Br. J. clin. Pharmac. (1981), **12**, 223–228

ONCE DAILY β-ADRENOCEPTOR BLOCKADE IN HYPERTENSION: AN AMBULATORY ASSESSMENT

STEWART MANN, M.W. MILLAR CRAIG, V. BALASUBRAMANIAN & E.B. RAFTERY

The Cardiology Department and Division of Clinical Sciences, Northwick Park Hospital & Clinical Research Centre, Watford Road, Harrow, Middlesex

1 The ambulant intra-arterial blood pressure of eighteen hypertensive subjects was monitored before and again after 3 months treatment with thrice daily sotalol (six patients), twice daily pindolol (six patients) and once daily pindolol (six patients).

2 Three patients in the sotalol group underwent a third study having changed to a once daily regimen; similarly six patients in the pindolol groups were restudied having crossed over to the alternative pindolol dosing regimen, total daily dosage being maintained in all cases.

3 Comparison of 24 h blood pressure curves before and after treatment showed effective daytime reduction but less consistent effects at night.

4 In the crossover experiments once daily and multiple daily dosing regimens produced identical patterns of reduction over 24 h in both blood pressure and heart rate.

5 It is inferred that in the treatment of hypertension, once daily dosing with standard preparations of β-adrenoceptor blocking agents is probably adequate.

Introduction

A multitude of β-adrenoceptor blocking agents are currently available for the treatment of hypertension and other conditions. Many of their pharmacological properties have been contrasted and emphasised by advertisers but perhaps the feature of greatest importance in treating hypertensives is the duration of action of the drug. Gatley (1968) and Marshall & Barritt (1977) are among those who have shown that patients with a symptomless condition will comply poorly with therapeutic instructions, especially where these involve several doses spaced throughout each day. Several effects of β-adrenoceptor blockers have a direct relationship with the concentration of the drug in the plasma and the pharmacokinetics of the more commonly used products indicate that three or four daily doses are required to maintain relatively constant levels. Some companies have recently introduced slow-release preparations of their products in order to get over this difficulty. However, where anti-hypertensive action is concerned the effects have often been shown to last considerably longer than expected and even compounds with a short elimination half-life in the plasma have been found to exert this action beyond 24 h from their last dose in a chronically maintained regimen (Reybrouck *et al.*, 1978; Gordon, 1976; Wilson, Morgan & Morgan, 1976; Traub & Rosenfeld, 1976).

We, and others, have assessed the profile of blood pressure reduction over the 24 h day in freely ambulant hypertensives by performing ambulatory monitoring before and later during treatment with one of a number of β-adrenoceptor blockers. We have used the 'Oxford' technique (Bevan, Honour & Stott, 1966) which uniquely allows the continuous recording of the intra-arterial pressure waveform in individuals whose activities are largely unrestricted. Several of these studies have suggested poor control by the drugs of blood pressure levels during the night and early morning (Millar Craig *et al.*, 1979; Millar Craig *et al.*, 1978). In order to compare the reduction profiles of once or multiple daily dosage regimens we have performed trials using two β-adrenoceptor blockers, one with a long elimination half-life (sotalol, 10–12 h) (Brown *et al.*, 1976) and another with a short half-life (pindolol 3–4 h) (Bobik, Jennings & Korner, 1977). A number of subjects in each trial agreed to a third study so that the effects of different regimens could be directly compared.

0306–5251/81/080223–06 $01.00

Methods

All 18 patients included in this study had been referred to the hypertension clinic of the hospital with uncomplicated essential hypertension. None had received anti-hypertensive medication during the 2 months prior to initial monitoring and during this time all had at least two blood pressure measurements in the clinic in excess of 150/100 mm Hg. Mean age was 48 years (range 20–64 years), and the group included four women. Mean clinic blood pressure prior to the first study was 170/105 mm Hg. All subjects gave informed consent and the study was approved by the hospital's Ethical Committee.

