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Bioavailability of rectally administered naproxen

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Summary

The pharmacokinetics of naproxen administered intravenously was studied in 8 healthy volunteers after a single dose of 250 mg of the drug. The influence of the dose on the pharmacokinetics of the drug administered rectally was also studied in 30 healthy volunteers divided into 4 groups, each receiving 125, 250, 500 or 750 mg. Plasma concentrations were determined by a spectrofluorometric method. Administered intravenously, naproxen showed values for the elimination half-life and distribution volume of 16.45 h and 7.14 litres, respectively. After rectal administration, the anti-inflammatory agent exhibited dose-dependent non-linear kinetics. The values of the elimination half-life found for the doses of 125, 250 and 500 mg were 15.69, 15.67 and 15.58 h, respectively, similar to those obtained after i.v. administration. However, at a dose of 750 mg, a value of 11.21 h was recorded. Naproxen is well absorbed rectally and the bioavailability showed values higher than 80%, which was slightly lower than those observed after oral administration.

Introduction

Among the different factors which govern the disposition of a drug, of prime importance is the influence exerted by the administration route employed, particularly with respect to the absorption and bioavailability processes.

The use of the rectum for systemic administration of drugs has been the objective of several studies (Dulac et al., 1978; de Boer et al., 1982), in which the efficacy of such formulations has been shown to be dependent upon the drug in question, the suppository base and patient factors. There is sound therapeutic justification for the preferential administration of a drug rectally rather than the oral route, which may in some cases lead to sequels of nausea, vomiting or side-effects or in people with GI disturbances where a delay in gastric emptying gives rise to a decrease in the absorption rate.

Naproxen is a non-steroidal anti-inflammatory agent with anti-inflammatory, analgesic and antipyretic properties frequently used in the treatment of rheumatic diseases (Berry et al., 1978) and which more recently has been used as an analgesic (Huskisson, 1983; Sevelius et al., 1980; Ylikorkala et al., 1980). Its therapeutic effect seems to be directly related to the serum levels reached as has been demonstrated by its use in the treatment of pain and inflammatory disease states (Sevelius et al., 1980; Day et al., 1982).

As in the case of other non-steroidal anti-inflammatory agents (NSAIDs), naproxen is lacking in bibliographical data concerning its rectal ab-

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sorption, despite the fact that rectal formulations for these NSAIDs are readily available and widely used. The aim of the present work was to study the pharmacokinetic behaviour and bioavailability of naproxen administered rectally at doses of 125, 250, 500 and 750 mg.

Materials and Methods

Drug

For i.v. administration, naproxen (Syntex, Palo Alto, CA), was used in a sterile solution in Sörensen's phosphate buffer pH = 7.8 at a concentration of 250 mg/8 ml. For rectal administration, naproxen was used in the form of suppositories containing 125, 250, 500 and 750 mg, using "Stearinum B" as the excipient.

Healthy volunteers

(1) In the first phase of the experiments, naproxen pharmacokinetics were studied after i.v. administration at a single dose of 250 mg. This study was carried out in 8 healthy volunteers (2 females) with an age range of 30–56 years, (mean ± S.D.: 43 ± 10 years) and a weight range of 58–70 kg (mean ± S.D.: 63.3 ± 4.2 kg).

(2) The second experimental phase looked at naproxen pharmacokinetics after the rectal administration of four different doses of 125, 250, 500 and 750 mg to 30 healthy volunteers (10 females) with an age range of 22–40 years (mean ± S.D.: 29 ± 6.1 years) and a weight range of 50–95 kg (mean ± S.D.: 66 ± 11 kg). The healthy volunteers were divided into 4 groups as follows:

A Dose: 125 mg; $n = 7$
B Dose: 250 mg; $n = 8$
C Dose: 500 mg; $n = 8$
D Dose: 750 mg; $n = 7$

In all cases patients complied in not passing stool until 7 h after administration. Informed consent was obtained from all participating and all studies were carried out under medical supervision.

Blood samples were withdrawn by direct puncture of the basilica forearm vein at 0, 0.5, 1, 1.5, 2, 3, 4, 5, 7, 12, 24, 30 and 36 h after dosing. The samples were collected in heparinized glass tubes and the plasma separated by centrifugation and stored at −20 °C until assay.

