ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, June 1991, p. 1085–1088
0066-4804/91/061085-04$02.00/0

Vol. 35, No. 6

Effects of Amoxicillin-Clavulanate Combination on the Motility of the Small Intestine in Human Beings

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Received 14 August 1990/Accepted 19 March 1991

The amoxicillin-clavulanate combination (Augmentin) frequently induces gastric complaints and diarrhea by an unknown mechanism. The aim of this study was to assess the effects of two orally therapeutic regimens of amoxicillin-clavulanate on small bowel motility in human beings. Duodeno-jejunal manometric recordings were performed in six healthy subjects treated in a cross-over double-blind study with placebo; amoxicillin-clavulanate, 1 g plus 250 mg per os every 12 h for 3 days; or amoxicillin-clavulanate, 1 g plus 250 mg per os every 12 h on day 3 only (1-day regimen). Recordings were all performed on day 3 during a diurnal fasting period, a fed state after a standard dinner, and a nocturnal fasting period. Amoxicillin-clavulanate did not affect the motility of the small intestine during the diurnal fast or the fed state. During the nocturnal fast, amoxicillin-clavulanate significantly increased the motility index of the nonpropagated contractions and tended to increase the duration and the amplitude of the propagated contractions. The same digestive motor effect was already observed on the first day of treatment (1-day regimen). This study demonstrates that the oral administration of a therapeutic regimen of amoxicillin-clavulanate is associated, in most cases, with the occurrence of small intestinal motor disturbances.

The amoxicillin-clavulanate combination (Augmentin), one of the most widely used antibiotics, frequently induces gastrointestinal side effects, such as nausea, vomiting, cramping (prevalence, 3 to 6%), or diarrhea (prevalence, 4 to 15%) (3, 5). These prevalences are higher than those reported with other orally administrated beta-lactams (10). These effects are usually minor and transient, but they sometimes lead to interruption of the treatment (3). As for other broad-spectrum antibiotics, disturbances of the normal gastrointestinal microflora are often incriminated, but there is no proof of this. The aim of this study was to test whether the oral administration of a therapeutic regimen of amoxicillin-clavulanate in healthy volunteers is accompanied by changes in small bowel motility, as reported previously for macrolide antibiotics (11).

MATERIALS AND METHODS

Subjects. Seven healthy male volunteers (ages, 22 to 28 years) were included in the study. No subject was taking any medication or had a history of gastrointestinal symptoms or surgery. The study was approved by the Ethical Committee of the Medical University of Rouen, and written informed consent was obtained from each subject.

Recording system. As reported previously (4, 6), intraluminal pressures were recorded from four side holes cut into an assembly of four polyvinyl tubes (internal diameter, 0.8 mm). The sensors were located at 5, 15, 25, and 35 cm from a rubber stall containing 2 ml of mercury and fixed to the tip of the tube to facilitate positioning. Radiopaque marks were inserted in the catheters near the side holes and at the tip to facilitate the fluoroscopic control of the position to the assembly. The probe was advanced so that the two proximal sensors were below Treitz's ligament, i.e., in the jejunum. The probe was then fixed to the nose to avoid migration during the recording period. Recording lumens were continuously perfused with distilled water with a low-compliance hydraulic infusion system. Pressures were measured with transducers (Gould Statham P23 ID) and were simultaneously recorded with a paper recorder (writing speed, 5 mm/min; Mingograph; Siemens) and digitized with a frequency of 5 Hz per channel to be stored in the hard disk of a computer (AT; IBM).

Study design. During this double-blind cross-over study, each volunteer underwent three tests in a random order with an interval of at least 1 week between each test. The motor effects of the following three regimens were compared: (i) amoxicillin-clavulanate (Laboratories Beecham, Paris, France), 1 g plus 250 mg per os, given every 12 h for 3 days; (ii) placebo given the first and second days and then amoxicillin-clavulanate, 1 g plus 250 mg per os, given every 12 hours on the third day; and (iii) placebo given for 3 days. Each test lasted 3 days. Subjects were ambulatory when they were treated on the first and second days, until the manometric recording was performed the third day. Manometric recordings started at 10 a.m. after an overnight fast, and were then continuous during 22 h. During recording, subjects remained in the supine position but were allowed to read and to watch television. Oral intake was strictly limited to a standard 750-kcal meal taken at 6 p.m. and to the tablets of antibiotics or placebo given at 10 a.m. and 6 p.m., according to the protocol regimen for each subject. Each standard meal consisted of one hard-boiled egg, minced beef, beans, mashed potatoes, one yogurt, compote of apples, and water. The compositions of the meals were constant: 50% carbohydrate, 30% fat, and 20% protein.

