Original Article

Efficacy and Safety of Phlogenzym — A Protease Formulation, in Sepsis in Children

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Abstract

- Background : Infections are a major cause of hospitalisation wherein the host mounts an inflammatory response against the infecting agent. Administration of proteolytic enzymes could regulate the host's immune system and help early recovery from sepsis.
- Objective : To test the efficacy and safety of an oral enzyme formulation, Phlogenzym (Mucos Pharma GmbH, Geretsried, Germany; constituents of each enteric - coated tablet were bromelain 90 mg, trypsin 48 mg, rutin 100 mg) as adjuvant therapy in treatment of sepsis in children.
- Subjects and Methods : Double-blind, randomised, controlled phase III study at a tertiary care centre wherein 60 eligible children aged one month to 12 years with sepsis were randomised to receive either phlogenzym (n=30; 17 boys) or placebo (n=30; 22 boys) tablets (1 tablet / 10 kg body weight up to maximum six tablets a day in two or three divided doses for 14-21 days) along with appropriate antibiotics and supportive treatment.
- Results : Median time taken for fever to subside was three days (range 1-12; 95% CI - 1.14 to 7.14) in the phlogenzym group vs four days (range 1-18; 95% CI - 3.52 to 11.52) in the placebo group ($p < 0.05$); haemodynamic support was needed for two days (range 1-3; 95% CI - 0.84 to 3.16) in the phlogenzym group but three days (range 1-8; 95% CI 0.76 to 5.24) in the placebo group ($p < 0.05$). The modified Glasgow coma scale score normalized in three days (range 1-14; 95% CI 4.62 to 9.62) in the phlogenzym group vs 5.5 days (range 1-18; 95% CI - 2.52 to 13.52) in the placebo group ($p > 0.05$). Oral feeds could be started in four days (range 1-15; 95% CI - 1.74 to 9.74) in the phlogenzym group vs five days (range 1-11; 95% CI - 1.26 to 11.26) in the placebo group ($p > 0.05$). Two patients died in the placebo group.
- Conclusion : Phlogenzym is effective as an adjuvant with antibiotics and supportive treatment for early improvement of pediatric patients with sepsis. (J Assoc Physicians India 2002;50:527-531)

Introduction

Sepsis is a common cause of hospitalisation in young children especially in the first year of life.[1] Drugs acting against the organisms responsible are presently the mainstay of treatment in these diseases.

Studies have shown that the host mounts an inflammatory response to these infecting agents and these inflammatory mediators influence the ultimate outcome of the illness.[2] Accumulating evidence indicates that TNF and other cytokines are major mediators of septic shock. Administration of anti-ICAM-1 antibody in rabbits inhibits the rise of plasma TNF activity and reduces endotoxin-induced shock.[3] Inflammatory cytokines trigger the production of mediators like phospholipase A_2, eicosoanoids, nitric oxide, endothelin-1, thrombodulin and adhesion molecules, and activate polymorphonuclear leukocytes.[4] Septic shock is characterised by a massive upregulation of adhesion molecules due to the presence of bacterial lipopolysaccharides (LPS) and elevated levels of proinflammatory cytokines. Levels of soluble adhesion molecules like sICAM-1, sELAM-1 and sVCAM-1 are elevated in patients with septic shock.[5] These molecules play a critical role in the interaction of circulating neutrophils with vascular endothelium during inflammation. Furthermore, in patients with high levels of adhesion molecules the prognosis was poor. Watanabe S, *et al*, have shown that administration of anti-CD 18 antibody prevents acute lethality and reduces shock.[6]

In spite of advances in therapy, the overall mortality from sepsis continues to be unacceptably high, at

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around 20-30%.[7,8] The resistance of organisms to commonly used antibiotics and the presentation of patients to hospital at an advanced stage of the disease could be responsible for the high fatality rates.[9] Various studies have confirmed that oral administration of proteolytic enzymes down-regulates and degrades the over-expressed, inflammation-relevant adhesion molecules.[10,11] These enzymes regulate TNF levels by promoting its faster clearance, by activating alpha-2 - macroglobulin to the 'fast' form, thus reducing the stimulus for expression of adhesion molecules. By down-regulating elevated serum cytokine levels, systemic enzyme therapy could offer a safe adjuvant treatment in sepsis.

