Some observations on the effects of a calcium channel blocker, nitrendipine, in early human pregnancy

M. R. LAWRENCE & F. BROUGHTON PIPKIN

Department of Obstetrics and Gynaecology, University Hospital, Queen's Medical Centre, Nottingham NG7 2UH

1 The effects of a dihydropyridine calcium channel antagonist, nitrendipine 20 mg orally, have been investigated in 24 women in the first trimester human pregnancy in a double-blind, placebo controlled study.

2 The effects on systemic arterial pressure, pulse rate (PR), blood loss at termination of pregnancy (TOP), plasma renin, renin substrate and aldosterone concentrations and platelet aggregation to adenosine diphosphate $0.5\ \mu\text{M}$, adrenaline bitartrate $0.1\text{--}1.0\ \mu\text{M}$, thrombin $0.05\ \text{u ml}^{-1}$ and sodium arachidonate $0.1\text{--}0.2\ \text{mM}$ were studied.

3 Administration of nitrendipine was associated with a statistically-significant fall in diastolic pressure (BPD) the magnitude of which was directly related to the individual peak concentrations of the drug ($P < 0.02$). No significant effects were observed on systolic pressure (BPS); PR rose slightly. Baseline variability of all three parameters fell in the nitrendipine-treated group over the first 2 h but then increased significantly (BPS, $P < 0.05$; BPD, $P < 0.025$; PR, $P < 0.005$).

4 There was a positive association in both placebo and treated groups between the rates of change of BPD and PR ($P < 0.005$ for both); nitrendipine exerted a highly significant ($P < 0.001$) effect on this association compatible with its effect as a vasodilator.

5 Blood loss consequent on TOP did not differ in the two groups (nitrendipine $104 \pm 16\ \text{ml}$; placebo $114 \pm 20\ \text{ml}$).

6 There were no significant differences in basal or stimulated hormone concentrations in the two groups.

7 The *ex vivo* platelet aggregatory response in whole blood to $0.1\ \text{mM}$ sodium arachidonate was inhibited by nitrendipine ($P < 0.05$); responsiveness to the other aggregatory agents studied was not changed.

8 There was a wide individual variation in both time to peak concentration of nitrendipine and the size of the peak, making classical pharmacokinetic analysis impossible. The median time after ingestion to peak concentration was 105 min; the median concentration was $7.8\ \text{ng ml}^{-1}$.

9 These data suggest that, in the context of the severe vasoconstriction and platelet aggregability of pregnancy-induced hypertension, further studies of this drug in pregnancy are warranted.

Keywords calcium channel blockers antihypertensive agents pre-eclampsia pregnancy trimester first platelet aggregation

Correspondence: Dr M. R. Lawrence, Department of Obstetrics and Gynaecology, University Hospital, Queen's Medical Centre, Nottingham NG7 2UH

Introduction

A systemic blood pressure equal to or greater than 140/90 mm Hg will develop in late gestation in some 10% of women in their first pregnancy. A proportion will develop severe hypertension with intense vasospasm, usually with proteinuria, and, in the most severe and life-threatening cases, a widely disseminated intravascular coagulation. Treatment is at present empirical, usually with sympatholytic agents, although there is no evidence of enhanced sympathetic activity in this condition (Assali *et al.*, 1952). Furthermore, the drugs currently used all cross the placenta and exert clinically-detectable effects on the newborn for several days after birth (Dumez *et al.*, 1981; Macpherson *et al.*, 1986). Ethical considerations forbid the introduction of a new class of drug for the treatment of pregnancy-associated conditions without the most careful consideration, and with the performance of such pilot studies as are possible.

There is increasing interest in the possible use of calcium-channel blockers in the treatment of hypertension in pregnancy. Nitrendipine (BAY e 5009) is one of the class of dihydropyridine calcium channel blockers which is a potent anti-hypertensive agent (Kazda *et al.*, 1983a). It has a somewhat longer duration of action than structurally-similar agents, allowing the possibility of once-daily dosage (Kazda *et al.*, 1983b). The dihydropyridines, however, in very high dosage (100 mg kg⁻¹), when administered in early pregnancy, have been associated with the development of minor skeletal anomalies in the primate *Cynomolgus*. Thus their use in very early pregnancy should be contraindicated.

