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Influence of cardiopulmonary resuscitation on plasma concentrations of nimodipine in the dog

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The influence of cardiopulmonary resuscitation on the plasma concentrations of nimodipine in the anaesthetized dog has been examined. Nimodipine was given as a bolus injection followed by a maintenance infusion. When, during the maintenance infusion, the dogs were subjected to cardiac arrest followed by external cardiac massage combined with artificial ventilation (basic life support), a fast and almost threefold increase in the steady-state plasma concentrations of nimodipine was observed. When the maintenance infusion of nimodipine was stopped immediately before cardiac arrest and basic life support, the nimodipine concentrations decreased. These results indicate that during basic life support, there is a decreased transfer of infused nimodipine from plasma to the tissues. This is also supported by the fact that for antipyrine, a drug with a smaller volume of distribution than nimodipine, the increase in plasma concentrations when infused during cardiac arrest and basic life support, was much smaller. When nimodipine was started after restoration of the spontaneous circulation (advanced life support) in dogs that had been subjected to cardiac arrest and basic life support, the plasma concentrations were not significantly higher than in control dogs. It can be concluded that the fate of nimodipine is markedly altered during basic life support but not in the period following restoration of spontaneous circulation.

There is much interest in the use of calcium entry blockers as cerebro-protective agents in patients resuscitated after cardiac arrest (Bircher 1985; Dearden 1985). During cardiopulmonary resuscitation, the cardiovascular system is severely compromised and this can markedly alter the fate of drugs as shown, e.g., for lignocaine (lidocaine) in dog and man (Chow et al 1981, 1983). Since such data are not available for calcium entry blockers, we studied the fate of a calcium entry blocker in a canine model of cardiac arrest. The dihydropyridine derivative, nimodipine, was chosen because it has been described as a preferential cerebral vasodilator (Kazda & Towart 1982) and because it has been shown to improve the neurological outcome when given after complete cerebral ischaemia in primates (Steen et al 1985). The results obtained show markedly elevated plasma concentrations when nimodipine was infused during cardiac arrest and external cardiac massage, but not when the drug was infused after restoration of spontaneous circulation.

METHODS

Mongrel dogs of either sex, 5·5–18 kg, were anaesthetized with ketamine given as an i.v. bolus injection of 7 mg kg^{-1} and followed by a continuous infusion of 0·2 mg kg^{-1} min^{-1} throughout the experiment. Muscle paralysis was obtained with gallamine (bolus injection of 1 mg kg^{-1}), followed by a continuous infusion of 0·01 mg kg^{-1} min^{-1} (Jackson et al 1984). Endotracheal intubation or tracheostomy was carried out and the animals were mechanically ventilated (tidal volume 20 mL kg^{-1}, rate 12 min^{-1}, FiO_2 0·3).

A rectal temperature probe was inserted, and a heating pad was applied to maintain body temperature at 39 °C. Arterial blood pressure was measured using a Statham pressure transducer connected to a catheter introduced via the left femoral artery; the tip of the catheter was located in the aortic arch and blood pressure was recorded on a Beckman dynograph type R recorder. Electrocardiographic registration was obtained from standard leads and displayed on an oscilloscope (Scopette, Corbin-Farnsworth, Inc.).

Drug administration and assay

Nimodipine was given in a femoral vein as a bolus injection of 18 μg kg^{-1} over 3 min followed by a maintenance infusion of 0·55 μg kg^{-1} min^{-1}, since, from data obtained in preliminary experiments (Huyghens et al 1985), it was calculated* that this dosing regimen would lead to a steady-state plasma

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* The infusion rate (Ko) was calculated using the formula C_{ss} = Ko/Vd Ke, where C_{ss} = steady-state plasma concentration, Vd = apparent volume of distribution, Ke = elimination constant. The loading dose (D) was calculated using the formula D = C_{ss} Vd.

concentration of approximately 7 ng mL^{-1}, the plasma concentration found in patients with subarachnoid haemorrhage treated with nimodipine (Allen et al 1983). Antipyrine was given as a bolus injection of 21 mg kg^{-1}, followed by an infusion of 0·2 mg kg^{-1} min^{-1}; it was calculated* from the data of Belpaire et al (1983) that this would lead to a steady-state plasma concentration of 30 μg mL^{-1}.

Blood samples for determination of drug plasma concentrations were withdrawn either via a catheter in the right jugular vein or via a catheter in the right femoral artery.

Nimodipine was determined in plasma by capillary gas chromatography with nitrogen detection (Rosseel & Bogaert 1987), while antipyrine was measured with gas chromatography with flame ionization detection (Van Peer et al 1978).

