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Central Origin of Respiratory Arrest in Beta-Blocker Intoxication in Rats

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Central Origin of Respiratory Arrest in Beta-Blocker Intoxication in Rats. LANGEMEIJER, J. J. M., DE WILDT, D. J., DE GROOT, G., AND SANGSTER, B. *Toxicol. Appl. Pharmacol.* **89,** 399–407. Propranolol HCl (7.5 $mg \cdot kg^{-1}$), timolol maleate (7.0 $mg \cdot kg^{-1}$), and sotalol HCl (10 $mg \cdot kg^{-1}$) were administered intracerebroventricularly (icv) to spontaneously breathing (SB) rats. The respiratory rate declined until the rats all died from respiratory arrest. Artificial ventilation resulted in survival of the rats for a 3-hr observation period. Intravenous (iv) administration of the same doses of the three beta blockers to SB rats did not result in either respiratory depression or death. Except for a decrease in heart rate (HR) the hemodynamic and respiratory parameters remained almost constant during the 3-hr observation period after iv administration to SB rats. After icv administration to SB as well as to ventilated rats no significant differences could be observed in the initial decrease in HR in comparison with iv administration. In SB rats at the end of the experiments a further decrease in HR was observed which might be ascribed to hypoxia since it did not occur in ventilated rats. After icv administration of each drug to the ventilated rats, mean arterial blood pressure showed a significantly greater decrease at the end of the 3-hr observation period than after iv administration. Plasma concentrations of the three drugs were determined just before death after icv administration in SB rats. In the other two groups they were measured at mean survival time and at the end of the experimental period. The plasma concentrations showed that the route of administration rather than the concentration of the beta blocker in plasma determines the occurrence of respiratory arrest. It was concluded that an overdoes of propranolol, timolol, or sotalol can cause a centrally mediated respiratory arrest. Furthermore, a central mechanism appears to be implicated in the decrease in blood pressure.

Treatment of patients suffering from beta-blocker intoxication is directed mainly toward antagonizing cardiovascular manifestations such as bradycardia, hypotension, and low cardiac output. Both clinical (Frishman *et al.*, 1979) and experimental (Strubelt, 1984) studies have shown beta sympathomimetics to be the most effective drugs in the treatment of the hemodynamic disturbances after beta-blocker overdosage. Nevertheless, in a number of clinical cases such treatment has failed to prevent a fatal outcome (Montagna and Groppi, 1980; Shore *et al.*, 1981; Laake *et al.*, 1981; Hong *et al.*, 1983; Jean *et al.*, 1984). This has led to the assumption that other properties in addition to beta blockade determine the clincial course after an overdose of a beta blocker (Hong *et al.*, 1983; Sangster *et al.*, 1984).

Experiments in reserpinized (De Wildt *et al.*, 1984) and nonreserpinized (Langemeijer *et al.*, 1986) isolated rat hearts confirmed this assumption. In these models an overdose of propranolol, timolol, or sotalol caused a de-

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crease in myocardial contractility which could not be explained by the action of these drugs upon the beta receptor nor by a local anesthetic effect.

Since the *in vitro* experiments were concerned only with the effect upon the isolated myocardium, in another series of experiments the three drugs were administered intravenously to intact rats (Langemeijer *et al.*, 1985). The results showed that the primary cause of death from an overdose of propranolol, timolol, or sotalol was respiratory arrest. Artificial ventilation significantly prolonged the survival time after administration of the same doses. The total doses administered before the ventilated animals died as a result of cardiovascular failure were significantly higher for each drug. Since there were no significant changes in the blood gas levels during artificial ventilation, a central cause of respiratory arrest was considered to be more likely than a neuromuscular cause. In order to determine whether the three beta blockers had a central effect on respiration, in the present study each drug was injected into the lateral cerebral ventricle of both spontaneously breathing and artificially ventilated rats.

