CLINICAL PRACTICE

Meta-analysis of value of propranolol in prevention of variceal haemorrhage

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A meta-analysis of all controlled clinical trials of beta-adrenoreceptor blocking drugs, principally propranolol, in the prevention of primary or secondary variceal bleeding has shown that beta-blockade significantly reduced the occurrence of variceal bleeding, deaths from variceal bleeding, and overall mortality. There was some heterogeneity between trials in the effect of beta blockade on secondary prevention. When only fully reported, randomised, placebo-controlled studies were included the heterogeneity disappeared, and the reductions in bleeding episodes and mortality became more striking. Separate analyses of primary and secondary prevention studies also showed clear reductions in occurrence of variceal bleeding and deaths. These results seem to indicate the value of beta-adrenoreceptor blocking drugs for the primary prevention of haemorrhage from large oesophageal varices. However, there is still a need for large multicentre trials of beta-blockade for primary prevention of variceal bleeding in patients without large varices and of comparisons between beta-blocker therapy with other treatments in secondary prevention.

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Introduction

In about a third of patients with oesophageal varices due to chronic liver disease bleeding from these vessels occurs in and represents a major threat to life expectancy. Since the first demonstration by Lebrec in 1980[1] that the beta-adrenoreceptor blocking agent, propranolol, could reduce portal pressure in portal hypertension its efficacy in preventing variceal haemorrhage has been assessed in many trials. Some trials have been primary, in which the drug was used to prevent haemorrhage in patients who have not bled; some have been secondary, with the drug being used to prevent rebleeding; and one was tertiary, in which the drug was used to control active haemorrhage. This tertiary study was uncontrolled,[2] included only 6 patients, and therefore cannot be used as a basis for determining therapeutic policy. Although the numerous primary and secondary prevention studies have been discussed in many reviews and leading articles, there has been little statistical analysis incorporating all the available evidence. Lewis et al[3] analysed the results of twenty studies but since then much additional data have accumulated. Here we present our meta-analysis of trials of beta-adrenoreceptor blocking drugs (beta-blockers) in portal hypertension.

In meta-analysis each treated group is compared with the controls from the same study, and the treatment effect is combined across all studies, to provide information both about the presence of any significant effect and about its size.[4,5] We have made extensive efforts to find all relevant studies by means of literature search and communication with recognised authorities in the field, and believe it is unlikely that any important work published or unpublished, has been overlooked. Combining primary and secondary prevention trials irrespective of the aetiology of liver disease is reasonable only when certain criteria are met by each trial: all patients had portal hypertension; and the beta-blocker-treated group was compared either with no active treatment or with an active treatment as long as it was given to both groups. We have combined the results of all such controlled trials of beta-blockers, most of which used propranolol.

Methods

All suitable trials identified by July, 1989, were included (table I). No further relevant trials had been identified by early 1990. The pooled data were analysed by the standard Mantel-Haenszel common odds ratio method for combining results across trials.[4,5] This method also allows the heterogeneity of the treatment effect from trial to trial to be explored, and provides convenient estimates of the size of the effect together with 95% confidence intervals. All significance tests are χ^2 tests and exact p-values are given. The treatment effect is expressed as the percentage reduction in the event rate relative to control. Separate analyses were also undertaken of primary and of secondary prevention trials.

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Results

All trials

1877 patients were included in all the twenty-six trials, 967 in the beta-blocker groups and 910 as control. Compared with control therapy β-blockade led to a 44% reduction in the number of patients with bleeding and rebleeding episodes, a similar (42%) reduction in deaths from bleeding, and a 24% reduction in all-cause mortality (table I). For bleeding events, the test of heterogeneity was highly significant (p = 0·001), which indicates that the effect of beta-blockade on this end-point might differ from trial to trial.

Primary prevention

There were 797 patients in the seven primary prevention trials (table I), and in nearly all these trials the presence of large oesophageal varices was an inclusion criterion. In the beta-blocker treated group the overall reduction in the number of patients with bleeding episodes was 47%, in deaths due to bleeding 45%, and in total mortality 22% (table II). No evidence of heterogeneity was found for bleeding events (p = 0·38), although there was a suggestion of heterogeneity of total mortality (p = 0·058). Inspection of the confidence intervals of the individual trial mortality results suggests that any variation in treatment effect is quantitative rather than qualitative (ie, all trial effects were in the same direction).

Secondary prevention

The test of heterogeneity for the rebleeding episodes in these studies (p = 0·0005) indicates that important differences might exist between the results of the secondary prevention trials (table II). This seems to be the source of the overall heterogeneity when all trials were analysed together.