'Clinic' pressures were all measured by nurses with no knowledge of the patient's treatment status using a standard mercury sphygmomanometer and measuring diastolic pressure at the 'Phase V' point (disappearance of sounds). Quoted readings were all taken in the afternoon and consisted of the mean of levels measured after 10 min supine rest and 2 min standing. The monitoring methods, described in detail elsewhere (Millar Craig, Hawes & Whittington, 1978; Millar Craig, Bishop & Raftery, 1978), consisted of the percutaneous insertion of a cannula into the non-dominant brachial artery and connection to a portable transducer-perfusion unit. Signals of blood pressure and electrocardiogram were recorded on magnetic tape using an ambulatory tape recorder ('Medilog I', Oxford Medical Systems). After setting up, the subjects left the hospital and were encouraged to follow their normal daily routine. Recording continued for at least 24 h in all cases. After editing out any periods of poor signal quality the recordings were processed using a hybrid computer system (Cashman, Millar Craig & Stott, 1979) which analysed hourly sections to derive mean values of heart rate, systolic and diastolic pressure.

After their first monitoring period the initial six subjects were treated with sotalol 80 mg thrice daily. They were seen every fortnight in the clinic and dosage increased incrementally until either diastolic pressure was consistently below 100 mm Hg or the trial maximum of 240 mg thrice daily was reached. At the next mutually convenient date a further monitoring period was undertaken. Subjects were then asked if they would be prepared to enter the second phase; the three who agreed changed their dosage regimen so that they took the same total daily dosage all at once each morning. After a similar interval a further monitoring study was performed.

The twelve subjects taking pindolol were managed similarly except that at the outset they were randomised to either once or twice daily therapy and were asked to cross over to the alternative regimen for the second phase. Dosage ranged from the starting total of 10 mg daily to a maximum of 30 mg daily. Four patients from the once-daily and two from the twice-daily group completed both phases.

Results

The groupings used to assess the effects of different regimens of therapy are described below and characterised in Table 1 by mean age, clinic pressure, interstudy interval and drug dosage. Circadian curves were in each case constructed by joining the average of pooled hourly mean values; the change in these between phases of a study being assessed by Student's *t*-test for paired observations.

Of the studies performed on patients taking

Table 1 Details of patient characteristics, clinic blood pressure, drug doses and interstudy intervals for the groups used in analysis of effects of different β-adrenoceptor blocker regimens (n = number of patients)

Study	n	*Mean age (years)*	*Mean pre-treatment BP (mm Hg)*	*Mean interstudy interval (weeks)*	*Mean pre-restudy BP (mm Hg)*	*Mean dose (mg/day)*
Sotalol Pre *v* three times daily	5	47	165/105	16	144/92	420
Sotalol three times daily *v* once daily	3	51	171/108	17	132/87 three times daily 148/100 once daily	440
Pindolol Pre *v* once daily	7	48	167/102	18	128/87	14
Pindolol Pre *v* twice daily	9	47	175/106	17	147/90	20
Pindolol once daily *v* twice daily	6	46	175/102	13	133/84 once daily 138/87 twice daily	15

sotalol, all were amenable to analysis except one pretreatment study of a patient who later completed both phases. Results contrasting pretreatment and thrice-daily therapy are therefore shown for the remaining five subjects in Figure 1. Substantial reduction of blood pressure throughout the day and night was apparent, but little difference between 06.00 and 09.00 h, especially in diastolic pressures. Results from the three patients who were monitored both during thrice-daily and once-daily therapy (Figure 2) agreed closely throughout the 24 h.

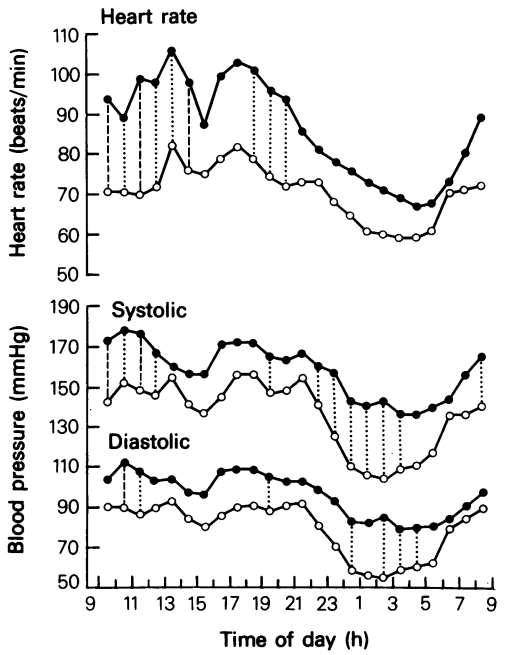

Figure 1 Circadian curves of heart rate, systolic and diastolic blood pressure in five patients before (●–●) and during (○–○) treatment with sotalol three times daily. Lines join pooled hourly mean values. Vertical lines indicate degrees of statistical significance (●...○, $P<0.05$; ●---○, $P<0.01$).

