CNS-related performance and haemodynamics of metoprolol-Oros and propranolol after single and 3 days dosing in healthy volunteers

A. L. VAN STEVENINCK, M. S. M. PIETERS, H. C. SCHOEMAKER, D.D. BREIMER & A. F. COHEN
Centre for Human Drug Research, University Hospital, Rijnsburgerweg 10, P.O. Box 9600, 2300 RC Leiden,
The Netherlands

- 1 The effects of metoprolol-Oros 14/190 once daily, propranolol 80 mg twice daily and temazepam 10 mg once daily on central nervous system (CNS) related performance and haemodynamic variables were evaluated in a double-blind, randomized, placebo controlled, crossover study in 12 healthy volunteers. Drugs were administered for 3 consecutive days except for temazepam, which was administered on days 1 and 3 only. Treatment effects were evaluated at 0, 2, 5 and 8 h on days 1 and 3.
- 2 Neither β -adrenoceptor blocker had significant effects in a battery of tests after single or 3 days dosing. Temazepam caused a decrease in saccadic peak velocity of $37.4^\circ \text{ s}^{-1}$ (95% CI: 6.0, 68.9) at 2 h and an increase of auditory reaction times of 11.5 ms (0.2, 22.8) at 8 h on day 1. No significant effects of temazepam were detected on day 3.
- 3 Both β -adrenoceptor blockers reduced exercise heart rate. Peak effects were measured at 2 h 40 min after propranolol but not metoprolol-Oros (difference, day 1: 20 (11, 29) beats min^{-1} , day 3: 13 (8, 19) beats min^{-1}). Both β -adrenoceptor blockers significantly reduced baseline exercise heart rate on day 3. Compared with day 1, metoprolol-Oros caused larger reductions of exercise heart rate at all times on day 3.
- 4 Metoprolol-Oros and propranolol caused similar reductions of systolic- and diastolic blood pressure on days 1 and 3. Temazepam caused a small reduction in diastolic blood pressure at 5 h 40 min on day 1 but was otherwise devoid of haemodynamic effects.
- 5 Results from this study indicate no evident effects of metoprolol-Oros 14/190 once daily and propranolol 80 mg twice daily on CNS-related performance after 1 and 3 days dosing.

Keywords metoprolol sustained release propranolol psychomotor-performance blood pressure exercise heart rate

Introduction

β -adrenoceptor antagonists are among the most frequently prescribed drugs for treatment of cardiovascular diseases. Although β -adrenoceptor blockers are generally well tolerated their use is occasionally limited by side effects. Tiredness, fatigue and lethargy are among the most common adverse events leading to discontinuation of β -adrenoceptor blocker therapy. Although these complaints are believed to result mainly from decreases in cardiac output and altered muscle metabolism, CNS-effects may contribute (McDevitt & MacConnachie, 1988). Other complaints indicative of central effects of β -adrenoceptor blockers include light-headedness, sleep disturbances, changes in mood and occasionally psychi-

atric symptoms. In view of these adverse effects many studies have been performed to evaluate potential effects of β -adrenoceptor blockers on CNS-related performance. However, the literature on CNS-related side effects of β -adrenoceptor blockers remains largely inconclusive. Comparison of results from different studies is difficult due to the variety of methods and the different drugs and dosages used. Such difficulties may partly be solved by concomitant assessment of the level of β -adrenoceptor blockade and by using methods which are in some way validated with respect to their sensitivity in revealing drug induced impairment. With a recent review indicating no tests with specific sensitivity to CNS effects of

β -adrenoceptor blockers (Dimsdale *et al.*, 1989), the choice of methods remains largely arbitrary. However, the use of tests which have been validated against low doses of sedative drugs and the incorporation of a low dose active control in studies might be recommended.

Sustained release formulations have been introduced for several β -adrenoceptor blockers in order to obtain therapeutic efficacy with once daily dosing, while avoiding high plasma levels which could be associated with side effects. The efficacy of sustained release β -adrenoceptor blockers, including metoprolol, has been demonstrated in several studies in hypertensive patients (Carruthers *et al.*, 1990; McInnes & Brodie, 1988a; Serlin *et al.*, 1983). Also, subjective tolerability of sustained release metoprolol appears to be similar to or slightly better than conventional β -adrenoceptor blocker therapy (Dimenas & Dahlöf, 1990). However, thus far no studies of potential effects of sustained release β -adrenoceptor blockers on objective indicators of performance have been published. Besides the potential beneficial effects, the possibility of deteriorated performance the morning after a dose of sustained release metoprolol should also be considered. Detrimental effects of β -adrenoceptor blockers on the quality of sleep have been reported (McDevitt & MacConnachie, 1988) and daytime performance might suffer when higher plasma levels are maintained at night.