METHODS

The experiments were performed on male rats (Wi/CPB, TNO, Zeist, The Netherlands) weighing 280–320 g. Five days before the experiments a cannula was placed into the lateral cerebral ventricle as described by De Wied (1976). The rats were anesthetized with pentobarbital (60 $mg \cdot kg^{-1}$, intraperitoneally) and placed in a stereotact. After exposure of the surface of the skull, a hole was bored, 1 mm posterior and 1 mm lateral to bregma, through which a PE 50 cannula was inserted into the lateral cerebral ventricle. The cannula was secured by means of two screws and dental cement and the skin was closed. At the end of each experiment methylene blue was injected in order to check the position of the cannula visually. After a 5-day recovery period the rats were anesthetized with urethane ($1.1\ g \cdot kg^{-1}$, intraperitoneally). All the rats were tracheotomized and placed in the dorsal position. In spontaneously breathing rats the cannula was connected to a Fleisch head (0000) in conjunction with a pneumotachograph (Godard). Respiratory rate and tidal volume were determined. In artificially ventilated rats the cannula was connected to a volume constant ventilator (Harvard Model 680 small-animal respirator). These animals were ventilated with room air at a frequency of 60 min^{-1} with a tidal volume of 3 ml. The right femoral vein was cannulated and saline (NaCl 0.9%) was administered using an infusion pump (Braun, 2.25 $ml \cdot hr^{-1}$). The right femoral artery was cannulated and the cannula was connected to a pressure transducer (Hewlett–Packard 1280 C). Blood pressure measurements (BP) were recorded (Hewlett–Packard 7758 A). Mean arterial pressure (MAP) was calculated as diastolic pressure plus $\frac{1}{3}$ pulse pressure. The electrocardiogram was taken from needle electrodes applied to the extremities subcutaneously. Standard leads I, II, and III were recorded on an ECG amplifier (Elema-Siemens). Heart rate (HR) was calculated from the R-peaks.

Throughout the experiments, rectal temperature was recorded and maintained at approximately 37°C by radiant heat.

Blood samples (0.8 ml) were taken from the right femoral artery for the determination of plasma concentrations of the beta blockers after discarding the first 0.1 ml of blood from the cannula.

Drug analysis. Propranolol, timolol, and sotalol were quantified in plasma by high-performance liquid chromatographic methods (De Groot *et al.*, 1985). A liquid chromatograph (Model 1884 B, Hewlett Packard) equipped with a reverse-phase column (Hypersil ODS, Shandon) and a variable-wavelength ultraviolet detector (Spectroflow 773, Kratos) operated at 225 nm (propranolol, sotalol) or 295 nm (timolol) was used. Propranolol concentrations lower than 1 $mg \cdot liter^{-1}$ were detected by a fluorescence detector (Model RF 530, Shimadzu) operated at 282 nm (excitation) and 334 nm (emission). Chromatographic separation was by ion-pair chromatography using sodium 1-heptane sulfonate as the ion-pairing agent. Internal standards were carazolol and practolol. The drugs were separated from plasma by solid-phase extraction procedures using ODS extraction columns (J. T. Baker).

Statistics. Statistical analysis was performed by Student's t test for paired and unpaired data; $p = 0.05$ was considered the limit of significance. Results are expressed as means ± SE.

Experimental protocol. The drugs used in the experiments were propranolol HCl, timolol maleate, and sotalol HCl. The three drugs were administered intracerebroventricularly (icv) in a volume of 20 μl of saline. Appropriate icv doses were derived from pilot experiments. From a dose–range finding study a minimal dose for each drug that resulted in death within a reasonable time interval was chosen for measuring the time course of hemodynamic and respiratory parameters. From the steep dose–lethality curve the lethal doses proved to be 7.5 mg of propranolol HCl, 7.0 mg of timolol maleate,

and 10 mg·kg^{-1} of sotalol HCl, respectively. The beta blockers were dissolved in 2 ml of saline at a concentration such that the requisite dose of each drug was contained in 20 μl of the solution. The pH of the solution was adjusted to between 7.3 and 7.4 by means of 1 N NaOH. The maximal volume of NaOH used was 0.1 ml.

