Perforated gastric ulcer complicating corticosteroid therapy in acute rheumatic fever

A. Klar[1], J. Moise[1], A. Brand[1], D. Seror[2], H. Hurvitz[1]

(1) Department of Paediatrics, Bikur Cholim General Hospital affiliated with the Hebrew University-Hadassah Medical School, Jerusalem, Israel ; (2) Department of Paediatric Surgery, Hadassah University Hospital, Mount Scopus, Jerusalem, Israel.

Abstract

We report an 11-year-old boy with acute rheumatic fever who presented with gastric perforation while treated with corticosteroids (CS). He had been treated initially with acetylsalicylic acid for 11 days, CS replaced the treatment with acetylsalicylic acid due to deterioration of carditis.

The possible pathogenesis is discussed. (Acta gastroenterol. belg., **2000**, 36, **236-238**).

Key words : corticosteroids, perforated, ulcer, rheumatic fever.

Introduction

Gastrointestinal complications associated with acetylsalicylic acid or CS therapy have been reported in paediatric patients (1). However, gastric perforation has rarely been reported (2). We report an 11-year-old boy with acute rheumatic fever who developed gastric perforation presumed to be a complication of CS treatment following acetylsalicylic acid therapy.

Case Report

An 11-year-old male patient whose medical history was unremarkable except for mild childhood asthma, was diagnosed in another hospital as acute rheumatic fever. The diagnosis of rheumatic fever was based on the modified Jones criteria (3) : carditis, diagnosed clinically by appearance of a new apical systolic heart murmur confirmed by echocardiography as mitral regurgitation, migratory polyarthralgia, fever of 39°, elevated ESR and CRP of 100 mg/L (N < 5) and an elevated anti streptolysin O titer of 800 todds unit. He was treated initially with acetylsalicylic acid (60 mg/kg/day) taken with meals and penicillin V-K 50 mg/kg/day (Rafa, ISRAEL) before meals, After improvement of his symptoms he was discharged to ambulatory follow-up on the same treatment. Ambulatory echocardiography on the 11th day of treatment demonstrated worsening of the carditis, with aortic and tricuspid insufficiency in addition to mitral insufficiency. He was admitted to our ward and the acetylsalicylic acid was discontinued and replaced by corticosteroid therapy. Prednisone 1.5 mg/kg/day was given as an anti inflammatory agent for the treatment of carditis and prevention of permanent valvular damage. Penicillin V-K 250mg × 2/day was continued. On the second day the patient complained of abdominal pain, antacid therapy, maalox 10cc × 3/day (Rhone – Poulenc ISRAEL) was added and his abdominal pain subsided. After 10 days of therapy the patient was discharged with instructions to continue therapy with prednisone, 1 mg/kg/day, maalox 10cc × 3/day and penicillin V-K 250mg × 2/day.

Eight hours after discharge he returned to the emergency room complaining of severe pain over the left shoulder. There was no fever, no complaint of nausea, nor vomiting. Examination of the abdomen revealed mild tenderness over the left lower quadrant without evidence of peritoneal irritation. Chest and abdominal x-ray revealed free air under the left diaphragm. Perforated viscus was diagnosed and the patient was transferred to the paediatric surgical service for an urgent operation.

On laparotomy, a small perforated gastric ulcer was found at the anterior aspect of the fundus, near the greater curvature, with a small amount of free turbid fluid surrounding it. The perforation was debrided and primarily sutured. The postoperative course was uneventful. Serology for Helicobacter-pylori was negative. Prednisone 1 mg/kg/day was continued and was tapered off over a month, cimetidine 150mg × 2/day was added. On follow up of 2 years the child is well with normal echocardiographic findings and on prophylactic treatment with penicillin V-K 250 mg × 2/day.

Discussion

Gastric perforation is an uncommon complication of peptic ulcer disease in children. In a recent review of the literature only 16 children with perforated gastric ulcer had been treated previously with steroids. Most of them had a significant debilitating underlying active illness (e.g. malignancy) (2). We are not aware of any reported case describing gastrointestinal perforation associated with CS or acetylsalicylic acid therapy in acute rheumatic fever although gastrointestinal bleeding has been reported in patients receiving acetylsalicylic acid therapy (4).

Keenan *et al.* found significant gastropathy, associated with none steroidal anti inflammatory drugs

Correspondence & reprint request to : A. Klar, M.D., Department of Paediatrics, Bikur Cholim General Hospital, POB 492, Jerusalem, 91004 Israel.

