EXPERIMENTS ON THE PHARMACOLOGY OF HYDROXYDIONE SODIUM SUCCINATE

BY

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The actions of hydroxydione sodium succinate ("Viadril") have been studied in chloralose or decerebrate cats, or cats otherwise untreated. It is virtually devoid of action at the neuromuscular, ganglionic, or peripheral adrenergic synapse. After rapid intravenous injection, hydroxydione produced a transient hypotension with little bradycardia and stimulated the respiration. These effects were over in 1 to 2 min. and were reduced if injection was slow or the hydroxydione diluted. Vagotomy did not alter the depressor response, but reduced the respiratory stimulation. In the untreated or the decerebrate animal, as much as five times the anaesthetic dose of hydroxydione was required to depress the respiration or blood pressure. Chloralose potentiated these depressant actions 5 to 10 fold. Both the circulatory and the respiratory depression appeared to be mediated centrally. Decerebrate rigidity was readily lessened by hydroxydione, but the pinna reflex and conjunctival reflex were relatively resistant to its action, and the knee jerk outstandingly so.

Fine transient muscular fasciculations, not unlike those produced by suxamethonium, have occasionally been observed by one of us during hydroxydione administration in man, occurring shortly after the onset of unconsciousness. They appear first in the muscles of the face, spread to the upper limbs and trunk, and die away after a few seconds. Such an observation suggested that hydroxydione might have some neuromuscular action. The possibility became more important in the light of the relaxation which hydroxydione anaesthesia can produce, especially in the pharynx and the larynx. The experiments described below started, therefore, with an investigation, in cats under chloralose, of the neuromuscular action of the drug. It was found, however, that even large doses of hydroxydione had no neuromuscular action. But in the animal under chloralose a somewhat unexpected depression of the respiration by hydroxydione was observed which prompted a fuller investigation of its pharmacology. One interesting finding has been the great potentiation of the respiratory depressant action of hydroxydione by the presence of chloralose.

METHODS

Cats were used for most experiments. After induction with ethylchloride and ether, anaesthesia was maintained with chloralose 60 to 80 mg./kg. The blood pressure was recorded by a siliconed, heparinized

cannula in one carotid artery. The respiration was recorded, after a tracheal cannula had been inserted, by the aid of respiratory valves and a respiration recorder on the expiratory side (Paton, 1949). When required, the twitches of the tibialis anterior muscle were recorded on the smoked drum with a steel spring myograph, in response to supramaximal excitation of the sciatic nerve through shielded electrodes in the thigh. Rectangular pulses of 0.5 m.sec. duration were delivered at varied frequencies, usually one every 10 sec. Action on an autonomic ganglion was tested by recording the contractions of the nictitating membrane with a lever of magnification about 5-fold and load about 2 g. writing frontally on the smoked drum, the membrane being excited to contraction by supramaximal preganglionic shocks through the cervical sympathetic nerve in the neck which had previously been separated from the vagus and divided from its central connexions. The contents of the eyeball were removed. Rectangular pulses of 0.5 m.sec. duration were applied, at 10 shocks per sec. either for a period of 15 sec. every min. or continuously, through platinum electrodes. To make injections a venous cannula was inserted into the femoral or jugular veins, and all injections were washed in with 2 ml. saline.

In some experiments decerebration was performed; a trephine hole was made in the parietal bone and, after incision of the dura, a transection made between the inferior and superior colliculi towards the pituitary fossa; the hemispheres were then removed. To reduce bleeding during the operation both carotid arteries were tied and a vertebral clamp adjusted to control bleeding as necessary. The animal was left for 0.5 hr. to 1 hr. before further dissection so that satisfactory clotting of the cerebral vessels could occur.

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In two cats induction of anaesthesia was performed with hydroxydione, the drug being made up in 1% procaine, and injected into a vein on the foreleg. When full anaesthesia had been produced one or more of the procedures just mentioned were used.

The doses of drugs are given in terms of their salts. These were hydroxydione sodium succinate ("Viadril," Pfizer), adrenaline tartrate, noradrenaline tartrate, acetylcholine chloride, histamine acid phosphate, succinylcholine di-iodide, *d*-tubocurarine chloride. The hydroxydione was normally made up as a 10% solution either in saline or, as described by Galley and Lerman

(1959), in 0.25% or 0.5% procaine. The procaine made no detectable difference to the effects seen.

