THE PRODUCTION OF HYPOTHERMIA

BY

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The effect of hypothermia in diminishing the body's oxygen consumption has led to a recent interest in this as an aid to anaesthesia in the poor-risk case and in major surgery. Man is equipped with a highly effective mechanism for combating the effects of cold, and the first step in the production of hypothermia must be to overcome this response. This can be achieved by deep anaesthesia (Bigelow *et al.*, 1950), the use of muscle relaxants (Krogh, 1916), or by the "lytic cocktail" or "liberation cocktail" introduced by the French workers Laborit and Huguenard (Huguenard, 1953).

We have compared the efficacy of these three methods in facilitating the production of hypothermia in the anaesthetized dog by means strictly comparable to those applied in man, and the individual constituents of the "lytic cocktail" have been studied. Their effect on the rate of fall of the rectal temperature after the application of ice, and on the amount of shivering produced, has been studied. We have also investigated the effect of hypothermia, induced with the aid of the constituents of the "lytic cocktail," on oxygen intake, heart rate, and respiration.

Methods

Unselected mongrel dogs were used, varying in weight (8–16 kg.) and age. Basal narcosis was induced by the intraperitoneal injection of 30 mg./kg. pentobarbitone in a 3% solution at approximately blood heat (Adams, 1944). Once the dogs were asleep endotracheal intubation with a cuffed tube was carried out by the aid of a topical application of 2% amethocaine or 2% lignocaine. Forty-five minutes after induction of anaesthesia adjuvant drugs were administered in doses as follows: pentobarbitone, 15 mg./kg.; D-tubocurarine chloride, 3 mg./kg.; chlorpromazine, 2 mg./kg.; pethidine, 4 mg./kg.; promethazine, 2 mg./kg. The "lytic cocktail" comprised all of the last three in the doses mentioned. With the exception of pentobarbitone (which was given intraperitoneally), all drugs were given by deep intramuscular injection mixed with 1,000 Benger units of hyaluronidase. Immediately the muscle relaxant was given the cuff of the endotracheal tube was inflated and the animals' respiration mechanically controlled with oxygen for periods of three to four hours. A similar procedure was adopted when respiration failed because of hypothermia. Fifteen minutes after injection of the adjuvants the animals were covered with ice-bags. Cooling continued for 90 minutes, when the animals were gradually heated up by the help of hot-water bottles and a hair-drier.

These doses of the constituents of the "lytic cocktail" are similar to those which are given to man. The total amount of pentobarbitone (45 mg./kg.) administered to those animals who received it as an adjuvant will result in deep anaesthesia (Adams, 1944). In the case of D-tubocurarine chloride, 3 mg./kg. was given, as we found that this will invariably produce apnoea over the period of our investigations, and it can be safely reversed some three to four hours later by neostigmine 5 mg. and atropine 2 mg.

In order to reduce the factor of individual susceptibility of the dogs to the drugs and to cooling, the experiment was planned so that during its course each animal received each of the adjuvants. As will be reported later, three dogs died during this study. In the case of two of these the death occurred when the last adjuvant drug was being investigated, so that the series with these is complete. In the third instance the fatality was with the first drug, and no readings obtained from this dog are included in the results.

Rectal temperatures were noted by a thermocouple every five minutes, and the presence or absence of shivering was noted at similar intervals. The heart rate was recorded every 15 minutes. Oxygen intake was measured by means of a direct recording of respiration on a spirometer containing oxygen. To reduce resistance to respiration all valves were removed from the instrument and a small soda-lime canister was inserted close to the endotracheal tube. Care was taken to see that the circuit was leak-proof, and at temperatures below 30° C. respiration was aided during the period of observation. This ensures full oxygenation of the blood and eliminates respiratory depression as a cause of decreased oxygen intake (Bigelow *et al.*, 1950). Another factor which may well interfere with the readings is the excretion of nitrogen by the dog when breathing from a spirometer containing oxygen. To overcome this a large flow of pure oxygen was administered by a T-piece once the endotracheal tube was in position, and between readings the animal was maintained on pure oxygen.

