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Cardiorespiratory depression and haemolysis due to thioridazine overdose in the rat

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The cardiovascular and respiratory effects of an intravenous overdose of thioridazine (125 mg kg^{-1} h^{-1}) were examined in either spontaneously breathing or artificially ventilated urethane-anaesthetized rats. In both groups Po_2, heart rate and mean arterial pressure decreased and atrioventricular and intraventricular conduction time, as well as QT time, increased similarly. Pco_2 and pH did not differ significantly except in spontaneously breathing rats where a severe acidosis occurred at the end of the experiments. Haemolysis was suspected. The same dose was administered intravenously to artificially ventilated rats. Plasma concentrations of the drug and its main metabolites, haematocrit and free plasma Hb were determined in separate groups. A severe haemolysis was observed. Thioridazine administered in the same doses intragastrically, intraduodenally or intraperitoneally resulted in lower plasma values than after intravenous administration and there was no haemolysis. Much higher oral doses produced haemolysis at 36 h, at which time plasma concentrations were not higher than those recorded after administration via the other non-intravenous routes. It is probable that the observed changes in cardiovascular and respiratory parameters are partly the result of haemolysis following thioridazine administration.

Since the introduction of thioridazine about 20 years ago, nine patients have taken this drug in overdose, five of whom died. In one, ventricular bradycardia (Donlon & Typin 1977) and in another, sinus tachycardia (Joubert & Olivier 1974) was observed. The cause of death of the others was not given (Eticknap & Gordon 1961; Donlon & Typin 1977). Of the recovered patients, two showed ventricular, and the other two supraventricular tachycardia (Burda & Captain 1968; Fletcher at al 1969; Burgess et al 1979). Serious arrhythmias such as ventricular fibrillation, ventricular tachycardia and sudden death have also been described in patients who had taken the recommended dose (Schoonmaker et al 1966; Fletcher et al 1969; Tri & Combs 1975; Fowler et al 1976; Chouinard et al 1978).

In the dog, the effects of therapeutic and toxic doses of thioridazine on myocardial electrophysiological properties were studied by Yoon et al (1979). The diastolic threshold, effective refractory period, and conduction time, were significantly increased and idioventricular automaticity was suppressed after therapeutic doses. At toxic doses these effects were more pronounced. The influence of thioridazine on the heart was studied in isolated ventricular muscle cells, Purkinje fibres (Arita & Surawicz 1973a), papillary muscle of the guinea-pig and of the rat (Landmark 1971: Hollander & Cain 1971; Arlock et al 1978), in the isolated heart (Landmark et al 1969) and in human atrial fibres (Arita & Surawicz 1973b). In these experiments thioridazine reduced the maximum rise of the action potential and slightly prolonged repolarization without altering the resting membrane potential significantly. There was also a reduced potassium efflux, a decreased excitability and an increased effective refractory period. To our knowledge, no further studies of the effects of an overdose of thioridazine on circulation and ventilation of laboratory animals has been reported.

We now report the results of a study of cardiorespiratory depression due to thioridazine.

MATERIALS AND METHODS

Procedures

Anaesthetized (urethane 1·1 g kg^{-1} i.p.), and unanaesthetized male rats, 300–350 g were given doses chosen for a restricted survival time (about 90 min) and manifestation of toxic phenomena.

Anaesthetized rats were tracheotomized. In spontaneously breathing rats, the cannula was connected to a Fleisch head (0000) in conjunction with a pneumotachograph (Godard). Respiratory rate, tidal volume and minute volume were determined.

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In artificially ventilated rats, the cannula was connected to a volume-constant ventilator (neonatal and infant 'Baby control', Roche) adapted for small animals (Tidal volume 3 ml, rate 80 min^{-1}).

The right femoral veins of the anaesthetized rats were cannulated. NaCl 0·9% (saline) was administered using an infusion pump (2·25 ml h^{-1}; Braun). The right femoral artery was cannulated. The cannula was connected to a pressure transducer (Hewlett Packard 1280 C). Pressure measurements were recorded (Gould). Mean arterial pressure (MAP) was calculated as diastolic pressure plus $\frac{1}{3}$ pulse pressure.

The electrocardiogram was taken from needle electrodes applied subcutaneously to the extremities. Standard leads I, II and III were recorded on an ECG amplifier (Elema-Siemens). Heart rate (HR) was derived from a cardiotachometer.

During the experiments blood samples were taken from the cannula of the right femoral artery and collected in heparinized capillaries or cups for the determination of blood gases (0·1 ml), haematocrit (Ht; 0·1 ml), plasma haemoglobin (Hb; 0·5 ml) and plasma thioridazine, mesoridazine and sulphoridazine concentrations (0·5 ml).