RESULTS

Actions on the Neuromuscular Junction

In the cat under chloralose a dose of hydroxydione (5 to 10 mg./kg.), which can produce severe respiratory depression, leaves the twitch of the tibialis in response to excitation of its motor nerve completely unaffected (Fig. 1, *a* and *b*). There are neither

FIG. 1.—Cat, 2.6 kg., chloralose. Intravenous injections. Record of blood pressure, respiration, and tibialis twitch. CO, bilateral carotid occlusion for 30 sec. AR, artificial respiration. NAD, noradrenaline. Sux, suxamethonium.

preliminary fasciculations to be seen nor potentiation of the twitch nor any sign of neuromuscular block. Even doses up to 100 mg./kg. (Fig. 1b), which produce profound circulatory effects in the cat under chloralose, are either devoid of any effect on the muscle twitch or even slightly potentiate it. In addition, a test was made of the interaction of hydroxydione with succinylcholine and *d*-tubocurarine. Succinylcholine given to a cat which was under the influence of 10 mg./kg. hydroxydione did not vary from its usual behaviour; and a dose of 20 mg./kg. hydroxydione during recovery from succinylcholine paralysis did not influence the course of recovery in any way. After a massive dose of hydroxydione (100 mg./kg.) the fasciculations normally seen were abolished (Fig. 1b), and the neuromuscular block produced came on a little more slowly and was somewhat prolonged. If so small a change in the action of suxamethonium is produced by a dose 5 to 10 times the normal human anaesthetic dose, any such effect must be negligible in practice. With tubocurarine, corresponding observations were made; after 100 mg./kg. hydroxydione, it was possibly a little potentiated, and had a more prolonged action. These observations imply that,

in a very large dose, hydroxydione has a slight ability to lessen specific depolarization of the endplate, a property shared, in much more intense form, by many anaesthetics.

Supporting evidence for the conclusion that hydroxydione had virtually no neuromuscular action was obtained indirectly in another way. In the decerebrate animal after total doses of hydroxydione up to 230 mg./kg., and with a dose of 500 mg./kg. after induction with hydroxydione, the knee jerk could still be elicited. The presence of a knee jerk necessitates intact neuromuscular transmission; this result is an even more cogent reason for rejecting any significant neuromuscular action.

Action on Autonomic Ganglia

Fig. 2 shows the effect of 10 mg./kg. hydroxydione on the response of the nictitating membrane to preganglionic excitation, a dose which produced the usual substantial sustained hypotension seen in chloralosed cats. Immediately after the injection, there was possibly a slight weakening of the response of the membrane to continued stimulation; and about 10 min. later, when the hypotension was fully developed, there was a doubtful reduction of the

FIG. 2. — Cat, chloralose. Intravenous injections. Response of nictitating membrane to preganglionic excitation at 10/sec., either for 15 sec. every min., or continuously.

FIG. 3.—Cat, chloralose. Record of carotid arterial blood pressure. Artificial respiration. Responses to nicotine (Nic) before and after 10 and 40 mg./kg. hydroxydione.

response to intermittent excitation. With a higher dose, of 40 mg./kg., the response to intermittent stimulation was definitely reduced; and with continued excitation, the response was not quite as well maintained as usual. Hydroxydione thus has a slight ganglionic action, around 1/300 of the potency of hexamethonium, detectable but not sufficient to account for the hypotensive action.

A test was also made of the effect of hydroxydione on the pressor response to nicotine (Fig. 3). At 10 mg./kg., the rise in blood pressure was hardly altered, although its time course was modified slightly. With 40 mg./kg., however, the action of 1 mg. of nicotine was abolished. This anti-nicotine action is more pronounced than would be expected from the effect of hydroxydione on ganglionic transmission; but it must be remembered that nicotine, in addition to exciting autonomic ganglia, also stimulates chemoreceptors and exerts other central actions.

The fact that the nictitating membrane response to preganglionic excitation was little altered by hydroxydione also implies that hydroxydione has a negligible action at the junction between the sympathetic nerves and smooth muscle, and on the responses of smooth muscle to the sympathetic transmitter. The latter point was tested directly. A large dose of hydroxydione, indeed, increases the rise in blood pressure produced by noradrenaline (Fig. 1b), presumably because the blood pressure is lower and the buffer mechanisms paralysed. In short, hydroxydione has little peripheral synaptic effect, whether tested on the sympathetic effector junction, the autonomic ganglion or the neuromuscular junction.

