

## Acute effects of doramectin on gastric acid secretion in anaesthetized rats - a short communication

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### ABSTRACT

To investigate the acute effects of doramectin on basal and histamine-stimulated gastric secretion in anaesthetised rats, twenty adult female Sprague-Dawley rats were anaesthetised and their stomachs were cannulated and perfused with saline. Basal gastric acid secretion was collected from all rats. Doramectin (300 µg.kg<sup>-1</sup>, n = 5 and 600 µg.kg<sup>-1</sup>, n = 5) was then administered to ten rats intramuscularly, followed an hour later by histamine (100 µg.kg<sup>-1</sup>) subcutaneously. In another 10 rats the histamine was administered an hour before the doramectin. There was no significant change in gastric acid secretion compared to when doramectin alone was administered. Histamine, produced a significant increase (P<0.01) in gastric acid secretion. Doramectin neither potentiated nor decreased the effect of histamine on gastric acid secretion.

**Key words:** gastric acid, doramectin, rats, gamma amino butyric acid

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### Introduction

Doramectin is an avermectin B1 produced from *Streptomyces avermitilis* and is a potent endectocide (SAEKI et al., 1997; TOUTAIN et al., 1997) widely used in veterinary medicine. It affects gamma amino butyric acid (GABA)-gated chloride channels (HARDER, 2002). Gamma amino butyric acid is an inhibitory transmitter in enteric interneurons (KRANTIS, 2000; TSAI, 2005).

The main stimuli for gastric acid secretion are acetylcholine released at or near the parietal cells by postganglionic neurons, gastrin released by G cells (in response to

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aromatic amino acids and the neuropeptide pituitary adenylate cyclase-activating peptide (PACAP)) in the antrum and proximal duodenum, and histamine from enterochromaffin-like (ECL) cells of the lamina propria (BERTACCINI, 1988; SOLL and WALSH, 1979; VARGA et al., 1993; WILKES et al., 1991). The ECL cells also have receptors for somatostatin, galanin and polypeptide YY, which inhibit the release of histamine (LAMBRECHT et al., 2006). ECL cells are distributed throughout the gastrointestinal (GIT) mucosa and control intestinal secretion, motility and absorption and also have GABA receptors (SCHAFERMEYER et al., 2004). GABA affects the release of somatostatin and gastrin from the antral mucosa of rats (HARTY and FRANKLIN, 1983). Given the distribution of GABA receptors in the regulatory cells of the gastrointestinal tract, it is possible that Doramectin may alter gastric secretions and predispose animals to gastric ailments associated with hyperacidity or achlorhydria such as ulceration and gastritis. We thus investigated the acute effects of doramectin on gastric acid secretion in rats.

#### Materials and methods

Twenty Sprague-Dawley female rats were used ( $240 \pm 45$ g body mass), which had been kept on a 12 hours light-dark regime and fasted for 18 hours prior to the experiments. The rats had drinking water *ad libitum*. The rats were anaesthetized with pentobarbitone (Rhone-Poulenc S.A)  $50 \text{ mg.kg}^{-1}$  intraperitoneally. They were tracheostomised to keep the airways patent. The abdomen was opened via a midline incision, the stomach was cannulated at the pyloro-duodenal junction with a polyethylene cannula. An orogastric cannula was placed so that the tip lay in the non-glandular portion of the stomach and was connected to an infusion-perfusion pump (Harvard Apparatus, St. Natrick, Mass) set to infuse  $1 \text{ mL.min}^{-1}$  of 0.9% saline. The stomach was perfused for 30 minutes to stabilize gastric secretion and then six basal acid collections were taken at 10-minute intervals in all rats. Following the basal collections, ten rats were injected with  $100 \text{ }\mu\text{g.kg}^{-1}$  histamine (Sigma-Aldrich, USA) subcutaneously, and gastric contents collected for 60 minutes. This was followed by either  $300 \text{ }\mu\text{g.kg}^{-1}$  Doramectin (Dectomax, Pfizer, USA) ( $n = 5$ ) or  $600 \text{ }\mu\text{g.kg}^{-1}$  ( $n = 5$ ) intramuscularly, and the gastric acid collected as before. In another 10 rats the procedure was reversed so that the rats received the Doramectin an hour before the histamine injections. All samples were collected at 10 minute intervals and were titrated against 0.01 M sodium hydroxide with phenolphthalein as an indicator to determine the total amount of acid secreted. Once completed all the rats were euthanased by an overdose of thiopentone.