No recording in the pindolol study required substantial editing but one subject who completed both phases was a night-worker. Since his pattern of circadian blood pressure variation was unusual (Mann *et al.*, 1980a) his results were excluded from the pretreatment comparisons but not the crossover study, where comparability of treatment effects rather than alteration of the shape of the curve was being assessed. For the comparison of pretreatment results with those obtained during pindolol given once daily (Figure 3) and twice daily (Figure 4) data from all subjects were used whether taking the particular regimen during the first or second phase of the study. As an unequal number from each initially allocated group completed both phases results of seven taking the once daily and nine taking the twice daily regi-

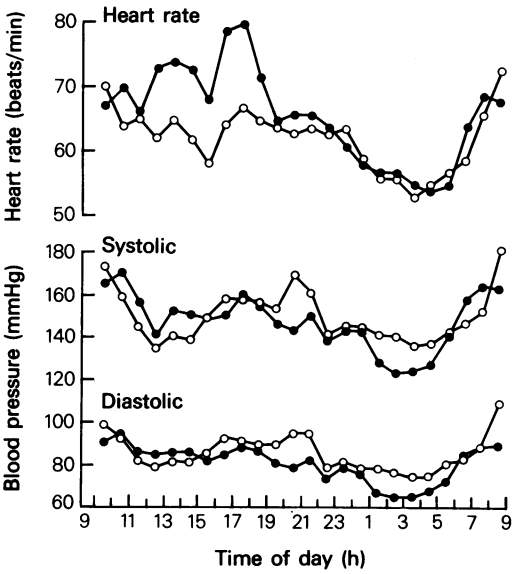

Figure 2 Comparison of 24 h heart rate and blood pressure in three patients taking sotalol either thrice daily (●–●) or once daily (○–○). No changes were statistically significant.

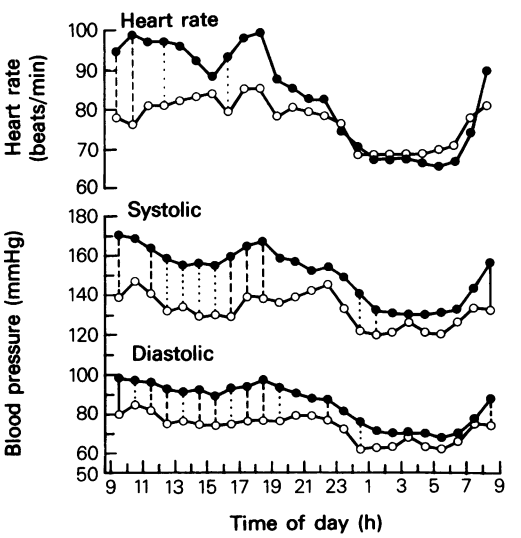

Figure 3 Comparison of 24 h heart rate and blood pressure in seven patients before (●–●) and during (○–○) therapy with pindolol once daily (statistics as Figure 1).

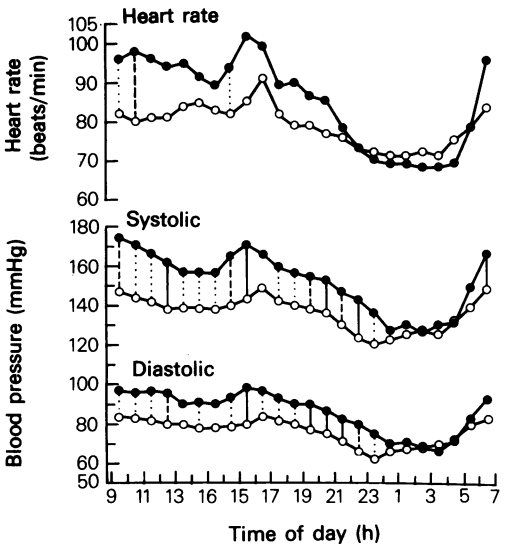

Figure 4 Comparison of 24 h heart rate and blood pressure in nine patients before (●–●) and during (○–○) therapy with pindolol twice daily (statistics as Figure 1, ●–○, $P<0.001$).