This study was conducted to evaluate the outcome of sepsis in children with an oral enzyme preparation, Phlogenzym (Mucos Pharma GmbH, Geretsried, Germany; constituents of each enteric - coated tablet were bromelain 90 mg, trypsin 48 mg, rutin 100 mg). The combination of animal serine proteases and vegetable cysteine proteases acts by modifying the biological response.[11]

Material and Methods

Patient eligibility

A double-blind, randomised, controlled, phase III clinical study of Phlogenzym, approved by the ethics committee of the institution, was carried out on the patients admitted in the pediatric intensive care unit. Out of 92 patients with sepsis admitted over 22 months, 60 children, aged one month to 12 years, were found eligible for recruitment. Informed written consent of the parents or guardians was taken.

Septic illness was diagnosed when the child had fever of more than 38°C, with or without hypotension, and weak peripheral pulses.[12] Detailed history, complete clinical evaluation including the modified Glasgow coma scale score,[13] haemogram, bacterial culture, metabolic work up, liver and renal biochemistry were done in all cases. The patient's protein-energy nutrition status was graded based on the Indian Academy of Pediatrics (IAP) classification.[14] Cerebrospinal fluid analysis, urine analysis, radiological and other tests were done as and when needed to aid in diagnosis. Children aged below one month and above 12 years, and those with concomitant diseases were excluded from the study.

Drug intervention

Patients were randomized into two groups. A computer-generated random sequence was used for allocation of patients to the study and control groups. The study group received Phlogenzym tablets and the control group received placebo tablets of the same colour, size and shape. The dose administered to both groups was 1 tablet/10 kg body weight daily in two or three divided doses, up to a maximum of 6 tablets/day for 14-21 days. As the children were small and had altered conscious level, the tablets were crushed, mixed with ample water and given via an indwelling nasogastric tube and orally when the child was fully conscious. Duration of treatment depended on the site and severity of infection.

For respiratory infections, CNS involvement in a child more than two years old, meningococcal sepsis, urinary tract infection, intraabdominal or generalized septicemia, the study medication and the antibiotics were given for 14 days. However, for CNS involvement in children less than two years old, cerebral abscess and cardiac infections the treatment was given for 21 days. The antibiotics were started empirically and later changed if necessary on receipt of the culture and sensitivity reports and supportive treatment was simultaneously given to all cases. For children less than three months old, antibiotic combination used was ampicillin and gentamicin or cefotaxime and gentamicin or amikacin. Antibiotic combinations given to children older than three months were ampicillin and chloromycetin or ampicillin and cloxacillin and chloromycetin or cefotaxime and amikacin depending on the infecting agent and the severity of infection. Fourteen patients (six in Phlogenzym group) received dexamethasone in the first 3-5 days of the illness and five cases (two from Phlogenzym group) received phenobarbitone.

Evaluation

Patients were evaluated on the basis of number of days for fever to subside, number of days for which haemodynamic support was needed, time taken for normalisation of modified Glasgow coma scale score, days required for commencement of oral feeds, complications and mortality, if any. All adverse events were noted. Haemogram, liver and renal function tests were repeated at the end of the study.

Statistical Method

The laboratory investigations in the Phlogenzym and placebo groups were compared using the unpaired t test. The nutritional status and the signs and symptoms were compared using the chi square test for proportions and for the efficacy parameters a non-parametric test (ie Mann-Whitney U test) was used.

Results

Out of 92 patients screened, 32 were excluded due to concomitant illness (n=22), death during screening (n=8) or refusal of consent (n=2). Of 60 patients enrolled in the study, 30 (17 boys) received Phlogenzym and 30 (22 boys) placebo. Most patients were from the low socioeconomic status. Mean height and weight was 77.1 cms and 9.1 kg in the study group and 72.3 cms and 11.6 kg in the control group, respectively. Patients were comparable in age and the clinical and biochemical features at presentation were similar in the two groups (Table 1). Localising signs of infection were absent in 14 children. Signs of respiratory,