Cardiac arrest and resuscitation procedures

Complete cardiorespiratory arrest was induced by an external transthoracic shock (60 Hz and 20–40 V AC) causing ventricular fibrillation (Vaagenes et al 1984) and by stopping mechanical ventilation.

Basic life support consisted of external cardiac compression either manually or with a Thumper mechanical resuscitator (Cardi 02, Michigan Instruments, Inc.) as specified in the section on experimental design. With both methods the compression force was adjusted to obtain a mean aortic pressure of about 35 mmHg. In the experiments with manual massage, the compression rate was 1 Hz and the ventilation was continued as before cardiac arrest; in the experiments with mechanical massage, compression rate was also 1 Hz and compression duration 0·5 s; after every fifth compression, diastole was prolonged by 0·5 s and the lungs were inflated to an inspiratory pressure of 15 cm H_2O at an FiO_2 of 1·0 (Rudikoff et al 1980). Sodium bicarbonate was administered as a bolus dose of 1 mequiv kg^{-1}, followed by a continuous infusion of 0·5 mequiv kg^{-1}/10 min (American Heart Association 1980) in the experiments where the dogs received only basic life support. Advanced life support consisted of the bolus administration of adrenaline (0·1 mg kg^{-1}) and sodium bicarbonate (2 mequiv kg^{-1}) into the aortic arch (Mullie et al 1982), followed by transthoracic defibrillation with a direct current countershock of 100 Joules. This countershock was repeated if necessary with successive increments of 50 Joules (Vaagenes et al 1984).

Experimental design

Nimodipine was given to 4 groups of animals. A first group of 4 control animals, not subjected to cardiac arrest, received a nimodipine infusion over 120 min.

A second group of 5 animals received a nimodipine infusion over 126 min; after 60 min of drug infusion, cardiorespiratory arrest was induced and was followed after 3 min by basic life support for 63 min, while the nimodipine infusion continued. External cardiac compression was done manually in 3 out of the 5 dogs.

In a third group of 4 animals the nimodipine infusion was stopped at the 60th min, i.e. at the moment of the induction of cardiorespiratory arrest; cardiac arrest was followed after 3 min by basic life support with mechanical massage for 63 min.

In a fourth group of 12 dogs, 6 were subjected to cardiorespiratory arrest followed after 3 min by basic life support (manual massage) for 3 min and then by advanced life support. Nimodipine was only started at 10 min after restoration of spontaneous circulation. The six other dogs also received nimodipine at the same dose regimen without having been subjected to cardiac arrest and resuscitation.

Antipyrine was given in two groups of animals. A first group of 7 animals received antipyrine over 126 min; after 60 min of drug infusion, cardiorespiratory arrest was induced and was followed after 3 min by basic life support for 63 min, while the antipyrine infusion continued. External cardiac compression was done manually in 2 out of the 7 dogs.

A second group of 7 animals received an antipyrine infusion only during 60 min, i.e. until the induction of cardiorespiratory arrest; cardiac arrest was followed after 3 min by basic life support for 63 min. External cardiac compression was done manually in 1 out of 7 animals.

Analysis of data

The values given are means ± s.e.m. To detect changes in plasma concentrations in the course of an experiment a two way-analysis of variance was carried out. The statistical significance of these changes was subsequently verified with a paired *t*-test. A Mann-Whitney U-test was used to compare the nimodipine group with the antipyrine group.

In the animals receiving nimodipine after restoration of spontaneous circulation and their controls (group 4), the area under the curve was calculated using the trapezoidal rule and a Mann-Whitney U-test was used to compare the resuscitated dogs with their controls.

RESULTS

Nimodipine plasma concentrations

Control dogs. With the dosing regimen used, steady-state plasma concentrations of nimodipine were

reached within 30 min and were maintained during the 120 min infusion as shown for 4 dogs (group 1) in Fig. 1. The mean steady-state plasma concentration after 60 min of nimodipine infusion in the control dogs and in the 9 dogs receiving nimodipine before cardiac arrest (see below) was 12·3 ± 1·6 ng mL^{-1}.