On each day of treatment, subjects filled out a questionnaire to record the occurrence of diarrhea, nausea, vomiting, abdominal pain, and any other disorder.

Data analysis. For each recording, three successive periods were considered for analysis: the diurnal fast (from the start of the recording to the beginning of the dinner), the fed

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TABLE 1. Small intestinal motor parameters in six subjects each treated with placebo, amoxicillin-clavulanate for 1 day, and amoxicillin-clavulanate for 3 days[a]

Recording period and motor parameter	Placebo	Amoxicillin-clavulanate regimen	
		1 day	3 days
Diurnal fast			
Phases 1 and 2, motility index (mm Hg · s · min^{-1})	145 ± 37	156 ± 60	161 ± 46
Phase 3			
Frequency (h^{-1})	0.6 ± 0.1	0.4 ± 0.1	0.6 ± 0.2
Duration (min)	5.6 ± 1.0	5.6 ± 1.1	5.9 ± 1.0
Amplitude (mm Hg)	21.3 ± 3.8	21.3 ± 5.3	22.1 ± 2.5
Fed state			
Duration (h)	6.5 ± 1.1	6.5 ± 2.7	7.3 ± 1.5
Motility index (mm Hg · s · min^{-1})	193 ± 30	196 ± 60	196 ± 56
Nocturnal fast			
Phases 1 and 2, motility index (mm Hg · s · min^{-1})	121 ± 14	138 ± 44	168 ± 30[b]
Phase 3			
Frequency (h^{-1})	0.8 ± 0.1	0.9 ± 0.2	0.8 ± 0.2
Duration (min)	5.0 ± 0.8	5.6 ± 1.2	7.0 ± 1.7[c]
Amplitude (mm Hg)	21.0 ± 4.3	20.5 ± 4.1	23.0 ± 4.3[c]

[a] Results are expressed as means ± standard errors of the mean.
[b] $P = 0.036$.
[c] $P = 0.059$.

state (from the beginning of the dinner to the return of the first phase 3 [defined below] after the meal), and the nocturnal fast (from the return of the phase 3 after the meal to the end of the recording).

Motor activities during each period were analyzed by previously described methodologies (9, 12).

During fasting, the three phases of migrating motor complexes were recognized visually. Phase 1 was defined as a period of quiescence without visible contractions. Phase 2 was defined as an intermittent motor activity occurring between phases 1 and 3. Phase 3 was characterized by a burst of uninterrupted rhythmic and regular contractions that lasted at least 2 min and that migrated down the intestine at least over the two distal pressure sensors. Phases 3 were analyzed manually; and their frequencies (per hour), durations (in minutes) and amplitudes (in millimeters of mercury [1 mm Hg = 133.3 Pa]) were calculated. Phases 1 and 2 were analyzed with a computer program that determined the area under the mobility tracing curve in millimeters of mercury · second. To allow comparison between studies, we defined a motility index calculated as the ratio of the area under the curve divided by time (in minutes) and expressed in millimeters of mercury · second · $minute^{-1}$.

The fed state was defined as an irregular contractile activity observed in all leads, beginning with the onset of the dinner and ending with the return of the first phase 3 after the meal. Its duration and the motility index, as described above, were calculated.

Lastly, the respective frequencies of each symptom that occurred during each regimen were studied.

In this report, all values are expressed as means ± standard errors. Statistical analysis was performed by using the Wilcoxon nonparametric test for paired data.