There is no naturally-occurring animal model for pregnancy-induced hypertension (PIH). We have, therefore, carried out studies of the effects of nitrendipine on various cardiovascular parameters in early human pregnancies which were not to progress to term, although the conclusions which can be drawn from these experiments in relation to PIH are necessarily limited by the different gestational ages of our study patients and those who develop PIH.

Methods

Twenty-four healthy women between 9–12 weeks gestation were studied. Various physical characteristics of the patients are summarised in Table 1. All had previously been accepted for therapeutic termination of pregnancy under the terms of the 1967 Abortion Act after counselling by a consultant gynaecologist unconnected with the project. The protocol had been approved by the

Table 1 Physical characteristics of patients in each group (mean $\pm$ s.e. mean)

	Placebo (n = 12)	Nitrendipine group (n = 12)
Age (years)	25.5 $\pm$ 1.5	24.7 $\pm$ 1.9
Weight (kg)	67.0 $\pm$ 3.4	64.8 $\pm$ 3.2
Median gravidity	1	2
Median parity	0	0.5
Gestation (days)	77.9 $\pm$ 2.0	78.6 $\pm$ 1.2

hospital Committee on Ethics, and all subjects gave informed, written consent for participation. No woman gave a positive history of renal, hepatic, cardiovascular or metabolic disease. All denied recent aspirin ingestion.

Patients were allocated in a random, double-blind manner to receive either nitrendipine 20 mg p.o. or an identical placebo (supplied by Bayer U.K. Ltd). Patients were studied supine in a warm, quiet research room. An indwelling venous cannula (Venflon 16G, Viggo AB, Helsingborg, Sweden) was placed in an antecubital fossa for blood sampling. Systemic arterial blood pressure and pulse rate were monitored automatically (Dinamap 845, Johnson & Johnson, England) at 5 min intervals during the first 90 min and at 10 min intervals thereafter. A schematic representation of the time-course of the experiment is given in Figure 1. Basal blood sample size was 15 ml, and an additional 10 ml was taken at 0, 45 and 90 min for platelet function studies. Blood for measurement of renin (PRC) and renin substrate (PRS) concentration was placed in tubes containing EDTA; that for aldosterone (ALD) and nitrendipine determination was placed in tubes containing lithium heparin. Samples were rapidly centrifuged at 1980g and 4°C; plasma was separated and stored at -20° C. The concentrations of ALD, PRC and PRS were determined by radioimmunoassay as previously described (Symonds & Craven, 1977; Tetlow & Broughton Pipkin, 1983). Plasma nitrendipine concentration was measured by gas chromatography/mass spectrometry (Miles Laboratories, Bridgend) with a limit of detection of 0.5 ng ml⁻¹.

Termination of pregnancy was carried out by cervical dilatation and suction curettage of the uterus 152–275 min (mean 222.0 $\pm$ 5.7) after the administration of nitrendipine or placebo. The anaesthetic regime was standardized, and consisted of the administration of intravenous midazolam and methohexitone, the dosages titrated against the state of consciousness of the patient. Oxytocin 5 u i.v. was given routinely at the end of the operation. The same surgeon performed all terminations.

Figure 1 Schematic protocol of the study.

Blood loss at termination of pregnancy and during the following 24 h was determined by the method of Hallberg & Nilsson (1964). The major contaminant of the evacuant will have been amniotic fluid; pilot studies showed this to be without effect on the accuracy of the spectrophotometric method. The recovery of known amounts of added blood was $96.8 \pm 0.6\%$. Studies of platelet function in whole blood were carried out using the method of Fox *et al.* (1982). Briefly, spontaneous platelet aggregation was determined during stirring in response to: adenosine diphosphate $0.5 \mu\text{M}$, adrenaline bitartrate $0.1\text{--}1.0 \mu\text{M}$, thrombin 0.05 u ml^{-1} and sodium arachidonate $0.1\text{--}0.2 \text{ mM}$ (all from Sigma Co Ltd, Poole, Dorset). The platelet aggregation was measured by counting the number of free platelets remaining after addition of the aggregating agent, using an Ultra-flo 100 Whole Blood Platelet Counter (Clay Adams Ltd, England).

Statistics

Arithmetic means $\pm$ s.e. mean are quoted where the data were normally distributed; the use of medians is indicated in the text. Where the data were normally distributed Student's paired and unpaired *t*-tests, one- or two-way analysis of variance (*F*-test; ANOVA) and linear regression analysis have been used as appropriate. Where data were not normally distributed Wilcoxon's tests for paired and unpaired data have been used.