(NSAID) in less than 1% of children with juvenile rheumatoid arthritis (5). However Dowd *et al.* found that 34% of children taking NSAIDs had some gastric or duodenal injury ; nevertheless none were hospitalized for complications such as haemorrhage or perforation (6).

Older studies suggested that prednisone is an independent risk factor for gastric mucosal injury (7). However, a recent large meta-analysis study including 6,602 patients on prolonged steroid therapy concluded that peptic ulcer is a rare complication of this treatment. (8). On the other hand another meta-analysis study has confirmed the danger of gastroduodenal injury in patients receiving both NSAIDs and CS. The risk being 15 times higher than that of nonusers of either drug (9).

Our 11-year-old boy with rheumatic fever developed gastric perforation on the 10th day of prednisone therapy, 10 days after cessation of acetylsalicylic acid. We hypothesize, that the treatment with acetylsalicylic acid initiated the gastric injury causing erosion or ulcer. Later the gastric erosions or ulcer were affected by the negative effect of CS on collagen synthesis, and on gastric ulcer healing (as found in animal experiments), eventually leading to perforation of the ulcer (10-12).

The location of this patient's ulcer, on the greater curvature, is similar to the recent description by Al-Assi *et al.* in their report of gastric ulcer sites in NSAID users (13).

Our patient's course indicates that not only does concomitant therapy with NSAID and CS increase the risk of peptic ulcer disease, but so does consecutive treatment with CS after acetylsalicylic acid therapy.

Acetylsalicylic acid is a non selective cyclooxygenase (COX) inhibitor and as such inhibits both COX I & COX II activity, affecting the cytoprotective role of prostaglandins in the gastrointestinal tract increasing the risk of gastrointestinal ulceration, now hypothesized to be COX-I mediated (14).

In children taking NSAID, misoprostol was reported to be an effective treatment of gastrointestinal tract symptoms (15,16).

In another study misoprostol and ranitidine treatment were equally effective for symptomatic relief of NSAIDs induced abdominal symptoms in children with arthritis (17).

Omeprazole has been found to be an effective agent for gastroduodenal prophylaxis in adult patients taking NSAIDs (18), in patient who use NSAIDs regularly, omeprazole healed or prevented formation of ulcers more effectively than did ranitidine (19).

In a study comparing omeprazole and misoprostol in adult patients treated for ulcer associated with NSAIDs a higher rate of healing was found in the omeprazole group (20).

In children omeprazole has been shown to be a safe and effective treatment for acid related diseases (21).

It is not clear whether prophylactic anti-ulcer treatment should be recommended in children taking NSAID, acetylsalicylic acid or CS and if so, which treatment is preferable.

We recommend that studies regarding the need and efficacy for gastroduodenal protective therapy in children taking NSAIDs, acetylsalicylic acid or CS should be conducted.

