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# Impact of parenteral *n*-3 fatty acids on experimental acute colitis

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The present study was undertaken to investigate the effects of parenteral lipid emulsions (LE) enriched with *n*-3 fatty acids (*n*-3 FA) in experimental acute colitis. Seventy-four adult male Wistar rats were randomized into six groups, five of which had acetic acid-induced colitis. The animals received a fat-free diet and water *ad libitum* in individual metabolic cages. By a central venous catheter, saline was infused (0·5 ml/h) into the control groups CS (without colitis) and CC (with colitis), while the test groups received specific LE for 7 days. The $n-3/n-6$ FA ratio and the lipidic compositions regarding long chain (LCT) and medium chain (MCT) triglycerides were: group L – 1:7·7 (LCT, $n = 12$), M – 1:7·0 (MCT and LCT, $n = 12$), LW-3 – 1:4·5 (LCT plus *n*-3 FA, $n = 12$) and MW-3 – 1:3·0 (MCT and LCT plus *n*-3 FA, $n = 13$). The frequency of diarrhea, oral intake/body weight ratio, intestinal alterations, macrophage cellularity were evaluated and colonic concentrations of leukotrienes ($LTB_4$, $LTC_4$), prostaglandins ($PGE_2$) and thromboxanes ($TXB_2$) were measured. Groups M, MW-3 and LW-3 had less diarrhea than the CC group ($P<0·05$). Average oral intake/body weight ratio in MW-3 animals was comparable to the CS and better than the CC group. *n*-3 FA treated rats (LW-3 and MW-3) presented less intestinal inflammatory alterations than CC rats. Mucosal ulcer formation in MW-3 group did not differ from CS rats. M and MW-3 rats had less macrophages in the colon than the CC group. Compared with CC group, lower concentrations of $LTB_4$ in the CS, LW-3 and MW-3 groups; of $PGE_2$ in the CS, M and MW-3 groups; and of $TXB_2$ in the CS and MW-3 groups were found. Mean concentrations of $LTC_4$ did not differ among the groups. Thus, a LCT-containing LE with a low *n*-3–*n*-6 ratio does not modify inflammatory colitis manifestations; LE with a high *n*-3–*n*-6 ratio reduces diarrhea, preserves oral intake–weight ratio, attenuates morphological consequences and decreases colonic concentrations of inflammatory mediators; MCT/LCT-containing LE with 1:3 *n*-3–*n*-6 ratio exerts the most profound beneficial impact on the inflammatory response.

**Inflammatory bowel diseases: Ulcerative colitis: Lipids: *n*-3 Polyunsaturated fatty acids: Inflammatory mediators: Fat emulsion**

## Introduction

Inflammatory bowel diseases (IBD) are afflictions of unknown etiology which involve genetic, environmental and immunological factors in the pathogenesis (Sartor, 1997; Rutgeerts, 1998).

Medical management of IBD is based on anti-inflammatory and immunosuppressive drugs (Teixeira *et al.* 1993; Habr-Gama, 1994). Nutritional therapy might be beneficial in different phases of the disease in order to affect nutritional status or to control active disease. Therefore, a suitable nutritional formula should include nutrients that provide energy and also modulate inflammation, while exerting minimum antigenic stimulus (Carpentier *et al.* 1997; Campos *et al.* 1998).

The nutritional efficacy of lipid emulsions (LE) is dependent on the omega-3–omega-6 fatty acid ratio (*n*-3–*n*-6 FA) as well as on the fatty acid chain length of the component triglyceride (Fürst, 1994). The potential benefits of supplemental fish oil have been emphasized in various inflammatory and immunological disorders (Morlion *et al.* 1997; Alexander, 1998; Fürst & Kuhn, 2000). The biochemical mode of action is thought to be due to a competition of the high amount of *n*-3 FA with arachidonic

**Abbreviations:** FO, fish oil; IBD, inflammatory bowel disease; LCT, long chain triglicerides; LE, lipid emulsions; LT, leukotrienes ($LTB_4$, $LTC_4$); MCT, medium chain triglicerides; *n*-3 FA, omega-3 fatty acid; *n*-6 FA, omega-6 fatty acid; PG, prostaglandins ($PGE_2$); TX, thromboxanes ($TXB_2$).