Metoprolol-Oros 14/190 is an osmotically driven drug delivery system (Theeuwes *et al.*, 1985) containing 190 mg metoprolol-fumarate which is released at a constant rate of approximately 14 mg h^{-1} for 8 h with a total release time of 24 h. Compared with conventional tablets a relative bioavailability around 60% has been demonstrated for metoprolol-Oros, while fluctuations in plasma levels were reduced (Feliciano *et al.*, 1990). However, the relative pharmacodynamic bioavailability, as assessed by exercise heart rate reductions, was found to be similar to conventional tablets.

This article describes a study of CNS-related performance and haemodynamic effects of metoprolol-Oros after 1 and 3 days dosing in healthy volunteers. In this study propranolol 80 mg twice daily served as a control for central- and haemodynamic effects. Temazepam 10 mg once daily was used as an active control for sedative drug effects. Tests used to evaluate CNS-related performance and subjective effects were; adaptive tracking (eye-hand coordination), analysis of smooth pursuit and saccadic eye movements, auditory reaction times, a visual search task, a word memory test and visual analogue scales. Although effects of β -adrenoceptor blockers have previously been detected using similar methods (Dimsdale *et al.*, 1989), no single test has demonstrated consistent results. However, the adaptive tracking test, eye movement analysis and visual analogue scales have previously been validated for increasing doses of temazepam (Steveninck *et al.*, 1991).

Methods

Twelve healthy non smoking volunteers (six female, six male, aged 19 to 29 years, weights 55 to 91 kg) were

recruited after formal approval of the study protocol by the Ethics Review Board of the Leiden University Hospital. All volunteers received a full medical examination and gave written informed consent before study entry.

Trial design

The study was a double-blind, placebo controlled cross-over experiment with treatment order randomized according to three 4×4 latin squares, balanced for preceding treatments. Drugs were administered for 3 consecutive days with washout periods of 4 days between occasions. Pharmacodynamic assessments were made on days 1 and 3, before and 2, 5 and 8 h after intake of medications. Study medications were: metoprolol-Oros 14/190 once daily, propranolol 80 mg twice daily, temazepam 10 mg once daily and placebo, all drugs being racemic mixtures. Temazepam was administered on days 1 and 3 only. It was replaced by placebo on the second day in order to avoid unnecessary sedation of subjects where no tests were scheduled. A double dummy technique, with identical placebos for metoprolol-Oros and for the capsules containing propranolol or placebo, was used for blinding of treatments. Six subjects were tested per day using staggered time schedules. Intake of medication was at 09.00 h for the first subject, followed at 20 min intervals by the other subjects. The second dose of propranolol or placebo was administered 9 h later on days 1 and 2. Medications were administered orally with 150 ml water. A single blood sample was obtained after the second test session to verify correct administration of medications.

Pharmacodynamics

Performance tests were executed in a quiet laboratory with subdued lighting. Tests were practised six times in two training sessions prior to the actual study. Each test session lasted 40 min and consisted of the following sequence of tests: 1) adaptive tracking, 2) smooth pursuit and saccadic eye movements, 3) auditory reaction times, 4) computerized visual search task, 5) word memory test and 6) visual analogue lines. Blood pressure and exercise heart rate were assessed at the end of each session of performance tests.

The adaptive tracking test was performed as described by Borland & Nicholson (1974), using customised equipment and software (Hobbs & Strutt, Beckenham, Kent, BP 3PQ U.K.). The average performance and the standard deviation of scores over 10 min were used for analysis. Eye movements were recorded using a micro-computer based system for sampling and analysis (Steveninck *et al.*, 1989). For signal registration disposable silver-silver chloride electrodes (Medicotest N-00-S, Olstykke, Denmark) were applied after skin resistance had been reduced to less than 5 kOhms. Head movements were prevented using an ophthalmological head support. Smooth pursuit eye movements were recorded with target frequencies ranging from 0.3 to 1.1 Hz and total amplitudes corresponding to 40 degrees of eyeball rotation. Four cycles were recorded for each stimulus frequency. The percentage of time spent in smooth pursuit was calculated for all frequencies and the average

