INVESTIGATION OF RESPIRATORY AND CIRCULATORY EFFECTS OF ETHAMIVAN IN THE DOG AND CAT

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SUMMARY

Intravenous injections of ethamivan caused apnoea, bradycardia and hypotension in anaesthetized dogs whilst a similar circulatory response without apnoea was seen in anaesthetized cats. Apnoea and bradycardia were abolished and hypotension was reduced by bilateral vagotomy. Premedication with atropine abolished bradycardia but did not modify the other responses to ethamivan. The effect of intravenous injection of ethamivan was not altered by premedication with mepyramine or hexamethonium. Ethamivan did not cause apnoea when injected into the left auricle, the carotid artery or the posterior aorta. The effect on heart rate and blood pressure when injection was made at these sites was variable. It was concluded that ethamivan stimulated a chemoreflex having receptors in the pulmonary circulation. The reflex was not, however, inhibited by intravenous infusions of procaine.

Ethamivan (vanillic acid diethylamide) has been shown to have respiratory stimulant effects in laboratory animals (Ginzel, 1952) and in man (Gardiner, 1958; Locket, 1959, 1960; Anderton et al., 1962). In the anaesthetized dog, however, it has been shown that this drug gives rise to apnoea, bradycardia and arterial hypotension of short duration; there is no effective increase in respiration (Campbell, Lawson and Sanford, 1962). This response was not modified by alterations in dose or in the rate of intravenous injection. The present investigation was made in an attempt to discover the site of action of this drug, and to obtain an explanation for the effects previously observed.

METHODS

Young adult dogs and cats of either sex were used. In most experiments general anaesthesia was induced with sodium pentobarbitone (30 mg/kg); in a few animals anaesthesia was induced and maintained by inhalation of a cyclopropane-oxygen mixture. Arterial blood pressure was recorded either from the carotid or femoral artery, and respiratory rate and force were recorded from the side arm of a tracheal T-piece. In some experiments kymographic records were obtained from a mercury manometer and Brodie’s tambour, but in the majority arterial pressure was measured by a strain-gauge transducer and respirations by a capacitance electromanometer connected to a 4-channel pen recorder (AEI type EPR).

In four animals the vagi were sectioned bilaterally in the mid-cervical region.

Routes of injection of ethamivan.

Intravenous injections were made into the femoral vein. Arterial injections were made into the carotid artery or into the posterior aorta through nylon cannulae introduced into the thyroid and right femoral artery respectively.

In order to carry out intra-auricular injections thoracotomy was performed on the left side, the pericardium incised; a nylon catheter was introduced into the left atrium and retained by means of a purse-string suture. The chest was then closed, manual inflation of the lungs being used to exclude air from the thorax. When further evacuation of air was required, a water drain and vacuum pump were used. Four animals were used in these investigations.

Recording cardiac contractions.

Electrocardiogram. The heart rate was monitored by a single lead and displayed on the 4-channel pen recorder.

Drugs. Sodium pentobarbitone solution, 60 mg/ml (Nembutal; Abbott); ethamivan solution, 50 mg/ml (Vandid; Riker); sodium bemegride...
solution, 25 mg/ml (Sodium Megimide; Aspro Nicholas); atropine sulphate solution, 2 mg/ml; mepyramine maleate solution, 50 mg/ml (Anthisan, May and Baker); hexamethonium bromide, 10 mg/ml (Vegolysen; May and Baker); and procaine hydrochloride (Planocaine; May and Baker). All drugs were given intravascularly, except mepyramine maleate which was given by intramuscular injection.

RESULTS

Effect of non-barbiturate anaesthesia.
Anaesthesia was induced and maintained with a cyclopropane-oxygen mixture administered by means of a close-fitting mask. Injection of ethamivan 10 mg/kg caused temporary bradycardia, hypotension and apnoea. These effects were indistinguishable from those seen when pentobarbitone was used as the anaesthetic agent.