Analytical technique

The plasma concentrations of naproxen were determined by a spectrofluorometric technique described elsewhere (Anttila, 1977). The excitation and emission wavelength values were set at 330 and 360 nm, respectively, using an AMINCO spectrofluorometer 408. The major metabolite of naproxen, 6-O-desmethylnaproxen was not seen to interfere with the drug analysis (Anttila, 1977).

Pharmacokinetic analysis

Administered both intravenously and rectally, naproxen follows a two-compartment open kinetic model (Wagner, 1974; Gibaldi and Perrier, 1975).

The plasma level curve may be expressed by the following equations:

$$C_p = A_0 \cdot e^{-\alpha t} + B_0 \cdot e^{-\beta t} \quad \text{for the i.v. route}$$

$$C_p = A_0 \cdot e^{-\alpha t} + B_0 \cdot e^{-\beta t} - C_0 \cdot e^{-K_a t}$$

for the rectal route

where α and β are the rapid and slow disposition constants, respectively, K_a is the absorption constant and A_0, B_0 and C_0 are the coefficients of the exponential equations.

The coefficients and exponentials of these equations were calculated from the experimental data using a non-linear regression program based on the Gauss-Newton iterative procedure (Pfeffer, 1973). The plasma concentration data (C_p) obtained were weighted according to a variance using the inverse of the square of concentration as the weighting factor ($W = 1/C_p^2$). The initial estimates of the pharmacokinetic parameters were obtained using an ESTRIP program (Brown and Manno, 1978). Calculations were carried out on a Hewlett-Packard 85 computer.

The following pharmacokinetic parameters were calculated from these values: the lag time (t_0), the

maximum plasma concentration (C_{max}); the time taken to reach C_{max} (t_{max}); the elimination microconstant (K_{13}), the plasma half-life of the drug ($t_{1/2_\beta}$); the distribution microconstants (K_{12}, K_{21}); the area distribution volume ($V_{d_{area}}$); plasma clearance (Cl_p) and the area under the plasma level–time curve $(AUC)_0^\infty$.

The bioavailability of rectally administered naproxen was calculated in each case from the AUC of the plasma levels according to the equation:

$$F = \frac{\left[(AUC)_0^\infty \cdot \beta/D\right]_{\text{rectal}}}{\left[(AUC)_0^\infty \cdot \beta/D\right]_{\text{i.v.}}}$$

where F is the fraction of dose absorbed and D is the dose administered per kg of body weight.

Statistical analysis

The pharmacokinetic parameters obtained after rectal administration of different doses of the drug, were compared statistically in order to determine the effect of the dose on the pharmacokinetic behaviour of the drug. The following pharmacokinetic parameters, AUC and C_{max} normalized with the dose administered, $t_{1/2_\beta}$, Cl_p, $V_{d_{area}}$ were subjected to a one-way analysis of variance (ANOVA) by the BMDP program (Dixon et al., 1981).

A p-value from ANOVA of less than 0.05 was considered acceptable evidence of a difference between parameters.

Results and Discussion

Fig. 1 shows the mean plasma level curve of naproxen obtained after i.v. administration of the drug. Table 1 shows the corresponding mean pharmacokinetic parameters. The rapid distribution phase exhibits a duration of nearly 9 h with a rapid disposition constant of 1.38 h^{-1}. The slow disposition phase shows a plasma half-life of 16.45 h. Naproxen is therefore a slowly eliminated drug, possibly due to the high degree of plasma protein binding (Calvo and Domínguez-Gil, 1983). This situation could equally account for the low value obtained for the apparent distribution volume (7.14 litres) probably involving an apparent error.

TABLE 1

Mean pharmacokinetic parameters (± S.D.) obtained after i.v. administration of a dose of 250 mg of naproxen

C_0	(μg/ml)	= 85.00 ±	14.62
α	(h^{-1})	= 1.38 ±	1.31
$\beta \cdot 10$	(h^{-1})	= 0.43 ±	0.08
$t_{1/2_\beta}$	(h)	= 16.45 ±	3.12
K_{12}	(h^{-1})	= 0.76 ±	0.82
K_{21}	(h^{-1})	= 0.56 ±	0.48
K_{13}	(h^{-1})	= 0.10 ±	0.03
$V_{d_{area}}$	(l)	= 7.14 ±	1.33
Cl_p	(ml/min)	= 5.07 ±	0.76
$(AUC)_0^\infty$	(μg·ml^{-1}·h)	= 842.65 ±	161.49

Fig. 2 shows the plasma levels curve obtained with the 4 doses of rectally administered drug and Table 2 shows the corresponding mean pharmacokinetic parameters.