of these percentages was used as the final parameter. Saccadic eye movements were recorded for stimulus amplitudes of 10, 15 and 20 degrees to either side with interstimulus intervals varying randomly between 4 and 8 s. Ten saccades were recorded for each amplitude and the average peak velocity, reaction time and accuracy were calculated after removal of artifacts. Auditory reaction times and word memory were tested using the 'FEPSY' software package (Instituut voor Epilepsiebestrijding, 2103 SW Heemstede, The Netherlands). Auditory reaction times were calculated as the average of 20 left- and 20 right-handed responses. Speed and accuracy of immediate recall were tested by asking subjects to identify as quickly as possible the position of a word in an original sequence of six words. Test parameters were the average reaction time and number of correct responses of 24 runs. A computerized visual search task was originally included in the battery of tests. However, because a lack of parallel test-screens caused large learning effects, results of this test were not analyzed. Visual analogue lines were used to quantify subjective effects on alertness, mood and calmness as described by Bond & Lader (1974). No analyses of single visual analogue scales were performed. On every third day of testing, specific enquiry was made about complaints of restless sleep, frequent awakenings or vivid dreaming during the preceding two nights. Responses were reported for later comparisons between treatments.

Blood pressures were measured after 3 min rest with subjects seated, using an automatic oscillometric blood pressure monitor (Nihon Kohden, MPV 7201). Sub-maximal exercise testing was performed on a bicycle ergometer (Lode-Excalibur, Lode, Groningen, The Netherlands) after prior assessment of individual work loads resulting in a heart rate of 150 beats min^{-1} . Cycling started at 100 W and the workload was subsequently increased in three steps of thirty seconds to the predetermined level which was kept for another 1.5 min. A single chest lead was used for cardiac monitoring during the exercise test and heart rates were read from the monitor at the end of the test.

Statistical analysis

Results were analyzed for both study days separately by repeated measures analysis of variance with the within-subject factors time and treatment. In case of significant treatment effects or treatment $\times$ time interaction in the overall analysis, differences at individual time points were sought with paired *t*-tests. Comparisons between days 1 and 3 were made in case of significant drug effects on either study day. No corrections were made for differences at baseline because the inherent assumption that baseline values are predictive for the course of all subsequent measurements on days 1 and 3 did not seem justified whereas the procedure would add the random error in baseline values to all subsequent measurements. Separate correction for 'baseline values' on day 3 could not be performed because the *a priori* assumption was that continued dosing of β -adrenoceptor blockers might affect these values. Statistical analysis of complete data sets was performed with SPSS/PC + V4.0.1 (SPCC Inc., Chicago, Illinois, U.S.A.). In case of missing data the analysis was performed with BMDP Statistical

Software Inc., Los Angeles, U.S.A.) which, using a restricted maximum likelihood approach, is capable of analysing such unbalanced data sets. Missing data did not exceed 3% of the total number of observations for any parameter. Differences from placebo are reported with 95% confidence intervals in parentheses.

Results

All subjects completed the study. No serious side effects occurred following any of the treatments. Complaints of restless sleep, or nightly awakenings were reported three times after metoprolol-Oros, once after propranolol and twice after placebo.

Performance tests

Metoprolol-Oros and propranolol did not have significant effects in any of the performance tests. Temazepam caused a decrease in peak velocity of large amplitude saccades at 2 h on day 1 (difference from placebo: -37.4 ($-6.0, -68.9$) $^{\circ}\text{s}^{-1}$, Figure 1). A similar decrease of saccadic peak velocity occurred on day 3 (Figure 2) but

Figure 1 Average changes in peak velocity of $\pm 20^{\circ}$ -saccades; day 1. $\circ$ = placebo, $\blacktriangledown$ = metoprolol-Oros 14/190 once daily, $\blacksquare$ = propranolol 80 mg twice daily, $\bullet$ = temazepam 10 mg. * temazepam different from placebo, $P < 0.05$.

Figure 2 Average changes in peak velocity of $\pm 20^{\circ}$ -saccades; day 3. $\circ$ = placebo, $\blacktriangledown$ = metoprolol-Oros 14/190 once daily, $\blacksquare$ = propranolol 80 mg twice daily, $\bullet$ = temazepam 10 mg.

Figure 3 Average changes in subjective alertness; day 1.
○ = placebo, ▼ = metoprolol-Oros 14/190 once daily,
■ = propranolol 80 mg twice daily, ● = temazepam 10 mg.