Results

On all occasions the normal temperature of the animal was taken as that immediately before the administration of the adjuvant drug—that is, three-quarters of an hour after the intraperitoneal administration of the basal narcotic. For

Fig. 1.—Relationship of oxygen intake to temperature. Minus values indicate continuous readings in the absence of shivering. x, Isolated readings taken when the animal was shivering.

the sake of simplicity all temperatures are recorded as variations from this normal. In order to compare the amount of shivering under various conditions a point system was adopted. The presence or absence of palpable shivering was noted at five-minute intervals, one point being recorded for every positive observation. The average of six observations with each of the drugs studied can be seen in Table I. This shows the fall in temperature which took place every 15 minutes and the total amount of shivering every 30 minutes. In each of these dogs preliminary studies of oxygen intake under the effects of 30 mg./kg. pentobarbitone revealed that there were negligible changes over the period from 40 to 180 minutes after the injection of the barbiturate. Thus any changes which we have recorded are due to the hypothermia or adjuvant drug. As in the case of temperature, the normal readings for oxygen intake, pulse rate, and respiratory rate were taken to be those recorded immediately before the administration of the adjuvant. Changes in oxygen intake are expressed as percentages of the normal, whilst alterations in pulse rate are recorded as absolute changes from normal.

FIG. 2.—Relationship of heart rate to temperature. Minus values recorded when no shivering was occurring. x, Readings taken during bouts of shivering.

Fig. 1, showing the relationship between oxygen intake and temperature (10 observations), demonstrates a fall in the former as the latter decreases. However, when shivering occurs there is a consistent rise in oxygen demands. The lowered temperature may be seen to have a similar relationship to heart rate and respiratory rate in Figs. 2 (25 observations) and 3 (10 observations) respectively; but here again rises are constantly provoked by the onset of shivering. Apnoea is apt to occur at a rectal temperature of 25° C., but severe respiratory depression has been noted at temperatures of 29° C. and under.

Cardiac arrest occurred in three dogs at temperatures of 23° C., 23.5° C., and 26.5° C., respiration being unaided in all cases. It is significant that lower temperatures (21° C.—22° C.) have been obtained without untoward effects in those animals in which respiration was fully controlled with oxygen.

FIG. 3.—Relationship of respiratory rate to temperature.

Discussion

From Table I a comparison of those recognized methods of facilitating the production of hypothermia can now be made. An analysis of the results obtained with deep anaesthesia, curarization, and the "lytic cocktail" is given in Table II. This expresses the average temperature fall obtained using these methods after 90 minutes' cooling as a percentage of that occurring with basal narcosis alone. The amount of shivering which occurred during the last hour of cooling is similarly expressed. It is apparent from Tables I and II that there is little to choose between these three methods as regards rate and amount of temperature fall, and abolition of shivering.

A similar analysis of the effects of the constituent drugs of the "lytic cocktail" is also shown in Table II. From this it may be seen that by far the most active constituent

TABLE I.—Effects of Various Drugs and Combinations of Drugs on Average Fall in Rectal Temperature in the Dog and Amount of Shivering After Covering with Ice. (See Text for Explanation of Method of Recording Amount of Shivering.)

Drugs	Dose, mg./kg.	Average Fall in Rectal Temperature °C.						Average Amount of Shivering		
		Time in Minutes after Covering with Ice						Time in Minutes After Covering with Ice		
		15	30	45	60	75	90	0-30	35-60	65-90
Pentobarbitone	30	0.8	1.5	2.7	3.7	4.5	5.2	2	4	5.4
Pentobarbitone 30 mg./kg. plus the following, given 45 minutes later:										
Pentobarbitone	15	1.5	3.4	5.1	6.7	7.6	9.1	0	0	0.5
p-tubocurarine chloride	3	1.2	3.2	5.0	6.6	8.1	9.5	0	0.6	0.8
"Lytic cocktail," comprising:										
Chlorpromazine	2	1.7	3.3	5.1	6.9	8.5	10.4	0	0	0.5
Pethidine	4									
Promethazine	2									
Chlorpromazine	2	2.2	3.3	5.6	7.5	9.0	10.6	0	0	0
Pethidine	4	1.0	2.3	3.5	4.9	5.7	6.5	0	2.3	3.2
Promethazine	2	1.1	2.6	4.0	4.7	5.2	6.0	1.2	3.5	5.7