After administration of the drug, the plasma concentrations are seen to rise progressively, reaching a maximum value 2–3 h later. After rectal administration, naproxen is absorbed rapidly in the dose range studied, as shown by the values of the absorption constants, which were 1.89, 1.88, 2.03 and 2.31 h^{-1}, for the doses of 125, 250, 500 and 750 mg, respectively. The lag time observed, between 0.27 and 0.44 h, is normal for drugs administered in solid form.

On increasing the dose, a progressive rise in the plasma levels of the agent may be seen together with a corresponding increase in the AUC values of the plasma level–time plot. The analysis of variance performed, Table 3, shows that parameters such as C_{max} and AUC normalised with the dose have statistically significant differences for the 750 mg dose ($p < 0.03$), suggesting a loss of linearity in naproxen kinetics for doses above 500 mg.

We have verified this using the non-linearity test proposed by Wagner (1975) and based on the use of normalized plasma concentrations. The normalized plasma concentration curves are shown in Fig. 3. It may be seen that the curves corresponding to the dose of 125, 250 and 500 mg are almost identical, whereas lower values are shown at a dose of 750 mg which has been confirmed by

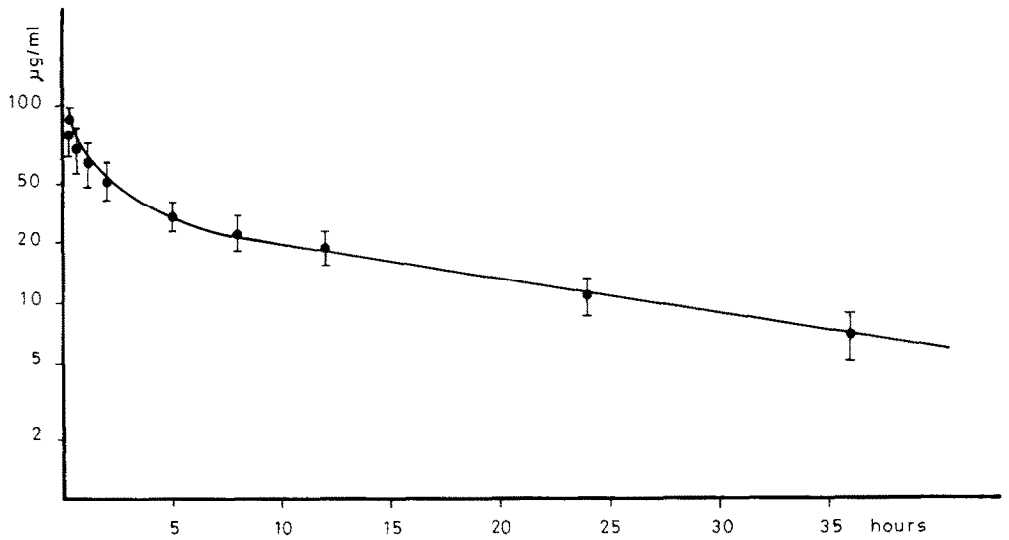

Fig. 1. Mean plasma levels curve obtained after i.v. administration of 250 mg of naproxen.

the results obtained in the statistical analysis. Such dose-dependent phenomena have been described after the oral administration of naproxen by Runkel et al. (1976) for doses greater than 500 mg.

