Low potential of dobutamine and dopexamine to block intestinal peristalsis as compared with other catecholamines

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Objective: Catecholamines are frequently used in critically ill patients to restore stable hemodynamics and to improve organ perfusion. One effect of short-term or long-term administration of catecholamines may be inhibition of propulsive motility in the intestine. We therefore analyzed the effect of doxepamine, dobutamine, and dopamine on ileal peristalsis and compared their action with that of epinephrine and norepinephrine, which have long been known to suppress intestinal peristalsis.

Design: In vitro study on excised guinea pig ileum segments.

Setting: Laboratory for experimental studies at the University.

Subjects: Isolated guinea pig ileum.

Interventions: Segments of ileum excised from guinea pigs were mounted in a tissue bath in Krebs-Henseleit solution and bubbled with 95% oxygen/5% CO₂. Luminal perfusion with the same solution was performed at a rate of 0.35 mL/min. The bath temperature was kept at 36.5°C. Peristalsis was recorded via changes in the intraluminal pressure. The drugs under investigation (dopamine, epinephrine, norepinephrine, dobutamine, and dopexamine) were added to the tissue bath.

Catecholamines are frequently used in critically ill patients with low cardiac output syndrome to improve global hemodynamics and/or regional perfusion. Their effects on the human splanchnic region may be divided into indirect effects, which result from beneficial or detrimental impact on splanchnic perfusion, and direct effects on intestinal motility. Experimental and clinical research on the effect of catecholamines on the gastrointestinal tract currently focuses primarily on their indirect effects because of changes in cardiac output and splanchnic perfusion (1–7). Despite the beneficial effects of catecholamines on cardiac output and overall splanchnic circulation, catecholamines do not necessarily improve blood flow to the gastrointestinal mucosa. Dopamine, for instance, increases splanchnic perfusion but causes a redistribution of blood flow from the mucosa to the muscularis, which may lead to mucosal dysfunction, promote bacterial translocation, and eventually give rise to multiple organ failure (8, 9).

A well-established action of the older catecholamines epinephrine and norepinephrine on the gut, which may limit their therapeutic usefulness, is the inhibition of propulsive intestinal motility (10–13). This effect is primarily a result of inhibition of acetylcholine release from enteric neurons (11, 13, 14). New catecholamines, such as dobutamine and dopexamine, have been introduced into clinical routine. They are used alone or in combination with traditional catecholamines with the aim of improving regional hemodynamic effects (1, 6). It is not known whether these catecholamines also inhibit peristalsis and, if so, how the potency of such effects compares with that of epinephrine and norepinephrine. We therefore set out to compare the actions of catecholamines currently in clinical use on peristalsis in the isolated guinea pig ileum. The experimental model, which uses a fluid-perfused segment of ileum, allows a quantitative assessment of direct drug effects on peristalsis independent of circulatory changes (15, 16). To allow comparison of the potency of five catecholamines (epinephrine, norepinephrine, dopamine, dobutamine, and dopexamine), concentration-response curves were constructed for each drug.

Measurements and Main Results: Low concentrations of each catecholamine, except epinephrine, caused a decrease in the pressure threshold, which reflects a stimulatory effect on peristalsis. Higher catecholamine concentrations caused a concentration-related increase in the threshold, cumulating in a complete block of peristalsis. The rank order of inhibitory potency was epinephrine > norepinephrine > dopamine > dobutamine ~ dopexamine. Dobutamine and dopexamine were about 500-fold less active than epinephrine in suppressing peristalsis.

Conclusions: This study shows that dobutamine and dopexamine have the least potential to block propulsive motility in the intestine, whereas epinephrine demonstrates the most adverse inhibitory effect. Because at low concentrations dobutamine and dopexamine even stimulate peristalsis, these drugs appear to be superior compared with other catecholamines with regard to their direct effects on intestinal motility. (Crit Care Med 2000; 28: 2893–2897)

Key Words: guinea pig; ileum; threshold; peristalsis; dopamine; epinephrine; norepinephrine; dobutamine; dopexamine; motility

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Table 1. Composition of the Krebs-Henseleit solution

<table>
<thead>
<tr>
<th>Substance</th>
<th>Concentration (mM)</th>
</tr>
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<tbody>
<tr>
<td>NaCl</td>
<td>119</td>
</tr>
<tr>
<td>KCl</td>
<td>4.75</td>
</tr>
<tr>
<td>CaCl₂</td>
<td>2.5</td>
</tr>
<tr>
<td>MgSO₄</td>
<td>1.5</td>
</tr>
<tr>
<td>NaHCO₃</td>
<td>25</td>
</tr>
<tr>
<td>KH₂PO₄</td>
<td>1.2</td>
</tr>
<tr>
<td>Glucose</td>
<td>11</td>
</tr>
</tbody>
</table>

pigs were killed, all procedures for care were executed in accordance with national and international guidelines for the care and use of laboratory animals.

