Original article

Preliminary clinical experience with a new natural compound in the treatment of oesophagitis and gastritis: symptomatic effect

Summary
The Authors describe a preliminary clinical investigation on forty patients with oesophagitic and gastric symptoms, ten of which were affected with reflux disease.
After oesophagogastroscopy and a urea breath test, they were administered a natural product based on hyaluric acid and chondroitin sulphate. The study was a double-blind trial versus placebo. The results were based on symptom analysis, and the natural compound showed statistically significant effectiveness against placebo. The pre-post treatment endoscopic investigations also showed improvement in inflammation and healing of the mucosa in both oesophageal and gastroduodenal pathologies.

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Introduction

Gastroesophageal reflux disease (GERD) is an acid-related disorder triggered by reflux of gastric contents into the oesophagus whose lower sphyncter (LES) becomes incompetent due to multiple causes. Hearthburn, the most common and distinctive symptom affects roughly 20-40% of western people whose 7% complains of daily symptoms; the seasonal prevalence of the disease in the general practice reaches even more than 50% of the population, and potential complications enclose erosive oesophagitis, Barretts oesophagus and adenocarcinoma. Functional dyspepsia is the commonest cause of dyspeptic symptoms in the world affecting roughly 25% of the population: its main features are recurrent pain or discomfort in the epigastric area, without coexisting irritable bowel syndrome, or ulcers; very often hyperchloridric secretion, gastric motility disturbances and psychosocial reactivity have been advocated in the physiopathology of such a so called gastritis and duodenitis. A very recent paper of Tomomitsu et al investigated the association between dyspeptic symptoms and endoscopic appearances enrolling 87 dyspeptic patients and 93 asymptomatic controls[1].
They found that friability in the antrum and duodenal ulcer scarring were independently associated with dyspeptic symptoms. The logistic regression analysis showed that both of

these endoscopic appearances were significantly more likely to be associated with dyspeptic symptoms. Among 18 dyspeptic patients with friability in the antrum, *H. pylori* infection was present in only three, and inflammation activity and severity of atrophy in the antrum by the updated Sydney System were mild in most patients. On this basis friability in the antrum was almost characterized by normal or high gastric acid secretion and, potentially hypergastrinemia. The symptomatic treatment of oesophagitis and gastritis is primarily approached with proton pump inhibitors to reduce the acid output and with buffering products that counteracts the hydrogenionic damage to the mucosa.

A recent our original approach to the problem was dedicated to identify and use some natural compounds able to buffer the acidity of the gastric fluid, as well as to inhibit the pepsin-induced mucosal rebound damage, but specifically addressed to steadily coat the epithelial surface as long as possible by means of an active principle able to stimulate the healing process with a very well known physiological repair mechanism.

The chemical composition of the compound investigated in our trial encloses Chondroitin sulphate (CS) and Hyaluronic acid (HyA) plus an adhesivity enhancer with the following rationale:

a) Chondroitin sulphate is a chemically safe and atoxic glycosaminoglycan family component with repeated disaccharide units made of glucuronic acid and galactosamine 1-beta sulphated group; the molecular structure had been identified by Babkin and Komarov, as an effective inhibitor of pepsin induced damage on the gastroduodenal mucosa, being with mucoitinsulphate, a main chemical component of the spontaneously secreted mucous by the parietal cells[2]. A primary attempt to Chondrotin sulphate treatment by mouth in gastroduodenal diseases was primarily tried on the man by Crandall & Roberts on 22 patients affected by duodenal peptic ulcer, with a definite symptoms improvement in 45%[3]. Levey and Sheinfeld, blocked in the Shay-ulcer model pf the rat, the gastric damage administering 25 mg Chondroitin sulphate by mouth[4].
b) Hyaluronic acid is an other outstanding atoxic biological molecule, characterized by a long dimeric cross-linked sugar (N-acetyl-D-glucosamine) linked with â-glucoronic acid.