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**Table 1.** Rectal and parenteral solutions infused and *n*-3–*n*-6 ratio in experimental groups

| Groups | Rats (*n*) | Rectal solution infused | Parenteral infusion | *n*-3–*n*-6 Ratio |
|---|---|---|---|---|
| CS | 12 | Saline | Saline | – |
| CC | 13 | acetic acid 10 % | Saline | – |
| L | 12 | acetic acid 10 % | LCT 100 % | 1:7·7 |
| M | 12 | acetic acid 10 % | MCT 50 % / LCT 50 % | 1:7·0 |
| L-W3 | 12 | acetic acid 10 % | LCT 90 % / FO 10 % | 1:4·5 |
| M-W3 | 13 | acetic acid 10 % | MCT 45 % / LCT 45 % / FO 10 % | 1:3·0 |

LCT – long chain triglycerides 10 % LE (Lipovenös®, Fresenius-Kabi, Germany).
MCT/LCT – medium and long chain triglycerides 10 % LE (Lipofundin® MCT/LCT (B. Braun-Germany).
FO – fish oil 10 % LE (Omegavenös®, Fresenius-Kabi, Germany).

acid (*n*-6 family) at the site of the membrane. Indeed this action reduces the synthesis of proinflammatory leukotrienes (4-series) and thromboxanes (2-series) and favours the anti-inflammatory 5 and 3 series, respectively (Roper & Phipps, 1994; Calder, 1996).

The goal of the present study was to investigate the effects of *n*-3 FA enriched LE on experimental acute colitis. Clinical, histological and inflammatory alterations induced in the presence of LE with variations in the *n*-3–*n*-6 ratio and in the triglyceride-fatty acid chain length were evaluated.

## Methods

Seventy-four male, adult, Wistar rats weighing 200–220 g were randomized according to rectal infusion and parenteral solutions and emulsions infused into six groups (Table 1). Ethical approval for this research was obtained by the Department of Gastroenterology (University of São Paulo Medical School, São Paulo). The animals were fed a fat-free oral diet and were housed individually in metabolic cages.

On the first day five groups of animals received a 2 ml rectal infusion of 10 % acetic acid and one group (CS) received physiological saline as described by MacPherson & Pfeiffer (1978). All the animals were subsequently infused with saline for 48 h by a central venous catheter. After that, the control animals (CS and CC groups) were continuosly infused parenterally with saline and the experimental groups (L, M, LW-3 and MW-3) received parenteral infusions of 10 % lipid emulsions. Parenteral volumes were provided through an infusion pump at 0·5 ml/h for 7 days. At completion of the study (tenth day) the entire colon was resected for further analyses (Fig. 1).

The frequency of diarrhea was monitored and the oral intake/body weight relation was assessed. After laparotomy, intestinal alterations (bowel dilatation and thickening, mesenteric inflammation, small bowel and epiploon adhesions) were evaluated and the entire colon resected. Each alteration added one point to each rat; thus, total points varied from 0 to 5. The average of each group was then calculated and compared to the other groups.

Intestinal fragments were taken from inflamed areas usually at the left colon and submitted to histological analysis. Regarding intestinal morphology, animals were separated in two groups according to the presence or absence of microscopic ulcers.

Macrophage cellularity was determined by immunehistochemistry using the alkaline phosphatase anti-alkaline phosphatase (APAAP) method (Noronha *et al.* 1995). Macrophage cellularity was divided according to scores of inflammation representing three features: number, distribution and location in relation to the basal membrane. According to these features, macrophage scores varied from 5 to 10 (Table 2).

Colonic concentrations of leukotrienes ($LTB_4$, $LTC_4$), prostaglandins ($PGE_2$) and thromboxanes ($TXB_2$) were determined by immune-enzymatic-assay (Pradelles *et al.* 1985).

Statistical analysis was made using the following methodology: Kruskal-Wallis test for oral intake/body weight ratio, inflammatory alterations and macrophage cellularity; Fisher Exact test for the frequency of diarrhea and histological analysis; Bonferroni's test for concentrations of inflammatory mediators. Significance level was $P<0·05$.

## Results

The results are shown in Tables 3 and 4 and the corresponding statistical analysis is summarized in Table 5.

Regarding feces consistency, groups M (11), MW-3 (11) and LW-3 (12) had a greater number of rats without diarrhea than the CC group (5) ($P<0·05$). All groups of animals had an average lower oral intake–body weight ratio when compared to the CS group (137·7), except MW-3 (129·8), in which the ratio was even higher than that of the CC group (106·8) ($P<0·05$). Rats treated with fish oil enriched emulsions (LW-3 and MW-3) showed less intestinal inflammatory alterations (1·1 and 0·9, respectively) than the CC rats (2·7) ($P<0·05$). Rats infused with MCT/LCT

