like the UK, France, and Brazil, while others have discontinued its use due to the competition with other setrons, like the USA and Germany.

Pharmacologically, Tropisetron is an antagonist at the 5-HT3 receptor, which is found in the central and the peripheral nervous system with a variety of different functions. In the central nervous system, it is connected to the generation of nausea, but also has anti-convulsant effect and affects pain signalling. It is also a partial agonist at the α7-nicotinic receptor (a subtype of the nicotinic acetylcholine receptor), which is involved in the formation of memories and attention. While all other setrons are all antagonist at the 5-HT3 receptor, only Tropisetron is reported to be an partial agonist at the α7-nicotinic receptor.[1] However, some other 5-HT3 receptor antagonist, which are not part of the setron group, can also serve as agonists at the α7-nicotinic receptor, for example a substance with the development name LY 278584.

Even further evidence does also suggest that Tropisetron influences an additional receptor signalling pathway, namely the α1 Glycine receptor. This receptor is widely distributed on the central nervous system. Tropisetron seem to bind this receptor at extremely low concentrations (1 pM). While it cannot activate the receptor by itself, it does sensitize the receptor for its natural ligand, glycine.[2] The mechanism of this interaction has been further explored, but it not clear how it contributes to the clinical application of Tropisetron.[3]

General Pharmacological Information

The intake of Tropisetron is confirmed to be effective via oral and intravenous administration. After oral administration, the absorption of Tropisetron is rapid with a high bioavailability of about 2 hours. It has a large distribution

volume, meaning that it permeates in most of the human body, including fat and brain tissue. It has a low first pass effect in the liver. An intravenous dose of 45 mg Tropisetron leads to almost no breakdown, while a dose of 10 mg will be broken down by around 30% through liver enzymes. However, the exact bioavailability is determined by the activity of the Cytochrome P450 System (CYP2D6) of the individual. In most people of western populations, the fast metabolizers are more common, with only 8 % off all people being slow metabolizers. Fast metabolizers need around 7 hours to eliminate half the drug from their system, while slow metabolizers need 42 hours.[4] At a 5 mg oral dose, oral bioavailability ranged between 27 % and 99 %.[5] In the blood, around 65% of Tropisetron is bound to proteins.

The breakdown of the drug mainly takes place at the indole ring system at the positions 5,6 and 7, where hydroxylation takes place, typically followed by conjugation with glucuronic acid and sulphate. Around 9% of the drug is eliminated unchanged in urine, while 70% are eliminated as conjugated metabolites via the same route. 15 % is eliminated by faeces.

Toxicology

The recommended clinical dose is 5 mg for 6 days to treat episodes of operative and chemotherapy induced nausea.[4] Tropisetron was well tolerated by volunteers when given as single oral doses of up to 150 mg or single intravenous doses of up to 100 mg. Headache, constipation and nonspecific tiredness were the most common adverse events at these dose levels, but occurred at similar frequencies during placebo treatment. Single oral doses of 200 mg Tropisetron given to 6 volunteers were associated with one severe migraine attack and one attack of severe abdominal pain with vomiting and postural hypotension. No single intravenous doses greater than 100 mg were tested. Multiple oral doses of Tropisetron of up to 50mg once daily for 14 days were tolerated well by volunteers. Seven-day treatment with Tropisetron 50mg twice daily was associated with headache and constipation. All of 3 subjects treated with 100 mg twice daily had severe adverse events, necessitating early discontinuation of treatment; they experienced hallucinations, severe headache, and constipation. Multiple intravenous doses of Tropisetron were well tolerated at levels of up to 100 mg per day for 14 days. On day 9 of treatment with Tropisetron 100 mg daily, 1 subject with a history of brain damage and a previous post-traumatic seizure suffered another seizure.[4]