Table 1 : Symptoms at inclusion of patients in the phlogenzym group and placebo group

Signs		Phlogenzym group n=30	%	Placebo group n=30	%
Fever		28	93.3	29	96.7
Hypothermia		05	16.7	06	20.0
Refusal of feeds		25	83.3	19	63.3
Loose motions		09	30.0	09	30.0
Vomiting		06	20.0	07	23.3
Convulsions		08	26.7	07	23.3
Altered sensorium		11	36.7	13	43.3
Oliguria		03	10.0	05	16.7
Skin lesions		05	16.7	02	06.7
Pulse	(Mean ± SD)	132.1 ± 18.7		123.6 ± 18.1	
Respiratory rate	(Mean ± SD)	47.4 ± 17.5		38.3 ± 11.8	
Systolic BP	(Mean ± SD)	85.0 ± 10.6		87.2 ± 11.6	
Diastolic BP	(Mean ± SD)	59.8 ± 5.4		60.8 ± 10.3	
	Good	04	13.3	02	06.7
Nutritional status	Average	19	63.4	21	70.0
	Poor	07	23.3	07	23.3
Protein energy	Grade I	05	16.7	08	26.6
malnutrition (IAP	Grade II	16	53.3	14	46.7
classification)	Grade III	04	13.3	03	10.0
	Grade IV	05	16.7	05	16.7

By unpaired 't' test and Chi square test; P > 0.05 not significant

central nervous and gastrointestinal system involvement were seen in 27, 14 and two children, respectively.

The pulse and respiratory rate and blood pressure were comparable in the two groups as were the nutritional and protein energy nutrition status (IAP grades). (Table 1) Laboratory investigations were comparable pretreatment ($p > 0.05$, Student's t test).

Efficacy Evaluation

Patients in the Phlogenzym group took three (range 1-12; 95% CI - 1.14 to 7.14) days for the fever to subside, whereas those in the placebo group required four days (range 1-18; 95% CI - 3.52 to 11.52) ($p < 0.05$). Haemodynamic support was required for two (range 1-3; 95% CI 0.84 to 3.16) days in the Phlogenzym group and three (range 1-8; 95% CI 0.76 to 5.24) days in the placebo group ($p < 0.05$). Patients in the phlogenzym group required three days (range 1-14; 95% CI 4.62 to 9.62) for the modified Glasgow coma scale score to normalise whereas patients in the placebo group required 5.5 days (range 1-18; 95% CI - 2.52 to 13.52) ($p > 0.05$). Oral feeds were started in four days (range 1-15; 95% CI - 1.74 to 9.74) in the Phlogenzym group and five days (range 1-11; 95% CI - 1.26 to 11.26) in the placebo group ($p > 0.05$). Abdominal distension was seen in one patient in the placebo group who was hypokalaemic. Two patients died in the placebo group with disseminated intravascular coagulopathy; there were no deaths in the phlogenzym group.

Discussion

A systemic inflammatory response is seen in association with sepsis and multiple organ failure is a common complication. Studies have shown that the pathophysiological effects of sepsis result from tissue damage caused by uncontrolled production of mediators of inflammation.[2] Early deaths are related primarily to acute effects of this systemic inflammatory response.

LPS interact with specific membrane receptors localized to mononuclear phagocytic cells and neutrophils. Binding of endotoxin to these cells, together with endotoxin-induced activation of the host vascular endothelium, initiates a series of signal transduction events that culminate in the release of numerous biochemical mediators. These mediators orchestrate complex biological interactions and amplification signals that lead to septic shock.[3] Antibiotics target the microorganisms while the deranged immunology continues. Killing of the bacteria further activates the immunological system. Also, in the late stage, antibacterial drugs are not effective.