The values obtained for the plasma half-life and plasma clearance of naproxen in the different rectal administration groups show the existence of statistically significant differences for the 750 mg

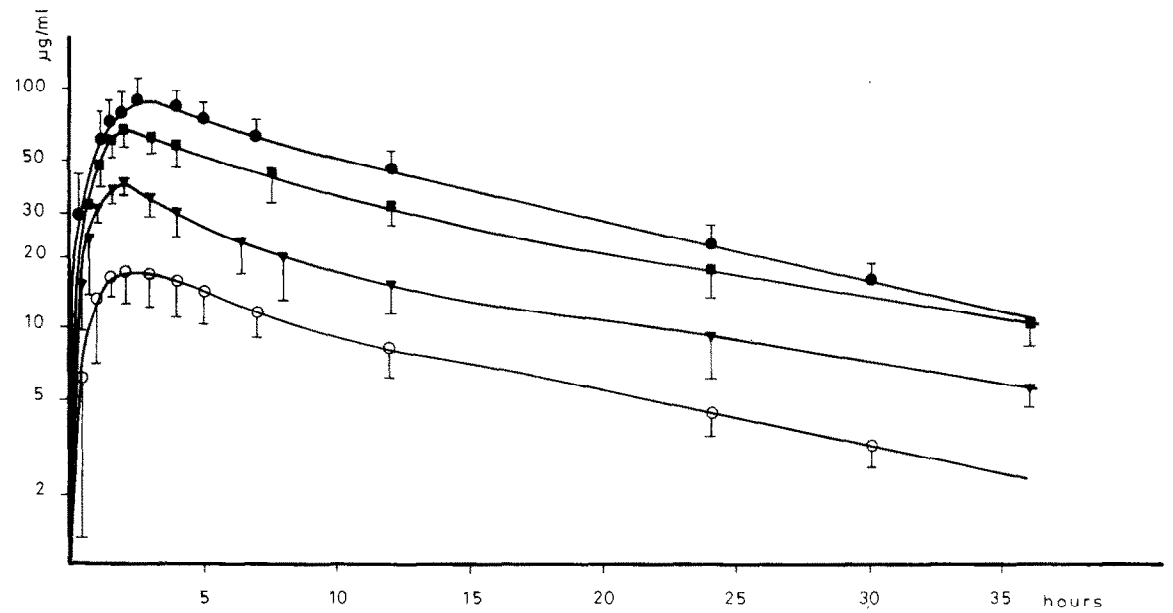

Fig. 2. Mean plasma levels curve of naproxen obtained after rectal administration of a single dose of: 125 (○), 250 (▼), 500 (■) and 750 (●) mg.

TABLE 2

Mean pharmacokinetic parameters (± S.D.) obtained for the four doses studied after rectal administration

Parameter		125 mg	250 mg	500 mg	750 mg
C_0	(μg/ml)	28.06 ± 9.50	98.49 ± 79.59	90.98 ± 27.30	125.35 ± 28.05
α	(h^{-1})	0.34 ± 0.11	0.64 ± 0.48	0.26 ± 0.09	0.27 ± 0.12
$\beta \cdot 10$	(h^{-1})	0.49 ± 0.17	0.46 ± 0.07	0.46 ± 0.08	0.62 ± 0.03
$t_{1/2_\beta}$	(h)	15.69 ± 5.90	15.67 ± 2.94	15.58 ± 2.98	11.21 ± 0.73
t_0	(h)	0.36 ± 0.21	0.37 ± 0.08	0.44 ± 0.06	0.27 ± 0.07
t_{max}	(h)	2.39 ± 1.85	1.43 ± 0.52	1.93 ± 0.47	3.43 ± 1.82
C_{max}	(μg/ml)	18.81 ± 5.64	40.26 ± 7.51	70.76 ± 16.07	86.03 ± 9.89
K_a	(h^{-1})	1.89 ± 0.99	1.88 ± 0.97	2.03 ± 0.71	2.31 ± 2.86
$(AUC)_0^\infty$	($\mu g \cdot ml^{-1} \cdot h$)	327.22 ± 48.43	679.33 ± 173.17	1 270.54 ± 257.32	1 572.76 ± 178.99
Cl_p	(ml/min)	5.63 ± 1.21	4.97 ± 0.96	5.13 ± 0.48	6.71 ± 0.94
$V_{d_{area}}$	(litres)	7.26 ± 1.77	7.74 ± 3.30	7.10 ± 0.74	6.49 ± 0.71

dose ($p < 0.01$), (Table 3). This decline observed in the plasma half-life value together with the increase in the plasma clearance value for high concentrations could be due to a decrease in the binding of the drug to plasma proteins, thereby accounting for the non-linear dose-dependent kinetics.

The values obtained for the distribution volume following rectal administration of the drug are very similar to those obtained after i.v. administration, and the difference between them is not statistically significant ($p > 0.2$).