Effects of Hydroxydione on Respiration and Blood Pressure

Animals under Chloralose.—In our first experiment, on a cat under chloralose, the somewhat startling observation was made that a dose of 10 mg./kg. of hydroxydione abolished the respiration in between 3 and 4 min. This is quite out of keeping with clinical experience (Lerman, 1956), so that a further analysis was made. In the chloralosed animal this dose always depressed respiration strongly, at least 40%. Even 5 mg./kg. had a distinct effect on respiration (Fig. 1a). Usually 20 mg./kg. would produce apnoea, but sometimes a higher dose was needed.

The immediate effect of hydroxydione on the respiration is usually a transient stimulation, occurring soon after the injection, increasing the minute volume sometimes as much as two-fold, sometimes only by 20 to 30%, with a rapid return to normal. It is after this that the depression of the minute volume occurs, accompanied by some slowing of respiration. Even with a large dose of hydroxydione there is some delay before respiratory paralysis ensues; and it probably cannot be produced in a shorter time than 2 or 3 min. The respiratory minute volume recovers again with time; after 10 to 20 mg./kg., recovery takes 30 to 60 min. During a reduction of respiration by hydroxydione, provided asphyxia is not produced, the minute volume often becomes more regular; spontaneous fluctuations, or reflex responses to rise or fall of blood pressure due to adrenaline or histamine or to stimulation of the cervical sympathetic trunk, are reduced. Thus, even in the experiment of Fig. 1a where the respiration was

already unusually stable, the respiratory effects of carotid occlusion and of 5 μ g. noradrenaline were reduced by 10 mg./kg. hydroxydione.

Accompanying the respiratory action is a somewhat complicated response of the blood pressure. First, with a dose of 10 mg./kg. or more, is a pronounced transient fall in blood pressure; this may be as much as 50 mm. cf Hg or more, according to the dose and speed of injection. It has a very short latency after the injection, and the blood pressure returns to the normal level in about 30 sec.

After this initial hypotension a second, pressor response up to 40 mm. and lasting 2 to 5 min. may be seen. There is no noticeable tachycardia during this time. The rise in blood pressure appears to occur only when there is a reduction of minute volume; but it is sometimes absent even when the respiration is depressed. This phase then passes into the third and main response, a slowly progressing hypotension which may reach its lowest point up to 15 or 20 min. after the injection; the blood pressure then slowly rises again, to return to normal at a time depending on the dose given.

The final prolonged hypotension appears to depend on a central vasomotor depression. The experiments on autonomic ganglia, mentioned earlier, exclude a peripheral paralysis of sympathetic effector organs as the cause, and this was confirmed by verifying that, for instance, the action of adrenaline and noradrenaline was unimpaired during the hypotension. (The depressor effects of histamine, and of histamine liberation, are also still demonstrable, although reduced as is usual when the blood pressure falls.) The hypotension is not accompanied by any marked bradycardia, and vagotomy did not influence it. The most reasonable explanation for it, therefore, is that it is due simply to reduction of central vasomotor tone. This conclusion was substantiated by finding that during the hypotension due to hydroxydione, the rise in blood pressure elicited reflexly by bilateral carotid occlusion was impaired despite the continuing effectiveness of autonomic transmission and of noradrenaline (Fig. 1*a*). With 5 mg./kg. hydroxydione (lowering the blood pressure by about 40 mm.) a considerable reduction of the carotid occlusion response occurred; with 10 mg./kg. (lowering the blood pressure to 60 mm.) it was virtually abolished (Fig. 1*b*) although 5 μ g. noradrenaline had a larger pressor effect than normal. Three hours later the carotid occlusion response had recovered considerably; the blood pressure was still low, but, after 7 hr. anaesthesia, this is of doubtful significance.

Decerebrate Animals

If the animal is decerebrated under ether, and an interval of 1 hr. or more allowed after ceasing ether administration, one can test hydroxydione on the respiration and circulation in the virtual absence of any other anaesthetic. When this is done, the initial respiratory stimulant and depressor actions are still present, with the same time course; the respiratory stimulation, indeed, is more pronounced than in the presence of chloralose. But the subsequent depression of the respiration is absent, until relatively enormous doses of hydroxydione are given. Similarly, the blood pressure, after the initial hypotension, returns permanently to its original level, and there is little sign either of the pressor effect or of the slow prolonged hypotension. Thus, in one animal, 140 mg./kg. hydroxydione given in divided doses over a period of 40 min. had nothing but a stimulant action on the respiration. In another, a single dose of 40 mg./kg., following previous divided dosage of 70 mg./kg. (itself ineffective), only stimulated respiration. In a third animal, it required 40 mg./kg. to depress minute volume by 25%. The blood pressure responses are harder to interpret, since the pressure tends to decline from its initial level in any case; but it appeared that no persistent hypotension occurred with doses under 40 mg./kg. and in one experiment 110 mg./kg. failed to reduce the blood pressure.

