Trimebutine: Mechanism of Action, Effects on Gastrointestinal Function and Clinical Results

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The actions of trimebutine [3,4,5-trimethoxybenzoic acid 2-(dimethylamino)-2-phenylbutylester] on the gastrointestinal tract are mediated via (i) an agonist effect on peripheral μ, κ and δ opiate receptors and (ii) release of gastrointestinal peptides such as motilin and modulation of the release of other peptides, including vasoactive intestinal peptide, gastrin and glucagon. Trimebutine accelerates gastric emptying, induces premature phase III of the migrating motor complex in the intestine and modulates the contractile activity of the colon. Recently, trimebutine has also been shown to decrease reflexes induced by distension of the gut lumen in animals and it may therefore modulate visceral sensitivity. Clinically, trimebutine has proved to be effective in the treatment of both acute and chronic abdominal pain in patients with functional bowel disorders, especially irritable bowel syndrome, at doses ranging from 300 to 600 mg/day. It is also effective in children presenting with abdominal pain.

KEY WORDS: TRIMEBUTINE; GASTRIC MOTILITY REGULATORS; IRRITABLE BOWEL SYNDROME; FUNCTIONAL BOWEL DISORDERS; CHILDREN

INTRODUCTION

Trimebutine has been used for many years to treat functional digestive disorders, mainly irritable bowel syndrome (IBS), in many countries. At the beginning of its clinical use, trimebutine was thought to act as a spasmylytic drug, acting directly on smooth muscle. Over the last decade, however, further knowledge has been obtained concerning its mecha-
nism of action, and several clinical trials have demonstrated its clinical benefit in IBS and some other functional bowel disorders.

It is therefore an appropriate point in time to summarize the data available on trimebutine in order to define more clearly its mechanism of action and its therapeutic indications. Trimebutine acts mainly as an opiate receptor agonist and differs from pure spasmolytic drugs such as phloroglucinol, mebeverine, tiemonium, and prokinetic drugs including metoclopramide, domperidone and cisapride. Moreover, the effects of trimebutine on the symptoms of patients with spastic colon, which suggests inhibition of motility, and on postoperative ileus, which implies stimulation of intestinal motility, indicate that trimebutine may modulate gastrointestinal motor activity.

In this review we first summarize the effects of enkephalins on digestive functions and especially on intestinal motility. We then examine the properties of trimebutine and its action on gut functions and, finally, the clinical results of studies evaluating the therapeutic efficacy of trimebutine in a variety of clinical disorders.

ACTION OF OPIATES ON DIGESTIVE FUNCTIONS

Among the oldest known pharmacological properties of opiates are their constipating effect, accounting for their use since antiquity as anti-diarrhoeal therapy, prior to their use as analgesics. The recent discovery of specific binding sites (opiate receptors) and their endogenous ligands (enkephalins) has considerably furthered our understanding of how opiates influence the gut, and has provided tools to reveal their level of action.

ENDOGENOUS OPIATES

Endogenous opiates were called ‘enkephalins’ because they were initially identified in brain extracts of several species and were classified as met- and leu-enkephalins, according to their specific C-terminal amino-acid residues. Enkephalins are derived from proenkephalin A. Their rapid degradation in the blood precludes the possibility of humoral transport and an action at a distant site. In contrast, enkephalins have been clearly identified in the myenteric plexus nerve terminals, especially in the duodenum and colon and in the pancreas. The family of opioid peptides also comprises β-endorphin and dynorphin, which display a more selective affinity for µ-receptor and κ-receptor types, respectively, while enkephalins appear to be more selective for δ receptors.

The existence of opioid receptors has been demonstrated on intestinal smooth muscle, using the model of isolated smooth muscle cells. The existence of enkephalin-immunoreactive nerve terminals at various sites, however, indicates that enkephalins may act at multiple levels to modulate gut motility, as enkephalin-containing nerve fibres have been found in prevertebral sympathetic ganglia, the anterior horn of the spinal cord, the vagus nerves and, of course, the brain.

ACTION OF OPIATES ON GASTROINTESTINAL MOTILITY

The regulation of gastrointestinal motility depends on the combined action of the myenteric plexus of the intraparietal enteric nervous system, the prevertebral ganglia and the central nervous system, via the parasympathetic cholinergic or non-cholinergic nonadrenergic and the sympathetic adrenergic pathways. The action of opiates on gut motility has been extensively studied; the results may, however, appear conflicting due to differences in aspects such as the species studied, the experimental procedures and the route of administration.
Opioid peptides are involved in the control of oesophageal motility, both locally and at the level of the central nervous system. Leu- and met-enkephalin exert opposite effects on the lower oesophageal sphincter pressure, but they appear to act on the nervous control of oesophageal motility by modulating the adrenergic and excitatory cholinergic activity, whereas the inhibitory vagal pathway seems to be unaffected.

