Benzathine penicillin G in prophylaxis of Helicobacter pylori infection

Helicobacter pylori infeksiyonu profilaksisinde benzathine penicilin G

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ÖZET: *Helicobacter pylori (Hp) enfeksiyonu tedavi edildikten sonra reenfeksiyon söz konusu olmabilmektedir. Bu çalışmanın gayesi, reenfeksiyonu önlemede depopenisilinin (Benzathine Penicillin G = BPG) faydalı olup olmayacağını araştırmak idi. Çalışma Hp eradikasyonu üçlü tedavi ile sağlanmış 68 nonülser dispepsili hasta alındı. Çeşitli nedenlerle 19 hasta çalışmadan çıkarıldı. Hp tespitinde üreaz testi ve histopatolojik inceleme kullanıldı. 68 hasta iki gruba ayrıldı: Grup A'daki 30 hastaya 6 ay süreyle ayda bir kez 1,2 milyon ünite BPG i.m. uygulandı. Kontrol grubunu oluşturan B grubundaki 38 hastaya ise hiçbir ilaç uygulanmadı. 6. aydan sonra tüm hastalarda Hp durumu araştırıldı. Çalışmayı 49 hasta tamamladı (Grup A'da 24, grup B'de 25 kişi). 6. aydan sonra Hp enfeksiyonu A grubunda hiç görülmedi (% 0), B grubunda ise 9 hastada görüldü (% 36). Gruplar arasındaki fark istatistiki olarak anlamlıydı ($p<0.05$). BPG Hp enfeksiyonunun önlenmesinde etkili görünmektedir. Bu sonuç özellikle, Hp reenfeksiyon oranının yüksek olduğu toplumlarda yaşayan ve sık nükseden peptik ülseri olan hastalar için önem arzetmektedir.*

Anahtar kelimeler: **Helicobacter pylori, reenfeksiyon, benzathine penicillin G**

GASTRIC Hp infection is increasingly acknowledged as an important cause of chronic active gastritis and there is good evidence showing a significant association with peptic ulcer disease (1-7). Recently attention has focused on a possible association between Hp gastritis and gastric carcinoma (8.9). For this reasons, treatment of Hp infection has great importance. But, after successful Hp eradication, reinfection may appear as a problem (10,16).

In this prospective study, whether BPG have a role in prophylaxis of Hp reinfection was investigated.

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SUMMARY: *Reinfection of Helicobacter pylori (Hp) may occur after successful eradication of infection. The aim of this study was to investigate if benzathine penicillin G (BPG) prevents reinfection or not. Sixty-eight non-ulcer dyspeptic patients who underwent successful Hp eradication were included in this study. During study, 19 patients dropped out of the study. Rapid urease test and histopathologic examination were used in determining of Hp. 68 patients were divided into two groups: 30 patients in group A used BPG 1.2 million i.u. (one i.m. injection monthly) for 6 months. 38 patients in group B did not take any medicine as control group. After 6 months Hp status was investigated in all patients. 49 patients (24 in group A, 25 in group B) completed the study. After 6 months, Hp infection did not appear in group A (0 %) whereas in group B, 9 patients (36%) were Hp (+). The difference between groups was significant statistically ($p<0.05$). BPG appears very effective in treating prophylaxis of Hp reinfection. This result may have great importance in patients with recurrent peptic ulcer disease.*

Key words: **Helicobacter pylori, reinfection, benzathine penicilline G**

MATERIALS and METHODS

Sixty-eight non-ulcer dyspeptic patients (52 male, 16 female; ranging in age from 19 to 68 years) who underwent successful Hp eradication (Bismuth subcitrate 300 mg/q.i.d., metranidazole 500 mg/b.i.d., amoxicilline 500 mg/q.i.d. for 15 days) were included in this study. The study was based on Hp status, endoscopic findings were not considered. In determining of Hp status; the parallelism of urease test (CLO test) and histopathologic examination were considered. The patients who have gastric surgery, the discordance of urease test and histopathologic examination and neglected BPG injections were excluded. So, 49 patients (39 male, 10 female) completed the study.