One of its natural functions is to control epithelial cells turnover by means of the CD44 and RAHMM receptors and to inactivate the free radicals and the reactive oxygen species (ROS) in the skin layer[5].

This molecule has largely been used as an effective skin ulcer healing compound, and several years ago we hypotesized that it might be beneficial also in oesophageal erosions and gastroduodenal ulcers[6].

In a previously unpublished clinical pilot trial we treated 20 adult patients affected by erosive oesophagitis and reflux with Hyaluronic acid by mouth twice daily along two weeks achieving a 76 % control of the symptoms. We used a 10% Hyaluronic acid sodium salt with a dynamic viscosity proportional to 4500 mPa*s administered with a spoon 3 hours after meals.

The plan to mix the molecules of HyA and CS, within an adhesive biopolymer, which might increase the mucosal surface adhesivity, was addressed to enhance the mucosa barrier either in the oesophagus or in the gastric and duodenal lumen.

Materials and methods

Trial design

Our study (double blind, crossing over drug versus placebo) enclosed 40 randomly selected patients (16 females and 24 males), aged between 6 and 87 years (average 55-85), with oesophagitis and gastritis symptoms characterized by heartburn, epigastric pain, dyspepsia, meteorism and belching; 22 patients had long standing reflux disease unadequately treated with proton pump inhibitors and antiacids. Ten cases underwent primarily the experimental protocol without any previous medical treatment. All the enrolled patients had such a severe symptoms score (see below) to require the use of PPI alone or PPI plus antacids. An informed consent was signed by each patient with the formal acceptance to self-administration of the nutriceutical compound under investigation, accepting the challenge of a two weeks placebo administration.

Treatments

Before being enrolled in the study, oesophagogastroscopy and urea breath test were per-

fomed on each one, to rule out any Helicobacter positive patient. Endoscopic reexamination was allowed twice. The patients signed an informed consent, and any previous disease-specific drug treatment was withdrawn 5 days before the start up of the investigation. They were randomized in two groups: 20 patients each, and submitted to oral administration of the drug to be tested and placebo.
The composition of our syrup was:
- Hyaluronic acid: 120 mg;
- Chondroitin sulphate: 300 mg;
- Excipients: Viscosity enhancers; preservatives; aroma; water q.s. 1200 mg

The viscosity of the syrup was 60 mPa.

Composition of the placebo was:
- 10% vaseline-oil/water emulsion;
- Viscosity enhancer;
- Preservatives;
- Aroma;
- Water q.s.:1200 mg.

The product and the placebo were manufactured in a private pharmacy accordingly with a galenic formula planned by one of the Authors (Palmieri), on the bases of a previous unpublished veterinary experimental trial on gastro oesophageal lesions healing in the horse.
The compounds were blindly administered with the following schedule: one spoon every 8 hours (far from meals) and two spoons at the bed time along two weeks. One week interval without administration. Two further weeks of treatment switching placebo and putative active principle in the groups. Symptoms

Table 1. Group A: start up with the drug-treatment and switched to placebo.