The decerebrate animal appeared, in short, to be something like 5 to 10 times more resistant than the chloralosed animal to the depressant effect of hydroxydione on respiration and blood pressure. So large a difference raised the question whether decerebration had removed some nervous structure necessary for the action of hydroxydione. This was tested by giving chloralose to three decerebrate animals. In one, which had received 140 mg./kg. hydroxydione with no depression of respiration, 40 mg./kg. chloralose (half the standard dose) produced apnoea in 3.5 min. In the other two, 60 mg./kg. chloralose itself depressed the respiration considerably; after a period of recovery, 10 mg./kg. hydroxydione was now itself able to produce apnoea. There was thus a powerful synergism between the two drugs in the decerebrate animal, each potentiating the depressant action of the other; it was of such a magnitude that a dose of hydroxydione, a small fraction of that necessary by itself to exert respiratory depressant action, combined with a dose of chloralose much smaller than normally employed, could cause complete abolition of respiratory movement. The fact that giving chloralose to the decerebrate cat allowed the depressant action of hydroxydione to be reproduced as in the intact cat under chloralose makes it

unnecessary to suppose that decerebration removes some nervous structure requisite for the action of hydroxydione.

The opportunity was also taken to make some qualitative observations in these decerebrate animals on muscle tone, the knee jerk, the conjunctival reflex and the pinna reflex. Decerebrate rigidity, and the clonic character of the response to tapping the quadriceps tendon, were obviously reduced by doses of 20 to 30 mg./kg. hydroxydione; but it proved generally impossible to abolish the reflexes, although the conjunctival reflex was weakened by large doses. A similar observation had been made in chloralosed animals: that even when apnoea was produced with hydroxydione, the knee jerk remained.

Induction of Anaesthesia with Hydroxydione

Having found that hydroxydione in the decerebrate cat appeared to be a remarkably safe anaesthetic, an induction of anaesthesia with hydroxydione alone was performed. In one animal a dose of 10 mg./kg. intravenously sedated the animal, and a further 10 mg./kg. 20 min. later deepened the sedation, and after another 20 min. interval a further 20 mg./kg. produced surgical anaesthesia. In another, approximately 80 mg./kg. in divided doses over 45 min. produced a similar effect.

Some of the observations previously made were then repeated (Fig. 4). Under these conditions, a dose of 10 or 20 mg./kg. hydroxydione had little or no depressant effect on respiration, and did not cause any prolonged hypotension. The usual transient hypotension, with a marked accompanying respiratory stimulation at the time of injection, was still seen. The promptness and transience of these two responses suggest that they are due to the presence of a high concentration of hydroxydione in the blood during its first circulation after the injection. This was confirmed by finding that both responses are much attenuated, either by making the injection slowly, or by diluting the injected solution ten-fold (Fig. 4a). Our first impression was that the hyperpnoea was secondary to the hypotension: for a similar phenomenon is often seen with depressor drugs. But, recorded on a fast-moving drum, the respiratory response sometimes precedes, by a few seconds, the hypotension, so that the latter can hardly be the sole cause of the respiratory change.

FIG. 4.—Cat, hydroxydione anaesthesia. Intravenous injections. Record of respiration and blood pressure. (a) Responses to hydroxydione 10 mg./kg. given in 0.23 ml. washed in with 2 ml. saline, except third injection in 2.3 ml. with 2 ml. washed in. (b) Responses to 10 and 20 mg./kg. hydroxydione on a 10 times faster drum. (c) Responses to 10 and 20 mg./kg. hydroxydione after cutting both vagi.

FIG. 5.—Cat. Hydroxydione anaesthesia. Record of respiration and blood pressure. Before the beginning of the record, 240 mg./kg. hydroxydione had been given over 2 hr. 40 min.

This analysis was confirmed by sectioning the vagi. As a result the hypotension produced by hydroxydione was reduced slightly, but its time course and the slight slowing of heart rate during the fall of pressure were unchanged. The respiration was more affected; the stimulant effect was much reduced; and in one experiment in which the first effect of hydroxydione had been to suppress one or two breaths before the stimulation of respiration, this transient apnoea disappeared. It appears, therefore, that the vagi play some part in the initial respiratory response to hydroxydione.