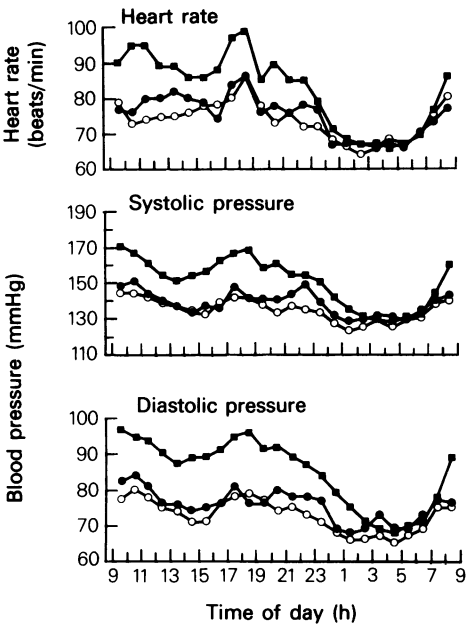

Figure 5 Comparison of 24 h heart rate and blood pressure in six patients before (■–■) and during therapy with pindolol once daily (●–●) and twice daily (○–○). There was no significant changes between once and twice daily reductions.

mens were available; the characteristics of each group (shown in Table 1) were however closely comparable. The profiles of blood pressure and heart rate control on either regimen and during both phases of the crossover study (Figure 5) were similar with little reduction during the later part of the night and the early morning. The crossover study confirmed the equivalence of once and twice daily regimens in the same patients. Here the individual changes from pretreatment levels produced by the two therapeutic regimens were compared and no corresponding hourly mean points were found to be significantly different (in all cases $P> 0.05$).

Discussion

In this trial, we have endeavoured (for the first time with these techniques) to use a crossover protocol to compare different therapeutic regimens.

The validity of the use of these methods of monitoring and analysis in assessing effects of treatment has been questioned (Sleight *et al.*, 1979) especially where physical activity has not been carefully standardised (Rowlands *et al.*, 1980). However, a study of the reproducibility of our techniques on a day-to-day basis has yielded encouraging results (Mann *et al.*, 1980a). With regard to this trial, a balanced crossover would have been ideal but difficult to achieve since up to 50% of subjects quite understandably decline to return for a third intra-arterial study. No order effect was observed however when the results were analysed separately for the five subjects taking multiple doses first (three sotalol, two pindolol) and the four initially on a once-daily regimen (all pindolol). To examine the relationship between the effects of a once daily and a multiple dosage regimen we felt it desirable to perform crossover studies despite the difficulty of repeating invasive studies more than once. This has necessitated the experimental protocols being initially somewhat tentative.

In an earlier report (Millar Craig *et al.*, 1979) we described the pattern of circadian blood pressure reduction produced by atenolol given in a once daily morning dose. Although daytime reduction was substantial, a much reduced effect was noted particularly for systolic pressure during the night and early morning periods, a feature suggesting inadequate 24 h control of blood pressure by the drug. However, it was pointed out that in the same patients the pattern of reduction had been the same on the subsequent (withdrawal) day and also when the dosage time had been changed to 23.00 h. Other studies have also been reported where acebutalol once daily (Mehta, Walsh & Goldberg, 1980) and oxprenolol thrice

daily (Millar Craig, Hawes *et al.*, 1978a) have produced a similar circadian pattern of reduction. By contrast other ambulatory studies of the effects of β-adrenoceptor blockers (Mann *et al.*, 1979; Floras *et al.*, 1979; Watson, Stallard & Littler, 1979) have shown more consistent pressure reduction throughout the day and night. Failure of nocturnal blood pressure reduction by a β-adrenoceptor blocker appears to be inconsistently related to the dosage regimen and possibly to the individual drug, perhaps being more a matter of individual response.

Sotalol clearly produced both daytime and night-time reduction of blood pressure when levels were compared with the pre-treatment study but early morning pressures were little affected. Pindolol in either regimen however appeared to have little effect during the later part of the night, and somewhat paradoxically this was more true with the twice daily regimen. The crossover studies of both drugs however showed that dosage regimen was unimportant in determining reduction patterns. This confirms previous work using non-invasive blood pressure measurement which has suggested equivalence of once and multiple daily dosing of β-adrenoceptor blockers, even of those with a short plasma half-life (Gordon, 1976).