	Patients (sex)	Age	Symptoms	Score drug	Score placebo (after crossing over)
1	B.C. (M)	38	Oesophagitis, gastritis, aerophagy	+	+
2	S.R.M. (F)	45	Reflux, pyrosis	+ + +	+
3	B.A. (F)	6	Reflux, epigastric pain	+++	++
4	G.C. (F)	42	Ovarian K., oesophagitis, gastritis, ascites	+ +	+
5	G.A. (F)	61	Reflux, gastritis, obesity	+ + +	+
6	N.G. (M)	45	Oesophagitis in diabetic	+ +	+
7	T.R. (M)	62	Oesophagitis and gastritis in coronary by pass	+ + +	+
8	B.F. (M)	7	Oesophagitis, aerophagy in steroid chronic treat	+ + +	++
9	O.F. (M)	42	Gastritis and pyloric ulcer (nitro- derivatives chronic. adm.)	+ +	+
10	M.D. (M)	41	Omeprazol resistant gastritis	+ +	+
11	C.A. (F)	82	Oesophagitis and biliary gastritis	+ + +	++
12	S.R. (F)	84	Oesophagitis and gastritis from biliary reflux	+ + +	++
13	M.D. (M)	51	Oesophagitis from chemotherapy	+ + +	+
14	B.E. (F)	68	Mucositis and oesophagitis from radiotherapy	+ + +	+
15	Z.G. (M)	66	Mycotic muco- oesophagitis from chemotherapy	+ +	+
16	T.F. (M)	49	Gastro-oesophagitis post-Helicobacter	+ + +	+
17	B.M. (F)	71	Oesophagitis in poliarthritic (>Iatrogenic)	+ + +	+
18	S.L. (M)	60	Gastroduodenitis in hepatopathic	+ +	++
19	R.A. (M)	54	Steroid-induced duodenal ulcer in R:A.	+++	+
20	Z.G. (F)	49	Oesophago-gastritis in biliary reflux	++	++

Table 2. Statistical analysis on group A data.

	Drug	Placebo
Mean ± SD	2,579 ± 0,368	1,316 ± 0,228
p-value (drug vs placebo)	2,22E-08	
F	50,824	
F-crit	4,113	

were scored daily as follows:

- +++ = complete disappearance of hearthburn and epigastric pain during the treatment
- ++ = less than 60 % reduction of hearthburn and epigastric pain with no more than three attacks of the symptoms admitted and very rare need of add antiacids to the experimental treatment
- + = less than 30 % reduction of hearthburn and gastritis with recurrent use of PPI and antiacids.

A final evaluation of symptoms relieve, as well as endoscopic short term check-up
On a 4 patients sample was done 4 weeks after the end of the trial

Statistical data interpretation

All the data groups are distributed normally, so we decided to used the analysis of variance (Anova). This statistical method evaluates data group of different populations. In all the comparison between placebo and drug, after crossing over, the p-value is minor than 0,05 and F obtained is major F-crit, thus reaching statistical significance.

Results

The treatment was completely safe and no dropout happened during the investigation. The compliance of the product (viscosity taste and

Table 3. Group B: start up with the placebo and switched to the drug.

	Patients (sex)	Age	Symptoms	Score drug	Score placebo (after crossing over)
21	C.M. (M)	44	Gastritis and reflux	+	+++
22	P.G. (F)	76	Gastritis and splenomegaly	+	++
23	B.C. (M)	38	PPI resistent gastritis and reflux	+	+++
24	M.D. (M)	62	Obesity diabetes gastritis and reflux	+	+++
25	B.G. (M)	71	Gastritis, liver transplant oesophagitis	+	++
26	G.P. (M)	66	Obesity gastritis oesophagitis	+	++
27	C.F. (F)	74	Cholangiocarcinoma,oesophagitis	++	+++
28	P.G. (F)	54	Gallstones biliary reflux	+	+++
29	B.S. (M)	61	Gastritis and oesophagitis fans-addicted	+	++
30	F.M. (F)	47	Gastritis and obesity	++	+++
31	T.W. (M)	59	Oesophagitis ,gastritis and thyroiditis	++	+++
32	S.I. (F)	87	Oesophagitis,gastritis hearth failure	+	++
33	A.R. (M)	55	Oesophagitis, gastritis and Gilbert syndrome	++	+
34	G.A. (F)	65	Oesophagitis, gastritis and Gilbert syndrome	++	+
35	F.G. (F)	52	Oesophagitis and lupus	+	+
36	M.M. (M)	37	Oesophagitis and duodenal ulcer	++	++
37	M.A. (M)	72	Gastritis and oesophagitis in cardiac valve	++	++
38	D.M.G.(M)	56	Gastritis and oesopagitis after morbid obesity surgery	+	++
39	G.A. (M)	73	Oesophagitis duodenal ulcer	++	+++
40	R.M. (M)	62	Gastritis and oesophagitis	+	++

Table 4. Statistical analysis on group B data.

