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

Peter C. Hayes  Jill M. Davis  John A. Lewis  Ian A. D. Bouchier

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.


Methods
All suitable trials identified by July, 1989, were included (table 1). 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. 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 $\chi^2$ 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 beta-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 II—Results of meta-analysis over all studies

<table>
<thead>
<tr>
<th></th>
<th>Total patients</th>
<th>Patients who bled</th>
<th>Deaths from bleeding</th>
<th>Total mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>All trials</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>967</td>
<td>260</td>
<td>70</td>
<td>207</td>
</tr>
<tr>
<td>Control</td>
<td>910</td>
<td>391</td>
<td>114</td>
<td>256</td>
</tr>
<tr>
<td>% reduction (95% CI)</td>
<td>44 (35, 51)</td>
<td>42 (24, 56)</td>
<td>24 (10, 35)</td>
<td></td>
</tr>
<tr>
<td>Treatment effect (p)</td>
<td>&lt;0.0001</td>
<td>0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity</td>
<td></td>
<td>0.334</td>
<td>0.197</td>
<td></td>
</tr>
<tr>
<td>Primary prevention</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>402</td>
<td>50</td>
<td>21</td>
<td>86</td>
</tr>
<tr>
<td>Control</td>
<td>395</td>
<td>92</td>
<td>38</td>
<td>107</td>
</tr>
<tr>
<td>% reduction (95% CI)</td>
<td>47 (28, 61)</td>
<td>45 (10, 67)</td>
<td>22 (0, 39)</td>
<td></td>
</tr>
<tr>
<td>Treatment effect (p)</td>
<td>&lt;0.0001</td>
<td>0.017</td>
<td></td>
<td>0.052</td>
</tr>
<tr>
<td>Heterogeneity</td>
<td></td>
<td>0.379</td>
<td>0.058</td>
<td></td>
</tr>
<tr>
<td>Secondary prevention</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>565</td>
<td>210</td>
<td>49</td>
<td>121</td>
</tr>
<tr>
<td>Control</td>
<td>515</td>
<td>299</td>
<td>76</td>
<td>149</td>
</tr>
<tr>
<td>% reduction (95% CI)</td>
<td>39 (30, 46)</td>
<td>40 (17, 57)</td>
<td>25 (07, 40)</td>
<td></td>
</tr>
<tr>
<td>Treatment effect (p)</td>
<td>&lt;0.0001</td>
<td>0.002</td>
<td></td>
<td>0.009</td>
</tr>
<tr>
<td>Heterogeneity</td>
<td></td>
<td>0.005</td>
<td>0.421</td>
<td></td>
</tr>
<tr>
<td>Selected trials</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>464</td>
<td>122</td>
<td>50</td>
<td>91</td>
</tr>
<tr>
<td>Control</td>
<td>416</td>
<td>174</td>
<td>57</td>
<td>124</td>
</tr>
<tr>
<td>% reduction (95% CI)</td>
<td>46 (35, 57)</td>
<td>51 (27, 68)</td>
<td>34 (16, 48)</td>
<td></td>
</tr>
<tr>
<td>Treatment effect (p)</td>
<td>&lt;0.0001</td>
<td>0.0004</td>
<td></td>
<td>0.0007</td>
</tr>
<tr>
<td>Heterogeneity</td>
<td></td>
<td>0.073</td>
<td>0.447</td>
<td></td>
</tr>
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</table>

There were 1080 patients in the nineteen secondary prevention trials. Beta-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—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) 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. However, the exciting findings by Lebrec and co-workers that propranolol reduced the risk of rebleeding from oesophageal varices could not be replicated in a largely similar trial in the UK, 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, 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. 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 varices44 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. 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. 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


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. 18 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.


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.12 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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