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EDITORIAL

Erythromycin and motilin as gastrointestinal prokinetic agents

Erythromycin, a macrolide antibiotic, was introduced into clinical use in the early 1950s and it has been widely used because of its efficacy and its minimal side effects [1]. However, it had been recognized that erythromycin often caused gastrointestinal symptoms [2,3]. The mechanisms of the gastrointestinal symptoms had not been known until 1984 when two groups of researchers independently found that erythromycin strongly contracted the gastrointestinal tract in the dog [4,5]. They also found that at lower doses, erythromycin initiated the interdigestive migrating motor complexes, strong gastric contractions that migrate into the intestine [4,5]. These findings have led to a great interest in searching for a possible use of erythromycin as a gastrointestinal prokinetic drug.

The interdigestive migrating motor complex (MMC), a typical gastrointestinal activity that occurs during the interdigestive (fasting) state, is a cyclical motor pattern which usually originates in either the stomach or duodenum, and migrates to the terminal ileum [6]. The MMC consists of three main phases: after a period of quiescence (phase 1), an irregular spiking activity occurs (phase 2), which is taken over by intense bursts of action potentials (phase 3 or activity front) [6].

Several substances are known to induce an MMC-like pattern: morphine, met-enkephalin, pancreatic polypeptide and somatostatin [7–10]. Although these substances induce contractions in the small intestine, they do not induce contractions in the stomach [7].

Motilin, a 22-amino acid peptide, is also known to induce an MMC-like pattern. Unlike other substances, motilin can initiate the MMC in the stomach. Injection of exogenous motilin induces gastric contractions which migrate to the intestine, contractions which are indistinguishable from natural MMCs [4]. In addition, injection of a motilin antiserum disrupts the natural MMC until plasma motilin concentration returns to the physiological level [11]. Furthermore, during the interdigestive state, plasma motilin concentration fluctuates, and there is a close correlation between the peak plasma motilin concentration and the occurrence of the MMC [12]. Interestingly, plasma motilin concentration increases only when phase 3 occurs in the stomach; the concentration decreases when phase 3 originates in the duodenum [12]. It is also known that motilin receptors are abundant in the stomach [13]. From these findings, motilin is considered to be involved in initiating the natural MMC in the stomach.

Erythromycin, at therapeutic doses (500–1000 mg), induces strong and continuous gastric contractions which do not migrate to the small intestine [5,12,14, 15]. In contrast, at lower doses (up to about 200 mg), it induces intermittent contractions in the stomach, and the contractions migrate into the intestine [12,14]. The frequency and amplitude of these co-ordinated gastrointestinal contractions are similar to those of a natural MMC [4,12,14]. This led to a hypothesis that erythromycin induces the MMC as a motilin receptor agonist. Binding studies have confirmed that erythromycin indeed displaces the binding of a radiolabelled motilin [16]. The stimulatory effect of erythromycin is decreased in animals tolerant to motilin [17,18]. Moreover, injection of erythromycin increases plasma motilin concentration in dogs [4], although it is not clear whether it is so in humans [12,14].

It has been known that motilin might accelerate gastric emptying [19,20]. It was a natural sequence to postulate that erythromycin might also speed up gastric emptying. This postulation was first shown to be true in healthy people as well as in patients with gastroparesis as a result of diabetes mellitus [21]. A number of subsequent studies have confirmed that erythromycin accelerates gastric emptying of both liquids and solids in patients with delayed gastric emptying because of several pathological reasons [22,23]. Erythromycin may also be effective in those patients in whom other gastric prokinetic drugs, such as metoclopramide or bethanechol, were ineffective [21,22].

Several other prokinetic effects of erythromycin have been reported. It increases the lower oesophageal sphincter tone, dilates the pylorus, and stim-

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ulates gallbladder emptying [18,23]. Patients with gastroparesis or with pseudo-obstruction of the intestine have several gastrointestinal symptoms, such as nausea, vomiting, abdominal pain, bloating and distension of the colon [22,23]. Erythromycin, at lower doses also reduces gastrointestinal symptoms in these patients [23].

In contrast to the potent prokinetic effect of erythromycin on the stomach, its effect on the intestines is weak [16,24]: erythromycin may either have no effect or even delay the intestinal transit [25]. One possible reason for the weak effect of erythromycin on the intestine is because of the distribution of the motilin receptor in the gastrointestinal tract. The concentration of the motilin receptor decreases aborally in the gastrointestinal tract [13]. Thus, the stimulatory effect of erythromycin may also decrease aborally. Another possibility is that erythromycin produces a prokinetic effect by inducing the phase 3 of the MMC. Strong contractions which occur during phase 3 expel remaining debris in the gastrointestinal tract distally, and they are thus called the interdigestive 'housekeeper' of the small intestine [6,26]. This 'housekeeper' function expels materials from the stomach, but it may not speed up the transit of food in the small intestine [27]. Therefore, if erythromycin produces the prokinetic effect by inducing the MMC, it would not markedly increase the transit time in the small intestine.