After a 30-min period of stabilization, a bolus of each drug was injected into the cerebral ventricle in the spontaneously breathing and in the artificially ventilated rats (n = 6 for each drug in both groups). In another group of spontaneously breathing rats (n = 6 for each drug), a bolus of the same dose of each of the three drugs was administered intravenously over a period of 2 min in a volume of 1 ml of saline. Three control groups (n = 6 in each group) were used. In two of them, 20 μl of saline was injected icv either into spontaneously breathing rats or into artificially ventilated rats. In the third group 1 ml of saline was injected intravenously (iv). The rats were observed for 3 hr or until no mechanical cardiac activity could be observed.

In the group of spontaneously breathing rats which had been given an icv injection, blood for the determination of the plasma concentrations of the drugs was withdrawn just before death occurred. In both of the other two groups blood samples were taken both at the mean survival time of the corresponding spontaneously breathing rats and at 3 hr after the start of the experiment.

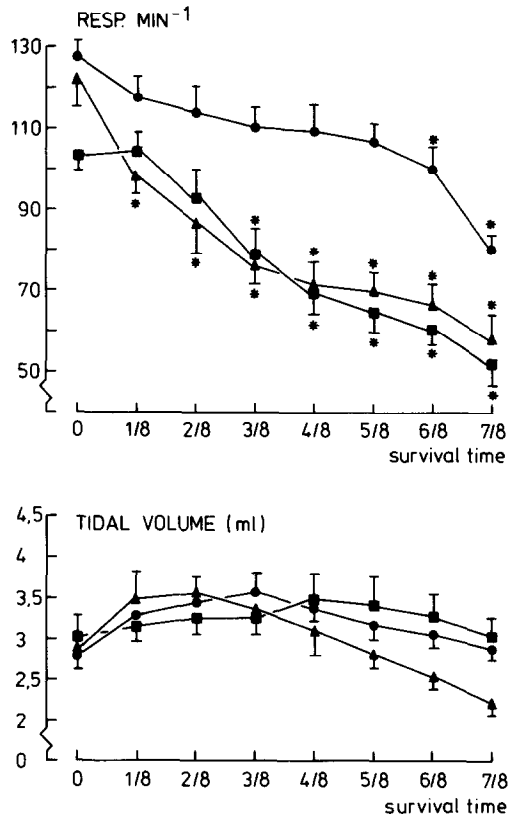

FIG. 1. The influence of an intracerebroventricular injection of propranolol HCl (▲; 7.5 mg·kg^{-1}), timolol maleate (■; 7 mg·kg^{-1}), and sotalol HCl (●; 10 mg·kg^{-1}) on respiratory rate and tidal volume in urethane-anesthetized rats measured from 0 to 7/8 of the total survival time. Mean values ± SE (n = 6). *Significantly different from preadministration values.

RESULTS

Control

In the three control groups in which saline was injected icv or iv no effect was observed and the respiratory and cardiovascular parameters remained constant throughout the 3-hr period during which the rats were observed.

Intracerebroventricular Administration in Spontaneously Breathing Rats

After icv administration of propranolol, timolol, or sotalol in spontaneously breathing rats, the animals died as a result of respiratory arrest after 13 ± 3, 39 ± 16 and 65 ± 11 min, respectively. The respiratory rate declined immediately after administration until at the end of the experiment no spontaneous respiration could be detected. The tidal volume rose until $\frac{3}{8}$ of the survival time, after which a decline was observed until the end of the experiment (Fig. 1). Immediately after the administration of propranolol MAP decreased until the end of the experiments. After timolol and sotalol, an increase of MAP was observed at first until $\frac{1}{8}$ of the survival time; thereafter MAP decreased. After the administration of each of the three drugs, there was a decrease in the heart rate until $\frac{1}{8}$ of the survival time. Thereafter this variable remained constant until it decreased at the end of the experiment (Fig. 2).