After cleaning, the ileum was first equilibrated in Krebs-Henseleit solution (Table 1) and bubbled with 95% oxygen/5% CO₂ for 1 hr. In a second step, segments of ileum with a length of 6 cm were taken and mounted in a small volume (22 mL) tissue bath (Mayflower, Hugo Sachs Electronics, Freiburg, Germany) in Krebs-Henseleit solution, which was bubbled with 95% oxygen/5% CO₂. The temperature of the tissue bath was kept at 36.5°C, whereas the pH of the Krebs-Henseleit solution was kept between 7.35–7.45.

Peristaltic contractions of the mounted ileum segment were elicited by luminal perfusion with Krebs-Henseleit solution at a rate of 0.35 mL/min using a REGLO-Digital MS-4/6–100 roller pump (Ismatec, Germany) against an aboral pressure of 5 cm H₂O. The peristaltic nature of the contractions was confirmed visually. Peristaltic contractions resulted in complete emptying of the segment. In total, 70% to 80% of the ileum segments developed repetitive peristaltic contractions and could be used for our experiments. Segments that did not show regular contractions were discarded. After a 15-min control period, the test drug was added to the organ bath and a 15-min test period was recorded. For each test drug and test concentration, a new segment was used.

Test Drugs. The drugs used in the study were dobutamine (Dobutrex, Eli Lilly, Indianapolis, IN), dopamine (Dopamin, Fresenius, Austria), dopexamine (Dopacard, Pisons plc, Pharmaceutical Division, UK), epinephrine (Suprarenin, Hoechst, Austria), and norepinephrine (Arterenol, Hoechst, Austria). Each test substance was first examined at a concentration of 1 nM. In the following experiments, the concentration was increased to evaluate the effect of different catecholamine concentrations on intestinal motility. The drugs were administered into the bath to the serosal surface of the ileum, in volumes not exceeding 1% of the bath volume.

Data Recording. Intraluminal pressure was measured at the oral end of the segment with a very low range differential pressure transducer (Validyne DP 45-XX, Hugo Sachs Electronics) and an amplifier (type 301, Hugo Sachs Electronics). Contractions were recorded with a Multi-Pen Recorder (R-OX, Hugo Sachs Electronics). The pressure curves of the mounted ileum segments were characterized by a slow initial rise of pressure to a threshold at which a peristaltic contraction was triggered (Fig. 1A). Then the cycle started anew. An increase in the threshold represents an inhibitory effect, whereas a decrease in the threshold reflects a stimulant action on peristalsis.

Data Analysis. Each segment served as its own control. Paired Student’s t-test was used for statistical analysis. A p of < .05 was considered to be significant. The recordings were analyzed for a shift in the pressure threshold required for triggering a contraction. The effects of different catecholamine concentrations on peristaltic activity were analyzed by measuring the distance between two consecutive contractions.

RESULTS

We tested five different catecholamines in at least six different concentrations. Analysis of the concentration response curves for pressure threshold showed significant qualitative and quantitative differences in the action of the different catecholamines on peristalsis. As shown in Figure 2, all catecholamines had a concentration-related increase in pressure thresholds, cumulating in a complete block of peristaltic activity. Epinephrine was the most effective inhibitor of peristalsis; significantly lower concentrations increased the pressure threshold as compared with the other catecholamines. Dopamine and dobutamine were the least potent inhibitors; higher concentrations were necessary to show an effect on the pressure threshold. The highest concentrations of each catecholamine used in the study resulted in a block of peristalsis. The concentration that led to this block of peristalsis was significantly lower for epinephrine and norepinephrine as compared with the other catecholamines (Fig. 2). Figure 2 also shows that all substances, except epinephrine, caused a small, but significant, reduction in the pressure threshold in their lower concentration ranges.

Effects of Different Catecholamines. Table 2 summarizes concentrations of maximum threshold reduction, half-maximum catecholamine concentrations and maximal inhibitory concentrations (block of peristalsis).

