UNDESIRABLE EFFECTS OF VANILLIC ACID DIETHYLAMIDE IN DOGS AND CATS

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SUMMARY

Vanillic acid diethylamide has been used experimentally in dogs anaesthetized by pentobarbitone. The main effects noted were depression of blood pressure and respiration. Isolated dog auricle preparations showed a decrease in both frequency and amplitude of contraction. In cats similarly anaesthetized there was a slight stimulatory effect on respiration lasting approximately one minute but a reduction in blood pressure also occurred.

INTRODUCTION

Vanillic acid diethylamide (VAD) was introduced by Ginzel in 1952 and was later acclaimed by some authors as the analeptic of choice in cases of barbiturate poisoning (Gardiner, 1958; Locket, 1959, 1960; Cole, Marks and Baum, 1960; Glynn, 1960).

The use of the compound was suggested following experimental work by Ginzel (1952) on rabbits either conscious, sedated by morphine or anaesthetized with urethane; cats under chloral hydrate narcosis; and isolated perfused hind limbs of dogs. His experiments and the subsequent clinical trials indicated that vanillic acid diethylamide had respiratory and circulatory stimulant properties as well as a potent action in reducing the depth of narcosis. Our preliminary trials on dogs, however, showed that the drug had severe depressant effects in this species.

An effective analeptic should stimulate respiration, giving an increased effective ventilation, and should also increase blood pressure if this is depressed. A decrease in the degree of central nervous depression, especially if accompanied by reduction in the recovery time, is also desirable. Experiments were, therefore, designed to assess the activity of VAD on respiration, blood pressure and duration of narcosis in the dog and cat.

METHODS

Cross-over tests.

Dogs were anaesthetized by intravenous injection of 33 mg/kg of a 6 per cent solution of sodium pentobarbitone. Thirty minutes after the induction of anaesthesia either a 5 per cent solution of vanillic acid diethylamide* or a 2½ per cent solution of sodium bemegride† was given intravenously. Continuous records of e.c.g. and respirations were made and intermittent records of systolic blood pressure were obtained by means of a sphygmomanometer cuff and pulsometer applied to the tail (Campbell, Lawson and Sanford, 1961). The tests were arranged in the manner described by Sanford (1958) and each dog was anaesthetized on three occasions separated by intervals of at least one week.

Effects on blood pressure and respiration.

In some experiments on dogs recordings were made in the manner described above. In other experiments on dogs and cats a continuous record of blood pressure was obtained by cannulation of the carotid artery. Tracings were made either by connection to a mercury manometer recording on smoked paper or to a Statham strain gauge transducer and electronic pen recorder. In these experiments respirations were recorded by inserting a T-piece in a cuffed endotracheal tube and connecting the side arm either to a tambour or to an electromanometer.

Isolated auricle preparations.

Young dogs 3 to 4 months of age were anaesthetized with sodium pentobarbitone. An incision was made in the left side of the thorax and between the 5th and 6th ribs, to permit free access to the thoracic cavity. The pericardium

*Vandil (Riker Laboratories Ltd.)
†Megimide Sodium (Aspro-Nicholas Ltd.)
was incised and the heart was removed as rapidly as possible and placed in oxygenated Tyrode solution containing twice the normal concentration of glucose at 30°C. Both auricles and the tissue joining them were dissected out in one piece and the preparation was suspended by threads inserted into the apex of each auricle. Contractions were recorded by a simple Starling heart lever writing on a smoked drum. The preparation did not usually contract spontaneously at first but could be induced to do so by a short period of electrical stimulation using square wave pulses of 20 V and 30 m.sec duration, delivered at a rate of one per 2 seconds.

RESULTS

Effects on sleeping time of dogs.

The recommended dose of 10 mg/kg of VAD given by intravenous injection produced no obvious reduction in the sleeping time of dogs given pentobarbitone.

Cross-over tests were carried out on three dogs. Intravenous injection of 28 to 33 mg/kg bemegride resulted in reductions in sleeping time of 36, 50, and 40 per cent respectively. Our intention was to give an equal dose of VAD but in the first dog the injection was stopped after 20 mg/kg had been given because of the persistent apnoea. This dose produced a reduction in the sleeping time of only 4.5 per cent. In the second dog 30 mg/kg VAD produced a reduction of 21 per cent. A slightly higher dose in the third dog, 33 mg/kg, caused convulsions and death.

In view of the relative inactivity of VAD in producing arousal without risk of toxicity, further tests were abandoned.