Long term data for using larger doses of Tropisetron is also available. Tropisetron was given at doses of 0.5 to 50 mg per day for up to 3 months in studies for indications other than chemotherapy-induced nausea, usually gastric emptying, and prevention of migraine headache. In these studies , constipation and headache were the most common adverse events.[4]

Animal Trials

A study found that Tropisetron does bind an important protein for the development of Alzheimer`s disease in a mouse with Alzheimer model. Mice also showed an increased spatial and working memory in the disease stages at a concentration of 0.5 mg/kg per day. The authors concluded that Tropisetron may be effective in treating mild cognitive impairment and Alzheimer's disease.[6]

The injection of harmful amyloid beta protein, as it occurs in the brain due to the changes in Alzheimer's disease, injected into brain of rats, lead to direct damage to brain tissue and acute signs of inflammation. Regular injections of Tropisetron of 1 µg did significantly reduce the inflammation and inhibited cognitive deficits experienced by those rats not treated with Tropisetron. Conversely, rats injected with mCPBG (a selective 5-HT3 receptor agonist) did experience higher rates of inflammation compared to the control group. This indicates that the activation of 5-HT3 receptors does play a role in inflammatory processes invoked by amyloid beta proteins.[7]

Interestingly, Tropisetron was also successful to reduce inflammation in the gastrointestinal system of rats which was irritated by a previous application of acetic acid, indicating Tropisetron has more general anti-inflammatory effects.[8] This anti-inflammatory effect was also theorized to play a role in

the finding that chemotherapy induced damage to the kidney was attenuated by additional Tropisetron in rats.[9]

Humans chronically treated with antipsychotic drugs usually suffer cognitive deficits. In a rat animal model, the injection of Tropisetron did improve the mental performance of these rats, indicating Tropisetron can potentially improve cognition in schizophrenic humans, which was later confirmed in clinical trials.[10]

Tropisetron has been discussed and trailed as a potential agent to treat pain. A rat model shows pain inhibition by Tropisetron may be dependent on pain type. While the administration of Tropisetron did inhibit pain caused either by mechanical damage or increased pain sensitivity, it did not show any effect on the pain experienced from cold exposure. Hence, using Tropisetron did treat pain might only work under specific conditions.[11]

Rats with damage to the optic nerve received an injection of Tropisetron. After 7 days, the molecular markers in the retina were evaluated. The results indicated that Tropisetron, along with ondansetron has potential neuro-protective effects.[12] This neuroprotective effect has only been published and studied recently and follow-up studies are expected.

Human Trials With Tropisetron

In cancer treatment induced nausea & general nausea

The first human trial was reported in 1987 on 11 cancer patients, who received 20 mg of the substance in two 15 min infusions.[13] The results showed it was more effective than previous common clinical practice using metoclopramide. Tropisetron also did not show any major adverse effects in this first trial. Another trial with 22 patients came to similar conclusions.[14]

In dose-finding studies, Tropisetron was shown to completely prevent nausea and/or vomiting in up to two-thirds of patients receiving high dose cis-platin treatment; in the majority of patients a single dose of Tropisetron was effective for at least 24 hours after chemotherapy. A 5 mg dose proved as effective as 10, 20 or 40mg, and somewhat more effective than a 2mg dose. Therefore, 5mg was determined to be the optimal daily dose for preventing the nausea and vomiting associated with the administration of chemotherapy.[4]

Further early clinical studies have been conducted by Clinical Research Department of Sandoz Pharma Ltd, in order to compare the substance to alternative anti-emetics. Tropisetron was compared with metoclopramide (either as monotherapy or in combination with benzodiazepines). These studies included a total of 582 patients, of whom 309 received Tropisetron, 51 received metoclopramide with or without benzodiazepines and 222 received an antiemetic cocktail based on high dose metoclopramide combined with dexamethasone and lorazepam or diphenhydramine. The results of these studies indicate that Tropisetron at a dose of 5 mg once a day is an effective and well tolerated single-agent antiemetic treatment that can be given without special precautions to all patients treated with aggressive chemotherapy. Compared with metoclopramide (with or without lorazepam), Tropisetron was more effective in preventing acute nausea and vomiting. Compared with the antiemetic cocktails, Tropisetron was equally effective in preventing acute vomiting and somewhat less effective in preventing acute nausea. Tropisetron was as effective as metoclopramide and somewhat less effective than the antiemetic cocktails in preventing delayed nausea and vomiting. However, when patients were followed up for more than 1 treatment course, anti-emetic cocktails were no longer superior to Tropisetron treatment and produced more adverse events.[4]