	Drug	Placebo
Mean ± SD	1,350 ± 0,239	1,316 ± 0,228
p-value (placebo vs drug)	2,31E-05	
F	50,824	
F-crit	4,113	

swallowing difficulty), was very favourable. The effectiveness was meaningful and impressive especially in kids with reflux and adults with biliary gastritis probably due to prompt neutralization of alkaline biliary fluid:

- 12 patients total symptoms remission;
- 7 patients less than 60 % symptoms reduction;
- 1 less than 30 % symptoms reduction.

Individual patients results are shown in Table 1,2,3,4 where we describe the diagnosis and the drug versus placebo or placebo versus drug comparison, in terms of different scores for each group: a remarkable effect of the nutriceutical compound has been observed, when administered at the trial start up, in the first group, and a minor benefit if adminstered after the placebo switch off, probably due to the prolonged impending symptoms along the trial course .

The hyaluronic-condroitinsulphate association

Figure 1. Oesophagitis case n°5.

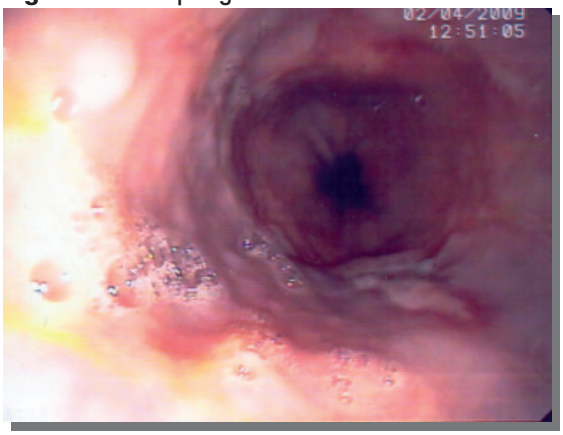


Figure 2. Oesophagus after therapy.

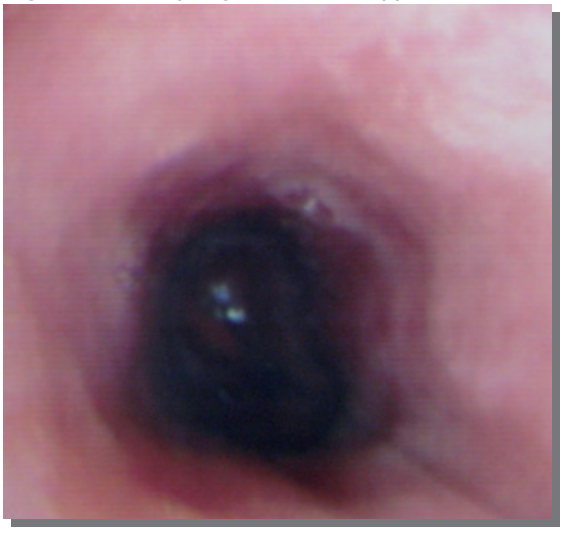


Figure 3. Piloric ulcer: case n°9.