Figure 4 Average changes in subjective alertness; day 3.
○ = placebo, ▼ = metoprolol-Oros 14/190 once daily,
■ = propranolol 80 mg twice daily, ● = temazepam 10 mg.

this did not reach statistical significance. However, the average baseline values on day 3 appeared to be increased for temazepam, which may have caused the lack of a significant effect. Effects of temazepam were not found for saccades with amplitudes of 10 and 15 degrees. An effect of temazepam on auditory reaction times occurred 8 h after drug intake on day 1 (reaction times increased

by 11.5 (0.2, 22.8) ms). No significant effects were detected in any of the other tests.

Subjective effects

No significant effects on subjective alertness, mood or performance were detected following any of the treatments. Although subjective alertness appeared slightly better following both β -adrenoceptor blockers on day 1 (Figure 3, $P = 0.055$), the effect was not apparent after 3 days dosing. Similar to saccadic peak velocity, subjective alertness at baseline on day 3 appeared to be increased for temazepam, with an apparent decline after intake of the drug (Figure 4).

Haemodynamic effects

Compared with placebo, both β -adrenoceptor blockers caused significant reductions in exercise heart rate at all times after intake of the first dose (Table 1). Following metoprolol-Oros, β -adrenoceptor blockade increased gradually over the first day. Exercise heart rates on the third day of dosing were significantly lower at all times compared with corresponding timepoints on day one (Table 1). Following propranolol, β -adrenoceptor blockade was more variable, with peak effects measured at 2 h 40 min after drug intake on both test days (difference from metoprolol-Oros; 20 (11, 29) beats min^{-1} and 13 (8, 19) beats min^{-1} , respectively on days 1 and 3). On day 3 baseline exercise heart rates were significantly lowered by both β -adrenoceptor blockers. Compared with placebo, significant reductions of systolic- and diastolic blood pressure occurred following both β -adrenoceptor blockers (Table 2). On the third day, only propranolol caused a significant reduction of systolic blood pressure at baseline while effects of metoprolol-Oros were larger at 8 h 40 min after intake. Diastolic blood pressures were not significantly different between metoprolol-Oros and propranolol although, compared with placebo, the effects of propranolol reached significance earlier on day 1. Neither β -adrenoceptor blocker caused significant reductions of diastolic blood pressure at baseline on the third day. Temazepam caused a small reduction in diastolic blood pressure at 5 h 40 min on day 1 but was otherwise devoid of haemodynamic effects.

Table 1 Exercise heart rate (beats min^{-1}); change from placebo (95% CI of difference)*

		Metoprolol-Oros	Propranolol	Temazepam
Day 1	0 h	2 (-4, 7)	0 (-3, 2)	1 (-2, 3)
	2 h 40	-15 (-21, -8)	-34 (-44, -25) [†]	3 (-1, 7)
	5 h 40	-24 (-30, -18)	-29 (-35, -23)	1 (-3, 5)
	8 h 40	-24 (-30, -19)	-30 (-52, -8)	0 (-2, 3)
Day 3	0 h	-20 (-28, -12) [‡]	-17 (-24, -11) [§]	1 (-2, 5)
	2 h 40	-27 (-33, -22) [‡]	-40 (-46, -34) [†]	0 (-2, 2)
	5 h 40	-30 (-35, -25) [‡]	-30 (-37, -24)	0 (-3, 4)
	8 h 40	-30 (-34, -26) [‡]	-25 (-32, -18)	0 (-3, 4)

*). Differences and confidence intervals have been rounded to integers.

[†]) Propranolol different from metoprolol-Oros ($P < 0.01$).

[‡]) Metoprolol-Oros day 3 different from metoprolol-Oros day 1 ($P < 0.01$).

[§]) Propranolol day 3 different from propranolol day 1 ($P < 0.01$).