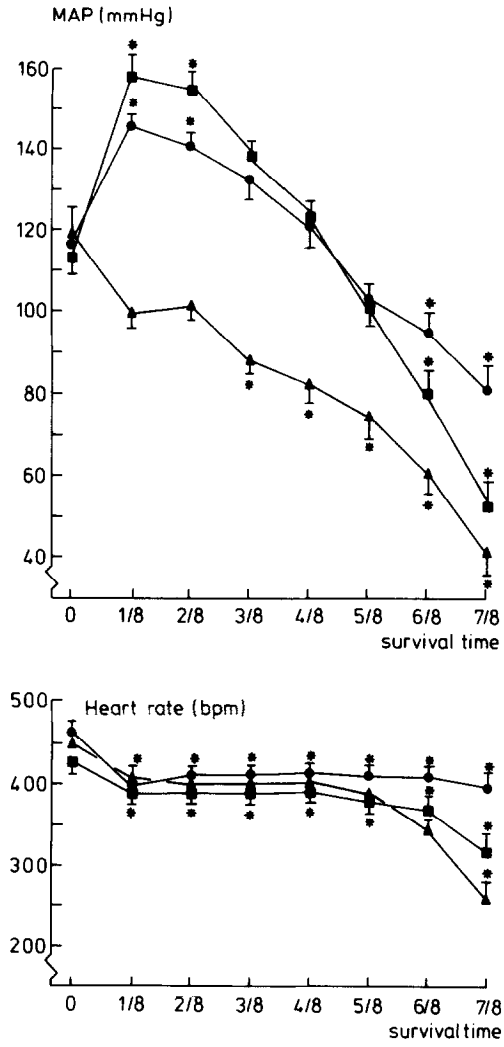

FIG. 2. The influence of an intracerebroventricular injection of propranolol HCl (▲; 7.5 mg·kg^{-1}), timolol maleate (■; 7 mg·kg^{-1}), and sotalol HCl (●; 10 mg·kg^{-1}) on mean arterial pressure and heart rate in urethane-anesthetized spontaneously breathing rats measured from 0 to 7/8 of the total survival time. Mean values ± SE (n = 6). *Significantly different from preadministration values.

Intracerebroventricular Administration in Artificially Ventilated Rats

After icv administration of the same dose of the three drugs in artificially ventilated rats as had been administered icv to the spontaneously breathing rats, none of the animals died during the 3-hr observation period. Administration of propranolol resulted in a significant decrease in MAP during the first hour and remained constant thereafter (Fig. 3). Timolol and sotalol produced a significant rise in MAP during the first 15 min. In the case of timolol, MAP then decreased significantly until 45 min after the beginning of administration, after which no further change was seen until the end of the experiment. After sotalol, a significant decrease was observed until 150 min after administration had started and thereafter MAP remained constant. The HR fell significantly during the first 15 min after administration of each drug but remained constant thereafter (Fig. 4).

Intravenous Administration in Spontaneously Breathing Rats

The same doses administered iv in spontaneously breathing rats as those administered icv resulted in a decrease in the respiratory rate with a constant tidal volume (data not shown). The MAP did not differ significantly during the experiments (Fig. 3). The HR fell during the first minute to the same extent as after icv administration. Thereafter it remained constant (Fig. 4).

Plasma Concentrations

Plasma concentrations determined in the three different groups are shown in Table 1. After icv administration in spontaneously breathing rats the plasma concentration of all three drugs was demonstrable and showed considerable variation. After icv administration in artificially ventilated rats plasma concentrations reached only one-half of the values of the concentrations determined at the same time in the spontaneously breathing rats. In the course of the experiments for propranolol and timolol a decrease, while for sotalol an increase, of the plasma concentration