The experiment of Fig. 4 was terminated by giving repeated doses of hydroxydione at 5 min. intervals, to examine the response to massive dosage (Fig. 5). After around 320 mg./kg., the blood pressure began to fail to return to its original level after each injection. After 480 mg./kg., each injection gave rise to a species of transient convulsion, which, after the last dose (total 600 mg./kg.), was more persistent and was at last accompanied by respiratory failure. It was remarkable that the knee-jerk could still be elicited, and not until effective respiration had ceased for several min. did it disappear.

DISCUSSION

Hydroxydione deserves attention as representing a type of anaesthetic structurally quite distinct from those in general use. Although, as a rule, the chemical structure of the general anaesthetics is less important than their physical properties, it may well be that the steroid nature of hydroxydione is responsible for some of its novel features. In discussing these, comparisons with other anaesthetics will be made.

As with other drugs given intravenously, the concentration in the blood is very high during the first one, possibly two, circulation times after the injection. Gray and Paton (1949) showed that, in the cat, an injection of volume about 3 ml. was only diluted about ten-fold in the blood in its first passage from a femoral vein to carotid artery; and that the injection "slug" was still detectable during the second circulation. We have concluded that the first response to hydroxydione, a fall in blood pressure and a stimulation of respiration, is due to this "slug effect"; for the time relations are correct, and this first response is greatly reduced by diluting the injected solution or by slow injection. The hypotension is accompanied by only a slight bradycardia and survives vagotomy, so that it is

not of the Bezold-Jarisch type. The respiratory response, primarily stimulant but occasionally preceded by one or two "dropped breaths," appears to depend in part on vagal pathways; the remainder may well be secondary to the hypotension. We have not analysed this initial response further, but it is not altogether a surprising consequence of the sudden exposure of the heart and lungs to a concentration of around 10^{-3} hydroxydione. It is of little significance for clinical practice, where a much greater dilution of the injected material will occur. It compares not unfavourably with thiopentone, with which immediate cardiac depression may be severe, and accompanied by apnoea.

The subsequent responses of the blood pressure and respiration depend on the intensity of the depression of vasomotor and respiratory centres. In the animal under chloralose, after a latency of a few minutes a slowing of respiration and reduction of tidal air lead to a fall of minute volume. There is a fall of blood pressure usually of similar time course, although sometimes the blood pressure may rise initially for a few min. during the early stages of the respiratory depression. Both respiratory and blood pressure depression reach their peak in 10 to 20 min. At this stage, spontaneous fluctuations or changes of reflex origin are reduced or abolished, although the responsiveness of the blood vessels to directly acting drugs (adrenaline, noradrenaline, histamine) is retained. Recovery is gradual; the effect of a dose of 10 to 20 mg./kg. lasts 30 to 60 min.

Although the reactions of the animal under chloralose allow the type and duration of action of hydroxydione to be studied conveniently, they give an erroneous picture of their magnitude. In the decerebrate or normal animal, it was not possible to produce apnoea with doses less than 140 mg./kg., and hypotension was equally slight; but under chloralose, 5 mg./kg. both reduced blood pressure and minute volume substantially. The mutual potentiation between chloralose and hydroxydione is an interesting phenomenon, and may well extend to other anaesthetics; Lerman (1956) has already commented on a potentiation by hydroxydione of nitrous oxide. More important for practice,

however, is an estimate of the safety of hydroxydione, expressed as the ratio of respiratory or circulatory depressant dose to anaesthetic dose. We have not made the systematic study necessary for this; but it is clear, from our own result (that roughly 50 mg./kg. will produce surgical anaesthesia) in conjunction with results reported elsewhere, that the safety factor is of the order of 5-fold, possibly higher. Some additional observations, which we have not described in detail, are relevant here. If apnoea is produced with hydroxydione, and allowed to continue for about 3 min. until circulatory failure occurs, it only requires artificial respiration and, if necessary, cardiac massage to restart quite a vigorous heart beat. At no time have we seen cardiac irregularities, even under such stringent conditions. It appears, in short, to be comparable with, or superior to, ether in its safety.

Finally, the lack of peripheral synaptic action is of interest. Ether is known to have quite a pronounced "curariform" action, shared in more or less degree by the other volatile anaesthetics. The barbiturates also have neuromuscular actions, and a power to block ganglia, which, with amylobarbitone, formed the basis of a test for neurogenic hypertension.

Hydroxydione thus presents features of considerable interest. It appears to be both safe and specific. Its time course of action differs from, say, thiopentone, but this merely means it must be used differently. If its principal disadvantage in practice (that of surface-activity, on which its local irritant effect in the tissues appears to depend) could be overcome, it, or similar compounds, would represent very valuable anaesthetic agents.

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