Additional experiments were performed in anaesthetized guinea-pigs, rabbits and dogs.

Drugs used

Thioridazine hydrochloride, mesoridazine besylate and sulphoridazine base were generously provided by Wander Sandoz (Basle, Switzerland). Urethane was purchased from OPG (Utrecht, The Netherlands).

The drugs were dissolved in saline.

Analyses

Arterial blood gas parameters (Po_2, Pco_2 and pH) were determined with a blood gas analyser (IL 413). Hb in plasma and Ht were determined with a spectrophotometer (Pye Unicam SP8-250) and a micro haematocrit centrifuge (MSE), respectively.

Thioridazine, mesoridazine and sulphoridazine in plasma were quantified by a high-performance liquid chromatographic method (publication in preparation). A liquid chromatograph (Model 1084B, Hewlett-Packard) was used, equipped with a reversed-phase column (Hypersil ODS, Shandon) and a variable-wavelength ultraviolet detector (Spectroflow 773, Kratos) operated at 264 nm. The mobile phase was 0·003 M sodium 1-heptane sulphonate in 0·01 M borate buffer (pH 8·2)/methanol (25/75) (flow rate 1·5 ml min^{-1}).

Trifluprομazine was used as an internal standard. The drugs were separated from plasma by combined bonded-phase/liquid-liquid extraction procedure.

Calculations

The results were presented at 1/8–7/8 of the total survival time. Results are expressed as mean ± s.d. The significance of differences between mean values in spontaneously breathing and artificially ventilated rats was evaluated using Student's *t*-tests for paired and unpaired data. A probability of 0·05 or less was considered statistically significant.

Experimental protocol

Intravenous administration in spontaneously breathing and ventilated rats

Thioridazine HCl was administered intravenously to spontaneously breathing (n = 6) and ventilated (n = 6) rats at a rate of 125 mg kg^{-1} h^{-1} after a steady state control period of 30 min. Blood gases and cardiovascular variables were determined. In two separate animal groups (each n = 6) the concentrations of the drug and metabolites in plasma and plasma concentrations of Hb and Ht, respectively, were determined. The animals were observed until no remaining QRS-complexes were registered.

Intravenous administration in spontaneously breathing guinea-pigs and rabbits and in ventilated dogs

Thioridazine HCl was administered intravenously to guinea-pigs (125 mg kg^{-1} h^{-1}; n = 2), rabbits 125 mg kg^{-1} h^{-1}; n = 2) and dogs (50 mg kg^{-1} h^{-1}; n = 2) after a steady state control period of 30 min Ht was measured. The animals were observed until no remaining QRS-complexes were registered.

Alternative routes of administration in spontaneously breathing anaesthetized and unanaesthetized rats

In anaesthetized rats a single dose of thioridazine HCl in 3 ml of saline was administered either through an intragastric cannula (250 mg kg^{-1}; n = 2) or intraperitoneally (125 mg kg^{-1}; n = 2). The concentrations of the drugs in plasma and Ht were determined. In conscious rats a single dose of thioridazine in 3 ml of saline was administered either intraperitoneally (660 mg kg^{-1}; n = 6) or orally (1 g kg^{-1}; n = 6). The Ht was determined. The thioridazine plasma concentration was measured at the end of the experiments. The anaesthetized rats were observed for 6 h, the unanaesthetized rats for 36 h.

RESULTS

Intravenous administration in spontaneously breathing and ventilated rats

After administration of 125 mg kg^{-1} h^{-1} to spontaneously breathing and ventilated rats the mean survival time was not different significantly (85·5 ± 12·0 min and 81·6 ± 11·0 min, respectively).

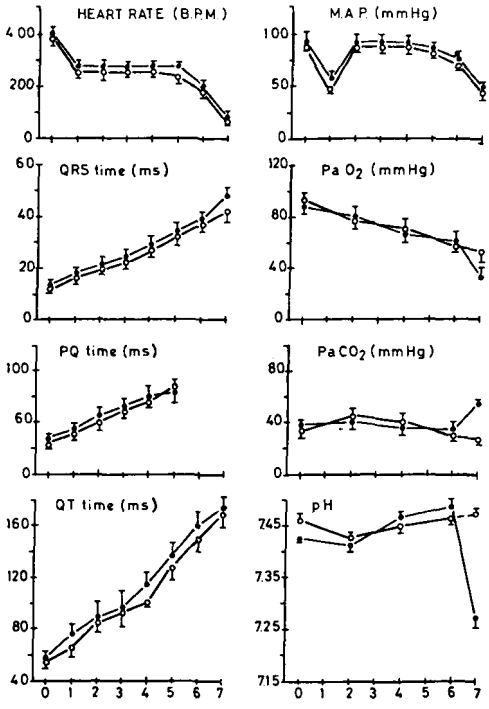

FIG. 1. The influence of an intravenous infusion of thioridazine HCl (125 mg kg^{-1} h^{-1}) on the cardiovascular system and arterial blood gases in urethane anaesthetized rats measured at 1/8–7/8 of the total survival time. ●—● Spontaneously breathing, ○—○ artificially ventilated rats. Mean values ± s.d. of 6 rats.

