Effect of ATP sensitive potassium channel modifiers on antinociceptive effect of metoclopramide

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Metoclopramide, a prokinetic drug, has been documented to produce antinociceptive response in animal models through opioid pathways. Morphine has been shown to act through ATP sensitive potassium channels (K_{ATP}) to produce antinociceptive response. However, such a possibility has not been examined for metoclopramide. The present study investigated this using pharmacological tools. Acetic acid induced abdominal constriction assay procedure was utilized to assess antinociception. The results confirmed that metoclopramide has antinociceptive response. Glibenclamide, a K_{ATP} channel blocker, pretreatment antagonized this response. Whereas, in minoxidil pretreated animals, metoclopramide elicited an enhanced antinociceptive response. Glibenclamide and minoxidil, which are known K_{ATP} channel blocker and opener respectively, interfered with metoclopramide antinociception. These finding are suggestive of a role for K_{ATP} channels in metoclopramide antinociception in mice.

Metoclopramide is an established prokinetic drug, which is commonly used for the management of vomiting. Besides this effect, an antinociceptive response has been reported in experimental as well as in clinical studies. Clinically, this drug was found to be useful for enhancing the analgesic effect of morphine after cesarean section and also in the management of ureteric colic. Experimentally, it has been reported that metoclopramide acts through opioid mechanisms since naloxone antagonises its antinociceptive action. Morphine has been shown to alter the functions of many neurotransmitters like acetyl choline, serotonin, gamma amino butyric acid, to elicit antinociceptive response. Similarly, metoclopramide was found to affect the cholinergic and adrenergic activity. At the cellular level, like morphine, metoclopramide has been demonstrated to modify the influx of calcium ions across the cell membrane to produce antinociceptive response.

One important mechanism by which morphine produces analgesic effect is by modifying ATP sensitive potassium (K_{ATP}) channels. Such a possibility for metoclopramide has not been investigated for its antinociceptive action. This was examined in the present study using pharmacological tools that modify K_{ATP} channels.

Metoclopramide was obtained as a gift from Shalaks Pharmaceuticals (P) Ltd, Mumbai, while glibenclamide from Micro Labs, Bangalore, minoxidil from Torrent Laboratories, Ahmedabad. Acetic acid glacial was purchased from Sarabhai, Wadodara. Except glibenclamide that was dispersed in 5% w/v Tween 80 in water for injection, all other drugs were dissolved in water for injection.

Randomly bred healthy adult Swiss albino male mice, weighing between 20-25 g were obtained from Central Animal House, JIPMER, Pondicherry and were housed (12-12 hr light and dark cycle, at room temperature 34°-35°C) in polypropylene cages under standard housing conditions in the departmental animal house. Food and water was provided ad libitum.

The antinociception was assessed by acetic acid induced abdominal constriction assay procedure. Acetic acid (glacial) was dissolved in purified water (0.6% v/v) and was administered intraperitoneally (10 ml /kg, ip). The number of abdominal constrictions during the following 15 minutes was counted. Any significant reduction in number of abdominal constrictions when compared to those obtained in vehicle treated mice, was considered as an antinociceptive effect. Each animal was subjected to antinociceptive test only once. The measurement of antinociception was made in a blind manner. In all the experiments, drugs were administered intraperitoneally.

Animals were divided into nine groups each consisting of six animals. The first group of animals received vehicle 15 minutes prior to acetic acid...
challenge. The second and third groups received metoclopramide 1.25 or 5 mg/kg; i.p 15 min prior to acetic acid challenge. These doses of metoclopramide were selected based on earlier studies. The role of K\textsubscript{ATP} channels in the antinociceptive action of metoclopramide was investigated using glibenclamide, a K\textsubscript{ATP} channel blocker, and minoxidil, a K\textsubscript{ATP} channel opener. The dose of these agents was selected based on earlier and pilot studies. Separate groups of animals received glibenclamide 10 mg/kg; i.p. or minoxidil 10 mg/kg; i.p. 15 min prior to either acetic acid or metoclopramide (1.25 or 5.0 mg/kg; i.p). Fifteen minutes after metoclopramide administration, the number of abdominal constrictions in these animals were measured after acetic acid challenge.

The data were analysed by using ANOVA followed by Dunnett’s ‘t’ test. Any difference with $P<0.05$ was considered as statistically significant response.

In line with earlier studies, metoclopramide per se in the doses employed (1.25 or 5 mg/kg), inhibited the number of abdominal constrictions elicited by acetic acid. The inhibition elicited by 1.25 mg/kg dose was not statistically significant, while 5 mg/kg metoclopramide treatment elicited a significant inhibition of abdominal constrictions. Glibenclamide (10 mg/kg; i.p) or minoxidil (10 mg/kg; i.p) per se failed to modify significantly the number of acetic acid induced abdominal constrictions when compared with those recorded in corresponding vehicle treated mice. However, in glibenclamide pretreated animals metoclopramide, in both the doses employed, failed to inhibit the abdominal constrictions.

On the contrary, in minoxidil pretreated animals, metoclopramide produced more inhibitory effect on the abdominal constrictions when compared with those observed in the absence of minoxidil.

Observations of the present study that glibenclamide antagonised the antinociceptive response of metoclopramide and minoxidil pretreatment enhanced the same response suggest that metoclopramide antinociception utilizes K\textsubscript{ATP} channels at the cellular level. This finding is akin to that observed for morphine wherein a similar antagonism of its antinociceptive action by glibenclamide has been demonstrated. As indicated earlier, both morphine and metoclopramide share yet another common action of modifying influx of calcium ions across the cell membrane to produce antinociceptive action. It is possible that both these mechanisms may be utilized by morphine as well as metoclopramide to produce antinociception at the cellular level. These observations lend further support to the suggestion that metoclopramide like morphine elicited antinociception through opioidergic pathways involving K\textsubscript{ATP} and calcium channels at the cellular level.

### Table 1—Effect of metoclopramide, glibenclamide, minoxidil alone or in combination on the acetic acid induced abdominal constrictions in mice.

<table>
<thead>
<tr>
<th>First Treatment (mg/kg; i.p)</th>
<th>Second Treatment (mg/kg; i.p)</th>
<th>Number of abdominal constrictions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle</td>
<td>None</td>
<td>30.80 ±2.80</td>
</tr>
<tr>
<td>None</td>
<td>Metoclopramide (1.25)</td>
<td>24.80 ±2.13</td>
</tr>
<tr>
<td>None</td>
<td>Metoclopramide (5)</td>
<td>12.25 ±1.18**</td>
</tr>
<tr>
<td>Glibenclamide (10)</td>
<td>None</td>
<td>3920 ±2.70</td>
</tr>
<tr>
<td>Minoxidil (10)</td>
<td>None</td>
<td>28.90 ±2.40</td>
</tr>
<tr>
<td>Glibenclamide (10)</td>
<td>Metoclopramide (1.25)</td>
<td>27.60 ±2.04</td>
</tr>
<tr>
<td>Glibenclamide (10)</td>
<td>Metoclopramide (5)</td>
<td>30.50 ±1.19**</td>
</tr>
<tr>
<td>Minoxidil (10)</td>
<td>Metoclopramide (1.25)</td>
<td>6.40 ±1.81**</td>
</tr>
<tr>
<td>Minoxidil (10)</td>
<td>Metoclopramide (5)</td>
<td>1.00 ±0.63**</td>
</tr>
</tbody>
</table>

*P<0.001 when compared with vehicle and none value.

**P<0.001 when compared with none - metoclopramide 5 mg value.

### References