TABLE I—TRIALS INCLUDED IN META-ANALYSIS

Author	Active therapy	Control	Size of study	Follow-up
Primary prevention				
Bosch et al[6]*	P	Pl	102	34 mo
Hayes et al[7]	P	Pl	95	1 yr
Ideo et al[8]	N	Pl	57	2 yr
Italian Multicentre Project[9]*	P	Vit K	174	22 mo
Lebrec et al[10]	N	Pl	106	1 yr
Pascal et al[11]	P	Pl	227	2 yr
Strauss et al[12]*	P	Pl	36	2 yr
Secondary prevention				
Burroughs et al[13]	P	Pl	48	21 mo
Cerbelaud et al[14]*	P	Unknown	84	2 yr
Colombo et al[15]	P	Pl	65	>1 yr
Gatta et al[16]	N	Pl	24	145 wk
Jensen[17]*	P+S	Pl+S	31	6 mo
Kiire[18]	P	Pl	50	1 yr
Kobe and Schentke[19]*	P	Nil	54	6–28 mo
Lopez Fuerte et al[20]	P	Pl	19	36 mo
Lebrec et al[21]*	P	Pl	74	2 yr
Marbet et al[22]*	P	Pl	20	2 yr
Mills et al[23]	P	Pl	81	2 yr
Pasta et al[24]*	P+C	H+C	89	2 yr
Queniet et al[25]*	P	Nil	99	18 mo
Robertson et al (unpub)*	P+S	Pl+S	55	1 yr
Sheen et al[26]*	P	Pl	36	<2 yr
Uribe et al[27]*	M	Pl	21	20 wk
Vickers et al[28]*	P+S	Pl+S	69	>1 yr
Villeneuve et al[29]	P	Pl	79	2 yr
Westaby et al[30]*	P+S	S	53	26 wk

*Did not satisfy strict criteria for fully reported, randomised, placebo-controlled study

Key Pl = Placebo; M = Metoprolol; Cim = Cimetidine, P = Propranolol, S = Sclerotherapy, N = Nadolol, H = Historical

TABLE II—RESULTS OF META-ANALYSIS OVER ALL STUDIES

—	Total patients	Patients who bled	Deaths from bleeding	Total mortality
All trials				
β-blocker	967	260	70	207
Control	910	391	114	256
% reduction (95% CI)	..	44 (35, 51)	42 (24, 56)	24 (10, 35)
Treatment effect (p)	..	<0·0001	0 0001	0 001
Heterogeneity	..	0 001	0·334	0 197
Primary prevention				
β-blocker	402	50	21	86
Control	395	92	38	107
% reduction (95% CI)	..	47 (28, 61)	45 (10, 67)	22 (00, 39)
Treatment effect (p)	..	<0·0001	0·017	0·052
Heterogeneity	..	0 379	0 266	0 058
Secondary prevention				
β-blocker	565	210	49	121
Control	515	299	76	149
% reduction (95% CI)	..	39 (30, 46)	40 (17, 57)	25 (07, 40)
Treatment effect (p)	..	<0·0001	0·002	0·009
Heterogeneity	..	0 0005	0 328	0·421
Selected trials				
β-blocker	464	122	30	91
Control	416	174	57	124
% reduction (95% CI)	..	46 (33, 57)	51 (27, 68)	34 (16, 48)
Treatment effect (p)	..	<0·0001	0·0004	0·0007
Heterogeneity	..	0·073	0·696	0 447

There were 1080 patients in the nineteen secondary prevention trials. β-blockade reduced the number of patients with rebleeding episodes by 39%, number of deaths from rebleeding by 40%, and total number of deaths by 25% (table II).

Further analysis of all trials

Heterogeneity in effect on bleeding and rebleeding episodes was further explored in a subset of trials, selected by applying stricter criteria—ie, the trials had to be randomised, placebo-controlled, with data analysed according to "intention to treat" principles, and final results (rather than interim findings or results obtained on early termination of the trial) had to be available. There were 880 patients in the eleven such trials. These trials showed little evidence of heterogeneity, but analysis confined to these trials enhanced treatment effects (table II).

Trials with propranolol

Analysis of studies examining only propranolol (and excluding the index Lebrec trial[1]) made very little difference to the results.