In the stomach, opioid peptides – either exogenous or endogenous – slow gastric emptying. This action is probably peripheral since administration of these opioid peptides by intra-arterial infusion induces sustained pyloric contractions and gastric relaxation, and both of these effects are reversed by naloxone. Morphine enhances antral motility when given intravenously or by intracerebroventricular injection. In contrast, met-enkephalin inhibits gastric motility when given either peripherally or intracerebrally.

Morphine and other opiates are known to delay intestinal transit. In rats, this delay is associated with decreased contractile activity. In contrast, morphine stimulates small bowel motor activity in dogs, sheep and man.

The complex nature of the relationship between the transit of digesta and intestinal motor activity does not, however, allow the prediction of the effect of a compound on intestinal transit based on its action on intestinal motility. When injected intravenously in dogs and in humans, morphine induces a premature phase III or activity front. Such ectopic activity fronts can be induced by morphine in the postprandial state and can be blocked by nalorphine methiodide, a peripheral mu-receptor antagonist. When an ectopic or premature phase III of the migrating motor complex (MMC) is induced by codeine in man during the postprandial period, however, the background myoelectrical activity of the phase II of this premature MMC is composed of spike activity similar to those observed during the disruption of the MMC, indicating that codeine-induced phase III activity is superimposed on the postprandial pattern induced by the meal.

It seems likely that the constipating effect of morphine can be largely explained by an action on the colon. In dogs, colonic motility is characterized by cyclical grouped colonic contractions occurring at 15-min intervals, independently of the digestive state. After intravenous injection of morphine, this cyclical pattern is disrupted and replaced by a 25-min period of continuous activity consisting of an increase in both tonic and phasic contractions. This pattern can also be induced by synthetic opiates such as loperamide. In man, morphine slows colonic transit, but increases phasic and tonic contractions; however, it decreases the number of propagated waves, which are also decreased in constipated patients. Naloxone has recently been shown to induce defaecation in constipated patients and to suppress the postprandial rectosigmoid motor response in human volunteers.

### LEVEL OF ACTION OF OPIATES ON REGULATION OF INTESTINAL MOTILITY

Opiate receptors are widely distributed, being found in the central nervous system, peripheral nerve terminals and myenteric plexus, and are even present on smooth muscle cells. The precise locus of action of opiates on the regulation of intestinal motility has not, however, been demonstrated in all species. Although a central action is probably involved in some effects of opiates on intestinal motility and colonic motility may be centrally mediated, the peripheral action of opiates on the myenteric plexus seems to be important. The action of opiates on the myenteric plexus has been extensively studied in vitro. In guinea-pigs,
enkephalins, acting mainly on μ-receptors, inhibit the contractions induced by transmural electrical stimulation. In this case, and in rabbit ileal strips, in which they inhibit motility, enkephalins are thought to block the release of acetylcholine by the cholinergic nerves of the myenteric plexus or to induce hyperpolarization of myenteric nerves (Fig. 1).

In other experiments, however, met- and leu-enkephalins also inhibited contractions induced by exogenous acetylcholine, cholecystokinin and prostaglandin E1, suggesting a direct action on smooth-muscle receptors. Enkephalins also inhibit the release of vasoactive intestinal peptide from myenteric neurons.

INFLUENCE OF OPIATES ON SECRETORY PROCESSES

In dogs, μ-opiate agonists and met-enkephalin reduce gastric acid secretion induced either by sham-feeding or by a meal of meat. This action of opiates is probably mediated both by central and peripheral pathways. In man, gastric acid secretion is stimulated by low doses of enkephalins or opiate agonists, but is inhibited at high doses.

Morphine, opioid analogues, β-endorphin and met-enkephalin reduce pancreatic exocrine secretion in rats, predominantly via a central action. In dogs, however, both morphine and met-enkephalin reduce bicarbonate and enzyme secretions in response to duode-
nal acidification and to secretin infusion, and a presynaptic inhibitory action of met-enkephalin on cholinergic neurons enhancing pancreatic secretion has been postulated.

Although the antidiarrhoeal effects of opioid agonists are largely attributed to an inhibition of propulsive activity rather than to an effect on intestinal secretion, opiates inhibit mucosal intestinal secretions stimulated by various secretagogues. Intravenous morphine increases intestinal absorption in fed, but not in fasted, dogs, suggesting a modulation of the influence of food on intestinal absorption. Although they are ineffective when administered peripherally, when injected into the brain at low doses, opiates increase basal water and electrolyte absorption and reduce cholera-stimulated intestinal secretion in conscious dogs. This effect, which is not related to motor changes, is reversed by naloxone and vagotomy and reproduced only by µ agonists.

