Effect Of Itopride hydrochloride on QT interval in adult healthy volunteers

Seema Gupta, Vinod Kapoor, B.M. Gupta, B. Kapoor, Ujala Verma, Vikram Gupta

ABSTRACT
The objective of the present study was to evaluate the effect of Itopride hydrochloride on QT interval in a randomized, placebo controlled, double blind, cross over study. Itopride hydrochloride in a dose of 50 mg three times a day was administered to ten healthy male adult volunteers followed by placebo with a washout period of one week. 12 lead ECG recordings (minimum three) were taken before and after the test drug. Corrected QT intervals (QTc) were measured by using Bazett's formula. Mean QTc interval values for individual drugs were analysed using two tailed paired t test and unpaired t test was used when post drug QTc interval values of Itopride and placebo were compared. No statistically significant change was observed in the QTc interval with Itopride and the results were comparable with that of placebo.

Introduction:
Treating patients with gastrointestinal symptoms caused by reduced gastrointestinal motility such as non-ulcer dyspepsia (NUD), gastroesophageal reflux disease (GERD), diabetic gastroparesis and functional dyspepsia presents a major challenge in clinical practice. Prokinetic agents such as Metoclopramide, Domperidone, Cisapride, Mosapride etc. are the mainstay of therapy in these disorders. All the drugs in this group are efficacious with modest prokinetic activity but the matter of major concern is their safety profile. The main side effects of Metoclopramide are extra pyramidal such as dystonic reactions and Domperidone though is devoid of extra pyramidal effects, is associated with galactorrhoea or gynaecomastia. Cisapride has the potential to cause QT prolongation on ECG, thus predisposing to cardiac arrhythmias and its use has been restricted by the US FDA. Mosapride too belongs to the same group and although its side effects are not well documented, it has drug interaction potential similar to that observed with Cisapride. In this context, a prokinetic agent with good efficacy and at the same time favourable tolerability profile is the need of the hour in the treatment of dyspepsia. Itopride hydrochloride, the new benzamide has recently gained much favour as a gastrokinetic agent due to several reasons such as dual mode of action, lack of significant drug interactions at the level of cytochrome P450 and a better safety profile.

Several non-cardiac drugs may prolong cardiac repolarisation (hence, the QT interval of the surface electrocardiogram) to such a degree that potentially life threatening ventricular arrhythmias (e.g. torsades de pointes) may occur especially in case of overdosage or pharmacokinetic interaction. Different classes of non-cardiac drugs reported to prolong the QT interval include histamine H1-receptor antagonists, antipsychotics, antidepressants, macrolides, fluoroquinolones and prokinetic agents etc., Among prokinetic drugs, Cisapride usage has already been restricted and the cardiac safety of Mosapride has also been questioned in few studies. Since Itopride belongs to the same benzamide group as Cisapride and Mosapride, it becomes mandatory to evaluate its cardiac safety profile. With this aim, the present study was undertaken to see the effect of Itopride on QT interval in adult healthy volunteers.

Material & Methods:
A randomized, placebo controlled, double blind, crossover study was conducted in the postgraduate department of pharmacology and therapeutics, Govt. Medical College, Jammu. Subjects were non smoking volunteers, judged healthy on the basis of medical history, physical examination, routine laboratory investigations and 12 lead electrocardiogram (ECG). They were not allowed to take any drug other than...
study drugs one week before inclusion and throughout the duration of their participation in the study. Written informed consent was taken from each volunteer for participation in the study and the protocol was approved by the local ethics committee.

During the study, 10 subjects (all males) in the age group of 18.5-22 years (20.45 ± 0.95) were given Itopride hydrochloride (Ganaton; Abbott India Ltd.) in the oral doses of 50 mg three times a day for one day and placebo (Glucose D) one capsule three times a day for one day separated by a washout phase of one week.

Procedure:
ECGs were recorded by a digital ECG Cardiomin 2k UNI-EM device. The subjects were allowed to rest for 10 minutes in the supine position in a quiet room. Several ECG recordings (minimum three) were obtained before and after administering the test drug. The placement of leads was the same for each recording and the same ECG machine was used for each subject. All ECG recordings were made simultaneously in 12-leads at a paper speed of 25 mm/sec (amplitude 1 mV = 10 mm) with the use of automatic recording mode. To avoid inter-reader variability all electrocardiographs were read by the same investigator who was blinded to the treatment assignment after all test periods were completed. The ECGs were analyzed by calculating RR and QT intervals. All the ECG recordings were carried out with lead II. However, occasionally another appropriate lead was selected if lead II was inadequate. The QT interval was measured from the onset of QRS complex to the end of T wave. In case of a prominent U wave, the dip or notch between the T and U wave was taken as the end of T wave. QT interval after measurement was standardized by converting it to QTc i.e. corrected QT interval. Because the QT interval is influenced by change in heart rate, it is customary to correct the interval to such changes (QTc).