Table 2 Blood pressure (mmHg); change from placebo (95% CI of the difference)*

		<i>Metoprolol-Oros</i>	<i>Propranolol</i>	<i>Temazepam</i>
<i>Systolic blood pressure (mmHg)</i>				
Day 1	0 h	-4 (-13, 5)	-4 (-13, 5)	-4 (-11, 3)
	2 h 40 min	-8 (-16, -1)	-13 (-27, 0)	-3 (-12, 7)
	5 h 40 min	-12 (-19, -5)	-9 (-18, -1)	-3 (-10, 4)
	8 h 40 min	-8 (-18, 2)	-12 (-22, -3)	-2 (-7, 4)
Day 3	0 h	-5 (-12, 2)	-11 (-19, -3) [†]	-3 (-13, 8)
	2 h 40 min	-12 (-20, -4)	-11 (-23, 0)	0 (-6, 7)
	5 h 40 min	-12 (-20, -3)	-11 (-20, -2)	0 (-12, 13)
	8 h 40 min	-12 (-22, -3)	-7 (-15, 0) [‡]	-2 (-9, 5)
<i>Diastolic blood pressure (mmHg)</i>				
Day 1	0 h	-1 (-5, 3)	1 (-5, 8)	-1 (-4, 3)
	2 h 40 min	-4 (-9, 1)	-8 (-14, -2)	-1 (-6, 4)
	5 h 40 min	-6 (-11, -2)	-8 (-12, -4)	-3 (-6, -1)
	8 h 40 min	-6 (-9, -3)	-7 (-12, -3)	-1 (-5, 2)
Day 3	0 h	-1 (-9, 6)	-3 (-9, 3)	0 (-7, 8)
	2 h 40 min	-5 (-9, -1)	-7 (-12, -1)	-2 (-7, 4)
	5 h 40 min	-8 (-13, -3)	-9 (-13, -5)	-1 (-5, 3)
	8 h 40 min	-8 (-11, -5)	-9 (-13, -5)	-1 (-4, 3)

*) Differences and confidence intervals have been rounded to integers.

†) Propranolol day 3 different from propranolol day 1 ($P < 0.01$).‡) Propranolol different from metoprolol-Oros ($P < 0.05$).

Discussion

Sustained release β -adrenoceptor blockers have been developed in order to enhance compliance to therapy while reducing side-effects which may be related to high plasma concentrations. Although there has been evidence for a reduction of side-effects related to peripheral β -adrenoceptor blockade such as exercise induced fatigue (Blomqvist *et al.*, 1988; Dimenas *et al.*, 1990a) and bronchoconstriction (Löfdahl *et al.*, 1988), there have been no indications of significant reductions in CNS-related side effects (Benfield *et al.*, 1986; Dimenas & Dahlof, 1990). However, studies thus far have focused on subjective tolerability of sustained release β -adrenoceptor blockers only (Dimenas *et al.*, 1990a, b; Houtzagers *et al.*, 1988). To our knowledge no studies have been published investigating their effects on objective indicators of performance.

Numerous studies have been performed to obtain objective evidence of central effects of immediate release β -adrenoceptor blockers. Various methods and different β -adrenoceptor blockers have been used, both in healthy volunteers and in patients. CNS-effects have been demonstrated in several studies but no unequivocal results have thusfar been obtained with any β -adrenoceptor blocker. In a recent review of 55 studies, only 17% of all observations were found to indicate impaired performance while 16% demonstrated improvement (Dimsdale *et al.*, 1989). Although the sensitivity of methods will obviously affect results, most studies did not include a reference drug with known effects on tests used in the study. Where reference drugs have been used, the relative potency of the drug should be considered. Obviously, a reference drug which causes extensive impairment of performance will not validate results when minimal drug

effects are sought. The lack of consistent data on the dynamics of central side-effects and the absence of clear relationships between effects and plasma levels make it hard to infer the effects of continuous β -adrenoceptor blockade from available data on straight release drugs. The focus of our study therefore was to assess potential CNS-related side effects of metoprolol-Oros using objective tests of performance. Because CNS-effects of β -adrenoceptor blockers have proved hard to detect, a low dose sedative and a highly lipophilic straight release β -adrenoceptor blocker were incorporated as controls.

Results from our study showed no evidence for changes in performance following metoprolol-Oros 14/190 or propranolol 80 mg twice daily after 1 and 3 days dosing. Although there was a tendency for increased subjective alertness following both β -adrenoceptor blockers on day 1, there was no evidence for such an effect after 3 days dosing. As effects of 10 mg temazepam were limited to changes in saccadic peak velocity, the possibility of a type-II statistical error as well as potential confounding factors should be considered when judging β -adrenoceptor blocker effects from these results. In a previous study effects of a 10 mg dose of liquid temazepam on saccadic peak velocity, smooth pursuit eye movements and subjective alertness were clearly demonstrated up to 150 min after drug intake, while the effects of 5 mg liquid temazepam on saccadic peak velocity and subjective alertness were just detectable (Steveninck *et al.*, 1991). As no other studies have demonstrated effects of benzodiazepines at comparably low doses, a type-II statistical error due to an overall lack of sensitivity of the tests used would seem unlikely. Crystalline temazepam was used in the current study in order to have capsules identical to those used for administration of propranolol and placebo. A relatively low dose was deliberately chosen