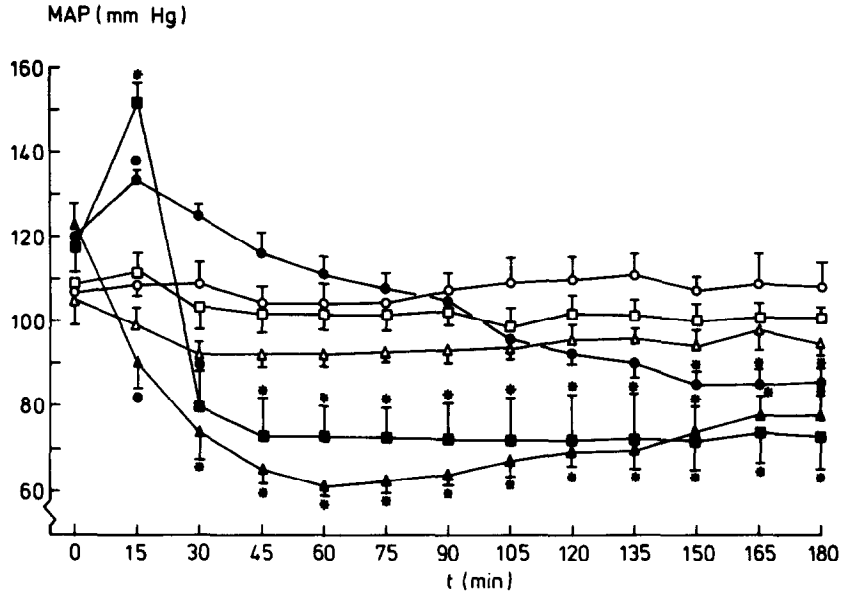

FIG. 3. The influence on mean arterial pressure of an intracerebroventricular injection of propranolol HCl (▲; 7.5 mg·kg^{-1}), timolol maleate (■; 7 mg·kg^{-1}), and sotalol HCl (●; 10 mg·kg^{-1}) in ventilated urethane-anesthetized rats and of an intravenous injection of propranolol HCl (△; 7.5 mg·kg^{-1}), timolol maleate (□; 7.0 mg·kg^{-1}), and sotalol HCl (○; 10 mg·kg^{-1}) in spontaneously breathing urethane-anesthetized rats. Mean values ± SE (n = 6). °Significantly different from preadministration values. *Significantly different from preadministration values and from values obtained after intravenous administration.

was observed. After iv administration the plasma concentrations determined at mean survival time were considerably lower for propranolol and timolol and higher for sotalol in comparison with icv administration. The plasma concentration was decreased for all three drugs at the end of the 3-hr observation period.

DISCUSSION

The clinical manifestations and course of a massive intoxication with a beta blocker cannot be attributed solely to beta blockade. Intoxicated patients usually exhibit bradycardia, hypotension, and a reduction in cardiac output. A noticeable feature is that in some patients the clinical condition suddenly deteriorates after a period of relative stability and that, despite treatment with β-adrenoceptor agonists, death occurs. Hong *et al.* (1983) and Sangster *et al.* (1984) have suggested that properties other than β-adrenoceptor blockade might be implicated in the clinical course of the intoxication or even in the fatal outcome.

In a previous study in which propranolol HCl, timolol maleate, and sotalol HCl were administered continuously iv to anesthetized spontaneously breathing rats, rats died from respiratory arrest (Langemeijer *et al.*, 1985). The sudden deterioration at the end of the experiments in hemodynamic parameters such as HR and MAP was due to hypoxia and respiratory acidosis resulting from the respiratory effects. When the rats were artificially ventilated, survival time was prolonged and death occurred from cardiac arrest after a much higher dose. Since there were no changes in blood gas levels during artificial ventilation, a central cause of respiratory ar-