RESULTS

Manometric recording. The main results of the study are summarized in Table 1. During the diurnal fast and the fed state, no motility parameter was significantly modified by either the 1-day or 3-day antibiotic regimen when compared with the placebo regimen. During the nocturnal fast, as shown in Fig. 1, the motility indices of phases 1 and 2 were significantly higher with the 3-day regimen than they were with the placebo regimen (168 versus 121 mm Hg · s · min^{-1}; $P = 0.036$). Moreover, during this period of nocturnal fasting, we found a trend for the phases 3 to be longer (7.0 versus 5.0 min; $P = 0.059$) and to be of higher amplitude (23.0 versus 21.0 mm Hg; $P = 0.059$) with the 3-day regimen than they were with the placebo regimen. The increased motility index with the 3-day regimen was observed in all six volunteers (Fig. 2), whereas the longer duration and the increased amplitude of the phases 3 were found in only five subjects (Fig. 3 and 4, respectively).

Side effects. Two subjects suffered from watery diarrhea, which occurred in both cases on the second and third days of the 3-day regimen. The subjects indicated no other adverse reactions.

DISCUSSION

The normal motility of the small bowel is now well recognized (12). The fasting pattern is characterized by the regular occurrence of bursts of migrating contractions (phases 3) which propel the lumen contents over a large distance; between two phases 3, the motor activity associates periods of motor quiescence (phases 1) and periods of irregular and nonpropagated contractions (phases 2). Eating interrupts this cyclic organization and induces a postprandial pattern characterized by irregular and permanent motor activity at

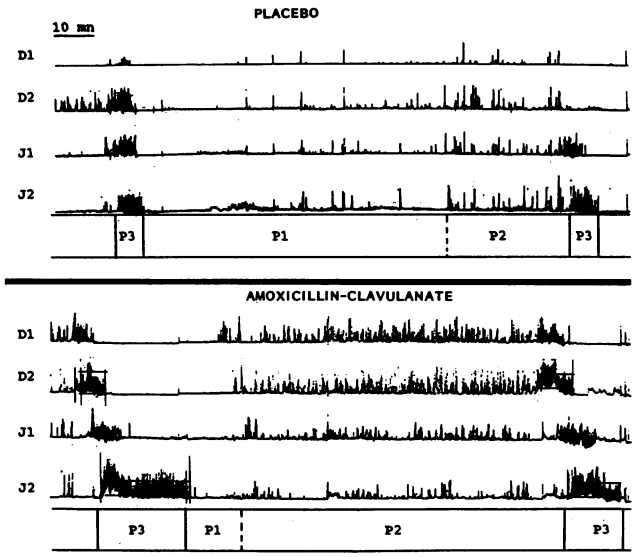

FIG. 1. Duodenal (D1, D2) and jejunal (J1, J2) motility recording during the nocturnal fast in a volunteer treated successively with placebo and amoxicillin-clavulanate for 3 days. Phases 1, 2, and 3 of the migrating motor complexes are indicated by P1, P2, and P3, respectively.

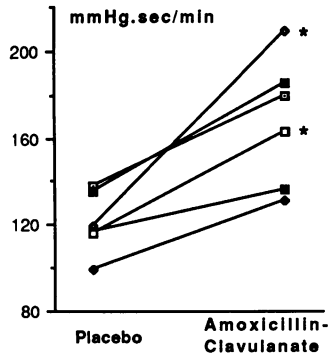

FIG. 2. Motility index calculated during the nocturnal fast in the six volunteers on day 3 of treatment with placebo and amoxicillin-clavulanate. The two subjects who experienced diarrhea with the antibiotic are indicated by asterisks.

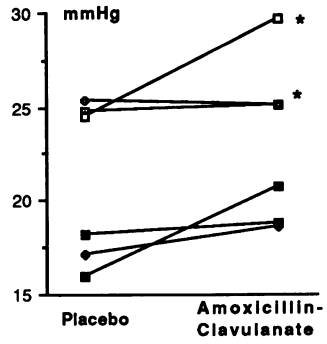

FIG. 4. Amplitude of intestinally propagated contractions (phases 3) during the nocturnal fast on day 3 of treatment with placebo and amoxicillin-clavulanate. The two subjects who experienced diarrhea with the antibiotic are indicated by asterisks.

all sites of the small intestine. Disturbances of small bowel motility have been reported, notably during intestinal bacterial overgrowth (12) and the administration of macrolide antibiotics (11). The manometric recording is a safe and well-codified method for studying small bowel motility in human beings (12). For the evaluation of the intestinal motor effect of a drug, manometric study is reliable, on the condition that a cross-over design is used. The variations of the normal motor patterns are important from one subject to another (9). Therefore, for the assessment of the motor effect of a drug, any subject needs to be considered as his or her own control.