Is erythromycin useful during the peri-operative period and in the intensive care unit? There may be several potential uses for the drug; however, the efficacy of the drug in these situations is still not clear and there are some limitations to its routine use. First, erythromycin may be given to accelerate gastric emptying peri-operatively or in critically ill patients. One of the useful features of erythromycin is that the onset time for the prokinetic effect is very short [21–23, 25]. It may thus effectively reduce gastric contents in patients with full stomachs who are to undergo emergency surgery. However, erythromycin sometimes fails to accelerate gastric emptying (and also sometimes fails to induce the MMC) even in healthy subjects [14,22,23]. In addition, the drug may not be effective at all in some groups of patients. One study showed that in children with intestinal pseudo-obstruction, erythromycin induced the MMC in most patients in whom spontaneous MMC had been present, whereas it almost always failed to induce the complex in patients in whom a spontaneous MMC had been absent [28]. It may also not reverse the delayed gastric emptying caused by injection of morphine [29].

Accelerated gastric emptying caused by erythromycin is not physiological. Normally, the rate of gastric emptying of liquids, digestible and indigestible solids are markedly different [30]: both liquids and digestible solids are emptied from the stomach during the digestive state, and liquids leave the stomach more rapidly than digestible solids which usually remain in the stomach until they are broken down [30]. In contrast, large indigestible solids remain in the stomach until both liquids and digestible solids have left; these indigestible solids are expelled from the stomach by phase 3 of the MMC during the interdigestive state [30, 31]. Erythromycin accelerates gastric emptying of both liquids and solids, and expels these two components at a similar speed [21]. It also accelerates gastric emptying of indigestible solids even when food is in the stomach (digestive state) [32]. Therefore, erythromycin may expel food that is only partly broken down into the intestine [33]. This may cause indigestion and the dumping syndrome. In fact, one study showed that in healthy humans, erythromycin effectively increased gastric emptying, but it also caused abdominal pain, bloating, diarrhoea and sweating, typical symptoms of the dumping syndrome [34].

Erythromycin may accelerate the recovery from post-operative ileus [35,36], but conclusions regarding its efficacy are still premature. In one study, either erythromycin or saline was given intravenously every 6 h starting 3 days after pancreaticoduodenectomy [35]. Although the duration of the necessity for nasogastric drainage was not different, the incidence of re-insertion of a nasogastric tube was significantly lower in patients in whom erythromycin was given. Gastric emptying of both liquids and solids was also significantly increased when examined on the tenth post-operative day [35]. However, the time to discharge from the hospital did not differ between the two groups. In another study, either erythromycin 250 mg or saline was given every 8 h after abdominal surgery [36]. There was no difference in the time to recovery from the post-operative ileus between the groups [36]. A recent report showed that an erythromycin derivative shortened the post-operative

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ileus in patients who had undergone cholecystectomy [37]. A motilin derivative also increases post-operative motility in dogs [38].

Hypomotility of the gastrointestinal tract is a major problem in critically ill patients [26,39]. The MMC is often impaired in mechanically ventilated, critically ill patients [39]. When the frequency of the MMC is reduced, bacterial overgrowth is likely to occur in the intestine [26,40]. One study showed that all patients, with either sparse or no MMC activity, had bacterial overgrowth in the small intestine [26]. In rats, disruption of the MMC by either morphine or phenylephrine resulted in bacterial overgrowth; recovery of the MMC reduced the number of bacteria in the intestine [40]. It seems reasonable to hypothesize that in critically ill patients, a low dose of erythromycin, which produces no antibiotic effects, inhibits bacterial overgrowth by inducing the MMC. There have been no studies in which this hypothesis has been assessed.

One limitation of the routine use of erythromycin is that the dose range for the prokinetic effect may be narrow. Erythromycin dose-dependently increases the frequency of the MMC when the dose is relatively low; however, when the dose is increasesd further, it causes only strong gastric contractions that do not migrate to the intestine. These strong gastric contractions may thus only cause gastrointestinal discomfort, such as abdominal pain, nausea and vomiting [5,15].

The incidence of gastrointestinal symptoms caused by a therapeutic dose of erythromycin may be higher in young people then older people [3], although this has not been studied formally. It is thus possible that the effective dose of erythromycin as a prokinetic drug may also vary between different age groups. If this is so, erythromycin at doses which acts as a prokinetic drug in elderly people, could merely induce gastrointestinal symptoms in younger people.

It is also not clear whether erythromycin loses its gastrointestinal prokinetic effects during long-term use [21,22]. Acute tachyphylaxis to motilin, erythromycin and their derivatives have been shown in *in vitro* studies [17]. Concurrent administration with other prokinetic drugs may prevent excessive doses of erythromycin, may produce greater prokinetic effects, and may reduce tolerance, if any, to each drug.

There is no doubt that the gastrointestinal prokinetic effect of erythromycin and motilin is potentially useful in clinical practice, and it seems that erythromycin is being used in the intensive care unit. At the moment, we are utilizing a side effect of erythromycin; what we need now is an erythromycin derivative which produces a more potent prokinetic effect but is devoid of antibacterial activity. Such erythromycin derivatives as well as motilin derivatives have already been developed [14,17,37,38]. Questions still remain as to whether erythromycin increases gastrointestinal motility entirely through the motilin receptor: there is no similarity in the structures of erythromycin and motilin, and there are several differences in their effect. It may be possible that erythromycin induces gastrointestinal symptoms through mechanisms other than the motilin receptor. The optimal structure of this group of drugs will be found through studies not only on erythromycin and its derivatives but also on motilin itself.

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