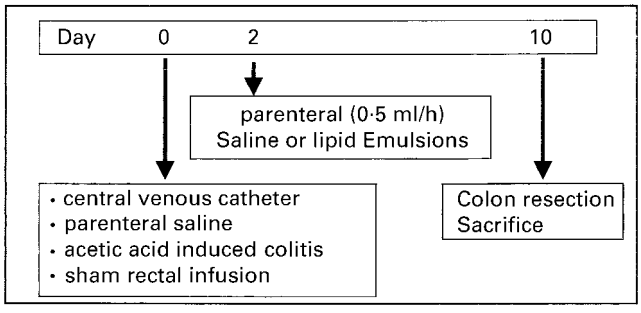


**Fig. 1.** Scheme of experimental plan.

**Table 2.** Colon macrophage cellularity. Scores related to number of macrophages, distribution and location

| Number | | Distribution | | Location | |
|---|---|---|---|---|---|
| value = 2 | | value = 1 | | value = 2 | |
| Low = 1 | High = 2 | Isolated = 1 | Grouped = 2 | Below BM = 1 | Upon BM = 2 |
| Final score | Final score | Final score | Final score | Final score | Final score |
| 2 × 1 = 2 | 2 × 2 = 4 | 1 × 1 = 1 | 1 × 2 = 2 | 2 × 1 = 2 | 2 × 2 = 4 |

BM = basal membrane.

**Table 3.** Results of physiological and inflammatory changes

| Variable | Groups | CS | CC | L | LW-3 | M | MW-3 |
|---|---|---|---|---|---|---|---|
| Feces | normal (*n*[a]) | 12 | 5 | 8 | 12 | 11 | 11 |
| Consistency | altered (*n*) | 0 | 8 | 4 | 0 | 1 | 2 |
| Oral intake/ | mean | 137·7 | 106·8 | 104·0 | 92·6 | 104·9 | 129·8 |
| body weight ratio | ± | 21·1 | 24·9 | 30·0 | 21·7 | 21·0 | 26·5 |
| Abdominal | mean | 0 | 2·7 | 2·5 | 1·1 | 2·0 | 0·9 |
| Alterations | ± | 0 | 1·8 | 1·9 | 1·6 | 1·4 | 1·7 |
| Mucosal ulcers | present (*n*) | 0 | 10 | 8 | 5 | 5 | 3 |
| | absent (*n*) | 12 | 3 | 4 | 7 | 7 | 10 |
| Macrophage | mean | 5·1 | 9·1 | 8·2 | 8·5 | 7·1 | 6·8 |
| cellularity score | ± | 0·3 | 2·2 | 1·7 | 1·7 | 1·6 | 1·7 |

[a] *n* = number.
± = standard deviation.

**Table 4.** Median values of pro-inflammatory mediators

| Eicosanoid | CS | CC | L | LW-3 | M | MW-3 |
|---|---|---|---|---|---|---|
| $LTB_4$ (ng/g) | 58·3 | 341·4 | 192·3 | 41·4 | 171·5 | 83·9 |
| ± | 18·2 | 61·5 | 20·5 | 16·0 | 56·0 | 33·2 |
| $LTC_4$ (ng/g) | 16·2 | 40·5 | 32·2 | 99·9 | 18·8 | 23·6 |
| ± | 9·6 | 27·0 | 230 | 226·6 | 11·9 | 24·5 |
| $PGE_2$ (pg/g) | 1626·8 | 7660·7 | 2553·7 | 3138·5 | 2148·6 | 2235·8 |
| ± | 378·2 | 167·4 | 584·8 | 186·5 | 423·4 | 681·5 |
| $TXB_2$ (pg/g) | 807·5 | 6416·4 | 1578·7 | 902·5 | 940·8 | 709·4 |
| ± | 60·4 | 235·3 | 676·0 | 75·5 | 57·2 | 54·0 |

LT = leukotriene; PG = prostaglandin; TX = thromboxane.
± = standard deviation.

**Table 5.** Results of statistical analysis and *P*-values of physiological variables, inflammatory changes and eicosanoids

| Variables | Statistical analysis | *P*- value |
|---|---|---|
| Normal feces | CC < LW − 3; M; MW-3 | $P=0{\cdot}0002$[a] |
| Oral intake/body weight relation | CC < MW − 3 | $P=0{\cdot}000001$[b] |
| | CS = MW − 3 | $P>0{\cdot}05$ |
| Inflammatory alterations | CC > CS, LW-3, MW-3 | $P=0{\cdot}0009$[b] |
| Macrophage cellularity | CC > CS, M, MW-3 | $P=0{\cdot}00003$[b] |
| Ulcers on histology | CC > CS, MW-3 | $P=0{\cdot}001$[a] |
| | CS = MW − 3 | $P>0{\cdot}05$ |
| Leukotriene $B_4$ | CC > CS, LW-3, MW-3 | $P=0{\cdot}0017$[c] |
| Leukotriene $C_4$ | No difference | $P=0{\cdot}3375$[c] |
| Prostaglandin $E_2$ | CC > CS, M, MW-3 | $P=0{\cdot}0049$[c] |
| Thromboxane $B_2$ | CC > CS, MW-3 | $P=0{\cdot}0138$[c] |