In this study, amoxicillin-clavulanate was given orally, because this method of administration is both the most common and most often responsible for gastrointestinal side effects (10). Two therapeutic regimens were studied. With the 1-day regimen, we expected to detect early disturbances because we have observed that gastrointestinal side effects sometimes occur in the first hours after drug administration. The motor effect of the 3-day regimen was studied because, in our experience, the incidence of gastrointestinal disturbances seems to be highest after this duration of treatment. Lastly, on the basis of a suspected dose relationship for the adverse effects of the drug (2), the highest recommended daily dosage regimen was used to increase the probability of observing gastrointestinal disorders.

The results of this study indicate that amoxicillin-clavulanate given orally at therapeutic doses markedly modifies the motility of the duodeno-jejunum in humans. A 3-day regimen of amoxicillin-clavulanate significantly increased the motility index during the nocturnal period and tended to increase the duration and the amplitude of the phases 3 during the same period. Moreover, a trend for an increase in the motility index and the duration of the phases 3 during the nocturnal fast was already observed after the first day of treatment (1-day regimen). During the diurnal fast, the motor effects of the two drug regimens did not appear to be significantly different. The fact that the motor effects of amoxicillin-clavulanate were more pronounced during the nocturnal fast than during the diurnal fast could be explained, in part, by the circadian variations of the small bowel motor patterns. It has been shown that intestinal motor activity is usually important during waking but is limited during sleeping (8). Therefore, the demonstration of an increase in motor activity was certainly more difficult during the diurnal than during the nocturnal part of the study.

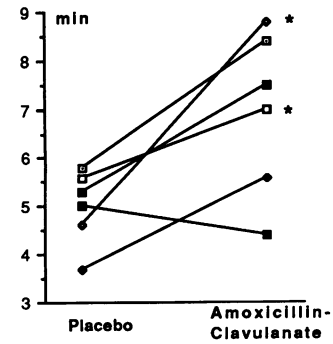

FIG. 3. Duration of intestinally propagated contractions (phases 3) during the nocturnal fast on day 3 of treatment with placebo and amoxicillin-clavulanate. The two subjects who experienced diarrhea with the antibiotic are indicated by asterisks.

The pathogenic mechanism of this motor effect remains unknown. Three hypotheses can be raised. (i) Disturbances of the normal gastrointestinal microflora seem unlikely because of the limited effect of the drug on the digestive microflora (1) and the usual low concentration of bacteria in the proximal gut, which is scarcely compatible with a mechanism of bacterial proliferation. (ii) The motor disturbances could be indirectly mediated by the release of an intraluminal mediator such as motilin, as was postulated for macrolide antibiotics (11, 15). (iii) Lastly, beta-lactam antibiotics interact directly with postsynaptic γ-aminobutyric acid receptors in the central nervous system (13). A similar direct effect of amoxicillin-clavulanate on the digestive tract could be involved, since such γ-aminobutyric acid receptors have been described in the myenteric plexus (14).

Digestive motor changes have been evoked previously to explain the gastric intolerance of macrolides (7). On the basis of the results of this study, it may be also tempting to correlate the adverse gastrointestinal effects of amoxicillin-clavulanate with the motor changes that we found. Indeed, the delay of occurrence of the motor disturbances is consistent with the clinical observations in patients, with gastrointestinal side effects usually being more pronounced after several days of treatment than after the first day of treatment. However, no definite conclusion can be raised on the basis of results of our study because we were unable to demonstrate an individual correlation between the motor

changes and the occurrence of side effects. Motor disturbances were demonstrated in five of six volunteers, but only two volunteers experienced digestive troubles.

In conclusion, this study demonstrates that the oral administration of a therapeutic regimen of an amoxicillin-clavulanate combination is associated, in most cases, with the occurrence of small intestinal motor disturbances. Further studies are needed to assess the respective roles of amoxicillin and clavulanate in the observed motor effects and to determine more precisely the involvement of these motor disturbances on the gastrointestinal symptoms that occur during amoxicillin-clavulanate therapy.

