THE PHYSIOLOGICAL ACTION OF ETHYL CHLORIDE, BROMIDE, AND IODIDE, AND OF 'SOMNOFORM'

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Although some of the anaesthetics mentioned in the title, particularly ethyl chloride, have now been in use for some years, and although considerable clinical experience has been accumulated, yet very little experimental pharmacological work seems to have been performed with these drugs. The only papers to which I have found reference are a short note by Cole,¹ and papers by Lebet,² and Ginsburg.³

Cole's experiments were performed with somnoform and ethyl bromide. He found that somnoform markedly increases the size and rate of contraction and the tone of the diaphragm, which remains in a state of strong tonic contraction, the heart still beating strongly. This effect is obtained after section of the vagi, and is, therefore, due to an action on the respiratory centre. With both somnoform and ethyl bromide small doses cause a rise of blood pressure and acceleration of the heart. With large doses, and especially after section of the vagi, a gradual fall takes place. With intact vagi the heart rate is increased by small doses and diminished by large ones. With vagi cut the usual effect is slowing.

The acceleration with intact vagi Cole attributes to a paralysis of the vagal nerve-endings by the ethyl bromide. He states that during

1. *Proc. Physiol. Soc.*, June 15, 1903 (*Journ. of Physiol.*, Vol. XXIX, p. 25).

2. *Bullet. Acad. de Médecine de Belgique* (4), XV, 5, p. 343.

3. *Inaug. Diss.*, St. Petersburg, 1893. I have not been able to gain access to the communications of Lebet and Ginsburg.

anaesthesia produced by somnoform or the bromide it is impossible to affect the heart by stimulation of the peripheral end of the cut vagus. He further states that it is either the ganglion cells or preganglionic endings which are affected. As will be seen below, I have been unable to confirm these statements.

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METHODS AND MATERIAL EMPLOYED

The experiments have been conducted upon forty dogs, two cats, and several frogs. The dogs and cats were anaesthetised, in the first instance, with ether, chloroform, or the A.C.E. mixture, and sometimes, in addition, by the intravenous or subcutaneous administration of morphia. In those animals in which a tracing of auricle and ventricle was taken curari was administered and artificial respiration maintained.

The drugs under investigation were administered by the tracheal tube. Respiration was recorded by means of a Marey's tambour, the volume of a limb, intestinal wall, or spleen by means of a piston recorder.¹ Blood pressure was taken from the carotid artery. A glass plethysmograph was used for recording changes in the volume of the limb, and an air oncometer made of gutta-percha for the intestine. The method described by Oliver and Schäfer² was employed for recording the effects upon the heart. A curved metal bar was pressed in the auriculo-ventricular groove, so that the movements of auricle and ventricle might be recorded independently.

The ethyl chloride used was partly that sold under the name of 'narcotile' by Bengué, of Paris, and partly 'kelène' from Fries Bros., of New York. The ethyl bromide was manufactured by Squibb, of New York. The somnoform was that prepared by A. Rousseau, Bordeaux. The ethyl iodide was for some experiments obtained from Kahlbaum, of Berlin, and in others a specimen kindly

1. The instruments employed were obtained from Allbrecht, of Tübingen. It has been found convenient to have the counterpoise of the piston recorder worked on a threaded rod, so as to facilitate accurate adjustment.

2. *Journal of Physiol.*, XVIII, p. 256. 1895

prepared for me by Mr. Thorwaldson in the chemical laboratory of the University of Manitoba.

The ethyl iodide was tested only for the purpose of making the investigation more complete, not with any idea of its being employed generally as an anaesthetic.¹ In order to obtain any marked effect it was necessary to place the bottle containing the drug in hot water in order to vaporise it more rapidly.

It is remarkable how uniform have been the effects of the drugs in different experiments. The results in different individual dogs have indeed varied widely in a quantitative sense, and idiosyncrasy plays a large part in the conditions affecting the action of these anaesthetics in dogs as in the human subject, but qualitatively the results of the administration can be predicted with tolerable certainty.

The differences in action between the chloride, bromide, iodide, and somnoform is one of degree only, and this degree seems to depend simply on the volatility of the drugs.² Somnoform is stated by Cole to be a mixture of 65 parts of ethyl chloride, 30 parts of methyl chloride, and 5 parts of ethyl bromide.³ The presence of methyl chloride does not appear to affect the results.

EFFECTS ON THE RESPIRATION

In small doses the rate and depth of respiration are markedly increased immediately on administration, gradually becoming normal after the anaesthetic is removed (See Fig. 1). This occurs in the majority of instances, though sometimes the rapidity is increased while the depth is unaffected, and occasionally the depth is increased while the frequency is unaltered. (See Fig. 2.)

With larger doses the respiration is often temporarily increased, just as with a small dose, but soon the breathing becomes shallower and less frequent. (See Figs. 5, 10, 11, 12.) With still larger doses the respiration stops completely—usually 2-3½ minutes before the heart ceases to beat. (See Figs. 3 and 4⁴.)

