Platelet Activity and Selective $\beta$-Blockade in Migraine Prophylaxis

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Migraine is associated with increased platelet activity and an incidence of cerebrovascular ischemic events. Because cerebrovascular events might result from platelet aggregation, enhancing platelet activity further in the treatment of migraine is not desirable. $\beta$-Adrenoceptor blockers effective in migraine prophylaxis include propranolol (nonselective) and metoprolol ($\beta_1$-selective), but it is uncertain how $\beta$-receptor subtype selectivity might influence platelet behavior in migraine. In 29 patients, comparable clinical responses were obtained with therapeutic doses during 1 month of treatment with propranolol, metoprolol, and the $\beta_1$-selective Li 32-468. Propranolol increased and metoprolol decreased platelet aggregation and ATP release, and the effect of Li 32-468 could be related to that of propranolol. These actions can be largely explained in terms of what is known of platelet $\beta$-receptors and therefore can be generalized to other effective $\beta$-blockers. Since altered platelet activity does not account for the efficacy of these agents in migraine, the actions of $\beta$-blockers on platelets should be considered as side effects. Those $\beta$-blockers inhibiting platelet activity should be preferred in migraine treatment, assuming equal efficacy, which implies the use of $\beta_1$-selective blockers.

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While migraine is ordinarily not a threatening disease, it might result in severe neurological damage. In some patients, whose susceptibility is difficult to predict, migraine is a risk factor for stroke. Platelet activation, with release of vasoconstrictor substances accompanied by embolization of platelet aggregates, is viewed as an important cause of stroke. Platelet activity is known to be altered in migraines, raised plasma $\beta$-thromboglobulin and serotonin levels indicate increased activity, and circulating platelet microaggregates are abundant. These facts suggest that drug therapy for migraine aimed at reducing platelet activity has a rational basis.

Propranolol is highly effective in migraine prophylaxis; in the past, it has been considered a first-line therapy. In high doses (640 mg daily), it has been reported to inhibit platelet activity and thromboxane generation, thus establishing a link between effective treatment and the platelet theory of migraine causation. But platelets possess $\beta$-receptors with characteristics of the $\beta_1$-subtype. Blockade of these receptors would be expected to release stimulation mediated by platelet $\alpha$-receptors and enhance, rather than inhibit, platelet activity. Propranolol is a nonselective $\beta$-blocker and would therefore inhibit $\beta_2$-receptors.

Other $\beta$-adrenoceptor blockers are also useful in migraine prophylaxis, efficacy being restricted to those without partial agonist activity but unrelated to $\beta$-receptor subtype selectivity. Metoprolol, a $\beta_1$-selective blocker without partial agonist activity, is significantly better than placebo, and controlled trials have found that it and propranolol have similar efficacy. Li 32-468 is a recently developed $\beta$-blocker also without partial agonist activity, and it has high $\beta_1$-selectivity in doses of <6 mg. These three drugs are therefore useful for studying effects of selective $\beta$-blockade in migraine. We administered each to migraine patients in comparable therapeutic doses and examined how platelet activity was altered.

Subjects and Methods

Twenty-nine patients took part in the comparative studies, 11 in a propranolol vs. metoprolol study and 18 in a propranolol vs. Li 32-468 study. All gave informed consent in terms approved by the Charing Cross Hospital Ethical Committee. They were selected for unequivocal diagnoses of classic or common migraine, with attacks recognized for at least 2 years and occurring at the time of entry two to five times per month. Symptomatic and other drug therapies were strictly limited to paracetamol (acetaminophen) and codeine. Good compliance with the study medications was confirmed from patients’ assertions and counts of tablets returned.

Propranolol vs. Metoprolol Comparative Study

The 11 patients were 18–45 (mean 41) years old; five had classic and six had common migraine. This study with two established effective drugs was organized as a double-blind crossover comparison. Each drug was taken for 4–5 weeks, 40 mg propranolol t.i.d. and 50 mg metoprolol t.i.d., and were approximately equivalent in $\beta_1$-blocking effect. The two drugs were formulated in matching tablets, and the order of treatment periods was random, with propranolol given first in four patients and metoprolol first in seven. Run-in and washout periods (each lasting 4 weeks), without placebo, preceded the first and second treatments.
During the four periods of the study, patients maintained diary cards indicating the days that they were affected by migraine attacks and the severity of symptoms scored on a three-point scale based on the extent of curtailment of routine daily activities (not at all, partial, and complete). A symptom score for each period was derived by adding all severity scores recorded in that period and correcting for 28 days (sum-of-severities score).²² Platelet aggregation and secretion (ATP release) were measured at the end of every period. Before venous sampling for this purpose, the last dose was omitted so that peak activity of the drug was not present.