![Image](https://example.com/image1.png)

**FIG. 1**

Effect of VAD on blood pressure and respirations of a dog anaesthetized with pentobarbitone.
**Effect on blood pressure and respiration.**

Dogs given an intravenous dose of 10 mg/kg of VAD showed a marked fall of systolic blood pressure immediately after the injection, followed by a secondary transient rise often above the pre-administration level (fig. 1). At the same time there was a pronounced bradycardia of short duration.

Injection of the drug also had a profound effect on respiration (fig. 1). Immediately after administration respiration ceased entirely. After a period of apnoea which lasted from 30 seconds to 2 minutes, small fast respiratory movements were seen. Over a period of 10 minutes the tidal volume increased and the respiratory rate decreased to the pre-administration level. Figure 2 shows the composite results of intravenous administration of 10 mg/kg VAD in ten dogs.

In dogs which were deeply depressed by pentobarbitone, VAD produced a smaller effect on the blood pressure but a similar effect on respirations. If apnoea was already present no stimulation of respiration occurred. Reducing the speed of injection did not alter after the final response.

Intravenous infusion of the drug at rates of 12.5 mg and 25 mg/min produced no change in blood pressure, heart rate, or respiration.

**Cats.**

The response to the drug in cats was somewhat different from that observed in dogs (fig. 3), in that apnoea was not seen. In the lightly anaesthetized cat, respirations were stimulated for 30 to 60 seconds, but in more deeply anaesthetized animals no change in respirations was noticed.

A fall in systolic blood pressure consistently followed the intravenous injection of VAD, but no bradycardia occurred; tachycardia developed after a few seconds but the heart rate had returned to the pre-administration level within 2 minutes.

**Isolated auricle preparations.**

The effect of the drug on the heart was demonstrated by means of preparations of isolated dog
auricles, VAD produced a reduction in rate and force of contraction in the dog auricle, which returned to normal after washing (fig. 4).

Toxicity.

Ten dogs were given intravenous doses ranging from 20 to 45 mg/kg. All animals which received more than 30 mg/kg developed convulsions and died within 3 minutes without regaining consciousness. One animal died after intravenous administration of 27.5 mg/kg.

DISCUSSION

The main indication for the use of an analeptic is in cases of severe respiratory depression. One of the more common causes of this is barbiturate poisoning, and Gardiner (1958) and Locket (1960) have reported favourably on the use of VAD in such cases.

We have not been able, however, to demonstrate any useful effect in dogs anaesthetized with pentobarbitone. Doses of 2.5 to 20 mg/kg of the drug did not stimulate respirations without first causing a period of apnoea. Such respiratory stimulation as did occur was of very short duration and might in part have resulted from carbon dioxide retention during the apnoic phase. The tachypnoea which followed was accompanied by a decrease in tidal volume so that the effective ventilation was reduced.

Intravenous injection of VAD in dogs, using doses of 2.5 mg/kg or more, consistently caused a fall in blood pressure. This was occasionally followed by a rise to a pressure greater than the pre-injection value but in most cases no secondary hypertension occurred. This fall in blood pressure might in part be caused by the direct depressant action of the drug on the heart illustrated by the results of experiments on the isolated dog auricle.

In cats, injection of VAD did not produce apnoea but no useful stimulation of respirations occurred. The effect on the blood pressure was similar to that observed in the dog although there was no marked bradycardia in this species. Ginzel (1952) made similar observations in cats narcotized with chloral hydrate and has reported both apnoea and hypotension following the injection of VAD in some animals. In a previous report of the action of VAD in dogs anaesthetized with morphine and chloralose, Auinger et al. (1952) found that intravenous injection of the drug caused transient hypotension and bradycardia and a slowing of respirations. These authors, however, described a greater stimulant effect than has been demonstrated in the present experiments.

Auinger et al. (1952) found also that dogs given VAD showed a rapid return of consciousness, but no arousal from barbiturate anaesthesia occurred in our experiments. Pedal and palpebral reflexes became stronger for a period of about 5 minutes after injection but did not persist. This is much less satisfactory than the arousing effect produced by VAD in dogs anaesthetized with morphine and chloralose.

FIG. 4

Response of isolated dog auricle to VAD. Fluid in the tissue bath was changed at W.
of bemegride in dogs and cats (Macfarlane and Bentley, 1957). Although potent stimulatory effects in man have been reported, no such effects have been seen in the dog and cat. At present we are unable to suggest any explanation for these differences.

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REFERENCES


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