1. Although the iodide undoubtedly has anaesthetic properties, yet its lack of volatility (boiling point 72° C.) and its nauseous odour would prevent its use for this purpose in the human subject.

2. The boiling point of the chloride is 12° C, of the bromide 38.4° C, of the iodide 72° C.

3. The proportions are given differently by some writers. Thus McCardie (*Brit. Med. Jour.* March 17, 1906, p. 616) gives it as ethyl chloride 65, methyl chloride 35, and ethyl bromide 5 parts.

4. This fact would appear to be of importance as indicating the value of artificial respiration in cases of an overdose of these drugs. I have in several instances restored an animal by artificial respiration after voluntary respirations had ceased for some time (30-90 seconds), and the blood pressure had fallen almost to zero. (See Fig. 12.)

Fig. 1. Dog, 11.7 K. A.C.E.—Ether. The tracing shows the effect of a small dose of ethyl bromide followed by a stimulation of the vagus while the animal is fully under the effect of the anaesthetic. The respiration is at first deepened and increased in rapidity, later becoming shallower, though still frequent.

Fig. 2. Ethyl chloride, 'small dose. Bitch, 8 K. Spleen, respiration, carotid blood pressure. A.C.E., morphia.

This effect occurs equally before and after section of both vagi as well as after the administration of nicotine and is probably due, as suggested by Cole, to a direct action on the respiratory centre. Whether the effect is primarily, or indeed chiefly upon the diaphragm as stated by Cole we cannot be certain.

In some instances the animal recovers after respiration has been in abeyance for one minute or even for a longer period, the respiration beginning with very small movements and gradually increasing in extent. (See Fig. 2.) As a rule the recommencing respiratory movements, although shallow, are very frequent. (See Figs. 3, 5, and 7.)

Fig. 3. Hind limb respiration. Carotid blood pressure. Dog, 10 K. A.C.E.—nicotine—both vagi cut. Ethyl chloride. Shows sudden stoppage of respiration with recovery. No steps taken to aid recovery. Ether-morphia-curari-nicotine. Both vagi cut.

With a fatal dose the respiration, after being stopped for two or more minutes, will usually become re-established for a few seconds before death; stopping finally at the same time as, or a few seconds before the heart. (See Fig. 4.)

Fig. 4. Dog, 4.8 K. Ethyl chloride, overdose, death. Sudden failure of respiration, interval of three minutes then fifteen respirations occur just before stoppage of heart.

Fig. 5. Intestine, respiration, carotid blood pressure. Dog, 9.6 K. A.C.E.—morphia. Both vagi cut. Ethyl bromide. Stimulation of peripheral end of vagus.

THE CAROTID BLOOD PRESSURE

With small doses there is generally a slight preliminary rise in blood pressure followed by a return to the normal. (See Fig. 6.)¹

Fig 6. Ventricle, auricle. Hind limb. Carotid blood pressure. A.C.E. morphia-curari. Ethyl bromide. Small dose at (1), larger dose at (2).

With larger doses the pressure rapidly falls. (In two instances in dogs the heart and respiration have ceased simultaneously). As pointed out by Cole the fall is more pronounced after section of the vagi. The tracings reveal the further fact that after the administration of atropine a more marked effect is liable to occur. In two animals, one of which was being anaesthetised with ethyl chloride, the other with ethyl iodide a rapidly fatal result occurred after atropine with an amount of the anaesthetic which before atropine had only produced a slight effect².

1. In this tracing the pressure falls below normal. Notice also the marked slowing of the heart, as shown both by the blood-pressure tracing, and the record of auricle and ventricle.

2. This would seem to denote that the use of atropine is contraindicated in cases of overdose from these drugs.

Fig. 7. Intestine, respiration, carotid blood pressure, Dog, 11.7 K. A.C.E. —ether. Both vagi cut. Somnoform.

Fig. 8. Ventricle, auricle, hind limb, carotid blood pressure. Dog, 6 K. Ether —morphine—curari. Ethyl iodide, large dose, stoppage of heart, blood pressure falling almost to zero. Recovery without interference.

THE HEART

With intact vagi the frequency of both auricle and ventricle is sometimes increased, though this does not always occur with small doses. A common result, even with small doses, is the diminution of the frequency and the extent of excursion of both auricle and ventricle (see Fig. 6). I find with Cole that the conduction of the auriculo-ventricular ring is depressed by large doses, the ventricle beating at half the rate of the auricle.

With the vagi cut, the heart is usually rendered less frequent and the excursions of both auricle and ventricle are diminished.

Fig. 9. Dog, 7.4 K. Ventricle, auricle. Intestine, carotid pressure. A.C.E.—morphia—curari. Vagi intact. Ethyl iodide. Shows increased frequency of heart after ethyl iodide.