Propranolol vs. Li 32-468 Comparative Study

This study involved one established effective drug and another of unknown effect in migraine. Furthermore, Li 32-468 was available continuously for only 1 month in these clinical trials because of incomplete toxicological development, which severely restricted the experimental design. Also, the optimal dose (2 or 4 mg) was not known. Patients were therefore selected for this study who were already on 60–320 (mean 159) mg propranolol daily as prophylactic treatment for migraine for periods ranging from 2 months to 3 years (mean 11.2 months). Eighteen patients aged 25–52 (mean 38) years took part; five had classic and 13 had common migraine. After 1 month of observation on their original therapy, Li 32-468 was openly substituted for propranolol. At the time of initial observation of efficacy, the dosages given were 2 mg b.i.d. in the first seven patients (Group 1) and 4 mg b.i.d. in the next 11 (Group 2). Li 32-468 was given for 4–5 weeks, and afterward, patients reverted to their original regimen of propranolol.

Clinically, these patients were assessed by their overall subjective impressions of Li 32-468 in relation to their original propranolol therapy. More objective (and, in particular, double-blind) assessments of this drug were not possible. Platelet aggregation and ATP release were studied in eight patients, four each from Groups 1 and 2, who were selected randomly. Mean doses of propranolol and durations of treatment in these eight were 180 mg daily for 19.5 months in Group 1 and 210 mg daily for 9.2 months in Group 2.

Platelet Activity Tests

Platelet aggregation was measured in vitro by the optical principle, using infrared light transmission in a Payton two-channel Lumi-aggregation module (model 1000; Buffalo, New York). ATP release was measured simultaneously in one channel by addition of firefly luminous organ extracts (luciferin-luciferase; Sigma Chemical Co., St. Louis, Missouri), which respond dose-dependently to ATP by producing visible light.

Peripheral venous blood was collected into 3.8% sodium citrate. Platelet-rich plasma (PRP) and platelet-poor plasma (PPP) were separated by centrifugation, and the platelet count of PRP was adjusted by dilution with PPP to within the range of 240–260 x 10⁷/l.

ADP and epinephrine were used to induce aggregation. A minimum of five concentrations ranging from 10⁻³ M to 10⁻² M were used in each test to produce dose–response curves. Many indexes of aggregation have been proposed, some with varying relevance to our study. We used the following based on previously recommended measurements: 1) as indicators of primary aggregation: height of the aggregation curve at 30 seconds (AGG 30) and slope of the primary curve (SLOPE), 2) as indicators principally of secondary aggregation: maximum height of the secondary curve (SEC PEAK) and height of the aggregation curve at 60 seconds minus the height at 30 seconds (60–30), and 3) for ATP release: peak height of the ATP release curve related to a curve derived from standard ATP concentrations.

These measurements for ADP and epinephrine gave 10 measurements altogether. Comparisons between different sampling occasions were based on readings from the dose–response curves: for aggregation, for an inducer concentration of 3.75 x 10⁻³ M (approximately midway between threshold and maximal); for ATP release, for 1 x 10⁻³ M (giving maximal or near-maximal secretion).

Results

Propranolol vs. Metoprolol Study

There were no significant differences between measurements of platelet aggregation and ATP release after run-in and washout, nor were there any consistent trends. Therefore, neither drug given as first therapy had a measurable long-term effect that might carry over into the second treatment period.

After 1 month of propranolol treatment, all measurements of aggregation increased relative to the period immediately before treatment. The effect was more marked with epinephrine than with ADP (Table 1). ATP release increased with both inducers. After 1 month of metoprolol treatment, all measurements of aggregation in response to ADP, and three of four in response to epinephrine, decreased (Table 1). ATP release decreased in response to both inducers, and these changes were significant (epinephrine: p < 0.05; ADP: p < 0.02; Student's t test). All measurements of aggregation were greater after propranolol than after metoprolol treatment; AGG 30, SLOPE, and 60–30 were significantly greater in response to epinephrine (Table 1). ATP release was greater after propranolol than after metoprolol, and this was significant in response to both inducers (Table 1).

Both drugs were associated with reduced sum-of-severities scores, propranolol by 26%, from a total of 177 before to 131 during treatment, and metoprolol by 16%, from 174 to 146. Though the observed response to propranolol was greater, the difference was not significant, and in any case, these measurements do not justify comparisons. Clinical response to either drug was unrelated to individual changes in platelet activity.
Propranolol vs. Li 32-468 Study

Clinical response to Li 32-468 in Group 1 (2 mg b.i.d.) was "as good as propranolol" in two patients and "not as good" in four patients; one patient in Group 1 suffered an adverse reaction (sinus tachycardia). In Group 2 patients (4 mg b.i.d.), nine rated Li 32-468 "better than or as good as propranolol" and two reported a worsening of symptoms. Overall, 11 patients (61%) found Li 32-468 at least as good as propranolol. This was the best judgment possible in the circumstances, and on this basis, with the higher dose of Li 32-468, the two drugs were comparable.