because the effects to be expected from metoprolol would be small. The use of crystalline temazepam has probably resulted in a slow and variable absorption with ensuing low plasma levels, which would explain the absence of detectable effects in most tests. However, the study design and conditions during the conduct of the study may also have induced variability in the results of performance tests. In retrospect, circumstances in this study (eight occasions, six subjects per day, a large number of performance tests and the arousal caused by bicycle exercise testing) may have reduced the sensitivity to small drug effects.

The lack of significant effects on saccadic eye movements after the second dose of temazepam appeared to result from differences at baseline as well as an increased overall variability. There were apparent increases in baseline values both for saccadic peak velocity (Figure 2) and for subjective alertness (Figure 4). In a previous validation study, these parameters have been shown to be highly sensitive indicators of sedative drug effects, with little variability in baseline values (Steveninck *et al.*, 1991). Possibly, treatment with temazepam on day 1 caused subjects to be more rested and hence more alert on day 3. As no baseline corrections were made in the statistical evaluation this would explain the apparent lack of temazepam effects on day 3.

Adverse effects on sleep have been reported following β -adrenoceptor blockers (McDevitt & MacConnachie, 1988). Although the incidence of insomnia was relatively low in a long-term surveillance study of metoprolol (The metoprolol surveillance study group, 1984), this may have been due to the use of insensitive methods or under-reporting with habituation to symptoms. Both subjective- and objective effects on sleep have been demonstrated for metoprolol with twice daily dosing (Kostis & Rosen, 1987) but not after single doses taken in the morning (Dimenas *et al.*, 1989). Consequently, more frequent disturbances of sleep and possibly deteriorated performance at morning might be expected following sustained release metoprolol due to elevated plasma levels at night. Although in our study complaints of disturbed sleep occurred most frequently following metoprolol-Oros, the incidence was low and did not allow adequate comparisons between treatments to be made. However, no evidence of deteriorated performance was found the morning after the second dose of metoprolol-Oros.

In general, comparisons between β -adrenoceptor blockers and across studies are complicated by the variety of methods and widely different doses used. Compatibility may be improved by studying side-effects at drug levels with comparable therapeutic efficacy. Although blood pressure response would be the most relevant parameter in this respect, it is not suitable in studies with normotensive volunteers due to inconsistent responses. Changes in resting heart rate have been used in some studies, but these may not accurately reflect β -adrenoceptor blockade (McDevitt, 1977). In this study we used submaximal exercise heart rate reduction as an indicator of the level of peripheral β -adrenoceptor blockade (Israili, 1979), as changes in exercise heart rate have been shown to

reflect plasma levels of β -adrenoceptor blockers (McInnes & Brodie, 1988b; Racine Poon & Moppert, 1985) while concentration effect relationships appear to be similar in healthy volunteers and in hypertensive patients (McInnes & Brodie, 1988b).

In our study, β -adrenoceptor blockade increased significantly between the first and third day following metoprolol-Oros. Therefore, comparisons with propranolol may best be made for the third day only. On this day exercise heart rate reduction was similar for both β -adrenoceptor blockers with the exception of peak effects which were measured at 2h 40 min after propranolol (Table 1). Although these peak effects did not cause significant effects on CNS-related performance, observations suggested a correlation between the extent of heart rate reduction and complaints of muscle fatigue and breathlessness during the exercise test. Relationships between exercise heart rate reduction and subjective ratings of leg fatigue and vitality have previously been demonstrated in young (Blomqvist *et al.*, 1988) and in elderly subjects (Dimenas *et al.*, 1990a). Consequently, the smoother course of β -adrenoceptor blockade following administration of metoprolol-Oros might reduce complaints of muscle fatigue and exercise intolerance.