All endoscopic procedures were performed following an overnight fast. No patients had sedation,

Tablo 1. *Hp reinfection rates in group A and B at the end of the 6 months follow-up period.*

Group	Hp rein fection	%
A (n= 24)	n= 0	0
B (n= 25)	n= 9	36

only topical pharyngeal anesthesia was performed. Endoscopic procedures were performed by Olympus Q 20 and Pentax FG-32 X endoscopes. Endoscopes and biopsy forceps were disinfected by glutaraldehyde solution for 10 minutes. During endoscopic procedures 2 antral and 2 corporal biopsies were fixed in 10 % neutral buffered formalin and processed on paraffin in the normal manner: Sections were stained with haemotoxylin and eosin and a modified Gram stain for the identification of Hp in tissue sections (11). Biopsies were examined by a single histopathologist (M.D.) without knowledge of patients details.

Eradication of Hp was defined as no evidence of Hp infection 4 or more weeks after stopping antimicrobial therapy.

After eradication, the patients were divided into two groups: 30 patients in group A used 1.2 million i.u. BPG injection i.m. monthly for 6 months (all patients have no penicillin allergy). 38 patients in group B did not take any medicine as control group. Probable allergic patients were included in group B. Both groups were comparable in age, sex and symptoms. After 6 months, Hp status was investigated in all patients (one month after the last BPG injection in group A) and the results were compared. At the end of the study, group A had 24 and group B had 25 patients.

In statistically analysis, Fisher's exact test was used. The study was approved by the Academy Ethical Practices Committee and the patients gave informed written consent to take part in the study.

RESULTS

At the and of the 6 months follow-up period; none patient in group A had Hp infection, but in group B 9 patients had Hp infection (9/25) again (Table 1). The difference between groups were highly significant statistically ($p<0.05$).

DISCUSSION

In this study, we found that BPG in very effective in prophylaxis of Hp reinfection.

BPG has been used widely in prophylaxis of rheumatic fever. Thamlikitkul and co-workers (23) investigated the pharmacokinetics of BPG (1.2 million i.u. given i.m.) and other antibiotics in prophylaxis of rheumatic fever. Based on the pharmacokinetic profiles, they suggested that 1.2 million i.u. BPG given every 4 weeks is an appropriate regimen for preventing the recurrence of rheumatic fever in Thai adults. In our study BPG was used in same manner.

For Hp eradication, penicillines (e.g. ampicillin, amoxicillin) are effective about 20% as monotherapeutic agent (12,13). So, the penicillines have been used in combined therapeutic regimens (14).

In literature there is only one study about using BPG in Hp eradication (15). In that study Wirth and co-workers used oral amoxicillin for two weeks and then it was substituted for one single injection of i.m. BPG in Hp positive patients. Additionally, patients were given ornidazole 500 mg t.i.d. for 14 days and 120 mg colloidal bismuth sub-citrate q.i.d. for 28 days. The eradication rate was found 50%. In literature we haven't encountered any study about using BPG in prophylaxis of Hp reinfection. For this reason, in this study we used BPG for prophylaxis of Hp infection, not for eradication.

A number of studies (10, 17-19, 21, 23-26) have shown that eradication of the organism reduces the rate of duodenal ulcer relapse, providing a strong rationale for eradicating Hp in duodenal ulcer disease. In these studies, when Hp was eradicated, the recurrence of duodenal ulcer ranged between 0 and 22% (in a year) compared, typically, with 70-80% when eradication treatment failed (27). So, the prophylaxis of Hp infection has great importance for clinicians.

Rune and co-workers (22) performed a randomized controlled trial of the relaps rate of duodenal ulcer during 12 weeks treatment with penicillin V (it has no effect on epithelial-cell integrity) or placebo in 170 out-patients from five centres. They found the relapse rate 9% during treatment with penicillin and 50% with placebo ($p<0.0001$). So, they concluded that, infection with penicillin-

sensitive bacteria, i.e. Hp, plays an important role for recurrence of duodenal ulcer disease and penicillin V suppresses this infection, but does not eradicate it.