Ginsburg¹ states that the vagus endings are unaffected by ethyl bromide, and attributes the quickening of the heart to the excitation of the accelerator. Although Cole states that ethyl bromide paralyses the vagal nerve endings, he agrees with Ginsburg that the drug may sometimes have a stimulating action on the accelerators.

I have been quite unable to confirm Cole's observation that ethyl bromide paralyses the vagus terminals, and this applies equally to ethyl chloride, ethyl iodide, and somnoform. Although in about twenty

1. Quoted from Cole.

experiments with the different drugs named, the vagus in the neck (cut or uncut) has been stimulated when the animal was fully under the influence of the anaesthetic, never has there been any diminution of the usual inhibitory effect. Often, on the contrary, the effect of vagus stimulation seems to have been exaggerated. (See Figs. 1 and 5). This point has been further investigated upon the frog's heart recorded by the suspension methods. In two or three experiments it has been impossible to abolish the vagus action on either pre- or post-ganglionic fibres with ethyl bromide. Moreover there cannot be any action on the ganglion cells since the effect can be induced after pouring the drug upon the heart.

Fig. 10. Intestine, respiration, carotid blood pressure. Dog, 9.6 K. A.C.E. —morphia. Ethyl chloride. Shows diminution in extent and in frequency of respiration with recovery.

MODE OF ACTION OF THE DRUGS

The fall of blood-pressure, which always occurs, except perhaps with minimal doses, seems to be due to diminished force and frequency of the heart-beat. On the other hand the slight temporary rise with small doses, or as a first stage with larger doses, is due to a preliminary increase in force and frequency of the heart.

The volume of a limb, of intestinal wall, or of spleen almost always follows passively the blood pressure. During the preliminary rise of blood pressure there is a slight temporary dilatation of these organs, but when the blood pressure has become lowered there

Fig. 11. Dog, 9.6 K. A.C.E.—morphia. Fatal dose of ethyl bromide. Intestine respiration, carotid blood pressure.

is a constriction of these organs. (See Figs. 2, 6, 8, 7, 11). Thus we may say that in most cases the drugs have no effect on the vaso-motor system, or directly on the muscular walls of the peripheral arterioles. The blood is pumped into or drained out of the various organs of the body according to the strength of the heart.

Occasionally, however, one gets the opposite result, though never to a marked degree. Fig. 9 shows a slight dilatation of the intestinal wall after administration of ethyl iodide, and in this instance the dilatation appears to correspond with the fall of blood pressure. My clinical experience, which only extends to ethyl chloride and ethyl bromide, bears out the results obtained by physiological experiment. Clonic spasms occur with about the same frequency in human beings as in

Fig. 12. Dog, 9·6 K. A.C.E.—morphia, ethyl bromide, overdose, blood pressure drops to 2·5 m.m. above zero. Heart and respiration both ceasing. Artificial respiration, recovery.

animals. It is stated by many anaesthetists that 'ethyl chloride is a cardiac stimulant and that if a full dose is administered it dilates the peripheral arterioles.' The stimulating effect upon the heart is at best only slight and transitory, and is followed by a much more significant and lasting depressant effect. As we have seen there is only a passive dilatation of peripheral arterioles, and in full doses the blood is drained from the splanchnic area and also from the limb.

1. Knight, *Brit. Med. Journ.*, March 17, 1906.

SUMMARY

1. Ethyl chloride, ethyl bromide, ethyl iodide, and somnoform all have practically the same physiological action. Such differences as exist between them are only of degree, and appear to depend on the extent of their volatility.

2. With small doses the respiration is increased in frequency and depth, with larger doses it is diminished in both these respects. With very large doses it may cease entirely some considerable time before the heart stops.

3. With small doses the blood pressure is slightly raised, but with larger doses may be depressed with or without a small preliminary rise. These effects occur with intact vagi, with both vagi cut, after full doses of atropine, and after nicotine.

4. The drugs do not paralyse the vagus nerve-endings. It is possible to obtain full vagus action when the animal is deeply under the influence of the drug.

5. The action of these anaesthetics upon the circulatory system appears to be almost entirely directly upon the heart. The volume of the spleen, intestinal wall, or limb follows passively the change in blood pressure.

APPENDIX

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Since Dr. Webster handed in his paper to me I have seen Cole's full paper in the *Brit. Med. Journ.*, June 20, 1903.

Cole points out that the chief danger in the use of somnoform being a paralysis of respiration, careful watch must be kept over the respiratory movements. He also notes that after cessation of the respiratory movements it is easy to restore the animal by artificial respiration. This has been fully confirmed by Dr. Webster, and the restoration by artificial respiration is well shown in his tracing, Fig. 12.

But as regards the effects of ethyl bromide and somnoform on the vagus, Webster's results are diametrically opposed to those of Cole. The tracings given by Webster show conclusively that full vagus effects can be obtained when the animal is completely under the influence of the drug.

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