**STRUCTURE AND MECHANISM OF ACTION OF TRIMEBUTINE**

Trimebutine [3,4,5-trimethoxybenzoic acid 2-(dimethylamino)-2-phenylbutyl ester] was originally synthesized by Jouveinal Laboratoires (Fig. 2).

The gastrointestinal effects of trimebutine are mediated by two mechanisms described below:

**FIGURE 2**

Chemical formula of trimebutine.

**AGONIST EFFECT ON OPIATE RECEPTORS**

The agonist effect of trimebutine on opiate receptors was first demonstrated in dogs. In vitro studies have subsequently shown that trimebutine and its metabolite (N-mono-desmethyl-trimebutine or nor-trimebutine) bind to µ, κ and δ opiate receptors located on brain membranes and myenteric synaptosomes. In contrast with morphine or loperamide, trimebutine does not bind with a higher affinity to any particular opiate receptor subtype. This lack of specificity of the binding of trimebutine to opiate receptors is confirmed by results obtained in isolated intestinal fragments submitted to transmural electrical stimulation. The affinity of trimebutine for opiate receptors is lower than that of enkephalins and dynorphin. The modulatory action of trimebutine may be due more to its effects on both cholinergic and adrenergic nerves than to a myogenic effect. In vivo, trimebutine acts in conscious as well as anaesthetized animals and its modulatory properties may result from a dual-effect – excitatory and inhibitory – on postsynaptic excitatory potentials of neurons of the inferior mesenteric ganglion.

**RELEASE OF GASTROINTESTINAL PEPTIDES**

In dogs, trimebutine, like morphine, increases blood levels of motilin under fasting and fed conditions, while it impairs the postprandial increase in gastrin, glucagon, pancreatic polypeptide, insulin, gastric inhibitory peptide and vasoactive intestinal peptide. It is not clear from these results, however, whether trimebutine modifies hormonal levels by acting directly on endocrine cells or on hormone metabolism or via an indirect effect on motility. Conversely, some motor effects of trimebutine could be the result of the interaction of trimebutine with hormones. For example, a local inhibition of vasoactive intestinal peptide release could partially explain the
action of trimebutine on intestinal motility via impairment of the inhibitory effect of vasoactive intestinal peptide.59

PHARMACOKINETICS OF TRIMEBUTINE

After oral administration in animals (rat, dog, mouse, rabbit), intestinal absorption of trimebutine is almost complete, as 94% of an oral dose of trimebutine is eliminated by the kidneys in the form of various metabolites. The peak plasma concentration is observed 1 h after ingestion.56 Fetal transfer is low: in pregnant rats given 30 mg/kg of 14C-trimebutine orally, the maximum level of radioactivity in the fetus and amniotic fluid does not exceed 0.02% of the dose. In suckling rats only 0.04% of the dose is excreted in milk within 8 h.56 Autoradiographic studies (in rat) have shown large amounts of trimebutine concentrated in the gut.53

In man, after a single oral dose of trimebutine (2 mg/kg), the peak plasma concentration is reached within 1 h and the plasma elimination half-life is about 1 h.

The main metabolite of trimebutine, nor-trimebutine, is formed in the liver and exerts the pharmacological properties of trimebutine, especially in the colon.53

PHARMACODYNAMIC EFFECTS OF TRIMEBUTINE

EFFECTS OF TRIMEBUTINE ON THE STOMACH

In a double-blind cross-over study in healthy subjects, oral trimebutine (200 mg) accelerated gastric emptying of liquids by 19%. The maximal effect was observed after 40 min.62 In 21 patients with chronic gastritis, the effect of trimebutine on gastric emptying was studied using the technique of acetaminophen assay in blood samples. Plasma acetaminophen levels, measured 15 min after ingestion and preceded by trimebutine treatment, were significantly higher (P < 0.05) than after placebo. Trimebutine significantly accelerated delayed gastric emptying (P < 0.025).63 In another study evaluating the effect of trimebutine (100 mg) on gastric emptying after a dyspepsia-inducing meal, however, no effect was observed.64 More recently, an oral dose of trimebutine (200 mg) was shown to shorten the lag time before gastric emptying and also to accelerate gall-bladder emptying during the early postprandial period.65

Few studies have evaluated the effects of trimebutine on gastric motor activity. In 18 patients with non-ulcer dyspepsia, intravenous trimebutine (1 mg/kg) induced a biphasic manometric response with a coordinated increase in motor activity during the first 10 min and a dramatic inhibition for the next 30 min.66

Finally, trimebutine does not alter basal gastric acid secretion or pentagastrin-stimulated secretion.67