The study was approved by the University of Zimbabwe Research board.

Data were presented as mean  $\pm$  standard deviation and statistically analysed using a one-way ANOVA with the level of significance set at  $P < 0.05$ .

## Results

Doramectin (300  $\mu\text{g.kg}^{-1}$  and 600  $\mu\text{g.kg}^{-1}$ ) alone did not significantly affect gastric acid output (Fig. 1). Administration of Histamine alone significantly increased gastric acid compared to basal secretion, however, doramectin neither potentiated nor attenuated the effect of histamine on gastric acid secretion.

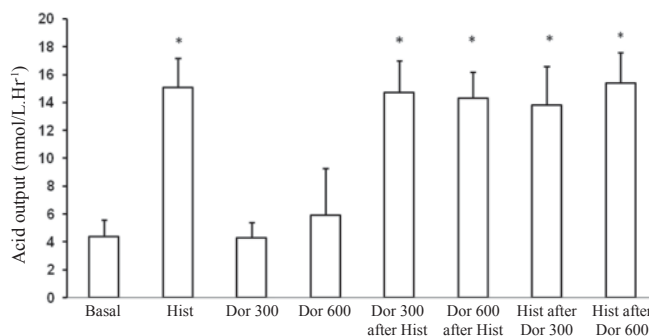


Fig. 1. Acute effect of doramectin and histamine on gastric acid output in anaesthetized rats.

\*Indicates data statistically significant ( $P < 0.01$ ) compared to basal gastric acid output. Hist = histamine, Dor 300 = doramectin 300  $\mu\text{g.kg}^{-1}$ , Dor 600 = doramectin 600  $\mu\text{g.kg}^{-1}$ .

## Discussion

The therapeutic doses of doramectin vary slightly from one species to another (ranging from 200  $\mu\text{g.kg}^{-1}$  in cattle, sheep and horses to 300  $\mu\text{g.kg}^{-1}$  in pigs). In this study we used a normal therapeutic dose (300  $\mu\text{g.kg}^{-1}$ ) and double the therapeutic dose (600  $\mu\text{g.kg}^{-1}$ ), neither of which significantly affected basal or histamine stimulated gastric acid secretion.

The infusion of GABA has been shown to increase gastric acid secretion in dogs (THIRLBY et al., 1988), however, we found that doramectin which causes the release of GABA and modulates GABAergic ionophores did not acutely affect gastric acid secretion in anaesthetised rats. Although most *in vivo* studies on the role of GABA in enteric function have focussed on the use of GABA directly or with GABAergic drugs such as baclofen, sodium valproate or diazepam and not the avermectins, when applied to isolated guinea pig ileum, avermectin B1a induced rhythmic longitudinal mechanical activity (KERR and ONG, 1986) indicating that at least *in vitro* the avermectins may affect GIT function. A case of toxicity has also been reported in humans due to exposure to emamectin benzoate (the 4'-deoxy-4'-epi-methyl-amino benzoate salt of avermectin B1) resulting in gastric erosion and transient gastrointestinal upset (YEN and LIN, 2004).

In cattle the time taken for doramectin to reach peak plasma concentrations following a subcutaneous injection was 5 days (TOUTAIN et al., 1997). Thus although we did not find any significant acute effects of doramectin on gastric acid secretion, it may not have been the case if the study had been over a longer duration.

Doramectin did not acutely affect gastric acid secretion in the anaesthetised rats but it is important though to emphasize that this study was performed on rats and the data thus may not be readily extrapolated to other species. It is recommended that further studies be carried out on other species in which doramectin is routinely administered and over a longer time course.