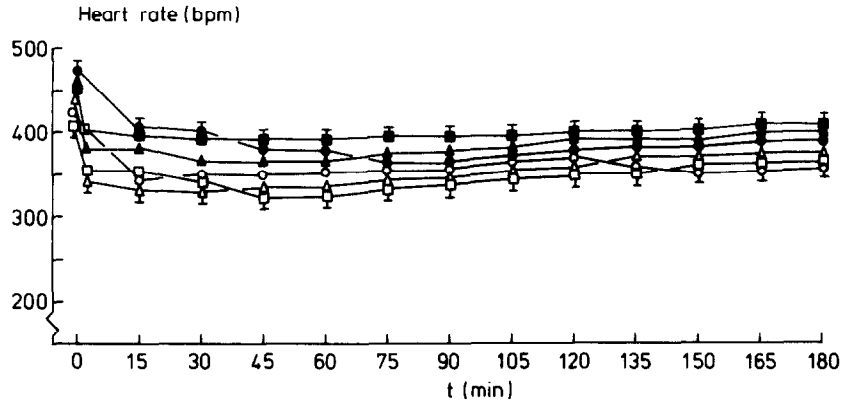

FIG. 4. The influence on heart rate after an intracerebroventricular injection of propranolol HCl (▲; 7.5 mg·kg^{-1}), timolol maleate (■; 7.0 mg·kg^{-1}), and sotalol HCl (●; 10 mg·kg^{-1}) in ventilated urethane-anesthetized rats and of an intravenous injection of propranolol HCl (△; 7.5 mg·kg^{-1}), timolol maleate (□; 7.0 mg·kg^{-1}), and sotalol HCl (○; 10 mg·kg^{-1}) in spontaneously breathing urethane-anesthetized rats. Mean values ± SE (n = 6). All values are significantly different from preadministration values at 0 min.

rest was considered to be more likely than a peripheral cause such as bronchoconstriction.

In the present study, in order to distinguish between central and peripheral effects, doses of each drug much lower than those in the above-mentioned study were administered icv as well as iv to spontaneously breathing rats. The pragmatically chosen icv doses were based upon the results of pilot experiments.

TABLE 1

PLASMA CONCENTRATIONS

Drug	Single dose (mg·kg^{-1})	icv in spontaneously breathing rats just before respiratory arrest	icv in ventilated rats		iv in spontaneously breathing rats	
			Mean survival time[a]	After 3 hr	Mean survival time	After 3 hr
Propranolol HCl	7.5	1.7 ± 0.5	0.82 ± 0.07	0.24 ± 0.02	0.50 ± 0.03	0.04 ± 0.004
Timolol maleate	7.0	0.94 ± 0.32	0.51 ± 0.07	<0.05	0.32 ± 0.02	<0.05
Sotalol HCl	10	1.18 ± 0.26	0.65 ± 0.10	0.99 ± 0.27	1.32 ± 0.17	0.28 ± 0.08

	Mean dose[b] after iv infusion (mg·kg^{-1})	iv in spontaneously breathing rats[c] just before respiratory arrest	Mean dose[b] after iv infusion (mg·kg^{-1})	iv in ventilated rats[c] just before cardiac arrest
Propranolol HCl	39 ± 2	3.3 ± 1.2 (n = 4)	88 ± 1	ND[d]
Timolol maleate	461 ± 17	160 ± 33 (n = 6)	700 ± 12	323 ± 65 (n = 4)
Sotalol HCl	253 ± 9	607 ± 235 (n = 5)	1800 ± 34	2280 ± 149 (n = 6)

Note. Plasma concentrations (expressed as mg base liter^{-1}) after a single intracerebroventricular (icv) or intravenous (iv) injection (n = 6 for each drug) or after a continuous iv infusion of propranolol HCl, timolol maleate, and sotalol HCl in urethane-anesthetized spontaneously breathing or ventilated rats. All values are expressed as means ± SE.

[a] Mean survival time is the mean time whereupon the spontaneously breathing rats died after icv administration.

[b] Results from previous experiments (Langemeijer *et al.*, 1985).

[c] Unpublished results from previous experiments.

[d] ND, not determined.

From a dose-range finding study a minimal dose for each drug that resulted in death within a reasonable time was chosen, which would allow measurements of changes in hemodynamic/respiratory parameters. Since no brain concentrations of the beta blocker were determined, it is not known if these doses are relevant to the concentrations achieved in the brain during toxicity with systemically administered beta blockers. The icv administration of propranolol HCl, timolol maleate, and sotalol HCl resulted in death from respiratory arrest. After iv administration of the three drugs all rats survived the 3-hr observation period. Also after icv administration of the same doses to artificially ventilated rats the animals survived the 3-hr observation period.

In comparison with the previous experiments, the doses required to produce respiratory arrest were 5–65 times higher after iv than after icv administration in spontaneously breathing rats. This confirms the hypothesis that the cause of respiratory arrest is related to a central mechanism.