After successful eradication of Hp infection, the rate of reinfection in one year is about 1-3% (29,30). But, Gliman et al (16) reported that, reinfection rates of Hp (within one year) in Peru, after successful eradication using triple therapy were 56%. This rate in our study is 36%; i.e. our result is as high as Gliman's. This discrepancies with other studies might be due to different socioeconomic status of different populations. In addition, antimicrobial regimens cannot eradicate Hp easily, and Hp can revert to coccoid form (20,31), and then coccoid form can have viability and Hp infection can reappear. For this reason, our reinfection rate may not be real reinfection rate, but may be reactivation rate, partly. We speculate that, BPG may suppress the reversion of coccoid form to viable form and it prevents recurrence of Hp infection.

1790 patients from 11 countries were enrolled in a prospective international study (28) to determine the incidence of allergic reactions to monthly i.m. BPG injections to prevent recurrences of rheumatic fever. The incidence of anaphylactic reactions was found 0.2%. This is a low incidence. In our study we didn't encounter any allergic reactions.

BPG is a cheap drug and available everywhere. In addition, one injection in a month seems as an advantage and because Helicobacter Pylori doesn't produce penicillinase, there isn't resistance problem againts BPG(14).

We havenot encountered any study about MIC (minimum inhibitory concentration) value of BPG for Helicobacter Pylori and secretion of BPG into gastric juice in literature. Only we know that, BPG is stable in the presence of gastric juice (32). More detailed studies about these subjects are necessary.

In conclusion, we can say that, because of the high recurrence rate of Hp infection in our study, the prophylactic regimens may be necessary, especially in patients who have recurrent peptic ulcer disease. BPG may be an appropriate prophylactic agent in non-allergic patients.

KAYNAKLAR

1. Rauws E AJ, Tytgat GNJ. Cure of duodenal ulcer associated with eradication of Helicobacter pylori. Lancet 1990; 335:1233-5.
2. Tytgat GNJ, Rauws EAJ. Campylobacter pylori and its role in peptic ulcer disease. Gastroenterol Clin North America 1990; 19:183-196.
3. Tytgat GNJ, Graham DY, Lee A, et al. Helicobacter pylori: Causal agent in peptic ulcer disease? J Gastroenterol Hepatol 1991; 6:103-40.
4. Marshall BJ, McGechie DB, Roger PA, Glancy RJ. Pyloric campylobacter infection and gastroduodenal disease. Med J Aust 1985; 142:439-44.
5. Goodwin CS, Armstrong JA, Marshall BJ. Campylobacter pyloridis, gastritis and peptic ulceration. J Clin Pathol 1986; 39:353-65.
6. Özden A, Ekinci C, Dumlu Ş ve ark. Üst gastrointestinal sisteme ait yakınmaları olan olgularda Helikobakter Pilori prevalansı. Gastroenteroloji 1992; 3:102-108.
7. Kaya N, Savran F, Ovalı E ve ark. Üst gastrointestinal sistem endoskopilerinde Helicobacter Pylori prevalansı. Gastroenteroloji, 1991; 2:338-343.
8. Recaverren-Arce S, Leon,Barua R, Cok J. et al. Helicobacter pylori and progressive gastric pathology that predisposes to gastric cancer. Scand J Gastroenterol 1991; 26 (Suppl. 181):51-7.
9. Forman D, Newel DG, Fullertan F et al. Association between infection with Helicobacter pylori and risk of gastric cancer: Evidence from a prospective investigation. Br Med J 1991; 302:1302-5.
10. Asaka M, Ohtaki T, Kato M et al. Causal role of Helicobacter pylori in peptic ulcer relapse. 1994; 29 (Suppl 7):134-138.
11. Trowell JE, Young AKH, Saul KJ, et al. Simple half Gram stain for showing presence of Campylobacter pyloridis in sections (letter). J Clin Pathol 1987; 40:702.
12. Oderda G, Vaira D, Holton J, et al. Amoxicillin plus tinidazole for Campylobacter pylori gastritis in children; assesment by serum Ig G antibody, pepsinogen I and gastrin levels. Lancet 1989; 1:690-692.
13. Rauws EAJ, Langenberg W, Houthoff HJ, et al. Campylobacter pyloridis-associated chronic active antral gastritis: A prospective study of its prevelance and the effects of antibacterial and antiulcer treatment. Gastroenterology 1988; 94:229-238.
14. Marshall BJ. Treatment strategies for Helicobacter pylori infection. Gastroenterol Clin North America 1993; 22:183-198.
15. Wirth HP, Wust J, Flury R, ct al. Atrial of modified triple therapy for the eradication of Helicobacter pylori in recurrent duodenal ulcer. Schweiz Med Wochenschr 1993; 123:1645-1649.
16. Gliman R, Barua RL, Ramos A, et al. High rates of recurrence of Helicobacter pylori after triple therapy in Peru. In: Takemoto T, Kawai K, Shimoyama T, Kimura K (eds). Helicobacter pylori and gastroduodenal disease. IJI Publishing 1991; 233-240.
17. Wang WM, Chen CY, Jan CM, et al. Long-term follow-up and serological study after triple therapy of Helicobacter pylori-associated duodenal ulcer. Am J Gastroenterol 1994; 89:1793-1796.
18. Forbes GM, Glaser ME, Cullen DJ, et al. Duodenal ulcer treated with Helicobacter pylori eradication: seven-year follow-up. Lancet 1994; 29; 343 (8892):258-260.
19. Logan RPH, Gummett PA, Polson RJ, et al. The recurrence of Helicobacter pylori in relation to dudenal ulcer. Rev Esp Enferm Dig 1990; 78 (suppl 1):72-73.