The cardiovascular parameters and the blood gases are shown in Fig. 1. Compared with the start of the experiments, in the spontaneously breathing rats the mean respiratory rate had decreased significantly. Mean tidal volume increased but not significantly during the experiments (data not shown). The course of Po_2, Pco_2 and pH was not significantly different in spontaneously breathing and ventilated rats, except at the end of the experiments when Pco_2 increased and pH decreased significantly in the spontaneously breathing rats. The course of MAP and HR and the changes in the ECG were not significantly different in spontaneously breathing and ventilated rats. MAP decreased immediately after the start of administration and returned within 15 min to the initial value. After a constant level for 1 h the heart rate decreased steadily.

Atrioventricular and intraventricular conduction time as well as QT-time increased. Disappearance of the P-wave and remarkable broadening of the QRS-complexes were observed at the end of the experiment. Thioridazine and mesoridazine plasma concentrations, Hb in plasma and Ht are shown in Fig. 2. The thioridazine and mesoridazine plasma concentrations and Hb in plasma increased and the Ht decreased steadily during the experiment. Sulphoridazine was not detected.

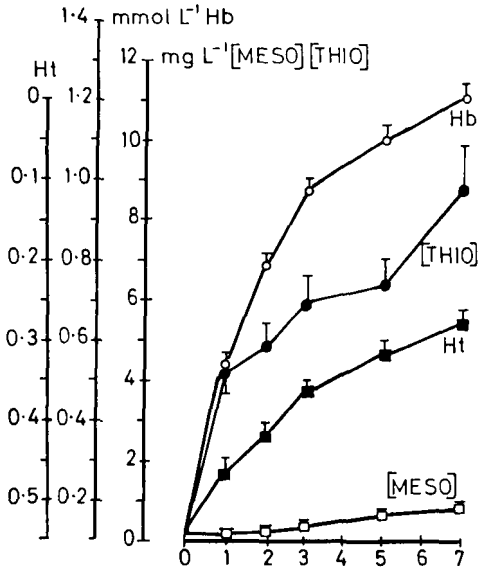

FIG. 2. The influence of an intravenous infusion of thioridazine (125 mg kg^{-1} h^{-1}) on Ht ■—■, Hb in plasma ○—○, thioridazine plasma concentration ●—● and mesoridazine plasma concentration □—□ in artificially ventilated urethane-anaesthetized rats measured at 1/8–7/8 of the total survival time. Mean values ± s.d. of 6 rats.

Intravenous administration in spontaneously breathing guinea-pigs, rabbits and in ventilated dogs

Ht was decreased in each species and the plasma was haemolysed (Fig. 3).

Alternative routes of administration in spontaneously breathing anaesthetized and unanaesthetized rats

After intragastric, intraduodenal and intraperitoneal administration of thioridazine no haemolysis occurred in anaesthetized rats. The thioridazine and mesoridazine plasma concentrations increased during the first hour. During the next hours a small rise was observed. The animals survived.

After oral and intraperitoneal administration of a higher dose to conscious rats a decrease of Ht was

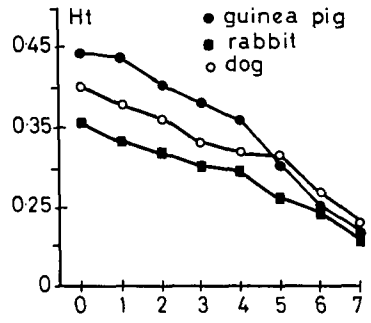

FIG. 3. The influence of an intravenous infusion of thioridazine (125 mg kg^{-1} h^{-1}) on the Ht in spontaneously breathing guinea-pigs, rabbits and in ventilated dogs measured at 1/8–7/8 of the total survival time (n = 2).

observed after 16 h and the plasma was haemolytic in appearance. At the end of the experiments thioridazine plasma concentration was 1·2 ± 0·2 mg $litre^{-1}$ after oral and 1·2 ± 0·3 mg $litre^{-1}$ after intraperitoneal administration.