Effect of premedication in dogs.
The typical response to an intravenous injection of ethamivan 10 mg/kg was not altered by premedication with mepyramine maleate 4 mg/kg, or hexamethonium bromide 2.5 mg/kg. Premedication with atropine sulphate 0.5 mg/kg, however, abolished bradycardia, though apnoea and hypotension still followed the injection of ethamivan. The effects of premedication by each of these drugs were tested in three dogs.

Effect of vagotomy.
Bilateral cervical vagotomy abolished the apnoea which followed injection of ethamivan 10 mg/kg in the anaesthetized dog (fig. 1a). However, abolition of apnoea did not reveal any respiratory stimulant action. Bemegride 10 mg/kg given to anaesthetized vagotomized dogs, on the other hand caused a marked temporary increase in respiratory rate (fig. 1b).

Ethamivan still produced hypotension in the vagotomized dog, but this was not accompanied by bradycardia.

In the cat, intravenous injection of ethamivan 10 mg/kg caused hypotension but not apnoea. Larger doses produced some stimulation of respiration (Campbell, Lawson and Sanford, 1959).

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**Fig. 1**

Vagotomized dog anaesthetized with pentobarbitone. Records of respiration, carotid arterial pressure and time (sec).

Effect of ethamivan 10 mg/kg (a). Effect of sodium bemegride 10 mg/kg (b).
FIG. 2
Vagotomized cat anaesthetized with pentobarbitone. Records of carotid arterial blood pressure, respiration and time (sec).
Effect of 10 mg/kg (a), and 30 mg/kg (b), of ethamivan given intravenously.

FIG. 3
Dog anaesthetized with pentobarbitone. Records of femoral arterial blood pressure, respiration, and time (sec).
Effect of ethamivan 5 mg/kg given into the femoral vein (a), left auricle (b), and carotid artery (c).
Following vagotomy, the response to ethamivan was unaltered and large doses still resulted in an increased rate and depth of respiration (fig. 2).

**Effect of injection by different routes in dogs.**

In these experiments a preliminary investigation was made to determine the minimum intravenous dose of ethamivan which would consistently cause apnoea when injected into the femoral vein. This dose (5 mg/kg) was then given successively into the left auricle (fig. 3b), the carotid artery (fig. 3c) and the posterior aorta. Injection at these sites never caused apnoea.

Left auricular and carotid injection had a variable effect on respiration. In some instances only very slight stimulant action was noted, while in others a fairly marked increase in depth and rate of respiration occurred, but did not persist for longer than 10-15 seconds. No consistent effect on the blood pressure was observed as a result of injection by these routes. Some dogs showed hypotension of short duration while in others an increase in blood pressure of similar duration was seen. Bradycardia was not marked, a slight reduction in heart rate being observed in association with the rise in blood pressure.

**Effect of infusion of procaine.**

Bevan and Verity (1961) have shown that infusions of procaine may inhibit the action of some drugs that stimulate chemoreflexes.

The effect of intravenous infusions of procaine on the response to ethamivan was therefore examined. An initial dose of 3 mg/kg procaine hydrochloride was followed by a continuous infusion of this drug. Several tests were carried out during different rates of infusion, during which ethamivan 10 mg/kg was given intravenously. Although rates of infusion of up to 2 mg/kg/min procaine were used apnoea and hypotension still occurred.

**DISCUSSION**

It is apparent that ethamivan has little or no central respiratory stimulant action in the dog. In man respiratory stimulation has been observed (Cole, Marks and Baum, 1960; Locket, 1960). Anderton et al. (1962) have shown that, in conscious human subjects, ethamivan stimulated respiration only when the alveolar Pco₂ levels were low.

A temporary depressant effect on respiration in the anaesthetized dog was previously reported by Auinger et al. (1952), whilst Ginzel (1952) found that a brief period of apnoea sometimes followed the injection of ethamivan in cats. We have not observed this response in cats, suggesting that it is inconstant in this species.