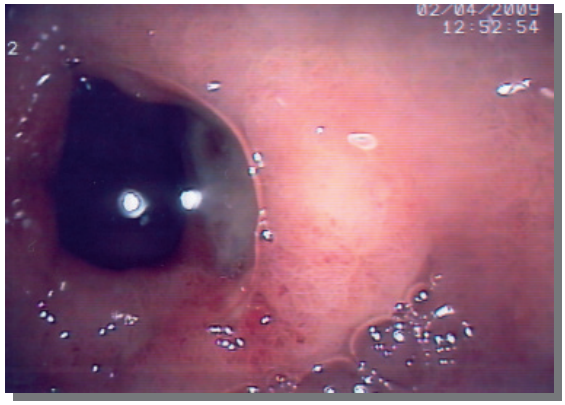
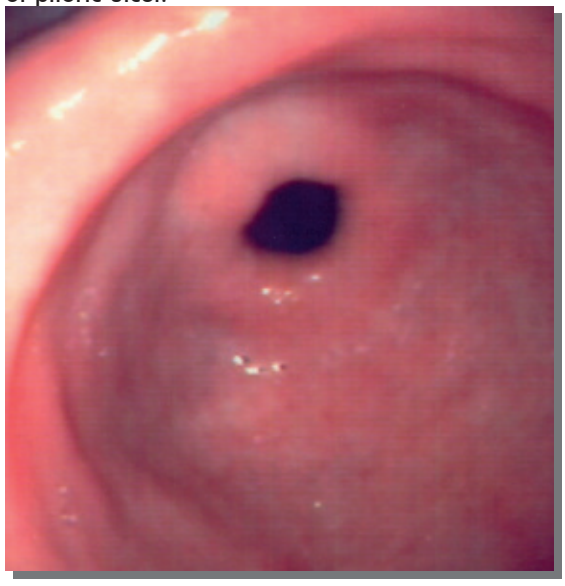


Figure 4. After therapy we can observe the absence of piloric ulcer.



was more effective in oesophagitic symptoms, control, but also gastroduodenitic improved during the treatment and in the short term follow-up (4 weeks) a smart improvement and excellent compliance was scored in the 7 years old kid with drug-resistent oesophagitis (case n°8).

Discussion

Our treatment schedule achieved quick symptoms improvement, accordingly with previous study of Bonfils & Cow who described the relationship between endoscopy[7], and pathological findings from the surgical specimen: accordingly with this Author the efficacy of Chondroitin sulphate, should be due not only to the affinity between its sulphonated molecular structure and the aminic groups of pepsin molecule, but also to the induction of a wide range of proteinated complexes (with haemoglobin and serum-globulins, for instance), coating steadily and protecting the deepithelized or ulcerated gastroduodenal areas[8].
Fialkova et al described skin ulcer healing promoter effect of the same compound in the rat with topical or systemic administration[9]. Harrison SE showed that Chondroitin sulphate is an excellent coating for intraocular lens implantation to avoid any damage to corneal epithelium[10]; according with this Author Chondroitin sulfate surpassed by far the protective qualities of other compounds: albumin was second best; Hyaluronic acid third. Comparisons with the commercially available Healon still revealed Chondroitin sulphate to be the most efficacious protective agent 40 hours lasting its effect. The concept of a protective layer by Chondroitin sulphate upon the surfaceal mucosal lesions of either oesophagus and stomach, are actually very appealing , because the good affinity of the compound for the injuryed surfaces, affords a very effective and strong protection[11-14].
More recently a clinical study of Steinhoff and Cow, in patients with interstitial cystitis, reported favourable symptomatic outcome by intravescical instillation of 0,2% highly purified Chondroitin sulphate solution with molecular weight 20-40.000 Daltons confirming antiinflammatory and healing properties of the compound in an other muscular-epithelial contractile organ[15].
The putative Ha action mechanism strongly supports the theory of inducing epithelial cells shifting (due to their increased motility at adequate Hyaluronic acid concentrations) to cover the submucosal connective tissue (which becomes more soft and hydrophylic due to the Hyaluronic acid availability) beneath the fibrin crust to repair the damaged mucosal layer.
The ulcers and erosions healing effect of Chondroitin sulphate is thus synergistically co-promoted by the Hyaluronic acid and the added adhesive biopolymer with a wide range of indications.

Conclusions

The nutriceutical product we tried has been shown very useful to control oesophageal and gastric symptoms of reflux and inflammation, even if we lack long term results and the final outcome of a long-run treatment. Our pre-post trial endoscopic investigations showed a smart improvement of the mucosa either in oesophageal or gastroduodenal pathology.

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