References

1. MATSUBARA T., MASON W., KASHANI IA., KLIGERMAN M., BURNS J.C. Gastrointestinal hemorrhage complicating , therapy in acute Kawasaki disease. J Pediatr, 1996, **128** : 701-3.
2. BICKLER S.W., HARRISON M.W., CAMPBELL J.R. Perforated peptic ulcer disease in children : Association of corticosteroid therapy. J. Pediatr. Surg., 1993, **28** : 785-7.
3. DAJANI A.S., AYOUB E., FREDRICK Z., BIERMAN F.Z., BISNO A.L., DENNY F.W., DURACK D.T., FERRIERI P., FREED M., GERBER M., KAPLAN E.L., KARCHMER A.W., MARKOWITZ M., RAHIMOTOOLA S.H., SHULMAN S.T., STOLLERMAN G., TAKAHASHI M., TARANTA A., TAUBERT K.A., WILSON W. Guidelines for the diagnosis of rheumatic fever Jones criteria, updated, 1992. Special writing froup of the committee on Rheumatic fever, endocarditis, and Kawasaki disease of the Council on Cardiovascular disease in the young, American Heart Association. *Circulation*, 1993, **87** : 302-307.
4. BERGMAN G.E., PHILIPPIDIS P., NAIMAN J.L. Severe gastrointestinal hemorrhage and anemia after therapeutic doses of aspirin in normal children. *J. Pediatr.*, 1976, **88** : 501-3.
5. KEENAN G.F., GIANNINI E.H., ATHREYA B.H. Clinically significant gastropathy associated with nonsteroidal antiinflammatory drug use in children with juvenile rheumatoid arthritis. *J. Rheumatol.*, 1995, **22** : 1149-51.
6. DOWD J.E., CIMAZ R., FINK C.W. Nonsteroidal antiinflammatory drug-induced gastroduodenal injury in children. *Arthritis & Rheumatism*, 1995, **38** : 1225-31.
7. MESSER J., REITMAN D., SACKS H.S., SMITH H J.R. CHALMERS T.C. Association of adrenocorticosteroid therapy and peptic ulcer disease. *N. Engl. J. Med.*, 1983, **309** : 21-4.
8. CONN H.O., POYNARD Y. Corticosteroids and peptic ulcer : Meta-analysis of adverse events during steroid therapy. *J. Intern. Med.*, 1994, **236** : 619-32.
9. PIPER J.M., RAY W.A., DAUGHERTY J.R., GRIFFIN M.R. Corticosteroid use and peptic ulcer disease : Role of nonsteroidal anti inflammatory drugs. *Ann. Intern. Med.*, 1991, **114** : 735-40.
10. CARPANI DE KASKI M., RENTSCH R., LEVI S., HODGSON H.J. Corticosteroids reduce regenerative repair of epithelium in experimantal gastric ulcers. *Gut*, 1995, **37** : 613-6.
11. WALSH WR, WIGGINS ME, FADALE PD, EHRLICH MG. Effect of delayed steroid injection on ligament healing using a rabbit medial collateral ligement model. *Biomaterials*, 1995, **16** : 905-10.
12. KAHN D.S., PHILLIPS M.J., SKORYNA S.C. Healed experimental gastric ulcer in the rat : re-ulceration resulting from cortisone administration. *Arch. Pathol.*, 1961, **38** : 177-87.
13. AL-ASSI M.T., GENTA R.M., KARTTUNEN T.J., GRAHAM D.Y. Ulcer site and complications : Relation to Helicobacter pylori infection and NSAID use. *Endoscopy*, 1996, **28** : 229-33.
14. RAZ A., WYCHE R.A., NEEDLEMAN P. Temporal and pharmacological division of fibroblast cyclooxygenase expression into transcriptional and translational phases. *Proc. Natl. Acad. Sci USA*, 1989, **86** : 1657-61.
15. AQRAWAL N.M. Epidemiology and prevention of non-steroidal anti inflammatory drug effects in the gastrointestinal tract. *Br. J. Rheumatol.*, 1995, **34** : 5-10.
16. GAZARIAN M., BERKOVITCH M., KOREN G., SILVERMAN E.D., LAXER R.M. Experience with misoprostol therapy for NSAID gastropathy in children. *Ann. Rheum. Dis.*, 1995, **54** : 277-280.
17. RASKIN J.B., WHITE R.H., JASZEWSKI R., KORSTEN M.A., SCHUBERT T.T., FORT J.G. Misoprostol and ranitidine in the prevention of NSAID-induced ulcers : A prospective, double-blind, multicenter study. *Am. J. Gastroenterol.*, 1996, **91** : 223-7.
18. CULLEN D., BARDHAN K.D., EISNER M., KOGUT D.G., PEACOCK R.A., THOMSON J.M., HAWKEY C.J. Primary gastroduodenal prophylaxis with omeprazole for non-steroidal anti-inflammatory drug users. *Aliment Pharmacol. Ther.*, 1998, **12** : 135-40.

19. YEOMANS N.D., TULASAY Z., JUHASZ L., RACZ I., HOWARD J., VAN RENSBURG C.J., SWANNELL A.J., HAWKEY C.J. A comparison of omeprazole with ranitidine for ulcers associated with nonsteroidal antiinflammatory drugs. *N. Engl. J. Med.*, **338** : 719-26.
20. HAWKEY C.F., KARRASCH J.A., SZCZEPANSKI L., WALKER D.G., BARKUN A., SWANNELL A.J., YEOMANS N.D. Omeprazole compared with misoprostol for ulcers associated with nonsteroidal antiinflammatory drugs. Omeprazole versus misoprostol for NSAID-induced ulcer management (OMNIUM) Study Group. *N. Engl. J. Med.*, 1998, **338** : 727-734.
21. SEIICHI K., KYOKO E., KUNIHIRO F., HIROO C., HIROSHI N. Effect of omeprazole in the treatment of refractory acid-related diseases in childhood : endoscopic healing and twenty-four-hour intragastric acidity. *J. Pediatr.*, 1996, **128** : 415-21.