[a]Fisher Exact test; [b]Kruskal-Wallis test; [c]Bonferroni's test.

plus fish oil LE (MW-3) were the only experimental group where mucosal ulcer formation assessed by histology was practicaly absent (ten rats) as seen in the control group without colitis (CS – twelve rats) ($P<0{\cdot}05$). Actually, macrophage cellularity scores were lower than in the CC group (9·0) only in rats infused with MCT/LCT LE alone (M group – 7·1) or enriched with fish oil (FO) (MW-3 group – 6·8) ($P<0{\cdot}05$).

The median colonic concentrations of eicosanoids indicated significantly lower concentrations of $LTB_4$ in *n*-3FA supplemented groups (LW-3 and MW-3) when compared to the CC group (41 and 84 *v.* 341 ng/g). Also, $PGE_2$ concentrations in M and MW-3 rats were lower than in the CC group (2148 and 2235 *v.* 7660 pg/g). $TXB_2$ concentrations in the MW-3 group were lower than those found in the CC animals (709 *v.* 6416 pg/g). $LTC_4$ median values were not different between the groups ($P>0{\cdot}05$).

## Discussion

Experimental models of colitis have been widely used to study the pathogenesis and therapy of IBD (Sartor, 1997). The intracolonic administration of acetic acid is a simple, low cost and reproducible method used in small animals (MacPherson & Pfeiffer, 1978; Moraes, 1987, 1989), and the resulting inflammation shares similarities with human IBD regarding histological aspects and eicosanoid metabolism (Sharon & Stenson, 1985). In the present study, differences in almost all variables were observed between the CC and CS groups, indicating that the model was effective in our hands.

Diarrhea, reduced oral intake and weight loss are common symptoms in IBD patients. Interestingly, in the present study LCT containing LE (L group) showed no anti-inflammatory effect on the mucosa, while supplemental *n*-3 FA ameliorated intestinal function (MW-3 group). The effect of *n*-3 FA in reducing IBD-associated symptoms is due to a reduced intestinal inflammatory response (less secretion, improved mucosal permeability, greater absorption) (McCall *et al.* 1989; Salomon *et al.* 1990; Grimminger *et al.* 1993*a*; Almallah *et al.* 1998) and improved colonic blood perfusion (Pomposelli *et al.* 1990; Pscheidl *et al.* 1992; Pscheidl & Böke-Pröls, 1997).

Anorexia is considered a feature of the metabolic response to pro-inflammatory cytokine elevation in rat colitis (Grimble, 1998). In this study, animals infused with MCT/LCT plus FO emulsion had a better oral intake–weight ratio than the other groups. It is recognized that while *n*-3 FA reduce the inflammatory response, *n*-6 FA have the opposite effect (Alexander, 1998). Furthermore, it was claimed that MCT promotes protein economy since the medium chain fatty acids are readily oxidized, so sparing amino acids from being used as energy (Jiang *et al.* 1993). The data from the present study suggest that *n*-3 FA supplementation in MCT/LCT LE preserved the oral intake–weight ratio because of reduced anorexia and protein catabolism. This experimental data emphasizes the potential clinical benefits of this formula in acute colitis.

In our investigation, less abdominal and intestinal inflammatory changes were found in FO treated groups at laparotomy, with reduced incidence of macroscopic alterations reflecting a lower degree of bowel injury. This observation supports the potential clinical benefit of supplemental *n*-3 FA in colitis. Our results are in good agreement with those obtained in trinitro benzero sulfonic acid (TNBS)-induced colitis in rats treated with *n*-3 FA supplemented total parenteral nutrition (Inui *et al.* 1996).

Rats receiving MCT/LCT plus *n*-3 FA (MW-3 group) exhibited greater protection against the development of severe morphological damage. Histological improvement (reduced ulcer formation, preservation of mucosal barrier and faster recovery after injury) has also been demonstrated in other experimental (Marotta *et al.* 1995; Shoda *et al.* 1995) and clinical settings (Stenson *et al.* 1992) by using supplemental *n*-3 FA.

