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## Is there still a place for metoclopramide as a prokinetic drug in critically ill patients?

Recently, regulatory agencies in North America and Europe re-evaluated the safety of metoclopramide. This resulted in recommendations and restrictions in order to minimize the risk of neurological and other adverse reactions associated with the use of metoclopramide. The side effects in non-ICU patients are as follows<sup>1</sup>:

1. Neurological adverse reactions, including extrapyramidal disorders, dyskinesia, dystonia, convulsion, hypertonia and tremor. The reported occurrence of tardive dyskinesia ranges from <0.01% to 23%. High occurrence is attributed to chronic use (months to years) of approximately 30±10 mg metoclopramide a day and concerns mostly older (60 ± 22 years) women. Of an estimated 15.9-million metoclopramide prescriptions in the UK in the period 1967-1982, extrapyramidal symptoms were reported with an incidence of 0.003%. Occurrence of akathisia is related to the rate of intravenous metoclopramide administration. After a bolus injection over 2 minutes 24.7% experienced akathisia, which was reduced to 5.8% in patients receiving the same dose in a 15-minute infusion.
2. Cardiac adverse reactions, including shock, hypotension, cardiac arrest, tachycardia, bradycardia, hypertension, cardio-respiratory arrest and circulatory collapse. Evidence is solely based on case-reports.

Delayed gastric emptying is commonly encountered in the ICU and may be present in 50 to 60% of all ICU patients. A recent retrospective analysis in ICUs in 21 countries demonstrated an enteral feed intolerance with 30.5% of patients after a median 3 days on enteral nutrition (EN) and patients with longer intolerance have longer lengths of stay and higher mortality<sup>2</sup>. Moreover, EN intolerance is associated with increase protein/caloric debt- which contributes to the worse outcome associated with EN intolerance. Metoclopramide is extensively used as an intravenous prokinetic drug to treat delayed gastric emptying and facilitate enhanced delivery of EN. However, metoclopramide is not officially registered for this specific indication in critically ill patients. The commonly used metoclopramide dosage in the ICU-setting is 10 mg four times daily. Limited information is available on metoclopramide dosing in renal failure. It is usually recommended to reduce the dose by 50% when creatinine clearance is 10-50 ml/min. Since the volume of distribution of metoclopramide is high, metoclopramide is only minimally removed by hemodialysis or peritoneal dialysis, and no supplemental dose is necessary after dialysis. During continuous renal replacement therapy 50% of the normal dose can be prescribed<sup>1</sup>.



### Are there (available) alternatives to metoclopramide?

At present, in many countries the only available alternative to metoclopramide is intravenous erythromycin. Erythromycin is generally considered to be effective and some investigators suggested that erythromycin is even more effective than metoclopramide as a single prokinetic agent<sup>3,4</sup>. Commonly, 200 mg intravenous erythromycin twice daily is used, but doses of 70 mg might be effective as well<sup>5</sup>. Use of erythromycin as a single agent may be hampered by the occurrence of tachyphylaxis within a few days and because of the concerns regarding its cardiac effects (QTc-prolongation) and the potential emergence of antibiotic resistance<sup>3,6</sup>. Besides erythromycin, no other alternatives are currently available.

### Tachyphylaxis of prokinetics

Tachyphylaxis was addressed in two studies<sup>4,7</sup>. Over time, all treatments became less effective with treatment failure *i.e.* tachyphylaxis occurring after 2, 3 and 6½ days for metoclopramide, erythromycin and combination therapy respectively. Combination therapy might be more effective because of the complementary actions of both prokinetics and the multiple mechanisms underlying delayed gastric emptying. The relevance of tachyphylaxis is still unknown, since combination therapy associated with delayed occurrence of tachyphylaxis did not result in improved survival or length of hospital stay. However, the power of the study might be insufficient to demonstrate significance<sup>4,7</sup>.

## Adjusting the dose of metoclopramide

Adjusting the maximum daily dose to 10 mg thrice daily according to the recommendations of the EMA should decrease the risk of neurological and other adverse reactions associated with metoclopramide<sup>8</sup>. However, evidence supporting the effectiveness of 10 mg thrice daily in critically ill patients is scarce, since most studies among these patients investigated the effects of 10 mg every six hours<sup>6</sup>. One study did investigate metoclopramide 10 mg thrice daily in the prevention of pneumonia in ICU patients who received nasogastric enteral feeding. Although metoclopramide thrice daily did delay the onset of pneumonia, this showed not to be of clinical significance as the risk of pneumonia and mortality were not reduced<sup>9</sup>. Thus, adjusting the metoclopramide dosage according to the recommendations of the EMA cannot be recommended as there is lack of evidence supporting this dosage regimen in critically ill patients. Efficacy has only been shown in studies using 10 mg qid.

## Recommendations for the use of prokinetics in ICU patients

At present, the only available alternative to metoclopramide is erythromycin, but both agents are commonly used as a combined strategy to improve gastric emptying and improve patient outcomes<sup>6</sup>. Some new prokinetic agents appear promising, but will not be available in the near future. We recommend to continue the off-label use of metoclopramide and not to exceed a daily dose of four times 10 mg. Attention must be paid to the reported side effects and the occurrence of tachyphylaxis, since this might be of major importance for patient safety and successful treatment. If intolerance to enteral feeding persists with use of metoclopramide, erythromycin should be added for another 24-48 hours. If this combination doesn't work it is probably better to stop both agents, and move to another route of feeding such as postpyloric feeding. In any case we recommend using the combination only during a maximum of 7 days for reasons of tachyphylaxis. In case of renal failure the dose of metoclopramide should be adjusted.

### Key Messages

- As neurological and cardiac side-effects have been rarely reported in critically ill patients and feeding intolerance is common and alternative therapeutic strategies are limited, we recommend continuing the off-label use of metoclopramide in critically ill patients to improve gastric emptying in patients with high gastric residual volumes to enhance enteral feeding.
- In order to limit side effects a slow infusion rate and dosages not exceeding a daily dose of four times 10 mg of metoclopramide is recommended, and dosages should be adjusted in case of renal failure.
- For reasons of tachyphylaxis and safety, a maximum duration of 7 days is recommended but shorter treatments periods would again limit the risk of side effects. Combination therapy with erythromycin can be considered if monotherapy is ineffective. In case of treatment failure with prokinetics, a postpyloric feeding tube should be considered.

### References

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