Discussion

Propranolol will reduce portal pressure in most patients with portal hypertension and reduce variceal blood flow in almost all.[31,32] However, the exciting findings by Lebrec and co-workers[33] that propranolol reduced the risk of rebleeding from oesophageal varices could not be replicated in a largely similar trial in the UK,[13] the discrepancy between the results of these two reports being attributed to differences in the type of patient included. After publication of the UK report enthusiasm for propranolol as secondary prevention of variceal haemorrhage waned. Subsequently many other trials have been reported, some differing in design—historical controls in one,[24] sclerotherapy in both arms in others (refs 17,26, and Robertson DAF, unpublished)—and some investigating different doses of propranolol or different beta-blockers. Taken singly none of the trials can be regarded as providing the definitive answer to the place of

propranolol in particular, or beta-blockade in general, in variceal bleeding. In fact their contrasting results have generated considerable debate, but the possibility remains that these are due, in no small part, to the play of chance.

Meta-analysis has been regarded with suspicion by many clinicians. However, as long as the strength and weaknesses of meta-analysis are realised, it remains a legitimate and powerful tool for drawing broad conclusions about treatment efficacy.[4,5] It is essential that sources of heterogeneity are explored and that the influence of trial inclusion on results of the analysis is examined. We found heterogeneity to be confined to the rebleeding data in the secondary prevention trials. The heterogeneity was apparently quantitative rather than qualitative in nature and, most importantly, was virtually abolished by the exclusion of trials that did not satisfy stricter criteria. This suggests that the less well controlled or the less fully reported studies are the ones giving the anomalous results. Interestingly, these excluded trials tended to be smaller than those satisfying our strict criteria. Contrary to experience in other clinical areas, the effects of treatment seemed to be slightly better after these exclusions, which lends some weight to the validity of the findings.

Another feature that supports the reliability of our findings is the consistency in the results between primary prevention trials, secondary prevention trials, and propranolol studies (with or without the index trial). The results were also internally consistent in that percentage reductions in bleeding events, rebleeding events, and deaths due to bleeding were all similar; the reduction in total mortality was consistent with an effect limited to deaths due to bleeding. Other causes of death, including liver failure, sepsis, and the development of hepatocellular carcinoma, would not be expected to be affected by propranolol.

Endoscopic sclerotherapy has also reduced the risk of rebleeding from oesophageal varices,[34] but it has not consistently improved survival; similar findings have been reported for portacaval surgery for variceal rebleeding. The effect of sclerotherapy on primary prevention of variceal haemorrhage, and that of portacaval shunts, have been disappointing. Sclerotherapy, like propranolol, is associated with a low incidence of side-effects, but those that do occur, such as oesophageal perforation, may be life-threatening. The technique also is demanding of both physician and patient time and is expensive.

Our results show that beta-blockade is effective in both primary and secondary prevention of variceal haemorrhage. However, because only 11% of the treated patients received a beta-blocker other than propranolol there is insufficient evidence that the effects seen are true class effects. The question that follows is how these results should influence clinical practice. Since no other therapy is effective in the primary prevention of variceal haemorrhage, our findings suggest that beta-blockade is indicated at least for those with large varices. However, in the group of patients who have already had a variceal bleed, both injection sclerotherapy and propranolol treatment are known to be effective in the prevention of rebleeding. The few trials that have compared these two treatments have shown little difference between them in effect on rebleeding and survival.[35] Propranolol has the advantage of being safe and cost-effective. Unfortunately compliance is likely to be poor, especially when probably a large proportion of the patients have alcoholic liver disease. In our recent study, up to a third of patients discontinued drug therapy during a 12 month treatment period, the dropout rate being equal in both the propranolol and placebo arms of the trial.[7] Compliance may be less of a problem with injection sclerotherapy.

In conclusion, meta-analysis of the existing controlled trials suggests that propranolol is a safe and effective means of reducing both the incidence of, and the mortality due to, bleeding from oesophageal varices. The combined data indicate that propranolol reduces the risk of bleeding or rebleeding by over 40%, and in both primary and secondary prevention it reduces mortality by about a quarter despite any doubts about compliance. The primary prevention trials, which included patients with large varices, and thus at high risk of bleeding, clearly show a beneficial effect, and on the strength of this analysis we would recommend long-term treatment with beta-blockers. However, for the many patients with portal hypertension without large varices a large prospective multicentre trial is indicated to determine which patients, if any, derive benefit. Further comparative trials of propranolol versus sclerotherapy are required to identify which is superior for secondary prevention of variceal haemorrhage.