The reason for the variability of nocturnal blood pressure control in different ambulatory studies remains obscure. It does not appear to be related to any pretreatment characteristics of the patients such as the height of the blood pressure or the nocturnal blood pressure fall, nor in our experience to fluctuations in patterns of activity and sleep. Its clinical significance is also still unclear but interestingly, good nocturnal blood pressure control was achieved by both non-β-adrenoceptor blockers we have studied – a centrally acting agent (Mann *et al.*, 1980b) and a diuretic (report in preparation).

Whilst it might appear unnecessary and even potentially dangerous to reduce a night-time blood pressure of, say, 135/70 mm Hg, this is a higher than normal level at that time. It is at present unclear whether damage from hypertension results from higher peak or mean levels or even rapidly changing blood pressure. Smirk, Veale & Alstad (1959) noted that 'basal' recordings made immediately after waking were a better predictor of future problems than 'casual' recordings, despite being considerably lower. Also we have found that the inconsistent control by β-adrenoceptor blockers has included the early morning period where blood pressure is rising rapidly. This period is temporally associated with a peak in the circadian incidence of hypertension-related pathological events (Millar Craig, Bishop *et al.*, 1978).

It may be argued that β-adrenoceptor blockade offers prognostic advantages to the hypertensive in other ways than merely by the blood pressure lowering effect. For example the control of exercise tachycardia, commonly used as a measure of clinical 'β-blockade' and regarded as directly relevant in the control of anginal symptoms, has been shown to be related to plasma levels of the drugs (Reybrouck *et al.*, 1978; Gugler *et al.*, 1975). One might, therefore, have expected ambulant heart rate to be sensitive to changes in dosage regimen. However, in our study the patterns were identical with either once-daily or twice-daily pindolol administration. The results might have been different if an agent with less intrinsic sympathomimetic activity (producing a more profound bradycardia) had been used. There is, of course, some residual inhibition of exercise tachycardia even 24 h after a single dose of pindolol (Aellig, 1976).

In summary we have demonstrated that when blood pressure is measured continuously throughout a subject's normal day and night the reduction produced by a β-adrenoceptor blocking agent was equivalent whether the drug was given on a once daily basis or by more complicated regimens. Barring the unlikely event of two independent but compensating errors the study also implies that long-term reproducibility of these techniques of recording and analysis is likely to be high.

We should like to thank Mrs Tarlika Vadgama and Mr S. Dashwood for technical help, Mrs J. Loveday and Mrs P. Lacey for secretarial assistance and Sandoz Products Ltd and Duncan Flockhart Ltd for financial support.

References

AELLIG, W.H. (1976). β-adrenoceptor blocking activity and duration of action of pindolol and propranolol in healthy volunteers. *Br. J. clin. Pharmac.*, **3**, 251–257.

BEVAN, A., HONOUR, A.J. & STOTT, F.D. (1966). Portable recorder for continuous arterial pressure measurement in man. *J. Physiol. (Lond.)*, **186**, 3P.

BOBIK, A., JENNINGS, G. & KORNER, P.I. (1977). Plasma pindolol levels and their significance in the assessment of cardiac β-adrenoceptor blockade. *Med. J. Austral.*, **2**, 3–5.

BROWN, H.C., CARRUTHERS, S.G., KELLY, J.G., McDEVITT, D.G. & SHANKS, R.G. (1976). Observations on the efficacy and pharmacokinetics of sotalol after oral administration. *Eur. J. clin. Pharmac.*, **9**, 357–372.

CASHMAN, P.M.M., MILLAR CRAIG, M.W. & STOTT, F.D. (1979). Hybrid system for fast data reduction of long-term blood pressure recordings. *Med. Biol. Eng. Comput.*, **17**, 629–635.

FLORAS, J., FOX, P., HASSAN, M.O., JONES, J.V., SLEIGHT, P. & TURNER, K. (1979). Assessment of the anti-hypertensive effect of atenolol using 24 h ambulatory monitoring of blood pressure. *Clin. Sci.* (Suppl. 5), **57**, 387s–389s.

GATLEY, M.S. (1968). To be taken as directed. *J. Roy. Coll. Gen. Practit.*, **16**, 39–44.