Intestinal macrophages have an important role in mucosal inflammation (Rogler *et al.* 1997). In the present study, the average scores of inflammation in the M and MW-3 groups were less than in the colitis control group (CC). This might indicate that the use of MCT/LCT emulsions is associated with reduced inflammation and macrophage recruitment. A growing body of evidence suggests that *n*-6 FA containing LCT emulsions are immunosuppressive and thus exert deleterious effects on immune cells (Cukier *et al.* 1997; Gelas *et al.* 1998), thereby affecting cytokine and eicosanoid synthesis and resulting in increased injury (Ulrich *et al.* 1996). Indeed, the greater proportion of *n*-3 FA (MW-3 group) in the present study might modify the profile of inflammatory mediator synthesis, stimulate cell defense mechanisms and result in less chemotaxis and cell adherence (Lee *et al.* 1985; Morlion *et al.* 1997; Grimm *et al.* 1998; Furst & Kuhn, 2000).

In the present work, mucosal $LTB_4$ concentrations were reduced in the *n*-3 FA treated groups when compared to the control group with colitis (CC). This may be a consequence of the known competition between eicosapentaenoic and arachidonic acids. Similarly, other studies showed that supplemental *n*-3 FA reduce levels of $LTB_4$ in IBD patients (Stenson *et al.* 1992) and in experimental colitis (Guarner *et al.* 1992; Inui *et al.* 1996; Nieto *et al.* 1998).

M and MW-3 were the only groups that had lower $PGE_2$ concentrations compared to the CC group. The same result was not found when comparing the LW-3 and CC groups. This could be attributable to the reduced (50 %) concentrations of LCT in M and MW-3 LE. We also observed a reduction in the concentration of $TXB_2$ in MW-3 treated rats, similar to the observations of Campbell *et al.* (1997); Yeh *et al.* (1997) with enteral or parenteral *n*-3 FA, respectively.

Administration of oral *n*-3 FA in IBD has presented contradictory results, either showing low effectiveness (Aslan & Triadafilopoulos, 1992; Greenfield *et al.* 1993; Loeschke *et al.* 1996; Lorenz-Meyer *et al.* 1996) or exhibiting some benefits like histological improvement and reduction in eicosanoid production (Guarner *et al.* 1992; Marotta *et al.* 1995; Shoda *et al.* 1995; Nieto *et al.* 1998). On the other hand, studies using parenteral provision of *n*-3 FA suggest that the venous route is more effective in the modulation of cytokine and eicosanoid patterns and thereby in the management of acute inflammation, even with short-term treatment (Grimminger *et al.* 1993*b*; Morlion *et al.* 1997; Tashiro *et al.* 1998; Hayashi *et al.* 1999). Particularly in IBD, favourable results have been reported in clinical (Ikehata *et al.* 1992; Grimminger *et al.* 1993*a*) and experimental studies (Inui *et al.* 1996) by using parenteral supplementation of *n*-3 FA.

An increased *n*-3–*n*-6 FA ratio might be associated with certain pharmacological advantages and less immunosuppressive effects (Fürst, 1994; Grimm *et al.* 1994, 1995;

Hayashi *et al.* 1999). On the basis of the effect on the $LTC_5/LTC_4$ ratio, it was proposed that the *n*-3–*n*-6 ratio should be between 1: 2 and 1: 4 (Morlion *et al.* 1997; Grimm *et al.* 1998).

In the present study the ratios of *n*-3–*n*-6 FA in the LE were 1:7·7 (group L), 1: 7·0 (M), 1:4·5 (LW-3) and 1: 3·0 (MW-3). Therefore it is not surprising that only the *n*-3 FA enriched emulsions revealed effective modulation of inflammation in this model of acute colitis.

The present results together with the available literature suggest that the parenteral provision of *n*-3 FA is a beneficial therapeutic approach for acute intestinal inflammation. The management of IBD patients by using immunomodulatory nutrients should be further scrutinized in controlled studies in order to evaluate if triglyceride composition (i.e. fatty acid chain length), duration of treatment and the use of different *n*-3–*n*-6 FA ratios could affect clinical results and immune status.

## Conclusions

An LCT-containing lipid emulsion with low *n*-3–*n*-6 FA ratio did not affect manifestations of colitis. The use of emulsions with high *n*-3–*n*-6 FA ratio reduced diarrhea, decreased inflammation changes, attenuated morphological injury and decreased concentrations of eicosanoids. The most profound beneficial impact was observed with MCT/LCT containing lipid emulsion where the *n*-3–*n*-6 FA ratio was 1:3.

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