In accordance with the results from this study, sustained release concentration profiles and continuous β -adrenoceptor blockade have previously been demonstrated upto 24 h after intake of 'Oros' drug delivery systems for metoprolol and oxprenolol (Feliciano *et al.*, 1990; McInnes & Brodie, 1988a). However, by contrast to previous studies in healthy volunteers (Woods *et al.*, 1985; Warrington *et al.*, 1985) we did find significant effects on systolic- and diastolic blood pressures following single and repeated doses of metoprolol-Oros and propranolol. As our subjects were healthy normotensive volunteers these pronounced effects on blood pressure may seem surprising. However, the strain imposed by lengthy tests sessions preceding haemodynamic measurements may have resulted in a slightly elevated adrenergic output, thus allowing decreases in blood pressure which might otherwise not have occurred.

In conclusion, no evidence was found for manifest changes in CNS-related performance or subjective effects following 1 and 3 days dosing of metoprolol-Oros 14/190 once daily or propranolol 80 mg twice daily in healthy volunteers. However, subtle changes in performance may have remained undetected in this study. As β -adrenoceptor blockade is more constant following metoprolol-Oros it may reduce complaints of exercise intolerance. In healthy volunteers metoprolol-Oros once daily causes similar reductions in blood pressure compared with propranolol twice daily.

The authors wish to thank; Jose Verloop for her skillful assistance during the study and Dr H. C. R. Brandenburg for preparation of propranolol and temazepam capsules and matching placebos. We thank Ciba Geigy, the Netherlands for supplying metoprolol-Oros and matching placebos and for financial support.