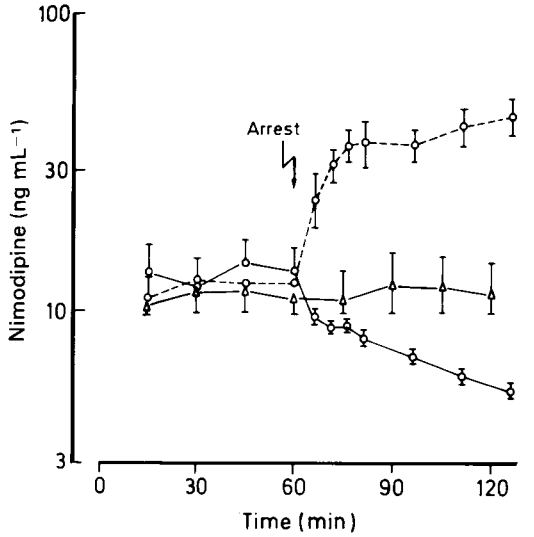

FIG. 1. Nimodipine plasma concentrations (mean ± s.e.m.) in control animals and during basic life support (BLS). Key: O- - -O, BLS under continuous nimodipine (n = 5); O——O, BLS after stopping nimodipine (n = 4); △——△, continuous nimodipine without BLS (n = 4).

Nimodipine infusion continued during basic life support. As shown in Fig. 1, the plasma concentrations of nimodipine increased markedly in the course of the 5 experiments of group 2 (two way-analysis of variance: $P = 0{\cdot}001$). The increase in plasma concentrations occurred soon after the start of basic life support: the mean plasma concentration after 13 min of basic life support, 36·9 ± 3·7 ng mL^{-1}, was 3 times higher than the average of the mean plasma concentrations at 45 and 60 min of infusion in the pre-arrest period, 12·3 ± 2·6 ng mL^{-1} (paired *t*-test: $0{\cdot}001 < P < 0{\cdot}01$).

Nimodipine infusion stopped before cardiac arrest. In 4 dogs (group 3) nimodipine was infused over 60 min and the infusion was stopped just before cardiac arrest and basic life support. In these experiments the plasma concentrations of nimodipine declined progressively during the 63 min of basic life support (two way-analysis of variance: $P < 0{\cdot}001$), as shown in Fig. 1.

Nimodipine infusion started after advanced life support. As shown in Fig. 2, the mean nimodipine plasma concentrations in the animals of group 4 that were subjected to cardiac arrest and resuscitation, were somewhat higher than in their controls. However, the AUC 3–60 min was not significantly different: 984 ± 148 ng mL^{-1} min^{-1} in the resuscitated dogs versus 804 ± 94 ng mL^{-1} min^{-1} in their controls (Mann-Whitney U-test: $P > 0{\cdot}05$).

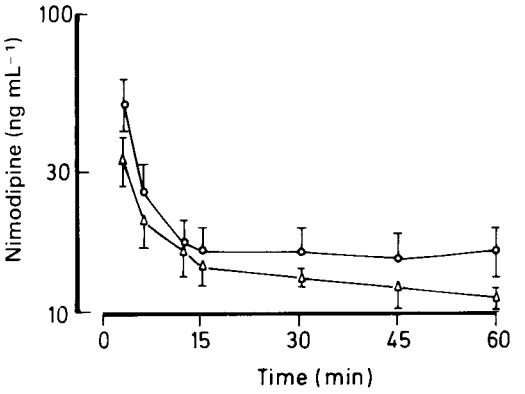

FIG. 2. Plasma concentrations (mean ± s.e.m.) of nimodipine given in dogs after resuscitation from cardiac arrest (O——O, n = 6) and in control dogs not subjected to cardiac arrest (△——△, n = 6).

Antipyrine plasma concentrations

Antipyrine infusion continued during basic life support. As shown in Fig. 3 the plasma concentrations of antipyrine increased significantly in the course of the experiments of group 1 (two way-analysis of variance: $P = 0{\cdot}001$). This increase occurred soon after the start of basic life support: the mean plasma concentration after 13 min of basic life support, 30·1 ± 7·7 μg mL^{-1}, was significantly higher than the average of the mean plasma concentrations at 45 and 60 min of infusion in the pre-arrest period, 18·7 ± 3·9 μg mL^{-1} (paired *t*-test: $0{\cdot}01 < P < 0{\cdot}05$).

Antipyrine infusion stopped before cardiac arrest. In 7 dogs (group 2) antipyrine was infused over 60 min and stopped before the induction of cardiorespiratory arrest and basic life support. As shown in Fig. 3 the plasma concentrations of antipyrine remained constant during basic life support.

Blood pressure during basic life support and after restoration of spontaneous circulation

The mean arterial blood pressures before cardiac arrest and during basic life support are shown in Fig.