Systemic enzymes have been shown to act as immunomodulators and anti-inflammatory agents and their role in surgical cases and chronic rheumatic conditions has been well documented. These agents act by

the following mechanisms[10,11,15] :

- Lysis of immune complexes by removing the Fc part from the immune globulin.
- Inhibition of immune complex deposition and fixation.
- Formation of an α-2 macroglobulin-enzyme complex, inhibiting the proliferation of cytotoxic T-cells.
- Modulation of cell surface (adhesion) molecules, preventing the binding of compounds with phlogogenic potential (e.g., C1q, membrane-attack complex, polymorphonuclear leucocytes)
- Inhibition of TGF-β formation

Trypsin and bromelain act on the C_H2 domain of ICAM-a, VCAM-1 and LFA-3 and inactivate them; they also break down excess cytokines in the vicinity of the inflammatory site, thereby reducing the intensity of the inflammation.[16] The nitric oxide and free oxygen radicals released by activated leucocytes are cleared by rutin.[17] An interesting observation made in septic shock is that the upregulation of monocyte cell surface adhesion molecule beta-integrin that takes place after LPS stimulation is not reversed by monocyte-deactivating cytokines like IL-4 or IL-10, but antioxidants have been proven to possess the ability to inhibit LPS-induced upregulation of beta-integrin. Rutin has proven antioxidant properties.[18] Thus, oral proteolytic enzyme preparations could be helpful in sepsis by normalising leucocyte activation and functioning and more importantly by limiting or preventing tissue injury due to the free-radical-scavenging properties of rutin.

In our study on children with sepsis, those treated with Phlogenzym in addition to standard treatment needed fewer days for the fever to subside and for withdrawal of haemodynamic support as compared to patients on standard treatment alone. Although oral feeds could be commenced earlier in the Phlogenzym group and improvement in modified Glasgow coma scale score was faster, the difference was not significant. Abdominal distension, probably secondary to hypokalaemia, was seen in one patient in the placebo group; two patients died in this group with disseminated intravascular coagulopathy. There were no deaths in the Phlogenzym group. This early response to treatment with Phlogenzym is important as it could reduce costs and help in early discharge of the patient.

Patients in our study being very young and altered due to their illness had to be given crushed tablets. Gastric juice tends to dilute the enzymatic activity[19] and this could have reduced efficacy of the Phlogenzym. Fourteen patients (six in the Phlogenzym group) received dexamethasone which being immuno-suppressive[20] would interfere with the enzyme functions. Nonetheless, our study suggests that enzymes have a place as adjuvant therapy in sepsis in children.

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Book Review

Human Sexuality Problems and Therapy, Editor **Dr. BT Tukol.** Published by Bharathi Publications, Jayanagar, Bangalore. Page 226. July 2001.

The branch of sexual medicine does not receive its due recognition in either the undergraduate or postgraduate syllabii in India and does not form an integral part of the medical curriculum. Hence knowledge about this field is often limited and very few doctors practise exclusively in this field in India.

This book contains talks given by well known practising sexologists in India during a Continuing Medical Education Programme at Bangalore Medical College. The editor has organised the chapters in a systematic manner and let the individual authors discuss various topics and give interesting case illustrations.

The initial chapter deals with the history of sexual medicine in the Western and Indian scenario, which is then followed by a chapter on human sexual response. The next few chapters deal with specific sexual problems like erectile dysfunction, premature ejaculation, orgasmic dysfunction, vaginismus etc. These chapters are quite comprehensive covering the epidemiology, etiology, diagnostic formulation and management both pharmacotherapy and psychotherapy wherever indicated. The book also contains chapters discussing topics like homosexuality where myths, problems faced by homosexuals as well as management is discussed. The next few chapters deal with male and female infertility and sexual problems in diabetics and hypertensives.

The latter part of the book covers psychotherapies and drugs like sildenafil citrate. Since HIV/AIDS is one of the worst epidemics to affect mankind in this century, a separate chapter has been devoted to it, covering aspects like epidemiology in India as well as etiology, prophylaxis. In the last part of the book a chapter dealing with sex and sexology in the new millenium, highlighting the social and attitudinal changes, effects of internet and sex, are discussed.

Dr. JV Bhatt has written a chapter on Teaching of Sexual Medicine to students, where he writes about the present status and brings up relevant questions of whether it should be made a separate examination subject and who should teach it.

Inspite of being a compilation of work by various authors it maintains a consistency and evinces interest to read from one chapter to another. The book is a useful addition to one's library and can be read by medical professionals to update themselves on sexual medicine as it especially covers aspects relevant to Indian population.

Sd/-
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