EFFECT OF TRIMEBUTINE ON THE SMALL INTESTINE

In fasted dogs, trimebutine – given either intravenously or orally – delays the appearance of phase III of the MMC in the stomach and duodenum by increasing the duration of phase II of the MMC in the intestine and by inducing a premature phase III, migrating along the entire intestine.53 The motor effects of trimebutine on the small intestine are prevented by previous intravenous injection of naloxone, but not by intracerebroventricular injection of naloxone, indicating that trimebutine acts peripherally to induce these effects.1 In the same study, trimebutine itself was shown to be ineffective when administered centrally. It has recently been shown that the effect of trimebutine on dog intestine is dependent on the phase of MMC at the time of drug injection.68
In stressed rats, trimebutine prevented stress-induced changes in intestinal motility, which consisted of a decreased duration of phase III of the MMC; diazepam did not reverse the effects of stress on small-intestine motility in this study. In man, trimebutine stimulates intestinal motility in both fed and fasted states. In the fasted state, intravenous injection of trimebutine (100 mg) induced a premature phase III of the MMC, which was very similar in duration and propagation velocity to a spontaneous phase III. When the injection of trimebutine was performed immediately after a spontaneous phase III or after the injection of naloxone, trimebutine did not induce additional phase III activity. In the fed state, intravenous trimebutine (100 mg) interrupted the fed pattern of intestinal motility and induced cyclical activity similar to that observed in the fasted state. In another study, trimebutine (600 mg) injected intraduodenally 20 min after a spontaneous phase III, also induced a premature phase III, which was related to the peak plasma trimebutine concentration.

In man, unlike the dog, trimebutine does not increase blood levels of motilin. Moreover, trimebutine was found to abolish the increase in plasma motilin observed in fasted subjects. In the same study, plasma levels of cholecystokinin and pancreatic polypeptide were not altered by the injection of trimebutine, while the prolactin level increased. By contrast, in another study, the plasma level of pancreatic polypeptide was increased following injection of trimebutine. Finally, trimebutine seemed to lower the plasma gastrin level in patients with chronic active gastritis.

**EFFECT OF TRIMEBUTINE ON COLONIC MOTILITY**

In dogs, trimebutine inhibits colonic spike activity recorded from electrodes implanted on the transverse colon. This effect is not reversed by naloxone, given either centrally or intravenously, indicating that trimebutine may influence colonic motility via receptors other than \(\mu\)-opioid receptors. Intracerebroventricular injection of trimebutine did not influence colonic motility in dogs.

The influence of trimebutine on colonic transit time was studied in constipated patients. In a randomized, double-blind, cross-over study, trimebutine 200 mg, three times daily significantly accelerated \((P < 0.05)\) the colonic transit time by 50%. In another study in patients with delayed colonic transit time (mean 105 h), colonic transit time was decreased to 60 h after trimebutine, but in patients with a normal colonic transit time before starting treatment, trimebutine did not alter transit time.

In man, trimebutine (100 mg, intravenously) did not alter colonic motility in fasted subjects, unlike morphine. Nevertheless, trimebutine may regulate colonic motility, as it increased the number of long spike bursts in constipated patients, but decreased the incidence in patients with diarrhoea-predominant IBS. The regulatory role of trimebutine has also been demonstrated in other studies, in which the colonic motor activity returned to normal with trimebutine in patients with either a hyperkinetic or a hypokinetic colon. In a more recent study, in which the colonic response to food intake appeared to be increased in the sigmoid colon of nine constipated patients, compared with healthy subjects, trimebutine (200 mg, orally) significantly decreased the excessive colonic activity observed in constipated patients, but did not modify the pattern of colonic motility in healthy subjects. This effect was statistically significant after 30 min and was maintained for at least 120 min. In another study with a similar design, however, trimebutine did not alter colonic motility in constipated patients.
**EFFECT OF TRIMEBUTINE ON STRESS-INDUCED CHANGES IN GUT MOTILITY**

Many reports have described changes in gut motility induced by various kinds of stress, in animals and in humans. The effect of trimebutine on stress-induced changes in gut motility has been evaluated in animals and, more recently, in humans. In rats, ‘travel-stress’ was induced by a train journey lasting several hours, and intestinal motility was monitored before and after the journey. Stress induced a significant decrease in the duration of phase III of the MMC (−30%; *P* < 0.001) lasting up to 48 h after the end of the journey. Trimebutine (166 μg/kg/h), administered intravenously during the stress, reversed the changes in intestinal motility, while diazepam had no effect on these changes.

In dogs, acoustic stress is known to induce gastric motor inhibition. A 1-h acoustic stress, started 40–50 min after a gastric MMC, delayed the onset of the next gastric MMC by 111%, while the jejunal MMC was not altered. Trimebutine (1 mg/kg, orally) abolished the effect of stress on gastric motility, but had no effect on gastric MMC latency when administered intravenously or centrally. The antagonistic properties of trimebutine on stress-induced modifications of gastric motility were inhibited by specific antagonists of *K* receptors. These results indicate that trimebutine mainly acts peripherally by inhibiting the effect of stress on gastric motility. Trimebutine may also act directly on peripheral receptors located in the gut wall.