The abolition of the apnoeic response in the dog following bilateral vagotomy suggested an effect of the drug on a reflex mechanism having an afferent pathway in the vagus. Such reflexes are well known and have been designated chemoreflexes* by Dawes and Comroe (1954) to distinguish them from the more specific chemoreceptor mechanisms. These authors defined three types of chemoreflexes: (1) a coronary (or Bezold-Jarisch) reflex causing bradycardia and a fall in arterial pressure; (2) a similar reflex from sensory receptors in the lungs, affecting arterial pressure and heart rate, and (3) a respiratory reflex arising from sensory receptors in the lungs. It would appear from our experiments that a pulmonary respiratory reflex causing apnoea is stimulated by the intravenous injection of ethamivan in dogs.

The cause of the circulatory effects of ethamivan is much less clear. Bradycardia was abolished by vagotomy but was also prevented by premedication with atropine. Hypotension still occurred after these procedures and does not appear to depend on stimulation of a chemoreflex. It has been emphasized by Dawes and Comroe (1954), however, that there are many difficulties inherent in an investigation of this type and the possible involvement of other chemoreflexes cannot be excluded.

Chemoreflexes may be elicited by a very diverse group of drugs, and species differences are also

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*The word "chemoreflex" as used by Dawes and Comroe denotes a reflex initiated by chemical substances whether they act upon true chemoreceptors, other types of sensory receptors or upon nerve fibres themselves. The word "chemoreceptor" is reserved to denote sensory nerve endings which normally respond to changes in their natural chemical environment in health or disease. Thus thoracic sensory receptors are not called chemoreceptors unless it is shown that these receptors are also stimulated by substances which are present under either physiological or pathological conditions.
encountered (Dawes, Mott and Widdicombe, 1951; Fastier, McDowall and Waal, 1959; Bevan and Verity, 1961; Dejours, 1962). Drugs which have been shown to stimulate chemoreflex responses include lobeline, veratridine, 5-hydroxytryptamine and various amidine derivatives such as 2-naphthylguanidine. None of these drugs has a close structural similarity to ethamivan. It may be of interest, however, that lobeline, in larger doses than those needed to elicit the chemoreflex, causes hyperpnoea and hypertension by stimulating the chemoreceptors of the carotid body (Bevan and Verity, 1961). Such an action was considered by Ginzel (1952) to be partly responsible for the stimulant effects of ethamivan.

Bevan and Verity (1961) also demonstrated that the chemoreflex effects of phenylbiguanide, 5-hydroxytryptamine and lobeline could be prevented by the intravenous infusion of procaine hydrochloride. In our experiments the effect of ethamivan was not abolished by an infusion of procaine at ten times the greatest rate used by these authors.

As species differences are a well marked feature of the chemoreflex response, it cannot be predicted that ethamivan would give rise to similar effects in man. Nevertheless it is of interest to find that a compound, intended for use as a respiratory stimulant, can in some species produce severe respiratory and circulatory depression.

REFERENCES


ETUDE DES EFFETS RESPIRATOIRES ET CIRCULATOIRES DE L'ETHAMIVAN CHEZ LE CHIEN ET LE CHAT

SUMMARY

Des injections intraveineuses d'ethamivan provoquaient une apnée avec bradycardie et hypotension chez les chiens anesthesiés alors qu'une réponse circulatoire analogue sans apnée était notée chez les chats anesthesiés. L'apnée et la bradycardie disparaisaient et l'hypotension était améliorée par vagotomie bilatérale. La prémédication par l'atropine faisait disparaître la bradycardie, mais ne modifiait pas les autres réponses à l'ethamivan. Les effets de l'injection intraveineuse d'ethamivan n'étaient pas modifiés par la prémédication par la mepyramine et l'hexaméthonium. L'ethamivan ne provoquait pas d'apnée après injection dans l'oreillette gauche, l'artère carotide ou l'aorte postérieure. L'effet de ces derniers modes d'injection sur le rythme cardiaque et la tension artérielle était variable. On a conclu de ces résultats que l'ethamivan stimule un chémoréflexe dont les récepteurs sont situés dans la circulation pulmonaire. Toutefois ce réflexe n'a pas pu être inhibé par la perfusion intraveineuse de procaine.

UNTERSUCHUNG DER WIRKUNG VON ETHAMIVAN AUF KREISLAUF UND ATMUNG BEI HUNDEN UND KATZEN

ZUSAMMENFASSUNG