Epinephrine. Concentrations <5 nM did not change the peristaltic activity of the ileum segment. Higher concentrations of epinephrine resulted in a concentration-dependent rise of the pressure threshold (Fig. 1B). At 100 nM, peristalsis was completely abolished (Fig. 1C). Epinephrine was the only catecholamine that did not decrease the threshold at lower concentrations (Fig. 2).

At lower epinephrine concentrations, the frequency of peristaltic contractions increased (Fig. 1A), whereas at higher concentrations peristaltic frequency was reduced (Fig. 1B).

Norepinephrine. Concentrations <5 nM did not alter peristaltic motility. Concentrations between 5 and 25 nM led to a significant reduction of the threshold with a maximal effect at 10 nM. Higher concentrations resulted in an increase in the threshold and a complete blockade of peristalsis at 1 μM. The frequency of peristaltic contractions was reduced at all concentrations tested.

Dopamine. There was no effect on peristalsis with dopamine concentrations <75 nM. A concentration of 100 nM led to a significant reduction of the threshold. Concentrations up to 5 μM resulted in a small increase of the threshold, whereas higher concentrations led to a pronounced increase in the threshold, which resulted in a complete block of peristalsis at 50 μM. The frequency of peristaltic contractions increased at dopamine concentrations between 10 and 25 nM. Higher concentrations of the drug reduced peristaltic frequency.

Dobutamine. Dobutamine added to the tissue bath at concentrations <1 μM did not influence peristaltic motility (Fig. 3A). Concentrations between 1 and 10 μM caused a significant reduction of the threshold. At bath concentrations of 15 to 25 μM, the drug caused a moderate concentration-related increase in the threshold. A concentration of 30 μM dobutamine led to a marked rise in the threshold, and at 50 μM, a complete block of peristalsis was seen (Fig. 3B, C). The peristaltic frequency was reduced by dobutamine at all concentrations tested.

Dopexamine. Dopexamine concentrations up to 1 μM did not alter peristaltic motility. Concentrations between 1 μM and 20 μM lowered the peristaltic pressure threshold. At 30 μM, no change in the threshold was found, whereas higher concentrations of the drug caused a marked increase in the threshold, and 50 μM dopexamine completely suppressed peristalsis. All concentrations caused an initial increase in the peristaltic frequency, whereas after a few minutes a decrease of frequency was found.
DISCUSSION

Our results demonstrate that catecholamines that are currently used in critically ill patients because of their cardiovascular effects differ markedly in their inhibitory and stimulatory actions on the peristaltic motility of guinea pig ileum in vitro. Dobutamine and dopexamine are ~500 times less potent in inhibiting peristalsis than epinephrine, which was the most active compound among the catecholamines tested. The rank order of inhibitory potency was as follows: epinephrine > norepinephrine > dopamine > dobutamine ~ dopexamine.

The relative potency of epinephrine and norepinephrine corresponds with the potency reported by Mc Dougall and West (10). To our knowledge, the effects of the other catecholamines on peristaltic motility have not been tested. The low inhibitory potency of dobutamine ($\beta_1$-adrenoceptor agonist) and dopexamine ($\beta_2$-adrenoceptor agonist and dopamine receptor agonist) is, however, consistent with the finding that $\alpha$-adrenoceptor agonists are more active in inhibiting acetylcholine release from enteric neurons and suppressing peristalsis than $\beta$-adrenoceptor agonists (13, 17, 18).

Other differences among the catecholamines concern the observation that all substances, except epinephrine, decreased the peristaltic pressure threshold at low subinhibitory concentrations, which means that they facilitated peristalsis at this concentration range. The relevance of this finding to propulsive motility in vivo remains to be determined.

Another difference relates to the steepness of the concentration-response curves for peristaltic inhibition. The curves for norepinephrine and dopamine were flatter than those for the other tested substances, which is likely to reflect the involvement of different receptors and/or mechanisms.

There were also differences in the catecholamine-induced changes of peristaltic frequency. Epinephrine, dopamine, and dopexamine increased the frequency, at least at subinhibitory concentrations. The increase in pressure thresholds at higher catecholamine concentrations was associated with a reduction of frequency. This was not evaluated further because peristaltic frequency in vivo is a complex variable dependent on infusion rate, intestinal compliance, peristaltic pressure threshold, and the efficiency of emptying.
Dobutamine and dopexamine have the least potential to block peristalsis; at low concentrations they even stimulate peristalsis. These drugs appear to be superior to other catecholamines with regard to their adverse effects on intestinal motility.