References

- Benfield, P., Clissold, S. P. & Brogden, R. N. (1986). Metoprolol, an updated review of its pharmacodynamic and pharmacokinetic properties and therapeutic efficacy, in hypertension, ischaemic heart disease and related cardiovascular disorders. *Drugs*, **31**, 376–429.
- Blomqvist, I., Westergren, G., Sandberg, A., Jonsson, U. E. & Lundborg, P. (1988). Pharmacokinetics and pharmacodynamics of controlled-release metoprolol: a comparison with atenolol. *Eur. J. clin. Pharmacol.*, **33** (Suppl.), 19–24.
- Bond, A. & Lader, M. (1974). The use of analogue scales in rating subjective feelings. *Br. J. med. Psychol.*, **47**, 211–218.
- Borland, R. G. & Nicholson, A. N. (1974). Human performance after a barbiturate (heptabarbitalone). *Br. J. clin. Pharmacol.*, **1**, 209–215.
- Carruthers, G., Shearer, R., Taylor, W. & Moore, M. (1990). A comparison of a controlled release (CR/ZOK) formulation of metoprolol, once daily, with conventional metoprolol tablets, twice daily, in mild to moderate hypertension. *J. clin. Pharmacol.*, **30**, S61–S65.
- Dimenas, E. & Dahlof, C. (1990). Tolerability and well-being with metoprolol in a controlled release (CR/ZOK) formulation: a review article. *J. clin. Pharmacol.*, **30**, S92–S97.
- Dimenas, E. S., Dahlof, C. G., Heibel, B., Moore, R. G., Olofsson, B. K., Westergren, G. E. & Lucker, P. W. (1990a). Subjective symptoms and pharmacokinetics/dynamics of metoprolol CR in elderly subjects – a comparison with atenolol. *Eur. J. clin. Pharmacol.*, **38**, 571–578.
- Dimenas, E., Dahlof, C., Olofsson, B. & Wiklund, I. (1989). CNS-related subjective symptoms during treatment with β_1 -adrenoceptor antagonists (atenolol, metoprolol): two double-blind placebo controlled studies. *Br. J. clin. Pharmacol.*, **28**, 527–534.
- Dimenas, E., Ostergren, J., Lindvall, K., Dahlof, C., Westergren, G. & de Faire, U. (1990b). Comparison of CNS-related subjective symptoms in hypertensive patients treated with either a new controlled release (CR/ZOK) formulation of metoprolol or atenolol. *J. clin. Pharmacol.*, **30**, S82–S90.
- Dimsdale, J. E., Newton, R. P. & Joist, T. (1989). Neuropsychological side effects of beta-blockers. *Arch. Intern. Med.*, **149**, 514–525.
- Feliciano, N. R., Bouvet, A. A., Redalieu, E., Castellana, J., Luders, R. C., Schwartz, D. J., Shum, L., Zak, S., Arnold, J. D. & Leese, P. T. (1990). Pharmacokinetic and pharmacodynamic comparison of an osmotic release oral metoprolol tablet and the metoprolol conventional tablet. *Am. Heart J.*, **120**, 483–489.
- Houtzagers, J. J., Smilde, J. G., Creyten, G. & Westergren, G. (1988). Efficacy and tolerability of a new controlled-release formulation of metoprolol: a comparison with conventional metoprolol tablets in mild to moderate hypertension. *Eur. J. clin. Pharmacol.*, **33** (Suppl.), S39–S44.
- Israili, Z. H. (1979). Correlation of pharmacological effects with plasma levels of antihypertensive drugs in man. *Ann. Rev. Pharmacol. Tox.*, **19**, 25–52.
- Kostis, J. B. & Rosen, R. C. (1987). Central nervous system effects of beta-adrenergic-blocking drugs: the role of ancillary properties. *Circulation*, **75**, 204–212.
- Löfdahl, C. G., Dahlöf, C., Westergren, G., Olofsson, B. & Svedmyr, N. (1988). Controlled-release metoprolol compared with atenolol in asthmatic patients: interaction with terbutaline. *Eur. J. clin. Pharmacol.*, **33** (Suppl.), S25–S32.
- McDevitt, D. G. (1977). The assessment of β -adrenoceptor blocking drugs in man. *Br. J. clin. Pharmacol.*, **4**, 413–425.
- McDevitt, D. G. & MacConnachie, A. M. (1988). Antianginal and β -adrenoceptor blocking drugs. In *Meyler's side effects of drugs*, edited by Dukes, M. N. G., pp. 359–389. Amsterdam: Elsevier Science Publishers.
- McInnes, G. T. & Brodie, M. J. (1988a). Evaluation of two oxprenolol oral osmotic (OROS) delivery systems in patients with essential hypertension. *Eur. J. clin. Pharmacol.*, **34**, 605–611.
- McInnes, G. T. & Brodie, M. J. (1988b). Concentration-effect relationships for oxprenolol in patients with essential hypertension. *Br. J. clin. Pharmacol.*, **25**, 539–545.
- Racine Poon, A. & Moppert, J. (1985). Concentration-effect relationship of oxprenolol in healthy volunteers: a retrospective analysis. *Br. J. clin. Pharmacol.*, **19**, Suppl. 2, 143S–149S.
- Serlin, M. J., Orme, M. L., MacIver, M., Green, G. J., Sibeon, R. G. & Breckenridge, A. M. (1983). The pharmacodynamics and pharmacokinetics of conventional and long-acting propranolol in patients with moderate hypertension. *Br. J. clin. Pharmacol.*, **15**, 519–527.
- Steveninck, A. L., van Cohen, A. F. & Ward, T. (1989). A microcomputer based system for recording an analysis of smooth pursuit and saccadic eye movements. *Br. J. clin. Pharmacol.*, **27**, 712P–713P.
- Steveninck, A. L., Kroon, J. M., Schoemaker, H. C., Pieters, M. S. M., Breimer, D. D. & Cohen, A. F. (1991). A study comparing the sensitivities of adaptive tracking, eye movement analysis and visual analogue lines to the effects of incremental doses of temazepam in healthy volunteers. *Clin. Pharmacol. Ther.*, **50**, 172–180.
- The metoprolol surveillance study group. (1984). A long term surveillance study of metoprolol in hypertensive patients. *Curr. Ther. Res.*, **35**, 491–500.
- Theeuwes, F., Swanson, D. R., Guittard, G., Ayer, A. & Khanna, S. (1985). Osmotic delivery systems for the β -adrenoceptor antagonists metoprolol and oxprenolol: design and evaluation of systems for once-daily administration. *Br. J. clin. Pharmacol.*, **19**, 69S–76S.
- Warrington, S. J., Barclay, S. P., John, V. A., Shotton, P. A. & Good, W. (1985). Comparison of single-dose pharmacokinetic and pharmacodynamic properties of two metoprolol Oros systems with different initial zero-order release rates. *Br. J. clin. Pharmacol.*, **19**, Suppl. 2, 225S–230S.
- Woods, K. L., Jack, D. B., Kendall, M. J., Halsey, A., O'Donnell, M. L., Warrington, S. J. & John, V. A. (1985). A multiple dose comparative study of the pharmacodynamic and pharmacokinetic behaviour of polymer-matrix and Oros dosage forms of oxprenolol in healthy volunteers. *Br. J. clin. Pharmacol.*, **19**, Suppl. 2, 117S–184S.

(Received 17 January 1992,
accepted 8 July 1992)