Regression analysis was performed on the raw data for each patient separately, to examine temporal changes in systolic and diastolic pressure and pulse rate over the first 2 h of the experiment. An example of this is shown in Figure 2.

Results

The two groups did not differ significantly with respect to any parameter indicated in Table 1.

Figure 2 Blood pressure (mmHg; ●—●) and pulse rate (beats min^{-1} ; ●---●) data plotted against time for a patient who received nitrendipine 20 mg p.o. at time zero. Superimposed are the corresponding regression lines for this patient from which the trend of changes seen during the first 2 h after ingestion were obtained.

No patient receiving nitrendipine reported any side effects, nor was any marked facial flushing seen.

Blood pressure and pulse rate

Basal effects Regression analysis for temporal trends of blood pressure or pulse rate in placebo-treated individuals showed approximately equal numbers to have experienced small falls or increases in these parameters over the first 2 h after tablet administration. Thus there were no statistically significant changes in these parameters over this time in the group as a whole. However, individual regression analyses in the nitrendipine-treated patients showed 10 of them to have experienced a fall in diastolic pressure over the first 2 h. The change in diastolic pressure from zero time was thus statistically significant ($P < 0.05$). The overall change in diastolic blood pressure was also statistically significantly dif-

Figure 3 Graphical representation of the shift in association between the rates of change of diastolic blood pressure (ΔBP) and pulse rate (ΔPR) in the nitrendipine group, compared with the placebo group: $\bullet$, nitrendipine group $y = 1.05x + 44.5$, $P < 0.005$; $\circ$, placebo group $y = 0.73x - 8.0$, $P < 0.005$.

ferent between the two groups ($P < 0.05$). There was no consistent change in either systolic blood pressure or pulse rate at this time, although the pulse rate showed a tendency to increase ($P < 0.1 > 0.05$).

Visual inspection of the data suggested an association between changes in diastolic pressure and changes in pulse rate (Figure 3). There was, indeed, a strong positive correlation between the rates of change with time of the two variables ($P < 0.005$ for both groups). As can be seen from Figure 3, the slopes of the lines relating the two variables were effectively identical for the two groups, but the intercepts on the y axis were highly significantly different ($P < 0.001$). There was a significant inverse correlation between peak plasma nitrendipine concentrations and the rate of change of diastolic blood pressure in individual patients ($P < 0.02$; Figure 4).

Effects during surgery There was no statistically-significant difference in pre-anaesthetic mean values of blood pressure or pulse rate in the two groups (Table 2). By 5 min after the induction of anaesthesia and start of the procedure, mean diastolic blood pressure in the placebo group had risen 6.0 ± 3.3 mm Hg and had reached $+7.6 \pm 2.2$ mm Hg ($P < 0.01$) by 10 min. There was also a highly significant rise in pulse rate by 5 min ($P < 0.001$) which had risen still further by 10 min ($P < 0.001$; Table 2). Systolic blood pressure did not change significantly during this period. Interestingly, in the nitrendipine-treated

Figure 4 The association between the peak plasma concentration of nitrendipine observed in individual patients and their corresponding rates of change of diastolic blood pressure (ΔBP) during the first 2 h after ingestion. $y = -6.56x + 31.62$, $P < 0.02$.

group, the diastolic blood pressure actually fell slightly in the 5 min after induction of anaesthesia, and only rose slightly in the following 5 min. The difference in response between the two treatment groups was statistically-significant ($P < 0.001$).

Table 2 Mean values ($\pm$ s.e. mean) for systolic (BPS) and diastolic (BPD) blood pressure and pulse rate (PR) at varying times before and after the ingestion of placebo or nitrendipine and during the operative procedure