By using the values of the AUC of the plasma levels it was possible to establish that the bioavailability of rectally administered naproxen in suppository form is optimal. The bioavailability values obtained range from 80% for the 250 mg dose to 90% for the 500 mg dose, there being no

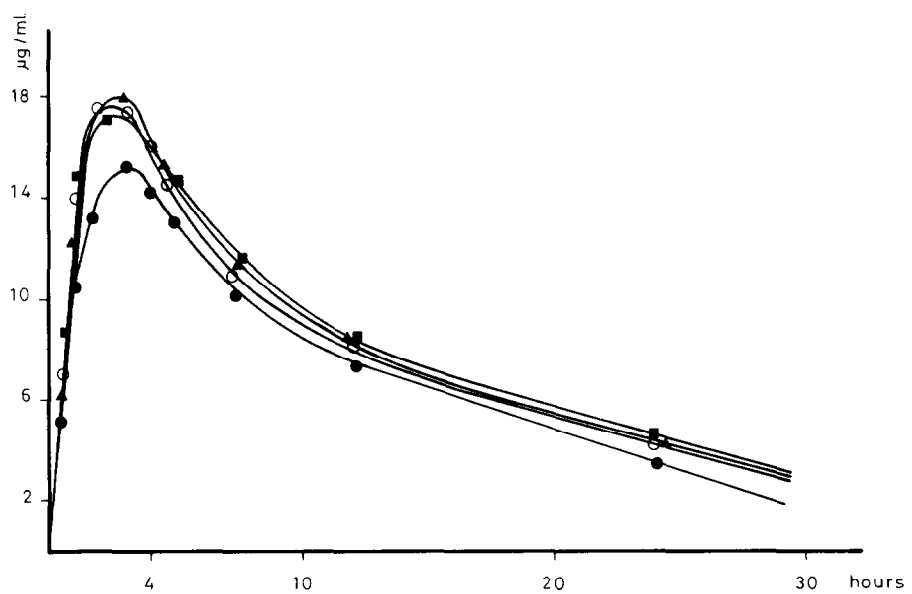

Fig. 3. Mean plasma levels curves normalised with the dose obtained with: 125 (○), 250 (△), 500 (■) and 750 (●) mg of rectally administered naproxen.

TABLE 3

Results of ANOVA test

Parameter	ANOVA	*p*-value
C_{max}/dose	A [a] vs B, C	> 0.3 (N.S.)
	B vs C	0.218 (N.S.)
	A, B vs D	< 0.008 (S.)
	C vs D	0.083 (N.S.)
$(AUC)_0^\infty$/dose	A vs B, C	> 0.8 (N.S.)
	B vs C	0.831 (N.S.)
	A, B, C vs D	< 0.03 (S.)
$t_{1/2_\beta}$	A vs B, C	> 0.8 (N.S.)
	B vs C	0.790 (N.S.)
	A, B, C vs D	< 0.01 (S.)
Cl_p	A vs B, C	> 0.1 (N.S.)
	B vs C	0.744 (N.S.)
	A vs D	0.087 (N.S.)
	B, C vs D	< 0.004 (S.)
$V_{d_{area}}$	A vs B, C, D	> 0.3 (N.S.)
	B vs C, D	> 0.2 (N.S.)
	C vs D	0.608 (N.S.)

[a] A, B, C and D correspond to the doses of 125, 250, 500 and 750 mg, respectively, administered rectally.

correlation between doses employed and bioavailability. The bioavailability values obtained are only slightly lower than those reported by other workers after the oral administration of similar doses (Runkel et al., 1972). However, these modifications do not affect the plasma concentrations of the drug significantly when compared with the serum levels obtained by us (Calvo et al., 1979) and other workers (Runkel et al., 1974) after oral administration of the drug. Such findings are similar to those reported previously for the bioavailability of naproxen in suppository form at doses of 300 (Sevelius et al., 1973) and 500 mg (Desager et al., 1976); in this latter study the bioavailability of the naproxen in the suppositories was 94.8% of the bioavailability of the drug in tablet form.

References

Anttila, M., Fluorometric determination of naproxen in serum. *J. Pharm. Sci.*, 66 (1977) 433–434.