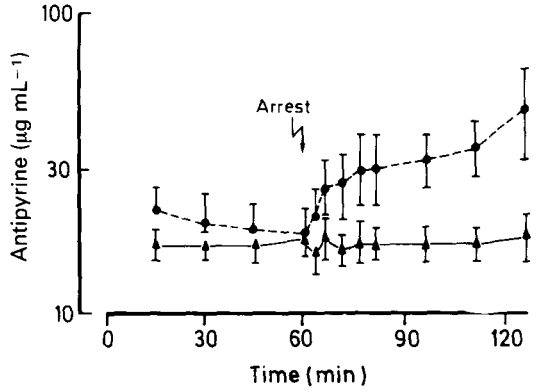

FIG. 3. Antipyrine plasma concentrations (mean ± s.e.m.) during basic life support (BLS). Key: ●——●, BLS under continuous antipyrine (n = 7); ▲——▲, BLS after stopping antipyrine (n = 7).

4. In the dogs receiving a continuous infusion of nimodipine during basic life support, the blood pressure before cardiac arrest was significantly lower than in those receiving a continuous infusion of antipyrine (Mann-Whitney U-test: $0{\cdot}03 < P < 0{\cdot}05$); the percentage decrease in blood pressure during basic life support was larger in the antipyrine group than in the nimodipine group (Mann-Whitney U-test: $P = 0{\cdot}05$).

In the dogs receiving nimodipine until cardiac arrest, the blood pressure before cardiac arrest was lower than that in dogs receiving antipyrine until cardiac arrest, but this difference was not significant; the percentage decrease in blood pressure during basic life support in the nimodipine and the antipyrine group was not significantly different.

The mean blood pressure values in the animals receiving nimodipine after restoration of spontaneous circulation (advanced life support), and in the control group not subjected to cardiac arrest but also receiving nimodipine, are summarized in Table 1. The mean blood pressure values found before cardiac arrest and before nimodipine infusion in both groups are comparable. During the infusion of nimodipine, however, the mean blood pressure was significantly lower in the resuscitated dogs than in the animals not subjected to cardiac arrest and resuscitation.

DISCUSSION

The aim of the present study was to investigate the influence of cardiopulmonary resuscitation on the pharmacokinetics of the calcium entry blocker, nimodipine, a substance of potential clinical interest as a cerebroprotective agent (White et al 1984; Steen et al 1985; Dearden 1985; Bircher 1985). With the dosing regimen of nimodipine used, steady-state plasma concentrations were achieved within 30 min of infusion and could be maintained over at least 2 h.

The mean steady-state plasma concentrations of nimodipine after 60 min of infusion and before cardiorespiratory arrest were higher than we expected on the basis of single dose kinetics. This can possibly be explained by the drug changing the liver blood flow and so its own elimination, as described for another dihydropyridine derivative, nifedipine (Hamann & McAllister 1983).

Table 1. Mean arterial blood pressure in mmHg (mean ± s.e.m.) during infusion of nimodipine in resuscitated and in control animals.

Animals resuscitated after cardiac arrest (n = 6)		Animals without cardiac arrest (n = 6)	
Before cardiac arrest and nimodipine	141 ± 11	Before nimodipine	138 ± 9
After cardiac arrest and during nimodipine		During nimodipine	
3 min	75 ± 7*	3 min	96 ± 12
15 min	63 ± 3*	15 min	107 ± 16
30 min	62 ± 5*	30 min	118 ± 17
60 min	64 ± 6*	60 min	120 ± 12

* Mann-Whitney U-test: $0{\cdot}005 < P < 0{\cdot}01$.

We first looked at the influence of cardiorespiratory arrest and basic life support on steady-state plasma concentrations, as this allows observation of the pharmacokinetic changes within the same animal. During basic life support following cardiorespiratory arrest, there was a fast and marked increase in the plasma concentrations with continuous infusion of nimodipine. This increase is probably related to the severe circulatory failure reflected by the profound drop in mean blood pressure during basic life support and could, from a theoretical point of view, be due to changes in elimination and/or distribution (Pentel & Benowitz 1984). A decrease in hepatic elimination, without a concomitant change in volume of distribution, cannot explain our results. Indeed, a decrease in hepatic clearance would only lead to such a marked increase in concentrations after a much longer period, as the half-life of nimodipine in intact dogs is around 0·5 h (Huyghens et al 1985). If the hepatic elimination stopped completely, again without a change in volume of distribution, on the basis of an estimate of the volume of distribution (around 2·5 L kg^{-1}, Huyghens et al 1985) it is possible to calculate that, under continuing infusion, after 13 min of basic life

support, the concentration increase could not exceed 3 ng mL^{-1}; in fact, it is more than 25 ng mL^{-1}. Therefore, it must be concluded that the distribution of the substance has changed. To see whether a transfer of nimodipine from tissues to plasma during basic life support could explain the fast increase in nimodipine plasma concentrations, the effect of basic life support on the plasma concentrations of nimodipine was studied in animals in which the infusion of nimodipine was not continued after the induction of cardiorespiratory arrest. As under these conditions a decrease in the plasma concentrations was observed, it is unlikely that transfer from tissues to plasma occurs during basic life support.