Another set of clinical studies was independently performed around the same time by a group based at the University of Torino, Italy. Their results showed Tropisetron 10 mg intravenously before chemotherapy did effectively reduce nausea and vomiting in about 85 % of all patients, with only minor side effects reported.[15] A later trial lower dose of 5 mg per treatment was also deemed effective and was in fact superior in efficacy compared to metoclopramide.[16]

Tropisetron combined with haloperidol, a substance similar to metoclopramide, was shown to be more effective than either substance alone by a different trail.[17] This combination was likely

not adopted into clinical practice due to the side effects of haloperidol. Compared to other -setrons, specifically ondansetron and granisetron, Tropisetron did show a comparative efficacy and safety in a literature review.[18]

Modern studies have identified the combination of fosaprepitant, Tropisetron and dexamethasone, all of which are individually used as anti-emetics, as one of the most effective ways to decrease nausea over a longer period of time during combined radio-chemotherapy.[19]

Trials that did not focus on nausea specifically associated with chemotherapy, but rather on nausea in emergency situations or after surgery, did conclude Tropisetron was more effective than metoclopramide and droperidol in such scenarios.[20] Even a dose of 2 mg was found to be equally effective compared to the standard dose of 5 mg in treating post-operative nausea and vomiting.[21]

Schizophrenia

Schizophrenia is spectrum of psychiatric conditions in which the patient generally suffers from hallucinations and loss of reality. Historically, antagonists at 5-HT receptor subtypes have been used as anti-psychotics (such has haloperidol and clozapine) to treat this and other psychiatric conditions. -Setrons, including Tropisetron, have been trialed for a similar use in patients with Schizophrenia. Tropisetron is especially interesting for psychiatric conditions due to its additional agonist at the α7-nicotinic receptor.

A small trial with 40 patients with schizophrenia showed that the quality of life and auditory sensory data has improved in the patient, with the notable exception of smokers.[22] Additional trials on a small scale have shown similar results and indicate that Tropisetron does have a positive symptomatic effect on patients diagnosed with schizophrenia.[23] This also includes deficits in cognition, as previous animal trials have suggested.[24]

Fibromyalgia

Fibromyalgia (or fibromyalgia syndrome) is a condition that is characterized by pain in different parts of the body, morning stiffness of the muscles, sleep disturbances and concentration impairment. The pain does not seem to be arise from the affected body parts, but rather is connected to a problem with the neuronal transmission and pain sensing in the central nervous system. -Setrons have been under investigation as candidates to treat this condition, although no official drug approval has been declared. Despite this, some clinicians have been prescribing -setrons to patients with Fibromyalgia (off-label use), including Tropisetron, since clinical studies have indicated its use to treat this condition.

In a group of 42 patients suffering from fibromyalgia, an intravenous dose of 2 mg Tropisetron (for one day or 5 days) led to a significant pain release. For those patients that received 5 consecutive daily doses, pain was reduced for weeks to several months, while those who had only received a single does did only reported pain relief for a few days.[25] A further phase-2 study with a prolonged administration duration of 28 days come to the conclusion that Tropisetron does decrease pain and symptoms in patients suffering from fibromyalgia.[26]