	BPS (mm Hg)	BPD (mm Hg)	PR (beats min ⁻¹)
<i>Placebo</i>			
Initial basal value	109.6 $\pm$ 2.8	63.4 $\pm$ 2.1	69.8 $\pm$ 2.7
120 min after tablet	109.4 $\pm$ 2.9	64.1 $\pm$ 2.2	69.9 $\pm$ 2.4
Pre-anaesthetic	112.9 $\pm$ 4.1	61.4 $\pm$ 1.9	71.4 $\pm$ 3.6
5 min post-anaesthetic	109.2 $\pm$ 3.9	67.4 $\pm$ 3.3	93.7 $\pm$ 4.4
10 min post-anaesthetic	115.3 $\pm$ 3.7	69.0 $\pm$ 3.3	99.3 $\pm$ 3.7
<i>Nitrendipine</i>			
Initial basal value	112.4 $\pm$ 1.9	64.4 $\pm$ 1.7	65.8 $\pm$ 2.5
120 min after tablet	112.8 $\pm$ 2.2	62.9 $\pm$ 1.2	69.9 $\pm$ 2.0
Pre-anaesthetic	116.6 $\pm$ 3.8	63.9 $\pm$ 2.6	75.1 $\pm$ 5.4
5 min post-anaesthetic	108.5 $\pm$ 2.1	62.8 $\pm$ 1.9	93.8 $\pm$ 4.8
10 min post-anaesthetic	112.9 $\pm$ 4.8	67.0 $\pm$ 3.3	105.5 $\pm$ 5.6

Again, there was no significant change in systolic blood pressure over this time. The pulse rate rose over both periods of observation ($P < 0.002$, $P < 0.001$ respectively; Table 2).

Blood loss consequent on termination of pregnancy

Neither at the time of termination itself nor in the subsequent 24 h was any significant difference observed in blood loss between the two groups. The mean overall loss in the nitrendipine treated group was 104 ± 16 ml while that in the control group was 114 ± 20 ml.

Hormones (Table 3)

Plasma renin concentration showed a tendency to increase over the 2 h following ingestion of nitrendipine or placebo, and this increase was statistically-significant in both groups ($P < 0.05$ for both). No overall trend was determined for PRS in either group, nor did the concentrations differ. There was a small fall in plasma ALD concentration over the first 45 min in both groups (median fall; nitrendipine: -9 ng dl⁻¹, $P < 0.01$; placebo: -7 ng dl⁻¹, $P < 0.05$). Thereafter neither trend nor difference could be discerned in either group. No association could be demonstrated between peak plasma nitrendipine concentrations and changes in any of the hormones measured.

Plasma nitrendipine concentrations

These experiments were not primarily designed to examine the pharmacokinetics of nitrendipine in human pregnancy. Nevertheless, the opportunity was taken to acquire some information as

sampling times for other purposes permitted. Figure 5 shows the wide individual variation in both time to peak concentration and the magnitude of such concentration. The peak concentration was observed at a median of 105 min (range 45–220 min). Maximal concentrations ranged between 3.2 – 14.4 ng ml⁻¹ with a median value of 7.8 ng ml⁻¹. Concentrations of the primary metabolite of nitrendipine (M4786) were also measured. Again, both the time to peak concentration and the concentration itself varied widely, between 45 min–12 h (median 160 min) and between 2.7 – 19.6 ng ml⁻¹ (median 9.3 ng ml⁻¹) respectively. The conventional pharmacodynamic analysis of such data could not therefore be attempted.

Platelet function

No differences in platelet aggregability were observed between treated and control groups in their responses to either adenosine diphosphate, thrombin or adrenaline bitartrate at either sampling time. There was statistically-significantly less aggregation in response to 0.1 mM sodium arachidonate after 2 min stirring in the nitrendipine-treated group 90 min after the ingestion of nitrendipine than in the control group ($P < 0.01$).

Discussion

Hypertension in pregnancy and its sequelae, are the features most frequently associated with maternal death during pregnancy (DHSS, 1986). The hypertension may be longstanding or may apparently arise *de novo* during the pregnancy

Table 3 Medians and ranges of plasma renin concentration (PRC; ngAl ml⁻¹ h⁻¹), renin substrate (PRS; µgAl ml⁻¹) and aldosterone (ALD; ng dl⁻¹) at various sampling times for the two groups of patients