Various techniques are available for this purpose but the formula most widely used is Bazett's formula which is as follows.

$$QTc = \frac{QT\text{ interval}}{\sqrt{R-R\text{ interval}}}$$

QT interval and RR interval were measured in seconds and QTc was expressed in seconds. The normal QTc interval was taken as = 0.44 seconds. The average of 3 sequential QTc values was used as a single QTc value for statistical evaluation. QTc interval and absolute changes in the QTc intervals after drug therapy or placebo administration (QTc post-treatment-QTc base line) were calculated.

**Statistical analysis**

The statistical significance between the baseline and post drug QTc interval values for individual drug was analyzed with the help of the 2 tailed paired t test. Unpaired t test was used for comparing the post drug QTc interval values of Itopride and placebo.

**Results**

All the 10 male healthy volunteers enrolled, completed the study and there were no dropouts. Treatment wise, all the 10 volunteers were assigned to receive Itopride and then placebo after a washout period of 7 days. The demographic and baseline data of these volunteers are given in Table 1. The mean QTc interval values in the E.C.G at baseline and after the drug therapy are depicted in Table 2. With regard to mean data, one day after oral administration of either Itopride or placebo, no significant change in the duration of repolarization was observed (Fig 1). When mean QTc interval with Itopride were compared with placebo, the results were comparable and statistically insignificant (P=0.78, two tailed unpaired t test).

**Discussion**

Itopride hydrochloride is a novel prokinetic drug which was introduced in India in 2002. It has been approved for the symptomatic treatment of disorders like non-ulcer dyspepsia, chronic gastritis, diabetic gastroparesis or functional dyspepsia. This drug was first developed by Hokuriku Seiyaker Co. Ltd. and has been marketed in Japan since September 1995. Itopride is unique and different from the available prokinetics because of its dual mode of action and lack of significant drug interaction. Itopride, by virtue of its dopamine D2 receptor antagonism, removes the inhibitory effects on acetylcholine release. It also inhibits the enzyme acetylcholine esterase which prevents the degradation of acetylcholine. The net effect is an increase in acetylcholine concentration, which in turn, promotes gastric motility, increases the lower esophageal sphincter pressure, accelerates gastric emptying and improves gastro-duodenal coordination. Following the restriction imposed on cisapride usage and the subsequent report of the arrhythmic potential of mosapride safety of a prokinetic drug has been a cause of concern. Therefore, there is need of a prokinetic agent that is not only effective but at the same time without serious side effects. Itopride may prove to be an alternative in this situation. As there is little data showing the effect of Itopride on cardiotoxicity, the present study was conducted to evaluate the effects of this drug on ECG.

In our study, there was no significant change in the QTc interval after administration of Itopride (Table 2). The results with Itopride were comparable with those shown with placebo (fig 1).

Our findings are consistent with those of Sawant et al (2000) who have reported no adverse effect of Itopride on QT interval in a randomized controlled open-label comparative trial of Itopride and Domperidone undertaken in patients with non ulcer dyspepsia/chronic gastritis. Kamath et al (2003) in a single blind randomized study who compared the efficacy and tolerability of Itopride hydrochloride and Metoclopramide in patients of NUD have also shown that none of the patients had abnormalities on ECG after treatment. Various other preclinical and clinical studies too indicate that this drug is devoid of potential to cause prolongation of QT intervals unlike Cisapride and Mosapride. In a post marketing study of Itopride and placebo, no significant change in the duration of repolarization was observed (Fig 1). When mean QTc interval with Itopride were compared with placebo, the results were comparable and statistically insignificant (P=0.78, two tailed unpaired t test).

**Table 1: Demographic & Baseline Data of volunteers.**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of volunteers(n)</td>
<td>10</td>
</tr>
<tr>
<td>Age (yrs) Mean±SD</td>
<td>20.4±0.95</td>
</tr>
<tr>
<td>Male</td>
<td>10</td>
</tr>
<tr>
<td>Body wt. in kgs(Mean±SD)</td>
<td>62.1±6.02</td>
</tr>
<tr>
<td>History of ulcerogenic drugs</td>
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surveillance study of itopride hydrochloride in a dose more than 50 mg 3 times a day for 2 weeks, 3741 patients enrolled by 918 doctors were evaluated and it was concluded that it is an effective and well tolerated drug in the management of functional dyspepsia and dyspepsia in GERD and diabetic patients. In this study none of the patients reported any cardiovascular event. Reckarkani AL et al in open label non-comparative study in patients with non-ulcer dyspepsia and other gastric motility disorders.

**Table 2**

<table>
<thead>
<tr>
<th></th>
<th>No. of Volunteers</th>
<th>Baseline QTc (sec)</th>
<th>Postdrug QTc (sec)</th>
<th>Change from baseline QTc</th>
<th>P-value</th>
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<tr>
<td>Itopride</td>
<td>10</td>
<td>0.422</td>
<td>0.43</td>
<td>0.008</td>
<td>0.49</td>
</tr>
<tr>
<td>Placebo</td>
<td>10</td>
<td>0.416</td>
<td>0.425</td>
<td>0.009</td>
<td>0.41</td>
</tr>
</tbody>
</table>

**Figure 1:**

Effect of Itopride & Placebo on Cardiac QTc Interval

**REFERENCES:**

8. Bazett HC. An analysis of the time...