Berry, H., Swinson, D., Jones, J. and Hamilton, E.B.D., Indomethacin and naproxen suppositories in the treatment of rheumatoid arthritis. *Ann. Rheum. Dis.*, 37 (1978) 370–374.

Brown, R.D. and Manno, J.E., ESTRIP, a BASIC computer program for obtaining initial polyexponential parameter estimates. *J. Pharm. Sci.*, 67 (1978) 1687–1691.

Calvo, M.V., Domínguez-Gil, A., Miralles, J.M. and de Pablo, F., Pharmacokinetics of naproxen in healthy volunteers and in patients with diabetic microangiopathy. *Int. J. Clin. Pharmacol. Biopharm*, 17 (1979) 486–491.

Calvo, M.V. and Domínguez-Gil, A., Binding of naproxen to human albumin. Interaction with palmitic acid. *Int. J. Pharm.*, 16 (1983) 215–223.

Day, R.O., Furst, D.E., Dromgoole, S.H., Kamm, B., Rose, R. and Paulus, H.E., Relationship of serum naproxen concentration to efficacy in rheumatoid arthritis. *Clin. Pharmacol. Ther.*, 31 (1982) 733–740.

De Boer, A.G., Moolenaar, F., de Leede, L.G.J. and Breimer, D.D. Rectal drug administration: clinical pharmacokinetic considerations. *Clin. Pharmacokin.*, 7 (1982) 285–311.

Desager, J.P., Vanderbist, M. and Harvengt, C., Naproxen plasma levels in volunteers after single-dose administration by oral and rectal routes. *J. Clin. Pharmacol.*, 16 (1976) 189–193.

Dixon, W.J., Brown, M.B., Engelman, L., Frane, J.W., Hil, M.A., Jennrich, R.I. and Toporek, J.D., *BMDP Statistical Software*, University of California, Los Angeles, 1981, p. 347.

Dulac, O., Aicardi, J., Rey, P. and Olive, G., Blood levels of diazepam after single rectal administration in infants and children. *J. Pediat*, 93 (1978) 1039–1041.

Gibaldi, M. and Perrier, D., *Pharmacokinetics* 1st edn., Marcel Dekker, New York, 1975, p. 48.

Huskisson, E.C., Non-steroidal anti-inflammatory drugs as analgesics. *Prescribers' J.*, 23 (1983) 10–15.

Pfeffer, M., COMPT, a time-sharing program for non-linear regression of compartmentals models of drug distribution. *J. Pharmacokin. Biopharm.*, 1 (1973) 137–163.

Runkel, R., Chaplin, M., Boost, G., Segre, E. and Forchielli, E.; Absorption, distribution, metabolism and excretion of naproxen in various laboratory animals and human subjects. *J. Pharm. Sci.*, 61 (1972) 703–708.

Runkel, R., Forchielli, E., Sevelius, H., Chaplin, M. and Segre, E., Nonlinear plasma level response to high doses of naproxen. *Clin. Pharmacol. Ther.*, 15 (1974) 261–266.

Runkel, R., Chaplin, M.D., Sevelius, H., Ortega, E. and Segre, E., Pharmacokinetics of naproxen overdoses. *Clin. Pharmacol. Ther.*, 20 (1976) 269–277.

Sevelius, H., Runkel, R., Pardo, A., Ortega, E., Varady, J. and Segre, E., Naproxen suppository: tissue response and comparative bioavailability. *Eur. J. Clin. Pharmacol.*, 6 (1973) 22–25.

Sevelius, H., Runkel, R., Segre, E. and Bloomfield, S.S., Bioavailability of naproxen sodium and its relationship to clinical analgesic effects. *Br. J. Clin. Pharmacol.*, 10 (1980) 259–263.

Wagner, J.C., Application of the Wagner-Nelson absorption method to the two-compartment model. *J. Pharmacokin. Biopharm.*, 2 (1974) 469–486.

Wagner, J.G., *Fundamentals of Clinical Pharmacokinetics*, 1st edn., Drug Intelligence Publications, Hamilton, IL, 1975, p. 247.

Ylikorkala, O., Puolakka, J. and Kauppila, A., Comparison between naproxen tablets and suppositories in primary dysmenorrhea. *Prostaglandins*, 20 (1980) 463–471.