Pantoprazole compound discovery and development

Abstract

Pantoprazole is an proton pump inhibitor, which inhibits the gastric acid secretion by blocking the proton pump or the H+K+ATPase in the gastric parietal cells of stomach. Pantoprazole was synthesized in the year 1987 and was launched in the year 1994 after development and clinical trials. Development of the lead compound timoprazole and the discovery of H+K+ATPase as an target, were the two most important discoveries which led to the generation of a new class of compounds, the proton pump inhibitors. In this review, the discovery and the stages of development of pantoprazole will be discussed.

Introduction

The gastric acid is secreted in the stomach by the parietal cells. The gastric parietal cells are known to have three stimulators viz. gastrin, acetycholine and histamine. Acetylcholine and Histamine exert their effect through the M3-Muscarinic and H2-Histamnic receptors respectively. Whereas, gastrin exerts its action via release of histamine. Antagonists of the cholinergic and histaminic receptors were the first agents used for the inhibition of gastric acid secretion. The side effects and low efficacy limited the use of cholinergic receptor antagonists[1] and the histaminic receptor antagonists were the first class of drugs to be clinically used for the treatment of acid related disorders. These classes of drugs were widely developed in the 1970’s and 1980’s.[1]

But, variability in response and phenomena’s like acid rebound and tolerance were observed in these class of drugs[2]. Thus there was a need of more

effective targets and drugs for the optimal inhibition of gastric acid. This search led to the discovery of a new target, the gastric acid pump-H+K+ATPase and a new class of anti-secretory drugs were born that is the Proton pump inhibitors[2]. Omeprazole was then synthesized in 1979 and was the first clinically used proton pump inhibitor launched in 1988 and then gradually pantoprazole was synthesized in 1986 and launched in 1994. Today pantoprazole is one of the first line drug used in the treatment of acid related disorder.

Initiation of research for new compounds:

In 1967 at Astra Hässle researcher Ivan -stholm initiated an innovative research project in gastrointestinal field in order to develop anti-secretory agents which could be used in the peptic ulcer diseases[4]. Their first idea was to inhibit the gastric stimulating hormone gastrin[4]. It was known from the various animal experiments that local anesthetic agents of the antrum blocks the release of gastrin. Therefore the researchers at Astra Hässle aimed at synthesizing a local anesthetic compound which could be administered orally and is orally active. But all the available local anesthetic agents were however, protonated in an acidic environment and therefore were inactive, thus the goal was to change the chemical structure of lidocaine which was an established local anesthetic agent of the Astra Hässle itself into a non-basic compound[4]. The shay rat or the gastric fistula rat was used as a screening model. A large number of compounds were synthesized by the researchers, but it was found that the anesthetic property of the compound induced toxic effects. The chemical development finally ended with compounds including carbamates which were devoid of local

anesthetic properties. Carbamates were found to be very effective inhibitors of gastric acid secretion in rat models but were rather ineffective in dog.[6-7] The most effective carbamate compound was H81/75 but however in 1971-72, when it was tested in humans it was found to be completely ineffective.

Instead of reviving this local anesthetic lead, the researchers undertook a literature search to look for new approaches. In 1972, the researchers found an abstract from an Hungarian pharmacological meeting in which a new anti-secretory agent called CMN-131 was described. CMN-131 was synthesized by French company Servier.[4, 5] In this abstract it was reported that CMN-131 induced inhibition of stimulated gastric acid secretion in rats as well as anesthetized dogs. But due to severe toxicological problems the research on this drug never continued.[4] By this time in 1973, Smith-Kline and French announced the development of Cimetidine, worlds first H2 receptor antagonist which inhibited the gastric acid secretion by blocking histaminic receptors[1]. Based on the structure of cimetidine, a benzimidazole ring was added to the structure of CMN-131and was tested on animal models this new compound was named as H124/26 .[4]This sulphide compound was then modified for stabilization into its sulfoxide analogue and thus a new compound called as Timoprazole was born which was found to be a potent inhibitor of gastric acid secretion. But, however timoprazole was found to show toxicities in the thyroid gland. It causes enlargement of thyroid gland, the possible reason for this toxicity was that the timoprazole inhibits the iodine uptake. Thus timoprazole was not further developed and it served as a lead compound for the development of new anti-secretory agents. Uptill now the target of timoprazole was unknown.

Discovery of H+K+ ATPase:

In 1977, George Sachs and John Forte discovered H+K+ ATPase pump commonly known as the proton pump or the gastric acid pump[3. 4]. From the experiments carried out on hog gastric mucosa, they showed that the exchange of H+ and K+ were responsible for the regulation of the gastric acid secretion and they also suggested that this was the terminal step in the acid secretory process of the parietal cell wall[4]. When acid secretory membranes are isolated from the parietal cells, they round up and form closed vesicles containing H+K+ ATPase. On the basis of imunohistological data from various organs with the help of antibodies against a crude preparation from the secretory membranes of the parietal cells, Sachs showed that the proto pump was localized in the gastric parietal cells.[4] This immunohistological data not only revealed strong immunoreactivity in the parietal cell region of the stomach, but also revealed some acitivity in the thyroid gland.[5]

Target identification:

On the basis of various pharmacological methods, like the isolated guinea pig atrium, it was found that timoprazole was neither an H2-histaminic receptor antagonist nor an anti-cholinergic drug. Furthermore there were no evidences supporting any anti-gastrin activity of the compound.[4, 5] Therefore, though timoprazole inhibited the gastric acid secretion in various animal based models but its exact mechanism and site of action due to which it can account for its anti-secretory activity was yet to be identified.