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REFERENCES

1. Lebrec D, Corbic M, Nouel O, Benhamou P. Propranolol—a medical treatment for portal hypertension. *Lancet* 1980; ii: 180–82.
2. Bleichner G, Parent A, Raffray Y, Squara P. Traitement des hemorragies dues a l'hypertension portale par le propranolol. *La Nouvelle Presse Medicale* 1981; **10:** 1072–73.
3. Lewis JA, Davis JM, Allsopp D, Cameron HA. β-blockers in portal hypertension, an overview. *Drugs* 1989; **37** (suppl 2): 62–69.
4. Lewis JA. Beta-blockade after myocardial infarction—a statistical view. *Br J Clin Pharmacol* 1982; **14:** 15S–21S.
5. Yusuf S, Petro R, Lewis J, Collins R, Sleight P. Beta blockade during and after myocardial infarction; an overview of the randomized trials. *Prog Cardiovasc Dis* 1985; **27:** 335–71.
6. Bosch J, Groszmann RJ, Grace N, et al. Propranolol in the prevention of the first haemorrhage from oesophageal varices: results of a randomised, double-blind, co-operative clinical trial. *J Hepatol* 1988; **7** (suppl 9): S12.
7. Hayes PC, Crichton S, Shepherd AN, Bouchier IAD. Propranolol in chronic liver disease: a controlled trial of its effect and safety over twelve months. *Quart J Med* 1987; **246:** 823–34.
8. Ideo G, Bellati G, Fesce E, Grimoldi D. Nadolol can prevent the first gastrointestinal bleeding in cirrhotics: a prospective randomised study. *Hepatology* 1988; **8:** 6–9.
9. Italian Multicenter Project for propranolol in prevention of bleeding. Propranolol for prophylaxis of bleeding in cirrhotic patients with large varices: a multicenter, randomised clinical trial. *Hepatology* 1988; **8:** 1–5.
10. Lebrec D, Poynard T, Bernau J, et al. A randomised controlled study of propranolol for prevention of recurrent gastrointestinal bleeding in patients with cirrhosis: a final report. *Hepatology* 1984; **4:** 355–48.
11. Pascall J-P, Cales P, Multicenter Study Group. Propranolol in the prevention of first upper gastrointestinal tract haemorrhage in patients with cirrhosis of the liver and esophageal varices. *N Engl J Med* 1987; **317:** 856–61.
12. Strauss E, de Sa MFG, Albano A, et al. A randomised controlled trial for the prevention of the first upper gastrointestinal bleeding due to portal hypertension in cirrhosis: sclerotherapy or propranolol versus control groups. *Hepatology* 1988; **5:** 1395.
13. Burroughs AK, Jenkins WJ, Sherlock S, et al. Controlled trial of propranolol for the prevention of recurrent variceal haemorrhage in patients with cirrhosis. *N Engl J Med* 1983; **309:** 1539–42.
14. Cerbelaud P, Lavingnolle A, Perrin D, et al. Propranolol et prevention des recidives de rupture de varice oesophagienne du cirrhotique. *Gastroenterol Clin Biologique* 1986; **10:** 18.
15. Colombo M, De Franchis R, Tommasini M, Sangiovanni A, Dioguardi N. β-blockade prevents recurrent gastrointestinal bleeding in well-compensated patients with alcoholic cirrhosis: a multicenter randomised controlled trial. *Hepatology* 1989; **9:** 433–38.
16. Gatta A, Merkel C, Sacerdoti D, et al. Nadolol for prevention of variceal bleeding in cirrhosis: a controlled clinical trial. *Digestion* 1987; **37:** 22–28.