Another study showed that Tropisetron was effective in treating a variety of fibromyalgia symptoms including sleep disorders and cardiovascular complaint, with the notable exception of gastrointestinal symptoms, which are a common side effect of -setrons.[27] More studies have shown that Tropisetron does help to alleviate the symptoms of fibromyalgia.[28]

Fibromyalgia can also be observed as a symptom of systemic sclerosis, a serious autoimmune disease with bad prognosis. Tropisetron did reduce paint and increase joint movability of two patients suffering from secondary fibromyalgia induced by systemic sclerosis.[29]

Pain

Paracetamol and Tropisetron both are used to reduce pain in various scenarios. Interestingly combining both substances did not lead to reduction of pain in a small-scale clinical study with 16 volunteers. This indicates that both drugs antagonize each other's effects.[30] The combination of paracetamol and Tropisetron to relief pain was explored in two further small clinical studies, but came to no conclusion due to the small group of patients.[31]

A study on 123 patients with chronic lower back pain showed that Tropisetron did not have an

positive effect on this patient group.[32] Interestingly, an earlier study on 25 patients did conclude that Tropisetron was indeed effective to reduce pain in such a scenario.[33] Further research for the treatment of chronic back with Tropisetron pain is necessary.

Other indications

A clinical trial for the treatment of obsessive-compulsive disorder on 108 patients showed that the addition of Tropisetron (5 mg twice daily) to the already established compound fluvoxamine did significantly increase the effectiveness of the treatment.[34]

A trial with 1508 patients focusing on the prevention of post-surgery delirium is currently being conducted.[35]

Conclusion

There is a lot of clinical evidence proving efficacy and safety of Tropisetron in several indications. The compound can generally be considered free of severe side effects at appropriate dosage. However, headaches and gastro-intestinal effects after ingestion of Tropisetron are to be expected in some cases, more specifically constipation, which is usually treated with laxatives in a clinical setting if it does manifest during treatment. Long term use can generally be assumed safe at normal clinical doses of 5 mg/day. Single doses of up to 150 mg orally have been tolerated by individuals, although at this dose or beyond, severe side effects may occur, which in cases of vulnerable individuals may be life-threatening.

The most widely accepted use of Tropisetron is to prevent nausea and vomiting, especially during chemotherapy and post-surgery. For motion sickness, they are reported to be ineffective because motion sickness is triggered by a neurological pathway that does not respond to 5-HT3 antagonists.[36]

Tropisetron is also reported to reduce pain, at least in certain painful conditions. While the evidence for the treatment of fibromyalgia is solid, it is unclear if Tropisetron can be used to combat most forms of trivial pain experienced in everyday life, like the common NSARs (Ibuprofen etc). If the source of pain is unclear, especially in suspected forms of psychosomatic pain, application of Tropisetron may prove to be effective, although more clinical evidence is needed.

The reported use of Tropisetron in treating schizophrenia and increasing the cognitive function of affected patients does pose the question if Tropisetron can enhance cognition under different conditions. Some animal experiments show it may be able to do this, but in these experiments, it is only used to prevent damage from toxic stimuli and not in healthy animals. A retrospective human study found cognitive improvements in post-operative patients.[37] This does also point to the fact Tropisetron can increase cognitive function under stress. It may also be used to treat the cognitive decline experienced in the early stages of Alzheimer's disease. More studies are needed, especially on the cognitive function of healthy individuals to confirm this. The unusual α7-nicotinic receptor agonism of Tropisetron may be responsible for this characteristic. Additionally, there seems to be an anti-inflammatory effect of Tropisetron which has only been explored in animal studies.

The effect and toxicity of tropisetron is strongly dependent on personal genetics because the rate of breakdown and oral bioavailability does depend in liver enzyme activity. This is a problem in a clinical setting, as testing everyone for their expected rate of Tropisetron breakdown would lead to high costs. Different ethnic groups may also experience a difference in the efficacy of Tropisetron due to this fact, although no major problems have been reported with Tropisetron despite it being used worldwide.

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