Sample time	Placebo group			Nitrendipine group		
	PRC	PRS	ALD	PRC	PRS	ALD
(min post-dosing)						
0	5.4 (1.2–12.6)	2.4(1.5–4.5)	27.0(13.0–65.0)	5.7(2.4–12.0)	2.6(1.1–4.0)	21.5(9.0–53.0)
45	6.8(1.8–12.0)	2.2(1.4–5.2)	18.8(13.5–52.0)	8.4(4.2–13.5)	2.6(0.8–4.6)	14.3(4.5–40.0)
90	6.0(1.2–10.2)	2.7(1.6–4.7)	17.8(11.0–34.0)	7.5(3.0–13.5)	2.8(1.1–4.6)	19.5(6.0–39.0)
120	8.3(1.5–10.6)	2.2(1.3–5.6)	23.0(11.0–34.0)	7.1(4.2–15.0)	2.8(1.0–4.3)	20.3(5.5–32.5)
pre-operative (214.5 ± 8.8)	8.3(2.4–18.0)	2.5(1.3–5.8)	24.8(13.0–62.0)	9.0(4.5–13.5)	2.4(1.0–3.9)	18.5(6.5–46.5)
300	9.0(3.0–24.0)	2.2(1.6–6.6)	24.0(14.5–54.0)	11.3(6.6–30.0)	2.7(1.4–4.4)	22.8(11.0–52.5)
480	10.8(3.0–27.0)	2.4(1.3–5.3)	32.5(19.0–60.0)	12.0(6.0–24.0)	3.1(1.2–5.2)	31.0(17.0–>80.0)
1440	12.0(6.0–48.0)	2.9(1.1–5.5)	45.0(10.0–77.0)	15.0(9.0–30.0)	3.4(1.1–4.5)	34.0(13.0–77.0)

Figure 5 Plasma concentrations of nitrendipine for the 12 individual patients receiving 20 mg nitrendipine p.o. at time zero.

(PIH) or may be a combination of both. The dihydropyridines are of demonstrable efficacy outside pregnancy (see Klein, 1984; Halperin & Cubeddu, 1986). Pilot studies in pregnancy where single doses have been given to severely hypertensive women showed that the dihydropyridines had a marked antihypertensive effect, without apparent deleterious foetal effects (Walters & Redman, 1984; Walker *et al.*, 1987).

Studies of the effects of nitrendipine in non-pregnant normotensive subjects have been reported (Debbas *et al.*, 1984; Kann *et al.*, 1984). They showed only a small effect on resting blood pressure in normotensive adults (Millar *et al.*, 1983; Debbas *et al.*, 1984) but an increasingly large effect as basal blood pressure rose. Our patients were normotensive women at a stage of pregnancy in which total peripheral resistance and systemic arterial pressure are falling towards a nadir (Christianson, 1976). The hypotensive effect of 20 mg nitrendipine was small, though statistically-detectable, in these patients. It appears possible that arteriolar dilatation is already close to maximal physiological values in these patients, so that the administration of a vasodilator has very little effect. In PIH however, a state of marked vasoconstriction, the effects would be expected to be substantially greater.

Following the acute administration of nitrendipine, unlike some other dihydropyridines, there is a small rise in heart rate, believed to be reflexly mediated, which is not maintained during chronic therapy (Andren *et al.*, 1982; Nannan *et al.*, 1984). A small overall rise in pulse rate was also seen in the patients of this paper (Table 2). The association between the rates of change of

diastolic pressure and pulse rate, which in the placebo group passes through the origin of the graph, presumably indicates the variation of response in individuals to the combined stimuli of supine recumbency and inevitable apprehension regarding the forthcoming operative procedure. Thus some patients showed the fall in systemic blood pressure and pulse rate usual during a period of rest, while those more apprehensive evidenced increases, presumably sympathetically-mediated, in both parameters. The parallel leftward shift of the association in the group treated with nitrendipine may reflect superimposed reflex adaptation of pulse rate to the vasodilatation evoked by the drug.

There was a statistically-significant difference in the response of the diastolic pressure during the operative procedure in the two groups, an early increase in the placebo group being contrasted with a small fall in the treatment group. Nitrendipine appears not to change the magnitude of the sympathetic response to various manoeuvres (Lehmann *et al.*, 1983; Franz & Wiewel, 1984; Nannan *et al.*, 1984), but a blunting of pressor response to exogenous adrenaline has been noted in conscious pregnant sheep in the presence of therapeutic plasma concentrations of nitrendipine (Lawrence & Broughton Pipkin, 1987). Cervical dilatation was begun during the first 5 min and will have evoked a catecholamine surge. The pressor effects of this surge could thus have been blunted by nitrendipine. Furthermore, manipulation of the cervix is associated with a substantial release of prostaglandins (Mitchell *et al.*, 1977). Studies *in vitro* have shown that in the presence of nitrendipine the

concentration-response curves of human vascular smooth muscle to E-series prostaglandins are shifted to the right (Broughton Pipkin & Chinnery, 1985). Thus some blunting of response to released prostaglandins may have occurred.