17. Jensen LS, Krarup N. Propranolol in prevention of rebleeding from oesophageal varices during the course of endoscopic sclerotherapy. *Scand J Gastroenterol* 1989; **24:** 339–45.
18. Kiire CF. Controlled trial of propranolol to prevent recurrent variceal bleeding in patients with non-cirrhotic portal fibrosis. *Br Med J* 1989; **298:** 1363–65.
19. Kobe E, Schentke K-U Unsichere rezidivprophylaxe von osophagusvarizenblutungen durch propranolol bei leberzirrhotikern—eine prospektive kontrollierte studie. *Klinische Medizin* 1987; **42:** 507–10.
20. Lopez Fuerte F, Cardenas Rojas JA, Esquivel Lopez A, Perches Vega A. Prevencion de la hemorragia por varices esofagicas en pacientas con cirrosis hepatica mediante la administracion de propranolol. *Rev Gastroenterol Mex* 1986; **51:** 187–90.
21. Lebrec D, Poynard T, Capron JP, et al. Nadolol for prophylaxis of gastrointestinal bleeding in patients with cirrhosis—a randomised trial. *J Hepatol* 1988; **7:** 118–25.
22. Marbet UA, Straumann A, Gyr KE, et al. Reduction in early recurrence of variceal bleeding by propranolol. *Scand J Gastroenterol* 1988; **23:** 369–74.
23. Mills P, Garden OJ, Birnie GG, Carter DC. Propranolol in the prevention of further variceal haemorrhage in cirrhosis. *Gastroenterology* 1987; **92:** 1755.
24. Pasta L, Pagliaro L, Simonetti R, et al. Propranolol for prevention of upper GI rebleeding in cirrhosis. *Ital J Gastroenterol* 1985; **17:** 136–38.
25. Queniet AM, Czernichow P, Lerkbours E, et al. Etude controlee du propranolol dans la prevention des recidives hemorragiques chez les patients cirrhotiques. *Gastroenterol Clinique et Biologique* 1987; **11:** 41–47.
26. Sheen IS, Chen TY, Liaw YF. Randomised controlled study of propranolol for prevention of recurrent esophageal varices bleeding in patients with cirrhosis. *Liver* 1989; **9:** 1–5.
27. Uribe M, Ballesteros A, Strauss R, Rosales J, Guevara L. Use of cardioselective beta-blockers in portal hypertension and advanced liver disease. *Gastroenterology* 1983; **2:** 1339.
28. Vickers C, Rhodes J, Hillenbrand P, et al. Prospective controlled trial of propranolol and sclerotherapy for prevention of rebleeding from oesophageal varices. *Gut* 1987; **28:** A1359.
29. Villeneuve J-P, Pomier-Layrargues G, Infante-Rivard C, et al. Propranolol for the prevention of recurrent variceal haemorrhage: a controlled trial. *Hepatology* 1986; **6:** 1239–43.
30. Westaby D, Melia W, Hegarty J, Gimson AES, Stellon AJ, et al. Use of propranolol to reduce the rebleeding rate during injection sclerotherapy prior to variceal obliteration. *Hepatology* 1986; **6:** 673–75.
31. Bosch J, Mastai R, Kravetz D, et al. Effects of propranolol on azygos venous blood flow and hepatic and systemic hemodynamics in cirrhosis. *Hepatology* 1984; **4:** 1200–05.
32. Cales P, Braillon A, Jiron MI, Lebrec D. Superior portosystemic collateral circulation estimated by azygos blood flow in patients with cirrhosis. Lack of correlation with oesophageal varices and gastrointestinal bleeding. Effect of propranolol. *J Hepatology* 1984; **1:** 37–46.
33. Lebrec D, Bernuau J, Rueff B, Nouel O, Bouyges M, Benhamou JP. Propranolol in prevention of recurrent gastrointestinal bleeding in cirrhotic patients. *Lancet* 1981; i: 920–21.
34. Westaby D, MacDougall BRD, Williams R. Improved survival following injection sclerotherapy for oesophageal varices: final analysis of a controlled trial. *Hepatology* 1985; **5:** 827–31.
35. Fleig WE, Stange EF, Huneck R, et al. Prevention of recurrent bleeding in cirrhotics with recent variceal haemorrhage: prospective, randomized comparison of propranolol and sclerotherapy. *Hepatology* 1987; **7:** 355–61.

Quality criteria for early signals of possible adverse drug reactions

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The main function of the World Health Organisation's International Collaborative Programme on Drug Monitoring is to provide a reliable early warning of possible health hazards caused by medicines. Described here is an attempt to devise criteria that would produce a well-founded early signal of an adverse reaction on the basis of reports sent in by national collaborating centres and combined in the WHO database. To reduce the frequency of spurious associations (false-positive signals) it is suggested that publication be delayed until a few case-histories meeting the suggested criteria have been sent in. The criteria were tested retrospectively against early published case-reports on drug-associated agranulocytosis. 19 suspected associations were examined and a signal in the database was defined by there being three or more cases containing stipulated information about the patient and the treatment. The WHO database had reports on all the associations, suggested criteria for a signal being met in 15 instances. This signal was present when the first case was published in 7 instances and within three months of first publication in 1. Moreover, in 3 instances where publication came first the cases presented had been collected by a national drug monitoring centre. The WHO databank has the potential to provide doctors and scientists with signals which then should be evaluated in detail.

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Introduction

In an analysis of how serious new adverse drug reactions (ADR) were detected, Venning found that the first suspicions for 13 of 18 reactions were generated by observations made by single physicians who had submitted them as case-reports.[1,2] These reports were usually published in journals. Thus, observations made by astute physicians have a high sensitivity in detecting new associations. Venning also analysed the proportion of similar first reports of suspected ADR that were subsequently verified.[3] 35 of 47 (74%) were verified within 18 years. However, only 7 of the 19 reactions that were less well

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