The plasma concentrations determined in the different experimental groups showed that the hydrophilic beta blocker, sotalol, was also able to cross the blood–brain barrier. Considerable concentrations of the drug appeared in the plasma within 38–92 min. The mean plasma concentrations after icv administration in spontaneously breathing rats just before respiratory arrest were (in $mg \cdot liter^{-1}$) 1.7 for propranolol, 0.94 for timolol, and 1.18 for sotalol. In earlier studies in which continuous iv infusions of the three beta blockers were applied to spontaneously breathing rats, respiratory arrest occurred at respective plasma levels of 3.3, 160, and 607 $mg \cdot liter^{-1}$ (unpublished results). This implies that the route of administration rather than the concentration of the beta blockers in plasma determines the occurrence of respiratory arrest and reinforces the conclusion that respiratory arrest after beta-blocker overdosage is of central origin. The plasma concentrations of the three drugs at the median survival time, following icv administration in ventilated rats, were lower than those obtained in spontaneously breathing rats. This could be explained by an impairment of the circulation at the end of the experiments in the spontaneously breathing group, causing changes in tissue distribution and in liver metabolism. After icv administration to ventilated rats the plasma concentrations of propranolol and timolol declined during the course of the experiment as a result of hemodynamically unaffected tissue uptake and metabolism in the liver. The plasma level of sotalol rose. This rise can be explained by the hydrophilic property of sotalol. Administration icv seems to operate as a depot and the drug passes the blood–brain barrier very slowly.

In addition to the respiratory effects, the effects of the drugs on HR and MAP were studied. Immediately after a single iv dose of the beta blocker, the HR decreased after each drug, without any change in MAP. This is in agreement with other studies in which the acute hemodynamic effects of both therapeutic and overdoses of iv-administered beta blockers were investigated. Man in't Veld and Schalekamp (1983) in a review of these studies showed that the combination of a fall in HR without changes in MAP was due to an increase in peripheral resistance. HR decreased after icv administration both in spontaneously breathing and in artificially ventilated rats as well as after iv administration in spontaneously breathing rats. After icv administration the interval at which the maximal fall was recorded varied with each drug. It occurred after 2 min in the case of propranolol and timolol but only after 15 min in the case of sotalol. If the decline in the HR can be interpreted as a peripheral action, this time difference might be explained by differences in lipophilicity. Propranolol and timolol are lipophilic beta blockers and can easily pass the blood–brain barrier. Sotalol, a hydrophilic beta blocker, passed the blood–brain

barrier more slowly as was shown from the plasma concentrations. A further fall in HR occurred at the end of the experiment in spontaneously breathing rats. This must have been caused by the respiratory arrest since it did not occur in ventilated rats. No changes in MAP were recorded after iv administration. After icv administration of the same dose to ventilated rats all the three beta blockers produced a decline in MAP throughout the experiment. In the case of timolol and sotalol this decline was preceded by an initial rise. This pointed to a central mechanism responsible for the hypotensive action of beta blockers after overdose.

At $\frac{7}{8}$ survival time the MAP was 40–60 mm Hg after the three drugs had been administered to spontaneously breathing rats. The strong hypotensive action and the negative chronotropic effect might have impaired respiratory control centers by hypoperfusion. So, the respiratory effect may be secondary to the cardiovascular effects. However this is unlikely since an earlier investigation showed that a MAP of 40–60 mm Hg can exist for 30 min without respiratory arrest occurring (Langemeijer *et al.*, 1985). In the present experiments the average length of time during which the MAP fell to between 40 and 60 mm Hg was less than 10 min. Moreover, recently we tried to prevent blood pressure reduction by concomitant infusion of propranolol with a strong vasoconstrictor like Bay K 8644 (to be published). However, despite the maintenance of blood pressure all the animals died. Also, in the final phase the blood pressure fell to very low levels and the reduction in respiratory rate was even potentiated.

The results of this study indicate that overdosages of beta blockers produce respiratory arrest which is central in origin and the primary cause of death. A central mechanism also plays a role in the decrease in MAP that occurs. It is not clear from these experiments whether this respiratory arrest and the hypotensive action are beta receptor mediated. Further studies are required to determine the exact mechanisms involved. In clinical practice a sudden deterioration which interrupts a fairly stable clinical course can easily be explained by the onset of respiratory arrest. It is evdident that attention must be directed toward maintaining ventilation in addition to improvement of hemodynamic parameters. It is essential to start timely artificial ventilation.

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