The dihydropyridines have been shown to relax both spontaneous and oxytocin-induced contractions of human uterine smooth muscle both *in vivo* and *in vitro* (Ulmsten *et al.*, 1978; Forman *et al.*, 1979, 1982). Menorrhagia has been described in association with nifedipine therapy in two case reports (Rodger & Torrance, 1983; Singh *et al.*, 1983), possibly related to a failure by the basal arterioles to constrict. One of the objects of this study was thus to ascertain whether the administration of nitrendipine shortly before termination of pregnancy was associated with an increased blood loss, since adequate uterine contraction is a major requirement for successful haemostasis at delivery. Our data show no evidence for an enhanced blood loss at termination in conjunction with nitrendipine therapy, the losses being effectively identical. Thus although individual idiosyncrasy to treatment cannot be ruled out, plasma concentrations of nitrendipine within the therapeutic range under these circumstances do not appear adversely to affect appropriate uterine contractility.

There was no detectable difference between the treated and placebo groups in the sequential changes of PRC, PRS and ALD concentration, which were presumably due to the operative procedure (Table 3). It has been suggested that the administration of dihydropyridines such as nifedipine and nitrendipine is associated with an increased activity of the renin-angiotensin system (RAS) without the expected parallel increase in plasma ALD (Millar *et al.*, 1983; Luft *et al.*, 1985). However, inspection of the published data suggests that where the RAS is activated, plasma ALD does rise, albeit to a proportionally lesser extent (Luft *et al.*, 1985). Where the administration of a dihydropyridine is without effect on basal PRC, as with the subjects cited by Millar *et al.* (1983) and those of this paper, then basal ALD concentration does not differ from those treated with placebo.

The median peak plasma concentration of nitrendipine was somewhat lower than that reported in two studies of normal non-pregnant adults (Aronoff, 1984; Kann *et al.*, 1984) but within a similar range for a third study (Lasseter *et al.*, 1984). The subjects in the non-pregnant studies were all male, and the dose per kilogram bodyweight will have been some 20% higher in the patients of this paper. There will however have been a greater volume of distribution and a higher proportion of body fat per kilogram in the

pregnant patients which, since nitrendipine is very lipid-soluble, would be expected to offset this difference. The time to peak concentration was remarkably similar in the various studies and was evidently not influenced in our patients by the somewhat slower rate of absorption from the gastrointestinal tract in pregnancy.

In this study, using whole-blood aggregometry (Fox *et al.*, 1982), no differences in platelet aggregation in response to either adrenaline, ADP or thrombin could be demonstrated following the administration of 20 mg nitrendipine. Dihydropyridines have been shown to decrease platelet aggregability to adrenaline, ADP and collagen in platelet rich plasma in normotensive non-pregnant subjects and those with cardiac disease (Fritschka *et al.*, 1986; Dale *et al.*, 1983). Whether the lack of response in the patients of this paper relates to the use of a whole blood aggregometry technique or to the fact of their pregnancy, with its associated increase in baseline platelet aggregability, is not at present known. There was however a diminished aggregation to 0.1 mM sodium arachidonate in these patients. PIH is associated with much enhanced platelet aggregability in whole blood (Burgess-Wilson *et al.*, 1986) and subsequent thrombocytopenia, believed to be consequent on an imbalance in prostacyclin:thromboxane production (see Broughton Pipkin & Symonds, 1986); this effect might therefore be of some therapeutic relevance.

In conclusion, we have shown that the administration of a stat dose of nitrendipine 20 mg p.o. to normotensive women in first trimester pregnancy is associated with a small fall in diastolic pressure, the magnitude of which is related to plasma nitrendipine concentrations; that there is a large individual variability in both the time to, and the absolute value of peak nitrendipine concentrations; that its effects both on blood loss consequent on termination of pregnancy and those plasma hormones measured were negligible, and that it evoked a small inhibition of platelet aggregation in response to 0.1 mM sodium arachidonate. Until the underlying cause of PIH is elucidated, the choice of treatment will continue to be empirical. However, the characteristic combination of intense vasoconstriction and platelet aggregability, in conjunction with the data presented above and other available information about nitrendipine suggest that further studies on its potential usefulness in the treatment of PIH are warranted.

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