VETERINARSKI ARHIV 75 (2), 111-118, 2005

Role of serum pepsinogen in detecting cows with abomasal ulcer

Matjaž Mesarič*

Veterinary Faculty, University of Ljubljana, Ljubljana, Slovenia

MESARIČ, M.: Role of serum pepsinogen in detecting cows with abomasal ulcer. Vet. arhiv 75, 111-118, 2005.

ABSTRACT

Serum pepsinogen activity was determined in the blood serum of 126 clinically healthy cows by the method of Paynter. After slaughter the cows studied were classified into three groups according to established macroscopic changes to the mucous membrane of the abomasum: a group without changes, a group with ulcers and a group with other changes. The prevalence of the appearance of abomasal ulcers was 7%. In the group of cows with ulcer the average activity of pepsinogen was statistically significantly higher than in other two investigated groups ($P<0.001$). We found that the extent of changes to the mucous membrane of the abomasum had statistically the most significant influence on the activity of pepsinogen ($P<0.001$). The number of changes had smaller, but still statistically significant influence on the activity of pepsinogen ($P<0.05$). On the basis of a confidence level of 95%, we determined 5.0 U/L as the upper boundary of serum pepsinogen activity, which still does not signify major changes to the mucous membrane of the abomasum. The use of serum pepsinogen promised to provide a simple serum test to evaluate absence of subclinical abomasal ulcers in cows with known parasitological status.

Key words: cattle, abomasums, ulcer, pepsinogen

Introduction

The prevalence of abomasal mucousal diseases in cows is becoming more frequent in modern intensive production (RADOSTITS et al., 2000; PALMER and WHITLOCK, 1984; KATCHUIK, 1992; CABLE et al., 1998). Clinical signs are often rather diffuse and non-specific and it would be of considerable help to find an association between abomasal ulcers and various clinical parameters. Gastroscopy has become an excellent tool to verify

* Contact address:
Dr. Matjaž Mesarič, Veterinary Faculty, University of Ljubljana, Cesta v Mestni log 47, 1000 Ljubljana, Slovenia; Phone: +386 1 4779 274, Fax: +386 1 4779 388, E-mail: Matjaz.Mesaric@vf.uni-lj.si

ISSN 0372-5480
Printed in Croatia

the diagnosis in humans, horses and dogs (ODERDA et al., 1988; SANDIN et al., 1999). In cattle practice this diagnostic method cannot be used due to presence of the forestomach and permanent secretion of abomasal juice.

Pepsinogen is an inactive form of pepsin, which is the most important proteolytic enzyme of gastric juice. Increased activation of pepsinogen into pepsin by enhanced acidity of gastric contents can cause ulcers in humans and animals (TANAKA et al., 1991; SAEZ-ALQUEZAR et al., 1978; VIANELLO et al., 1988). In human serum pepsinogen was elevated by different diseases including gastric and duodenal ulcers (SAMLOFF et al., 1986). An increase in pepsinogen reflects mucousal damage as a consequence of an Ostertagia infection in cattle (XIAO et al., 1992; BERGHEN et al., 1993; SCHAW et al., 1997; SCOTT et al., 1999). Elevated pepsinogen levels induced by non-parasitic diseases in cows such as abomasitis catarrhalis acuta, abomasal ulcerations and left or right abomasal displacement were not confirmed (VÖRÖS et al., 1984; ZADNIK and MESARIČ, 1999). Pepsinogen activity of cattle with abomasal ulcer with fatal haemorrhage was abnormally high only in half of investigated animals (AUKEMA and BREUKINK, 1974). However, no exact investigations were made to determinate the role of serum pepsinogen in detecting abomasal ulcers in cattle.

In our contribution, the applicability of serum pepsinogen activity for the diagnosis of changes to the mucouse membrane of the abomasum in cows was under investigation.