20. Bode G, Mauch F, Malfertheiner P. The coccoid forms of Helicobacter pylori. Criteria for their viability. Epidemiol Infect 1993; 111:483-490.

21. George LL, Borody TJ, Andrews P, et al. Cure of duodenal ulcer after eradication of Helicobacter pylori. Med J Aust 1990; 153:145-149.

22. Rune SJ, Justesen T, Hansen JM, et al. Presentation of duodenal ulcer recurrence with penicillin. Ugeskrlaer 1994; 11: 156:221-223.

23. Coghlan JD, Gilligan D, Humphries H, et al. Campylobacter pylori and recurrence of duodenal ulcers; a 12 month follow-up study. Lancet 1987; ii: 1109-11.

24. Marshall BJ, Goodwin CS, Warren JR, et al. Prospective double-blind trial of duodenal ulcer relapse after eradication of Campylobacter pylori. Lancet 1988; ii: 1437-41.

25. Borody T, Noonin S, Cole P, et al. Recurrence of duodenal ulcer and Campylobacter pylori infection after eradication. Med J Aust 1989; 151:431-435.

26. Blum AL, Armstrong D, Dammann H, et al. The effect of Helicobacter pylori on the healing and relapse of duodenal ulcer. Gastroenterology 1990; 98:A22.

27. Axon ATR. Helicobacter pylori therapy: effection peptic ulcer disease. J Gastroenterol Hepatol 1991; 6:131-137.

28. International Rheumatic Fever Study Group. Allergic reactions to long term benzathine penicillin prophylaxis for rheumatic fever. Lancet 1991; 337:1308-1310.

29. Tytgat GNJ, Noach LA, Rauws EAJ. Helicobacter pylori infection and duodenal ulcer disease. Gastroenterol clinics of North America, 1993; 20:127-139.

30. Cutler AF, Schubert TT. Long-term Helicobacter pylori recurrence after successful eradication with triple therapy. Am J Gastroenterol 1993; 88:1359-1361.

31. Bode G, Malfertheiner P, Strohle A, et al. Polymorphism in Helicobacter pylori-a key function in recurrence of infection? Med Clin 1992; 87:179-184.

32. Raynolds JEF. Benzathine penicilline. Martindale. The extra pharmocopoeia, ed 30, p 122, 1993, London, The Pharmaceutical Press.