In man, a recent study investigated the influence of trimebutine on stress-induced changes in jejunal motor activity. Overall, trimebutine (200 mg, orally, three times daily) reversed the effect of stress on jejunal motility. While fasting, the periodicity of MMC was prolonged under stressful conditions compared with the resting state. Trimebutine, given before stress was applied, corrected the periodicity of MMC to the values observed in the resting state. After a meal, mental stress decreased the contractile amplitude of jejunal contractions compared with postprandial contractile activity under resting conditions. Again, trimebutine abolished the effects of stress on postprandial contractile activity of the jejunum. By contrast, after trimebutine, there was no modification of the frequency of contractions nor of the number of clustered contractions induced by stress.

**EFFECT OF TRIMEBUTINE ON SENSORY THRESHOLDS**

Enhancement of visceral perception has been demonstrated in patients with functional bowel disorders, and particularly in patients with IBS. The colonic thresholds of pain perception are lowered in these patients compared with controls. Pharmacological manipulation of these visceral perception thresholds is an interesting target for new drugs in the field of IBS.

Results from a recent study in animals showed that trimebutine may influence the activity of visceral afferents. In conscious rats, and in humans, rectal distension induces a rectocolonic reflex characterized by inhibition of colonic motility. In this model, trimebutine significantly decreased the intensity of this inhibitory reflex at a dose of 5 mg/kg (intraperitoneally). Further, the abdominal contractions induced by rectal distension were reduced by trimebutine at the intraperitoneal dose of 10 mg/kg. In another model, hypersensitivity to rectal distension was induced in rats by rectal inflammation with trinitrobenzenesulphonic acid (L. Bueno, Personal Communication). In inflamed animals, the threshold volume of rectal distension producing abdominal cramps was lowered to 0.4 ml compared with 0.8 ml in non-inflamed rats. After treatment
of the animals with trimebutine (10 and 20 mg/kg, intraperitoneally), a normal threshold for abdominal cramps, i.e. 0.8 ml, was restored. These results demonstrate that trimebutine is able to modify visceral sensitivity by reducing the visceral pain produced by colorectal distension. This action of trimebutine on visceral sensory afferents may explain partly its beneficial effect in the treatment of IBS (see below).

**Clinical Effects of Trimebutine**

Since trimebutine is available in many countries, in various forms (Table 1), extensive clinical experience has accumulated, showing that it is active in many indications with a good safety profile (Tables 2 and 4). Trimebutine is available at various dose strengths; the usual daily dose is between 300 mg (3 x 100 mg) and 600 mg a day (3 x 200 mg).

**Irritable Bowel Syndrome**

Irritable bowel syndrome (IBS) is a frequent cause of patients being referred to gastroenterologists. The diagnosis of IBS is based on the clinical history when endoscopic and laboratory tests have excluded an organic disease. IBS is usually chronic and characterized by the association of abdominal pain with change in bowel habits, presence of mucus in the stools, etc. The clinical course of patients with IBS may be characterized by periods of quiescence or by sudden attacks of abdominal pain, which may interfere with the patient's work, social and family life.

The aetiology of IBS is not clear and may differ between patients. In some it is a sequel to a severe acute gastroenteritis (traveller's diarrhoea). IBS may be exacerbated by specific constituents in the diet (caffeine, dairy products, alcohol), and by exposure to mental stress. Trimebutine has been shown to be effective in IBS; the results of clinical trials have indicated the therapeutic protocols to be used in different conditions. In IBS patients, it is important to distinguish between the treatment of acute attacks of abdominal pain and maintenance therapy, which is mainly based on the use of musculotropic drugs modulating gastrointestinal motility and drugs acting on intestinal transit.

### Table 1

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<tr>
<th>Debridat®</th>
<th>Dose strength of one unit</th>
<th>Daily number of units</th>
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</thead>
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<tr>
<td>Tablets</td>
<td>100 mg (maleate)</td>
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<tr>
<td>Capsules</td>
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<tr>
<td>Slow-release tablets</td>
<td>300 mg (maleate)</td>
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<tr>
<td>Injection</td>
<td>50 mg (maleate)</td>
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<tr>
<td>Oral suspension</td>
<td>24 mg/5 ml (base)</td>
<td>45 – 90 ml</td>
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<tr>
<td>Sachets</td>
<td>74 mg (base)</td>
<td>3 – 6</td>
</tr>
</tbody>
</table>

*Debridat is the registered trade name of Jouveinal Laboratoires, Fresnes, France; trimebutine is also marketed under the following tradenames (by licensees): Ibutin®, Inductan®, Lamotris®, Modulon®, Polibutine®.*
**TABLE 2**