Materials and methods

Blood samples were taken from 126 clinically normal cows before slaughter from tail vein (v. caudalis mediana). Serum was separated with centrifugation and frozen at -20 °C until examination. Pepsinogen activity in serum was determined via the method by PAYNTER (1994). After slaughter the abomasum was opened via curvatura minor, the entire mucousa was thoroughly examined and samples for histopathological examination were taken. Number, extent and location of established macroscopic changes of abomasal mucousa were recorded. With regard to macroscopic changes of mucousa, cows were divided into 3 groups: group without changes (n = 22), group with other changes (n = 90) and group with ulcers (n = 14). In group with other changes we have classified cows with abomasitis and erosions. The estimated macroscopic changes of abomasal mucousa were verified by histopathological examination.

The data were statistically evaluated by means of the analysis of variance (ANOVA), the multiple classification analysis and Youden index (ARMITAGE, 1971). Furthermore, in a series of serum pepsinogen determinations the true positive rate was plotted against the false positive rate to find optimal cutoff values, according to the receiver-operating characteristic (ROC) curve approach (METZ, 1978; ZWEIG and CAMPBELL, 1993).

Results

Results of histopathological examination matched with macroscopic distribution of the changes of abomasal mucousa. Fourteen abomasal ulcers were reported; 12 of type I and 2 of type II. The prevalence of the appearance of abomasal ulcers in our research was 0.07 (7%).

Table 1. Mean pepsinogen activities in cows with changes to the abomasal mucosa

Abomasal mucosa	n	Pepsinogen (U/L) x ± SD	P value	
Without changes	22	3.14 ± 1.06	<0.05	<0.001
Other changes	90	4.27 ± 2.70		
Ulcers	14	6.44 ± 2.80	<0.01	

ANOVA: F = 18.122; P< 0.001

Serum pepsinogen activity from all three groups is depicted in Table 1. The lowest mean pepsinogen activity was found in the group without changes. In the group of cows with abomasal ulcers statistically significant higher mean activity of pepsinogen was found, compared to the group without changes (P<0.001) and the group with other changes (P<0.05). Mean activity of pepsinogen was in the group with ulcers twice as high as in the group without changes.

Table 2. Predictive value of serum pepsinogen in cows with abomasal ulcer

	Abomasal ulcer		
Serum pepsinogen	Yes	No	Total
< 5.0 U/l	4	81	85
> 5.0 U/l	10	31	41
Total	14	112	126

Positive predictive value = 10/41 = 0.24 (24%); Negative predictive value = 81/85 = 0.95 (95%) Sensitivity = 10/14 (71.4%); Specificity = 81/112 (72.3%); Youden index = 0.44; Prevalence of abomasal ulcers = 0.07 (7%); Relative risk = 5.2; $\chi^2 = 8.95$ (P< 0.01)

Group without changes to the mucous membrane of the abomasum comprised the most homogeneous group in their serum pepsinogen distribution (x ± SD: 2.67 - 3.61 U/L). The greatest dispersion of serum pepsinogen was found in the group with abomasal ulcers (x ±

SD: 4.93 - 7.93 U/L). It was established that pepsinogen activities in blood of cows above 5.0 U/L revealed that abomasal mucousa was severely affected.

Table 3. Influence of location, number and extent of changes to the mucous membrane of the abomasum on serum pepsinogen by multiple comparison analysis

Influence	F-value	P-value
Location	0.69	0.504
Number	3.49	0.034*
Extent	24.99	0.0001***

*P<0.05; ***P<0.0001

The positive and negative predictive values were calculated by analysing results using a 2×2 contingency table (Table 2), grouping animals into those with pepsinogen activity greater than 5.0 U/L or less than or equal to 5.0 U/L, and whether or not cows had a documented abomasal ulcer. Results indicate that cows with elevated serum pepsinogen activity were 5.2 times (relative risk = 5.2) more likely to have abomasal ulcer than those with low or normal activities. The specificity of the method for pepsinogen determination for establishing abomasal ulcers was 72%, and sensitivity 71%. The positive predictive value for pepsinogen activity was 24%. More impressively, the negative predictive value of pepsinogen activity was 95%. Via Chi-square test a statistically significant (P<0.01) association was established between pepsinogen activity above 5.0 U/L and the presence of abomasal ulcers.