Therefore, the fast increase in plasma concentrations of nimodipine may be explained by a decreased transfer of the nimodipine infused during basic life support, from the plasma compartment to the tissues. A similar explanation has been given for the high plasma concentrations of lignocaine seen during basic life support in dogs (Chow et al 1983).

If this explanation holds true, it might be expected that for drugs with a smaller volume of distribution there would be a smaller increase in concentration. For antipyrine, which has a volume of distribution equal to body water, the relative increase of the plasma concentrations measured after 13 min of basic life support is indeed smaller than for nimodipine (55 ± 14% versus 256 ± 80%; Mann-Whitney U-test: $P = 0{\cdot}01$). The smaller increase with antipyrine cannot be explained by a difference in haemodynamic effects of the drugs. Indeed, the mean arterial blood pressure in the nimodipine group before cardiac arrest was lower than in the antipyrine group, probably because of the peripheral vasodilatory properties of nimodipine (Kazda et al 1982), but during basic life support the mean arterial pressure in the antipyrine group was not different from the nimodipine group. Therefore, the percentage drop in blood pressure was even more pronounced in the antipyrine group than in the nimodipine group.

In the experiments in which the infusion was stopped before cardiorespiratory arrest, the nimodipine plasma concentrations decreased, while under similar conditions the antipyrine plasma concentrations remained unchanged. This cannot be explained by haemodynamic differences, since the percentage decreases in blood pressure, as well as the values of the mean arterial blood pressure during basic life support in the antipyrine group, were not significantly different from those in the nimodipine group (Fig. 4). A possible explanation for this discrepancy might be that antipyrine is metabolized oxidatively while nimodipine is dehydrogenated and demethylated, but also hydrolysed (Meyer et al 1983), a step that does not require oxygen. Hence, it might be speculated that under the hypoxic conditions of basic life support, the antipyrine metabolism decreases while nimodipine continues to be metabolized. Obviously further experiments, with measurement of metabolites of nimodipine, are needed to test this hypothesis.

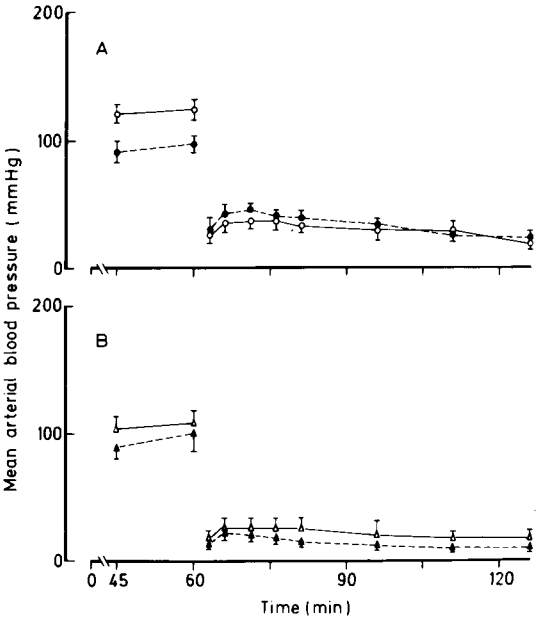

FIG. 4. Mean arterial blood pressure (mean ± s.e.m.) before cardiac arrest and during basic life support (BLS) under continuous drug infusion (upper panel) and in the experiments in which drug infusion was stopped before cardiac arrest (lower panel). Key: ○——○, BLS under continuous antipyrine (n = 7); ● · · · ●, BLS under continuous nimodipine (n = 5); △——△, BLS after stopping antipyrine (n = 7); ▲ – – – ▲, BLS after stopping nimodipine (n = 4).

Since important changes in nimodipine disposition occur during basic life support, we also investigated whether such changes occur in the post-resuscitation period. In these experiments nimodipine was started after restoration of spontaneous circulation since this corresponds with the clinical situation in which nimodipine is administered after cardiopulmonary resuscitation (Roine et al 1987). Although the plasma concentrations of nimodipine in the resuscitated animals tended to be higher throughout the 60 min infusion period, there was no significant

difference with the control animals. These results suggest that the drug disposition of nimodipine is not markedly altered in the post-resuscitation period. However this does not exclude that with longer cardiorespiratory arrest and resuscitation times, as present in some patients, the fate of nimodipine may still be altered in the post-resuscitation period. Therefore a study of the pharmacokinetics of nimodipine administered to patients resuscitated from a cardiorespiratory arrest is necessary.

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