Placebo-controlled clinical trials with trimebutine in patients with irritable bowel syndrome

<table>
<thead>
<tr>
<th>Reference no.</th>
<th>Study design</th>
<th>Daily dose of TMB (mg orally)</th>
<th>Treatment duration</th>
<th>No. of patients</th>
<th>Assessment criteria</th>
<th>Results(^a)</th>
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<tbody>
<tr>
<td>77</td>
<td>Double-blind Cross-over</td>
<td>600</td>
<td>2 × 4 weeks</td>
<td>20</td>
<td>Abdominal pain</td>
<td>TMB (60) &gt; Placebo (20) (P &lt; 0.001)</td>
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<td></td>
<td></td>
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<td></td>
<td>Constipation</td>
<td>TMB (50) &gt; Placebo (20) (P &lt; 0.001)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CTT</td>
<td>TMB &gt; Placebo (P &lt; 0.05)</td>
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<tr>
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<td>Double-blind</td>
<td>300</td>
<td>4 weeks</td>
<td>40</td>
<td>Abdominal pain</td>
<td>TMB (85) &gt; Placebo (20) (P &lt; 0.001)</td>
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<tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Constipation</td>
<td></td>
</tr>
<tr>
<td>97</td>
<td>Double-blind Cross-over</td>
<td>600</td>
<td>2 × 3 days</td>
<td>40</td>
<td>Clinical global impression</td>
<td>TMB (67.5) &gt; Placebo (5) (P &lt; 0.001)</td>
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<tr>
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<td>Double-blind Cross-over</td>
<td>300</td>
<td>3 days</td>
<td>26</td>
<td>Clinical global impression</td>
<td>TMB (42) &gt; Placebo (19) (\text{NS})</td>
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<td>6 months</td>
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<td>TMB = Placebo</td>
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<td>2 months</td>
<td>60</td>
<td>Abdominal pain</td>
<td>TMB (53) &gt; Placebo (30) (P &lt; 0.05)</td>
</tr>
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</table>

TMB, trimebutine; CTT, colonic transit time; NS, not significant.

\(^a\)Numbers in brackets are the percentages of patients who obtained a good response to treatment.
### Clinical trials with trimebutine compared with other drugs in patients with irritable bowel syndrome

<table>
<thead>
<tr>
<th>Reference no.</th>
<th>Study design</th>
<th>Daily dose (mg orally)</th>
<th>Treatment duration</th>
<th>No. of patients</th>
<th>Assessment criteria</th>
<th>Results*</th>
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<td>Double-blind Cross-over</td>
<td>TMB 600 MBV 450</td>
<td>2 x 1 week</td>
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<td>TMB = MBV</td>
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<td>TMB 600 MBV 400</td>
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<td>Abdominal pain</td>
<td>TMB &gt; MBV $P &lt; 0.05$</td>
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<tr>
<td>99</td>
<td>Double-blind</td>
<td>TMB 600 MBV 400</td>
<td>4 weeks</td>
<td>199</td>
<td>Abdominal pain</td>
<td>TMB &gt; MBV $P &lt; 0.0001$</td>
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<td></td>
<td></td>
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<td></td>
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<td>Duration of pain</td>
<td>TMB &gt; MBV $P &lt; 0.001$</td>
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<td>114</td>
<td>Double-blind</td>
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<td>28</td>
<td>Clinical global impression</td>
<td>TMB = PB</td>
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<tr>
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<td>Double-blind</td>
<td>TMB 450 FN 300</td>
<td>4 weeks</td>
<td>240</td>
<td>Abdominal pain Stool frequency</td>
<td>TMB (71) &lt; FN (85) $P &lt; 0.05$</td>
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<td>116</td>
<td>Double-blind</td>
<td>TMB 300 CIS 7.5 or 15</td>
<td>?</td>
<td>381</td>
<td>Clinical global impression</td>
<td>TMB = CIS</td>
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</table>

TMB, trimebutine; CIS, cisapride; FN, fenoverine; MBV, mebeverine; PB, pinaverium bromide.

*Numbers in brackets are the percentages of patients who obtained a good response to treatment.
TRIMEBUTINE IN ATTACKS OF ABDOMINAL PAIN IN IBS. An attack of abdominal pain is a frequent reason for referral of an IBS patient. In this situation, spasmylytic drugs may exert an analgesic effect, but do not influence the motility changes observed in these patients.\(^9\) They are also effective in relieving pain from other organs (e.g. urinary tract, female genital tract) and this may lead to misinterpretation of a favourable clinical outcome.

Optimal treatment of the acute symptoms of IBS requires drugs that act specifically on the gastrointestinal tract and are rapidly effective. A few studies have evaluated the effect of trimebutine in short-term treatment (3 – 15 days).