The indexes of platelet aggregation were consistently lower in Group 1 than in Group 2 after Li 32-468 treatment (Table 2). Measurements of change in ATP release varied widely in baseline measurements obtained during propranolol therapy. In the two groups together, all but one measurement of aggregation and both of ATP release showed reductions after Li 32-468 compared with previous levels during propranolol treatment (Table 2). None of these differences was significant, but the overall trend was consistent and more marked with the lower dose of Li 32-468.

Discussion

Therapeutic doses of propranolol and metoprolol have opposite effects on platelet activity in migraineurs: propranolol increased and metoprolol decreased measurements of both aggregation and secretion. These effects were observed consistently in response to the two inducing agents. Platelet aggregation measurements with Li 32-468 at 2 and 4 mg b.i.d. are more difficult to interpret because Li 32-468 treatment followed propranolol without a washout period. That the trend toward reduction in aggregability during Li 32-468 treatment was small but more marked with the lower dose suggests that the increased platelet activity during propranolol treatment was being partially replaced by a similar effect of Li 32-468.

Recent evidence suggests that platelet β-receptors31,32 are of the β2 subtype.19,33 Better established are α2-receptors on platelets,34-37 through which endogenous catecholamines reduce platelet cAMP levels and thereby promote platelet activation. Platelet cAMP is believed to be the principal modulator of platelet responsiveness in vivo.38-40; cAMP levels are maintained thereby promote platelet activation. Platelet cAMP is believed to be the principal modulator of platelet responsiveness in vivo.38-40; cAMP levels are maintained by the enzyme adenylate cyclase, the activity of which is governed by the balance between α2- and β2-receptor stimulation.41

On this basis, our findings can be largely explained. Propranolol, a potent and nonselective β-blocker, inhibits the β2-receptors on platelets, and by releasing α2-receptor-mediated activity, it increases the sensitivity of platelets to endogenous catecholamines.42 This adequately accounts for increased platelet aggregation and ATP release, particularly with epinephrine induction, in migraineurs taking propranolol. The observed effects of Li 32-468 also follow this reasoning if this drug is a less potent β2-blocker than propranolol and the doses used. There is some evidence for this, but unfortunately, Li 32-468 loses its selectivity at higher doses.26 Metoprolol, which is much less active at β2-receptor sites, would not have this effect. Actual inhibition of platelet activity is more difficult to explain, but receptor mediation is unlikely because both epinephrine- and ADP-induced activation were blocked.

Substantial support for our findings comes from recent evidence that, at doses similar to those we used, propranolol decreases and metoprolol increases cAMP levels.43 In the past, propranolol has been thought of as an antiplatelet drug.44-46 but this is a misconception except perhaps at high doses. In vitro, propranolol in concentrations exceeding usual therapeutic levels has

| Table 1. Propranolol vs. Metoprolol Study: Effects of Propranolol and Metoprolol on Platelet Aggregation and Platelet ATP Release in 11 Patients with Migraine |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
|                                  | P                               | M                               | P vs. M                          | p                              |
| Epinephrine                      |                                  |                                  |                                  |                                |
| AGG 30                           | 64 ± 17                         | 74 ± 21                         | 60 ± 34                          | 46 ± 19                         | P>M                             | <0.02                           |
| SLOPE                            | 92 ± 24                         | 95 ± 22                         | 82 ± 43                          | 73 ± 31                         | P>M                             | <0.05                           |
| SEC PEAK                         | 195 ± 82                        | 228 ± 49                        | 227 ± 42                         | 216 ± 74                        | P>M                             | NS                              |
| 60–30                            | 60 ± 18                         | 72 ± 23                         | 53 ± 29                          | 55 ± 20                         | P>M                             | <0.05                           |
| ATP release                      | 1,030 ± 550                     | 1,373 ± 873                     | 1,346 ± 590                      | 700 ± 400                       | P>M                             | <0.05                           |
| ADP                              |                                  |                                  |                                  |                                |
| AGG 30                           | 88 ± 19                         | 91 ± 19                         | 94 ± 25                          | 84 ± 22                         | P>M                             | NS                              |
| SLOPE                            | 149 ± 36                        | 153 ± 38                        | 156 ± 53                         | 139 ± 41                        | P>M                             | NS                              |
| SEC PEAK                         | 214 ± 41                        | 223 ± 39                        | 211 ± 43                         | 204 ± 41                        | P>M                             | NS                              |
| 60–30                            | 91 ± 30                         | 100 ± 39                        | 92 ± 29                          | 89 ± 24                         | P>M                             | NS                              |
| ATP release                      | 1,188 ± 935                     | 1,492 ± 1,990                   | 1,571 ± 860                      | 634 ± 300                       | P>M                             | <0.05                           |