TABLE II.—The Fall in Rectal Temperature that Occurred After Covering with Ice for 90 Minutes and the Amount of Shivering that Occurred During the Last Hour of the Cooling Expressed as a Percentage of the Observations Made Under Similar Conditions with Basal Narcosis Alone

	Percentage of Similar Readings with Basal Narcosis Alone	
	Fall in Rectal Temperature at 90 min.	Amount of Shivering, 35-90 min.
Recognized methods of facilitating the production of hypothermia:		
(a) Deep narcosis	+75	-95
(b) Curarization	+83	-85
(c) "Lytic cocktail"	+100	-95
Individual constituents of the "lytic cocktail":		
(a) Chlorpromazine	+104	-100
(b) Pethidine	+25	-42
(c) Promethazine	+15	-2

in facilitating the production of hypothermia is chlorpromazine. Pethidine, while moderately effective in eliminating shivering, has comparatively little effect in aiding the fall in temperature. The effects of promethazine appear to be negligible. A graphic representation of the rate of temperature fall obtained with chlorpromazine, pethidine, and promethazine (Fig. 4) demonstrates a steady fall in temperature with chlorpromazine. In the case of pethidine and promethazine the onset of shivering causes a marked

FIG. 4.—Rate of fall of rectal temperature when animal was immersed in ice with (a) chlorpromazine, (b) promethazine, (c) pethidine. * Average time after beginning of cooling to onset of shivering. ---- Hypothetic continuation of the steady fall in temperature that occurred with pethidine and promethazine before the onset of shivering.

reduction in the rate of temperature fall. A hypothetical continuation of the steady fall occurring before the onset of shivering shows that neither of these drugs would have been as effective in facilitating the fall in temperature as chlorpromazine. A possible explanation of this may be the occurrence of clinically undetectable shivering. That this can occur has been shown by previous electromyographic studies (Göpfert and Stuffer, 1952).

It is not the purpose of this paper to consider the mode of action of these drugs in facilitating hypothermia, but one point, however, seems worthy of mention. A dog in which hypothermia has been induced with the aid of pethidine will

show a very marked increase in the degree of shivering following the intramuscular administration of n-allyl-nor-morphine (3 mg./kg.). It is interesting to conjecture whether this is due to a reversal of the analgesic effect of pethidine in regard to thermal sensation (Evans, 1952) or whether it is due to a reversal of its central effects.

The fall in oxygen intake which we have observed during hypothermia closely resembles that reported by Bigelow *et al.* (1950). He induced hypothermia by cooling dogs sufficiently anaesthetized to eliminate shivering, and made no use of the "lytic cocktail." It is difficult to make a comparison with the findings of Churchill-Davidson *et al.* (1953), as these workers do not give sufficient details of their method of measuring oxygen consumption.

This could suggest that, provided shivering be eliminated, a fall in oxygen intake occurs with hypothermia irrespective of how this is produced.

Summary and Conclusions

A study has been made of the production of hypothermia facilitated by (1) deep anaesthesia, (2) curarization, (3) the "lytic cocktail." All three appear to be equally effective.

The active constituent of the "lytic cocktail" appears to be chlorpromazine. Pethidine decreases shivering somewhat while producing but little fall in temperature. Promethazine seems to have little effect.

Observations have been made on the effect of hypothermia on oxygen intake, pulse rate, and respiratory rate. All three are depressed at lowered temperatures, irrespective of how these are obtained.

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