GORDON, R.D. (1976). Initial treatment of the young hypertensive: thiazide diuretic or β-adrenoreceptor-blocking agent in a single daily dose? *Clin. Sci. mol. Med.*, **51**, 631s–633s.

GUGLER, R., HOEBEL, W., BODEM, G. & DENGLER, H.J. (1975). The effect of pindolol on exercise-induced cardiac acceleration in relation to plasma levels in man. *Clin. Pharmac. Ther.*, **17**, 127.

MANN, S., MILLAR CRAIG, M.W., ALTMAN, D.G., MELVILLE, D.I. & RAFTERY, E.B. (1979). The effects of metoprolol on ambulatory blood pressure. *Clin. Sci.*, **57** (Suppl. 5), 375s–377s.

MANN, S., MILLAR CRAIG, M.W., MELVILLE, D.I., ALTMAN, D.G., CASHMAN, P.M.M., RAFTERY, E.B. (1980a). Physical activity and the circadian rhythm of blood pressure. *Proceedings of the 3rd International Symposium on Ambulatory Monitoring.* London: Academic Press.

MANN, S., MILLAR CRAIG, M.W., MELVILLE, D.I., CASHMAN, P.M.M. & RAFTERY, E.B. (1980b). An ambulatory trial of guanfacine. *Br. J. clin. Pharmac.*, **10**, 103S–108S.

MARSHALL, A. & BARRITT, D.W. (1977). Drug compliance in hypertensive patients. *Br. med. J.*, **1**, 1278–1279.

MEHTA, S., WALSH, T. & GOLDBERG, D.A. (1980). Single daily dosage of acebutolol to control hypertension. *Proceedings of the 3rd International Symposium on Ambulatory Monitoring.* London: Academic Press.

MILLAR CRAIG, M.W., MANN, S., BALASUBRAMANIAN, V., RAFTERY, E.B. (1978a). Blood pressure circadian rhythm in essential hypertension. *Clin. Sci. mol. Med.*, **55** (Suppl. 4), 391s–393s.

MILLAR CRAIG, M.W., HAWES, D.W.C. & WHITTINGTON, J.R. (1978b). New system for measuring ambulatory blood pressure in man. *Med. Biol. Eng. Comput.*, **16**, 727–731.

MILLAR CRAIG, M.W., BISHOP, C.N., RAFTERY, E.B. (1978c). Circadian variation of blood pressure. *Lancet*, **i**, 795–797.

MILLAR CRAIG, M.W., KENNY, D., MANN, S., BALASUBRAMANIAN, V. & RAFTERY, E.B. (1979). Effect of once-daily atenolol on ambulatory blood pressure. *Br. med. J.*, **1**, 237–239.

REYBROUCK, T., AMERY, A., FAGARD, R., JOUSTEN, P., LIJNEN, P. & MEULEPAS, E. (1978). β-adrenoceptor blockers: once or three times a day? *Br. med. J.*, **1**, 1386–1388.

ROWLANDS, D.B., STALLARD, T.J., WATSON, R.D.S. & LITTLER, W.A. (1980). The influence of physical activity on arterial pressure during ambulatory recordings in man. *Clin. Sci.*, **58**, 115–117.

SLEIGHT, P., FLORAS, J., JONES, J.V. & HASSAN, M.O. (1979). Effect of once-daily atenolol on ambulatory blood pressure. *Br. med. J.*, **1**, 491.

SMIRK, F.H., VEALE, A.M.V. & ALSTAD, K.S. (1959). Basal and supplemental blood pressures in relationship to life expectancy and hypertension symptomatology. *N.Z. med. J.*, **58**, 711–735.

TRAUB, Y.M. & ROSENFELD, J.B. (1976). Once-a-day pindolol in hypertension. *Clin. Pharmac. Ther.*, **21**, 588–592.

WATSON, R.D.S., STALLARD, T.J. & LITTLER, W.A. (1979). Influence of once-daily administration of β-adrenoceptor antagonists on arterial pressure and its variability. *Lancet*, **i**, 1210–1213.

WILSON, M., MORGAN, G. & MORGAN, T. (1976). The effect on blood pressure of β-adrenoreceptor-blocking drugs given once daily. *Clin. Sci. mol. Med.*, **51**, 527s–528s.

(Received August 4, 1980)