Interpretation of frequency changes is therefore controversial (19). Furthermore, in contrast to changes in thresholds, which were constant during the whole observation period for each of the catecholamine concentrations tested, influences on peristaltic frequency were not constant.

The opposite effects of low and high concentrations of four of the five tested catecholamines on motility are most likely attributable to stimulation of different receptors. Stimulation of different receptors at different catecholamine dosages has been demonstrated for the effect of dopamine on blood vessels. Low-dose dopamine (≤3 μg/kg/min) has a vasodilatory effect because of a stimulation of dopaminergic receptors. Doses >5 μg/kg/min cause a stimulation of α-receptors and a vasoconstriction. In the present study, we have also observed dose-dependent switches of direct catecholamine effects. Except in the case of epinephrine, lower concentrations caused a reduction of the pressure threshold, and therefore a stimulation of intestinal contractility.

The present observations concerning the peristaltic pressure threshold indicate that dobutamine and dopexamine have the least potential to block propulsive motility in the gut. This low potency in suppressing intestinal propulsion favors the use of dobutamine and dopexamine in critically ill patients, although this recommendation is only based on their effects on intestinal motility and does not take their effects on gut perfusion into account. Milder disturbances of intestinal motility are frequently seen in the intensive care setting. Serious abdominal complications are known to occur in 1.4% of patients after cardiac surgery and have a total mortality of 14.5% (20). Risk factors for severe abdominal complications in cardiac surgery include advanced age, prolonged aortic cross-clamping time, low cardiac output, and multiple organ failure.

In experimental studies of pharmacologic effects on intestinal motility, addition of a pharmacologic substance to the organ bath rather than through the mesenteric vessels is commonly performed. Our data suggest that neither the timing nor quantitative aspects of the actions of catecholamines on the ileum are influenced by a possible diffusion barrier. As shown in Figures 1 and 3, the catecholamines had an immediate effect on peristaltic activity, which suggests that the time that is needed for diffusion of the catecholamine to their receptors was not a limiting factor of our preparation.

In addition, as shown in the Figures 1 and 3, the catecholamine effect did not increase during the observation time, which suggests that there was no diffusion barrier which would have been overcome with time and which might possibly have influenced the quantitative aspect of the catecholamines.

Although caution must be observed when our data from the guinea pig are applied to intensive care patients, some comparisons may shed light on potential clinical implications. Arterial plasma concentrations reach 23.9 nM in healthy volunteers after infusion of epinephrine at a rate of 0.2 μg/kg·min⁻¹ (21). In guinea pig ileum, comparable concentrations of epinephrine resulted in a stimulation of peristaltic frequency (Fig. 1A). There was no marked effect on the threshold of peristalsis at this concentration, but because the concentration-response curve of epinephrine is very steep, only slightly higher concentrations already cause a considerable inhibition of peristaltic contractility of the guinea pig ileum (Fig. 2). Infusion of norepinephrine in humans at a rate of 0.2 μg/kg·min⁻¹ resulted in arterial plasma concentrations up to 44.1 nM (21). In the guinea pig ileum, comparable concentrations caused a marginal increase of the threshold. Because the concentration response curve of the effects of norepinephrine on motility is flatter, the margin of safety for the therapeutic use of norepinephrine may be bigger as compared with epinephrine.

Plasma concentrations of dobutamine at an infusion rate of 10 μg·kg⁻¹·min⁻¹ reach about 0.6 μM, and plasma concentrations of dopexamine at an infusion rate of 4 μg·kg⁻¹·min⁻¹ reach 0.4 μM (22, 23). As can be seen in Figure 2 these concentrations have no effect on intestinal motility. Higher concentrations would stimulate motility, before at even higher concentrations inhibition of motility would occur. From the point of ileal motility, our data therefore support the suggested of Meier-Hellmann et al. (4) and Levy et al. (1) that a combination of norepinephrine and dobutamine may be preferable over an epinephrine monotherapy. This combination of drugs has also recently been suggested to be used in septic patients, by the Task Force of the American College of Critical Care Medicine (24).
In conclusion, our in vitro study compared the different effects of clinically used catecholamines on intestinal motility. We demonstrated that these catecholamines differed profoundly in their action on intestinal motility. Of the tested substances, dobutamine and dopexamine have the least potential to block peristalsis; at low concentrations they even stimulate peristalsis. These drugs appear to be superior to other catecholamines with regard to their adverse effects on intestinal motility.

REFERENCES