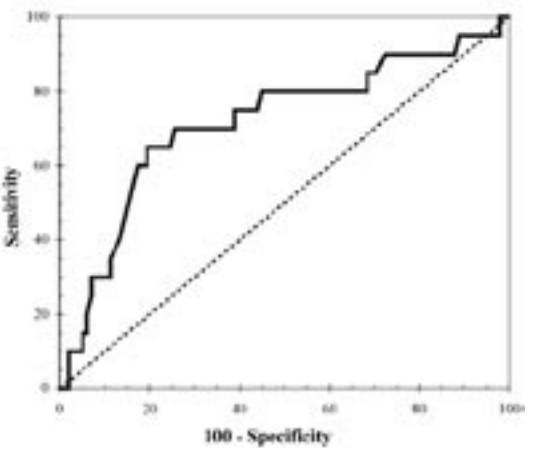

Fig. 1. Receiver-operating characteristic (ROC) curve of serum pepsinogen activity in the diagnosis of abomasal ulcer

Figure 1. illustrates the ROC curve of the serum pepsinogen activity in the diagnosing of abomasal ulcer. The curve-suggested cutoff for serum pepsinogen activity was 5.5 U/L (sensitivity = 65%, specificity = 81%) and area under the ROC curve was 0.769. The likelihood ratio for a positive test would be 3.35 and, for a negative test, 0.43.

The extent of changes to the mucous membrane of the abomasum had a statistically significant ($P<0.001$) influence on the activity of pepsinogen (Table 3). The number of changes had smaller, but still significant influence on the activity of pepsinogen ($P<0.05$). Location of changes has no influence on the activity of pepsinogen.

Discussion

The use of serum pepsinogen activity promised to provide a simple serum test to diagnose or evaluate cows with subclinical abomasal ulcer. Our present data confirm that serum pepsinogen activities were significantly higher in cows with established abomasal ulcer than in cows with other changes, and without changes, to the mucouse membrane of the abomasum.

Since our group without changes to the mucous membrane of the abomasum comprised individual cows without established histopathological findings of abomasum we considered it valid to infer a range of normal values arising from the results of this group. In fact, the distribution of serum pepsinogen activity was rather homogeneous in this group. No serum pepsinogen activities below 1.0 U/L were established in group without changes in comparison with the other investigated group of cows. The greatest frequency of elevated serum pepsinogen activity is related to the existence of abomasal ulcer and also to the presence, in some cases, of other changes to the mucous membrane of the abomasums.

On the basis of a confidence level of 95%, we determined 5.0 U/L as the upper boundary of activity of serum pepsinogen, which still does not signify major changes to the mucous membrane of the abomasum. The established upper boundary of serum pepsinogen is equal to that determined by PAYNTER (1994). Elevated serum pepsinogen activity defined by the study population itself was associated with a relative risk of 5.2 for abomasal ulcer. Direct calculations of the predictive value of an elevated pepsinogen activity revealed that only about 24% of cows develop abomasal ulcer. More impressive is that low normal pepsinogen activity indicated the absence of abomasal ulcer in 95% of cows. This high negative predictive value may reflect the relatively low prevalence of abomasal ulcer (7%) in our study population. The values obtained for the area under the ROC curve indicate the moderate accuracy of this test. The curve-suggested cutoff for plasma pepsinogen activity (5.5 U/L) resulted in estimates of sensitivity and specificity within the 5.0 U/L cutoff's CIs. Similarly, the Youden index of serum pepsinogen activity indicates moderate accuracy in diagnosing abomasal ulcer. These data may be explained by the fact that abomasal ulcers are heterogenic conditions and that acid peptic over

secretion may not be the main pathogenetic factor in all abomasal ulcers. There are also conflicting findings about how serum pepsinogen passes from peptic cells to the blood in cattle. There are two main theories about increasing serum pepsinogen activity. The first involves increased epithelial and vascular permeability allowing pepsinogen to leak into the blood (JENNINGS et al., 1966; MURRAY, 1969), and the second involves the direct hypersecretion of pepsinogen into the blood from zymogenic cells in a retrograde direction (McKELLAR et al., 1986; FOX et al., 1989). Our finding of significant influence of the extent and number of changes to the mucous membrane of the abomasum on the raised serum pepsinogen confirmed the statement that the concentration of serum pepsinogen is a good reflection of the damage to the abomasal mucousa.