ACKNOWLEDGMENTS

We thank B. Parent, C. Helluin, and C. Roussignol for technical assistance and M. Delannoy for secretarial assistance.

This work was supported in part by a grant from the Laboratories Beecham, Paris, France.

REFERENCES

1. **Brumfitt, W., I. Franklin, D. Grady, and J. M. T. Hamilton-Miller.** 1986. Effect of amoxicillin-clavulanate and cephradine on the fecal flora of healthy volunteers not exposed to a hospital environment. Antimicrob. Agents Chemother. **30**:335–337.
2. **Crokaert, F., M. P. Van Der Linden, and E. Yourassowsky.** 1982. Activities of amoxicillin and clavulanic acid combinations against urinary tract infections. Antimicrob. Agents Chemother. **22**:346–349.
3. **Croydon, P.** 1984. Worldwide clinical review of Augmentin. *In* Postgraduate medicine, progress and perspectives on beta-lactamase inhibition: a review of Augmentin, p. 71–78. Custom Communications, New York.
4. **Ducrotte, P., E. Koning, F. Guillemot, C. Guedon, E. Lerebours, P. Denis, and R. Colin.** 1989. Jejunal motility during cyclic total parenteral nutrition in patients with Crohn's disease. Gut **30**: 815–819.
5. **Gehanno, P., M. Simonet, N. Moisy, and M. Veron.** 1989. Etude comparative randomisée dans l'otite moyenne aigue de l'enfant entre Oracéfal* 50 mg/kg/j versus Oracéfal* 100 mg/kg/j versus Augmentin* 50 mg/kg/j. Réunion Interdisciplinaire de Chimiothérapie Anti-Infectieuse, Paris, abstr. 192.
6. **Guedon, C., P. Ducrotte, J. A. Chayvialle, E. Lerebours, P. Denis, and R. Colin.** 1988. Effects of intravenous and intraduodenal fat on jejunal motility and on plasma cholecystokinin in man. Digest. Dis. Sci. **33**:558–564.
7. **Itoh, Z., M. Nakaya, T. Suzuki, H. Arai, and K. Wakabayashi.** 1984. Erythromycin mimics exogenous motilin in gastrointestinal activity in the dog. Am. J. Physiol. **247**:G688–G694.
8. **Kumar, D., E. E. Soffer, D. L. Wingate, J. Britto, A. Das-Gupta, and K. Mridha.** 1989. Modulation of the duration of human post-prandial motor activity by sleep. Am. J. Physiol. **256**: G851–G855.
9. **Ouyang, A., A. G. Sunshine, and J. C. Reynolds.** 1989. Caloric content of a meal affects duration but not contractile patterns of duodenal motility in man. Digest. Dis. Sci. **34**:528–536.
10. **Todd, P. A., and P. Benfield.** 1990. Amoxicillin-clavulanic acid: an update of its antibacterial activity, pharmacokinetic properties and therapeutic use. Drugs **39**:264–307.
11. **Tomomasa, T., T. Kuroume, H. Arai, K. Wakabayashi, and Z. Itoh.** 1986. Erythromycin induces migrating motor complex in human gastrointestinal tract. Digest. Dis. Sci. **31**:157–161.
12. **Vantrappen, G., J. Janssens, J. Hellemans, and Y. Ghoos.** 1977. The interdigestive motor complex of normal subjects and patients with bacterial overgrowth of the small intestine. J. Clin. Invest. **59**:1158–1166.
13. **Williams, P. D., D. B. Bennett, and C. R. Comereski.** 1988. Animal model for evaluating the convulsive liability of beta-lactam antibiotics. Antimicrob. Agents Chemother. **32**:758–760.
14. **Wood, J. D.** 1987. Physiology of the enteric nervous system, p. 67–105. *In* L. R. Johnson (ed.), Physiology of the gastrointestinal tract, 2nd ed. Raven Press, New York.
15. **Zara, G. P., H. H. Thompson, M. A. Pilot, and H. D. Ritchie.** 1985. Effects of erythromycin on gastrointestinal tract motility. J. Antimicrob. Chemother. **16**(Suppl. A):175–179.