Lüttecke\(^9\) showed that trimebutine, 200 mg, orally three times daily for 3 days, was more effective than placebo in relieving abdominal pain in 39 IBS patients. Abdominal pain was significantly decreased in 27 patients after trimebutine, but in only two after placebo \((P < 0.001)\). In another study evaluating a 3-day treatment, trimebutine, 200 mg, orally, three times daily, was more effective than placebo in relieving acute pain, but no difference was observed between trimebutine, 100 mg, three times daily, and placebo.\(^9\) A study comparing the effects of trimebutine, 600 mg, with mebeverine, 450 mg, in a cross-over design \((2 \times 1 \text{ week})\) is presented in the same report: both treatments were equally effective in terms of pain relief.\(^9\)

FOUR WEEK THERAPY WITH TRIMEBUTINE. In a controlled cross-over study including 20 IBS patients with moderate-to severe-pain, Moshal\(^6\) observed significant relief of symptoms by trimebutine, 200 mg, three times daily, as compared with placebo (Table 2). In a double-blind double-placebo randomized study, trimebutine 600 mg (200 mg, three times daily) was more effective than mebeverine (400 mg/day) in the reduction of the frequency \((P < 0.0001)\), duration \((P < 0.001)\) and intensity \((P < 0.04)\) of these pain attacks (Table 3).\(^7\) Patients enrolled in this study had been selected on the basis of Manning's criteria and had severe IBS with at least three abdominal pain attacks every day. In another study, trimebutine (600 mg) was also more effective than mebeverine (400 mg/day) in patients treated for 4 weeks for abdominal pain.\(^10\) Many of these patients presented with signs of non-ulcer dyspepsia.

MAINTENANCE THERAPY FOR IRRITABLE BOWEL SYNDROME WITH TRIMEBUTINE. The effect of long-term treatment with trimebutine (600 mg) in IBS patients was evaluated in a randomized controlled study.\(^11\) This study did not show any difference between trimebutine and placebo regarding the occurrence of symptoms related to IBS during the 6-month follow-up. It should be stressed, however, that all of the patients in this study, unless they were treated with placebo or trimebutine, received a supplement of dietary fibre which may have improved symptoms by itself. Moreover, the efficacy of trimebutine and placebo was only evaluated at the end of treatment.

Trimebutine (100 mg, three times daily) was also evaluated compared with placebo in a 2-month double-blind study.\(^12\) Abdominal pain was decreased in more patients treated with trimebutine (52/59) than in patients receiving placebo (30/60; \(P < 0.05\)).

CONSTIPATION

In constipated patients, trimebutine (600 mg/day) significantly improved abdominal symptoms after an 8-week course of treatment; the improvement of symptoms was correlated with its action on colonic transit time measured by the pellet method.\(^7\) In another study including constipated patients, trimebutine accelerated the colonic transit time but failed to increase the frequency of bowel movements.\(^7\) Finally, in a trial in
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IBS patients, the stool frequency was increased after trimebutine.\textsuperscript{105}

In a recent study, 24 patients (12 with normal colonic transit and 12 with delayed transit) with chronic idiopathic constipation were evaluated by measuring their stool frequency, colonic transit time and myoelectrical activity.\textsuperscript{104} They were treated for 2 months with placebo and trimebutine (100 mg, twice daily) in a crossover design. Trimebutine significantly shortened the colonic transit time and stimulated propagated myoelectrical activity, but only in patients with delayed transit times. In view of these results, trimebutine may be helpful for patients with chronic idiopathic constipation and delayed colonic transit time.

In an open, non-placebo-controlled study, trimebutine effectively relieved constipation in IBS patients with moderate constipation (< three bowel movements/week). After one month of therapy (trimebutine, 300 mg/day, orally), stool frequency increased in 86% of patients. Clinical interview revealed that this objective improvement of the number of stools was considered by the patients to constitute an improvement of their constipation-related symptoms in 82.5% of cases.\textsuperscript{105} Global assessment of the efficacy of trimebutine in the treatment of IBS-related symptoms (abdominal pain, bloating, altered bowel habit) was considered to be good in 78.5% of patients and moderate in another 18.1%. Improvement was obtained in most patients after 2 days of treatment.