The routine determination of serum pepsinogen activity represents, according to data obtained and the use of other known diagnostic methods, an important parameter of diagnostic help. The method is of limited value in animals with unknown or unfavourable parasitological status, since a higher serum pepsinogen level was also established in other forms of abomasitis caused by *O. ostertagi*. Low or normal levels of serum pepsinogen activity (<5.0 U/L) may be useful as a predictor for low susceptibility for major changes to the mucous membrane of the abomasum.

Conclusion

The use of serum pepsinogen promised to provide a simple serum test to diagnose or evaluate subclinical abomasal ulcers in cows with favourable parasitological status. Our present data confirm that serum pepsinogen activities were significantly higher in cows with abomasal ulcer compared to cows without.

References

ARMITAGE, P. (1971): Statistical Methods in Medical Research. Blackwell Scientific Publication, Oxford, pp. 82-125.

AUKEMA, J. J., H. J. BREUKINK (1974): Abomasal ulcer in adult cattle with fatal haemorrhage. Cornell. Vet. 64, 303-317.

BERGHEN, P., H. HILDERSON, J. VERCRUYSSE, P. DORNY (1993): Evaluation of pepsinogen, gastrin and antibody response in diagnosing ostertagiasis. Vet. Parasitol. 46, 175-195.

CABLE, C. S., W. C. REBHUN, S. L. FUBINI, H. N. ERB, N. G. DUCHARME (1998): Concurrent abomasal displacement and perforating ulceration in cattle: 21 cases (1985-1996). J. Am. Vet. Med. Assoc. 212, 1442-1445.

FOX, M. T., D. GERELLI, P. SHIVALKAR, D. E. JACOBS (1989): Effect of omeprazole treatment on feed intake and blood gastrin and pepsinogen levels in the calf. Res. Vet. Sci. 46, 280-282.

JENNINGS, F. W., J. ARMOUR, D. D. LAWSON, R. ROBERTS (1966): Experimental *Ostertagia ostertagi* infections in calves: studies with abomasal cannulas. Am. J. Vet. Res. 27, 1249-1257.

KATCHUIK, R. (1992): Abomasal disease in young beef calves: surgical findings and management factors. Can. Vet. J. 33, 459-461.

McKELLAR, Q. A., J. L. DUNCAN, J. ARMOUR, P. MCWILLIAM (1986): Response to transplanted adult *Ostertagia ostertagi* in calves. Res. Vet. Sci. 40, 367-371.

METZ, C. E. (1978): Basic priciples of ROC analysis. Semin. Nucl. Med. 8, 283-298.

MURRAY, M. (1969): Structural changes in bovine ostertagiasis associated with increased permeability of the bowel wall to macromolecules. Gastroenterology 56, 763-772.

ODERDA, G., F. ALTARE, D. DELL'OLIO, N. ANSALDI (1988): Prognostic value of serum pepsinogen I in children with peptic ulcer. J. Pediatr. Gastroenterol. Nutr. 7, 645-650.

PALMER, J. E., R. H. WHITLOCK (1984): Perforated abomasal ulcers in adult dairy cows. J. Am. Vet. Med. Assoc. 184, 171-174.

PAYNTER, D. I. (1994): Pepsinogen activity, determination in serum and plasma. In: Australian Standard Diagnostic Techniques for Animal Diseases, Benalla, pp. 1-4.

RADOSTITS, O. M., D. C. BLOOD, C. C. GAY (2000): Veterinary Medicine. 9th ed. Bailliere Tindall, London, pp. 291-307.

SAEZ-ALQUEZAR, A., M. A. MARCHESE, T. V. S. BEZERRA, J. C. ANDREOLI, D. S. PARRA, J. F. PONTES (1978): Serum pepsinogen: correlation of techniques and analysis of levels found in different diseases of the stomach and duodenum. Clin. Chim. Acta, 90, 163-169.