Data are mean ± SD in arbitrary units of light transmission except for platelet ATP release, where data are mean ± SD in picomol/500 μl platelet-rich plasma. p calculated by Student's t test. P, propranolol; M, metoprolol; AGG 30, height of aggregation curve at 30 seconds; SLOPE, slope of primary curve; SEC PEAK, maximum height of secondary curve; 60–30, height of aggregation curve at 60 seconds minus height at 30 seconds; ATP release, peak height of ATP-release curve.
be found to inhibit platelet aggregation.\textsuperscript{17-19} In vitro exposure to drugs might not reflect situations in vivo,\textsuperscript{49} but 640 mg propranolol daily administered over pro-
longed periods did inhibit platelet aggregation in hypertensive patients.\textsuperscript{18} In that study, plasma concen-
trations of propranolol were presumably relatively high, and sympathetic tone was abnormal.

Although treatment periods in our study were short, plasma concentra-
tions of propranolol and metoprolol were presumably relatively high, and sympathetic tone was abnormal.

Our study was not primarily concerned with assessing efficacy, but both propranolol and metoprolol have been effective in therapeutic trials in migraine.\textsuperscript{17-20,24} Although treatment periods in our study were short, this efficacy was reflected in our patients, and 11 of 18 patients (61%) on Li 32-468 judged it comparable in efficacy to propranolol. Thus, the clinical effect of platelet inhibition appears to relate to \(\beta\)-selectivity. There is a need to review the place in migraine treatment of \(\beta\),-blockers of known efficacy because it is strongly arguable that one of these, and not a nonselective agent like propranolol, should be first-line therapy.

\begin{table}
\centering
\begin{tabular}{|l|c|c|c|c|c|c|}
\hline
 & \multicolumn{2}{|c|}{Group 1} & \multicolumn{2}{|c|}{Group 2} & \multicolumn{2}{|c|}{Groups 1 and 2} \\
\hline
 & P & L & P & L & P & L \\
\hline
Epinephrine & & & & & & \\
AGG 30 & 90 ± 28 & 49 ± 26 & 78 ± 35 & 88 ± 22 & 84 ± 30 & 68 ± 30 \\
SLOPE & 59 ± 22 & 41 ± 24 & 51 ± 12 & 50 ± 23 & 55 ± 17 & 45 ± 23 \\
SEC PEAK & 158 ± 89 & 149 ± 51 & 206 ± 33 & 188 ± 38 & 190 ± 53 & 168 ± 47 \\
60 - 30 & 56 ± 16 & 38 ± 19 & 82 ± 41 & 70 ± 18 & 69 ± 32 & 54 ± 24 \\
ATP release & 304 ± 317 & 752 ± 119 & 1,096 ± 700 & 673 ± 396 & 950 ± 634 & 713 ± 330 \\
\hline
ADP & & & & & & \\
AGG 30 & 95 ± 11 & 72 ± 18 & 91 ± 31 & 89 ± 13 & 93 ± 22 & 80 ± 17 \\
SLOPE & 147 ± 14 & 114 ± 38 & 141 ± 48 & 135 ± 26 & 144 ± 33 & 124 ± 32 \\
SEC PEAK & 185 ± 28 & 159 ± 6 & 206 ± 17 & 202 ± 21 & 195 ± 24 & 181 ± 27 \\
60 - 30 & 85 ± 20 & 69 ± 28 & 73 ± 39 & 92 ± 20 & 79 ± 30 & 80 ± 26 \\
ATP release & 528 ± 620 & 581 ± 462 & 1,122 ± 1,096 & 660 ± 634 & 818 ± 858 & 620 ± 501 \\
\hline
\end{tabular}
\caption{Propranolol vs. Li 32-468 Study: Effects of Propranolol and Li 32-468 on Platelet Aggregation and Platelet ATP Release in 8 Patients With Migraine}
\end{table}

Data are mean ± SD in arbitrary units of light transmission except for platelet ATP release, where data are mean ± SD in picomol/500 \(\mu\)l platelet-rich plasma. \(n = 4\) patients for each group.

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