**TRIMEBUTINE IN NON-ULCER DYSPEPSIA**

Trimebutine has been evaluated in several controlled studies in patients with non-ulcer dyspepsia (Table 4).\textsuperscript{106 - 108} At oral doses ranging from 400 to 600 mg/day, trimebutine improved symptoms related to dyspepsia; its efficacy was similar to that of metoclopramide.\textsuperscript{108}

**TRIMEBUTINE AND PATHOLOGICAL STATES OF INTESTINAL MOTILITY**

In a double-blind controlled study, trimebutine (400 mg, intravenously) shortened the period of postoperative ileus in patients who had undergone abdominal surgery.\textsuperscript{109}

In patients with idiopathic intestinal pseudo-obstruction, trimebutine (100 mg, intravenously) induced phase III of the MMC, despite the absence of any spontaneous phase III in these patients.\textsuperscript{110}

**TRIMEBUTINE IN PAEDIATRIC GASTROINTESTINAL DISORDERS**

In children, gastrointestinal disorders, especially functional bowel disorders, are frequently characterized by altered bowel habit - either constipation or diarrhoea - often but not always accompanied by abdominal pain. In 20 young patients (age range 4 – 14 years) with such disorders, trimebutine proved effective in relieving abdominal pain after 8 days of treatment and also in decreasing the frequency of stools in children with diarrhoea.\textsuperscript{111}

In another open, non-controlled study, 38 children (19 boys and 19 girls) with possible functional bowel disorders, suspected because of the simultaneous presence of abdominal pain, altered bowel habit and migraine-like headache, were treated with trimebutine (6 mg/kg orally, three times daily) for 1 month. The efficacy of trimebutine was evaluated clinically. Abdominal pain improved in nearly all patients after 1 months of trimebutine. Constipation and diarrhoea were also improved in two-thirds of patients. Improvement of symptoms was significant after 1 week of treatment.\textsuperscript{112}

Finally, trimebutine efficacy was evaluated in five children with severe gut disorders characterized by dramatic changes in intestinal motility requiring prolonged total parenteral nutrition.\textsuperscript{113} These infants (mean age 11.7 ± 6.8 months) had severe pseudo-
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TMB, trimebutine; MCP, metoclopramide.

*Numbers in brackets are the percentages of patients who obtained a good response to treatment.
obstruction, with absence of MMC in three cases. Basal recording of duodenal motility under fasting conditions showed absence of MMC and hypomotility. After trimebutine (3 mg/kg, intravenously), a phase III-like activity occurred in four patients, 88 ± 121 min after drug infusion; in two patients this was accompanied by the development of clinical signs of peristalsis, which were absent before injection. These results for trimebutine in children with severe pseudo-obstruction appear to be similar to those obtained in adults with similar intestinal motility disorders.110

**SAFETY OF TRIMEBUTINE**

The mass of clinical experience of using trimebutine confirms the safety of this drug. Reported side-effects, including skin rash (in less than 2% of patients), sleepiness (in 0.08%) and, very rarely, some cases of headache, dry mouth, constipation, diarrhoea, vomiting, asthenia and dizziness (each, in less than 0.01%). In many of the published studies, side-effects occurred at the same frequency in patients treated with trimebutine as in those treated with placebo. The daily dose of trimebutine (up to 600 mg, orally) did not influence the rate of side-effects.

In children, no significant adverse effects were reported in any of the available studies, showing that trimebutine is well tolerated at doses of up to 6 mg/kg.

**CONCLUSION**

The results of the clinical studies summarized in this paper, and our increasing knowledge of the pharmacodynamic effects of trimebutine, demonstrate that trimebutine is an effective treatment for abdominal pain and altered bowel habit in IBS patients. Trimebutine acts by regulating intestinal and colonic motility.

Trimebutine is indicated in the treatment of attacks of abdominal pain in these IBS patients as well as in maintenance therapy. Pain attacks in IBS may be defined as a sudden increase in the severity of symptoms interfering with the patient's daily life. The dramatic intensity of the symptoms may occasionally require referral of patients to exclude other diseases. In the case of abdominal pain attacks, trimebutine should be given at a dose of 200 mg, three times daily, orally. Intravenous administration should be used when necessary. The rapid improvement of symptoms and the global efficacy of trimebutine indicate that this dose regimen should not be given for more than 2–4 weeks.

In patients with mild-to-moderate symptoms, trimebutine should be given orally at a dose of 100 mg, three times daily. This dose of trimebutine has been shown to be more effective than placebo in relieving IBS symptoms in nearly all controlled studies. Trimebutine induces only a few minor side-effects and the huge clinical experience with this drug shows that it can be prescribed without restriction, except during the first 3 months of pregnancy. Trimebutine is also well tolerated in children, in whom it has been shown to be effective in the treatment of functional bowel disorders and severe intestinal motility disorders.

Trimebutine acts on intestinal motility but also, as shown recently, on visceral perception which, on the basis of recent research, is one of the main targets of drug therapy in IBS. The future of trimebutine will include clinical trials evaluating the prescription of trimebutine in doses adjusted to the severity of the symptoms in IBS patients. These controlled trials may also more clearly define subsets of patients for whom trimebutine should provide the greatest clinical benefit.
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