SAMLOFF, I. M., G. N. STEMMERMANN, L. K. HEILBRUN, A. NOMURA (1986): Elevated serum pepsinogen I and II levels differ as risk factors for duodenal ulcer and gastric ulcer. Gastroenterology 90, 570-576.

SANDIN, A., J. SKIDELL, J. HÄGGSTRÖM, K. GIRMA, G. NILSSON (1999): Post-mortem findings of gastric ulcers in Swedish horses up to one year of age: a retrospective study 1924-1996. Acta Vet. Scand. 40, 109-120.

SCOTT, I., A. DICK, J. IRVINE, M. J. STEAR, Q. A. MCKELLAR (1999): The distribution of pepsinogen within the abomasa of cattle and sheep infected with *Ostertagia* spp. and sheep infected with *Haemonchus contortus*. Vet. Parasitol. 82, 145-159.

SCHAW, D. J., J. VERCRUYSSE, E. CLAEREBOUT, J. AGNEESSENS, P. DORNY (1997): Gastrointestinal nematode infections of first-season grazing calves in Belgium: general patterns and the effect of chemoprophylaxis. Vet. Parasitol. 69, 103-116.

TANAKA, Y., K. MINE, Y. NAKAI, N. MISHIMA, T. NAKAGAWA (1991): Serum pepsinogen I concentrations in peptic ulcer patients in relation to ulcer location and stage. Gut 32, 849-852.

VIANELLO, F., M. PLEBANI, A. PICCOLI (1988): Role of serum pepsinogen in detecting ulcer disease. Clin. Chim. Acta 172, 335-340.

VÖRÖS, K., C. MEYER, M. STOBER (1984): Pepsinogenaktivität von Serum und Harn sowie Pepsinaktivität des Labmagensaftes labmagengesunder und nicht-parasitar labmagenkranker Rinder. Zbl. Vet. Med. A 31, 182-192.

XIAO, L., H. C. GIBBS, C. R. WALLACE (1992): Effects of *Ostertagia ostertagi* infection on secretion of metabolic hormones in calves. Am. J. Vet. Res. 53, 2019-2022.

ZADNIK, T., M. MESARIČ (1999): Fecal blood levels and serum proenzym pepsinogen activity of dairy cows with abomasal displacement. Israel J. Vet. Med. 54, 61-65.

ZWEIG, M. H., G. CAMPBELL (1993): Receiver-operating characteristic (ROC) plots: a fundamental evaluation tool in clinical medicine. Clin. Chem. 39, 561-577.

Received: 27 January 2004
Accepted: 1 March 2005

MESARIČ, M.: Uloga serumskog pepsinogena u otkrivanju čira sirišta krava. Vet. arhiv 75, 111-118, 2005.

SAŽETAK

Uporabom metode po Paynter-u, kod 126 klinički zdravih krava određivana je aktivnost serumskog pepsinogena u krvnom serumu. Nakon klanja, promatrane krave razvrstane su u tri skupine prema ustanovljenim makroskopskim promjenama u mukoznoj membrani sirišta: skupina bez promjena, skupina s čirom i skupina s drugim promjenama. Prevalencija pojavnosti čira sirišta iznosila je 7%. U skupini krava s čirom, prosječna aktivnost pepsinogena bila je statistički značajno viša u odnosu na druge dvije istražene skupine ($P<0,001$). Ustanovljeno je da proširenost promjena u mukoznoj membrani sirišta ima statistički najznačajniji utjecaj na aktivnost pepsinogena ($P<0,001$). Broj promjena imao je manji, ali još uvijek statistički značajan utjecaj na aktivnost pepsinogena ($P<0,05$). Na temelju razine pouzdanosti od 95%, kao gornja granica aktivnosti serumskog pepsinogena utvrđeno je 5,0 U/L što još uvijek ne označava veće promjene u mukoznoj membrani sirišta. Uporaba serumskog pepsinogena, kao pokazatelja u jednostavnom testiranju na supklinički čir sirišta, čini se opravdanom u krava s poznatim parazitološkim statusom.

Ključne riječi: govedo, sirište, čir, pepsinogen