During this time, the proton pump was discovered and there were evidences that the activation of this newly discovered proton pump, present in the

secretory membranes of the stomach parietal cells, was the final step of the gastric acid secretion. Also, the imunohistological data obtained using antibodies reveled strong immunoreactivity in the parietal cell region of the stomach and also some activity in the thyroid gland. On the basis of these facts coupled with the knowledge of the side effects of timoprazole on the thyroid gland, discussed earlier, raised an intriguing question in the minds of the scientists that could H+K+ ATPase, be the target of site of action of timoprazole. Research was initiated in this area in parallel to the further development of the benzimidazole compounds. With the help of the various pharmacological techniques such as the isolated gastric vesicles, it was indeed shown that the substituted benzimidazoles inhibited the gastric acid secretion by the inhibition of the H+K+ ATPase pump. Studies showed that the pre-incubation of isolated vesicles with substituted imidazoles resulted in inhibition of gastric acid secretion only when the conditions were acidic[4, 5]. This was really a breakthrough finding. This finding was further verified in experiments where the compound solvent was acidified[4]. All these facts and findings were the first indication that the substituted benzimidazoles had to be probably be transformed in other forms in order to bring about the active inhibition of the proton pump. Protonation of the compound was the first step in the transformation of compounds. These findings were followed by a series of experiments using various different types of test systems, in order to study the interactions of substituted benzimidazoles with the H+K+ ATPase pump. Several binding studies were carried out with substituted benzimidazoles which showed specific binding to the H+K+ ATPase.[3, 4] All the studies and findings showed that the substituted benzimidazoles

inhibited the gastric acid secretion by binding to the H+K+ ATPase pump and thus inhibiting its action.

Optimization of timoprazole:

Due to the various toxicological effects of timoprazole on the thyroid gland due to the inhibition of the iodine uptake, timoprazole was not suitable for further development. Therefore the researchers were in search of a new compound and a new possible approach. In order to optimize the lead compound timoprazole various studies were carried out, so that an compound devoid of toxicities could be developed.

A literature search of the chemistry of thiourea compounds showed few substituted mercapto-benzimidazoles having no effect on the iodine uptake by the thyroid[4, 5]. Thse substituted mercapto-benzimidazoles analogues were introduced into the structure of timoprazole. Various tests and experiments showed that the above analogue of timoprazole had a considerable anti-secretory actitvity and also was devoid of any inhibitory action on the uptake of iodine. This potent anti-secretory compound obtained after the introduction of mercapto-benzimidazole substituent’s in the structure of timoprazole was named as picoprazole.[5, 4]

The first toxicological studies of picoprazole showed necrotizing vasculitis in the small intestine of dogs[4]. However it was later found out that the toxic effect of picoprazole was an non-drug related phenomenon. The second toxicological studies carried out with picoprazole was rather successful. Picoprazole was then tested in human volunteers, where it showed very potent anti-secretory activity with a long duration of action.[4, 5]

Development of pantoprazole:

As discussed earlier, these compounds were only effective in inhibition of gastric acid secretion, if an only if the ATPase was making acid. As this compound was a weak base the steps that were thought then to result in inhibition of ATPase activity and acid secretion involved accumulation of the compound in the acid space of the isolated or intact gastric vesicles or in the parietal cell canalicullis during H+ transport, followed by a conversion of compound to its active form to account for acid dependence.[1] The conversion of compound to its active form is acid dependent. It was then postulated that these compounds acted as pro-drugs which can only react with the H+/K+ ATPase, if they are converted into their active form in an acid dependent manner. The active form of this compounds are the sulfenic acid or sulfenamide form. Further studies showed that the final structure of the compound generated in the acidic solution was a result of tetracyclic planar rearrangement of the compound, which leads to compounds containing a highly -SH reactive sulfenamide group.[1] However it is not clear whether the sulfenamide or the sulfenic acid or its dehydro form is responsible for binding to the H+/K+ ATPase covalently. In order optimize the acid stability of the lead compound and to generate selectivity for maximal accumulation at the site of action and for proper activation in the acidic space of the parietal cells, chemists changed and introduced new substituents on the heterocyclic ring of the lead compound which lead to the development and synthesis of Omeprazole in the year 1979[5]. It was found to be the most powerful inhibitor of stimulated gastric acid release[5]. Omeprazole was devoid of toxicities. Omeprazole was launched in 1988 and it was the first clinically used proton pump inhibitor.

In order to develop more acid stable and effective compounds various modifications were done and in 1986 Byk Guilden synthesized Pantoprazole. [3] It was tested in both in vivo and in vitro and was found to be a potent anti secretory agent. studies on human volunteers' was successful and it also suggested that pantoprazole had greater acid stability and target selectivity than omeprazole[2]. In addition its pharmacokinetic and metabolic profile was also different[2]. In 1987 sodium salt of pantoprazole was synthesized as the salt was more stable, more soluble and was more compatible with other excipients used in the formulation finally after seven years of clinical development pantoprazole was launched in 1994 for the first time in Germany.