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#### References

- BERTACCINI, G. (1988): Receptors involved in the regulation of gastric acid secretion. *S. Afr. Med. J.* 11, 3-4.
- HARDER, A. (2002): Chemotherapeutic approaches to nematodes: current knowledge and outlook. *Parasitol. Res.* 88, 272-277.
- HARTY, R. F., P. A. FRANKLIN (1983): GABA affects the release of gastrin and somatostatin from rat antral mucosa. *Nature* 303, 623-624.
- KERR, D. I., J. ONG (1986): Gamma-aminobutyric acid dependent motility induced by avermectin B1a in the isolated intestine of the guinea pig. *Neurosci. Lett.* 65, 7-10.
- KRANTIS, A. (2000): GABA in the mammalian enteric nervous system. *News Physiol. Sci.* 15, 284-290.
- LAMBRECHT, N. W. G., I. YAKUBOV, C. ZER, G. SACHS (2006): Transcriptomes of purified gastric ECL cells and parietal cells: identification of a novel pathway regulating acid secretion. *Physiol. Genom.* 25, 153-165.
- SAEKI, H., T. FUJII, S-I. FUKUMOTO, K. KAGOTA, A. TANEICHI, S. TAKEDA, M. TSUKAGUCHI (1997): Efficacy of doramectin against intestinal nematodes and sarcoptic mange mites in naturally infected sheep. *J. Vet. Med. Sci.* 59, 129-132.
- SCHAFFERMEYER, A., M. GRATZL, R. RAD, A. DOSSUMBEKOVA, G. SACHS, C. PRINZ (2004): Isolation and receptor profiling of ileal enterochromaffin cells. *Acta. Physiol. Scand.* 182, 53-62.
- SOLL, A. H., J. H. WALSH (1979): Regulation of gastric acid secretion. *Ann. Rev. Physiol.* 41, 35-53.
- THIRLBY, R. C., M. H. STEVENS, A. J. BLAIR, F. PETTY, L. CRAWFORD, I. L. TAYLOR, J. H. WALSH, M. FELDMAN (1988): Effect of GABA on basal and vagally mediated gastric

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acid secretion and hormone release in dogs. *Am. J. Physiol. Gastrointest. Liver Physiol.* 254, G723-731.

TOUTAIN, P. L., D. W. UPSON, T. N. TERHUNE, M. E. MCKENZIE (1997): Comparative pharmacokinetics of doramectin and ivermectin in cattle. *Vet. Parasitol.* 72, 3-8.

TSAI, L. H. (2005): Function of GABAergic and glutamatergic neurons in the stomach. *J. Biomed. Sci.* 12, 255-266.

VARGA, G., D. CAMPBELL, L. BUSSJAEGER, T. SOLOMON (1993): Role of gastrin and cholecystokinin receptors in regulation of peptone-stimulated gastric acid secretion in conscious rats. *Eur. J. Pharmacol.* 250, 37-42.

WILKES, J. M., M. KAJIMURA, D. R. SCOTT, S. J. HERSEY, G. SACHS (1991): Muscarinic responses of gastric parietal cells. *J. Membr. Biol.* 122, 97-110.

YEN, T-H., J-L. LIN (2004): Acute poisoning with emamectin benzoate. *Clin. Toxicol.* 42, 657-661.

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**ERLWANGER, K., T. CHANGARA, S. SAJENI, D. MASARA: Akutni učinci doramektina na lučenje želučane kiseline u anestetiziranih štakora. *Vet. arhiv* 80, 533-537, 2010.**

**SAŽETAK**

Dvadeset odraslih Sprague-Dawley štakorica bilo je podvrgnuto anesteziji radi istraživanja akutnih učinaka doramektina na bazalno i histaminom potaknuto želučano lučenje. U njihove želuče bile su postavljene kanile te su bili isprani fiziološkom otopinom. Bazalno izlučena želučana kiselina bila je skupljana od svih štakorica. Nakon toga štakoricama je u mišićje bio primijenjen doramektin (300 µg.kg-1, n = 5 i 600 µg.kg-1, n = 5), a sat kasnije potkožno i histamin (100 µg.kg-1). Drugoj skupini od 10 štakorica histamin je bio primijenjen jedan sat prije doramektina. Nije ustanovljena značajna promjena u lučenju želučane kiseline nakon davanja samog doramektina u odnosu na bazalno lučenje. Histamin je potaknuo značajno povećanje ( $P < 0,01$ ) lučenja želučane kiseline. Doramektin nije ni pojačao ni smanjio učinak histamina na lučenje želučane kiseline.

**Ključne riječi:** želučana kiselina, doramektin, štakori, gama-aminomaslačna kiselina

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