DISCUSSION

The aim of the present study was to elucidate the pathophysiological mechanisms causing death in thioridazine poisoning. On the basis of the physiological effects and of the observations in intoxicated patients a deleterious influence of this drug on haemodynamics might be anticipated. Considering the lack of information on the influence on haemodynamics as such, the present experiments were made in intact animals. By analogy with other central nervous acting drugs, an influence of thioridazine on the respiration was to be expected (Sangster et al 1979). Because changes in respiration influence the cardiovascular system, thioridazine was studied both in spontaneously breathing and artificially ventilated anaesthetized rats.

Surprisingly, the dose of thioridazine administered till death, did not differ in spontaneously breathing and artificially ventilated rats. Usually, respiratory arrest is caused by doses lower than those causing cardiac arrest. Furthermore, in both types of experiments Po_2 decreased. The course of Po_2 could not be explained by decreased alveolar ventilation. Thus, a disturbed O_2 absorption in the lung caused by thioridazine had to be considered. Gross examination of the organs of the animals disclosed no abnormalities of the lung but the kidneys were swollen and the urine was dark red. Haemolysis was suspected.

The experiments were repeated. From the time-dependent decrease of haemotocrit, as well as increase of Hb in plasma, it was concluded that thioridazine induced haemolysis after i.v. administration. To exclude species-specific effects thioridazine was administered intravenously to guinea-pigs, rabbits and dogs. In these species haemolysis was also induced.

For therapeutic purposes thioridazine is only available as an oral formulation. Haemolysis due to thioridazine in man has not been reported (Dukes 1975). Similar doses as in the earlier experiments were administered intragastrically (i.g.), intraduodenally (i.d.) and intraperitoneally (i.p.) to anaesthetized rats. No haemolysis was demonstrated. However, the plasma thioridazine concentration did not exceed 1·7 mg $litre^{-1}$. After i.v. administration much higher concentrations—up to 11·2 mg $litre^{-1}$—were achieved.

The strong anticholinergic effects of thioridazine, as well as the anaesthesia, might have interfered with the absorption of thioridazine from the gastrointestinal tract. Therefore thioridazine was administered orally in much higher doses to the conscious rat. In these experiments haemolysis was demonstrated. The plasma thioridazine concentration at the end of the experiments (36 h) was not higher than after i.g., i.d. or i.p. administration. Higher concentrations during the experiments cannot be excluded because these experiments lasted much longer. Therefore, the degree of haemolysis could not be correlated with the plasma thioridazine concentration.

Disturbances of O_2 absorption in the lungs in relation to haemolysis have not been reported. Since an effect of thioridazine on erythrocytes may be assumed, effects on other cellular constituents of the blood cannot be excluded. Possibly, aggregation and activation of granulocytes causing pulmonary oedema are responsible for the decreased Po_2. An effect on the lung itself, causing a diffusion disturbance or a disturbance in perfusion-ventilation ratio, has also to be considered.

In both spontaneously breathing and artificially ventilated rats, thioridazine induced electrocardiographic changes indicating a disturbance of atrioventricular and intraventricular conduction and a lengthening of ventricular repolarization. Considering the course of the heart rate, the extent of these changes is unrelated to changes in heart rate. The electrocardiographic changes develop gradually, seem to be dose related, and correspond with the known electrophysiological effects of thioridazine.

In both types of experiments (spontaneously breathing and artificially ventilated), thioridazine caused an initial decrease of MAP and heart rate.

Thereafter, MAP increased to the original value whereas heart rate remained more or less unchanged. Finally MAP and heart rate decreased. At that stage of the experiments a marked hypoxia had developed. The spontaneously breathing animals also had a severe respiratory acidosis.

The initial decrease of MAP seems to be related to the observed decrease of heart rate which may be accompanied by a decrease of cardiac output. Whether the decrease of MAP is partly caused by a decrease of systemic vascular resistance due to the adrenergic blocking effect of thioridazine cannot be concluded from these experiments. As far as the final deterioration of the circulation and the resulting cardiac arrest are concerned, hypoxia with or without respiratory acidosis seems to be a major determinant.

From these experiments it can be concluded that thioridazine is capable of inducing haemolysis and a disturbed O_2 absorption in the lungs. Because these phenomena are observed particularly after i.v. administration and as intoxications in man occur solely after oral (self) administration it is possible that these effects have been overlooked during the treatment of intoxicated patients. Only after completing a prospective study in man with regard to haemolysis it can be assessed whether the i.v. administration of thioridazine in anaesthetized rats is a suitable model for studying the pathophysiological mechanisms causing death in thioridazine poisoning.

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