Systemic Effects of 2-isovaleryl-1,3-indandione. (22176)

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(Introduced by J. H. Wills.)
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The 2-acyl-1, 3-indandiones possess anticoagulant properties which make the more potent compounds useful as rodenticides(1-4). A typical acyl indandione, 2-isovaleryl-1, 3-indandione (Isoval) was found by Kabat *et al.*(2) to possess no significant effects on blood pressure, respiration, or plasma prothrombin time in cats after slow intravenous administration of 20 mg/kg for 2.5 hours. However, these authors noticed that after oral doses of 100-300 mg/kg given to rats and rabbits, labored respiration, progressive muscular weakness, hyperexcitability, pulmonary congestion, venous engorgement and systolic standstill resulted.

During our study of prolonged plasma coagulation time produced by Isoval in rabbits, we noticed that intravenous injection of comparatively large doses resulted in extremely rapid death (within 2 minutes). Because such an acute effect had not been reported previously it was decided to investigate this action of Isoval and related compounds.

Methods. Cats of mixed breed and sex were used. The animals were anesthetized with pentobarbital and tracheotomized for artificial respiration or for recording respiration by means of Stathan strain gauge attached to pneumotachograph. In some animals, respiratory recordings were made by means of an intrathoracic cannula. The right carotid artery was cannulated and connected to mercury U-tube manometer for blood pressure recording. All injections were made through a polyethylene tube cannula inserted into the right femoral vein. Spinal sections were performed through dorsal incisions at approximately the C-4 level. The sodium salt of Isoval is soluble in water to about 20 mg/cc. When solutions of greater concentration were required, the substance was dissolved in diethylene glycol monoethyl ether. The effect of epinephrine on the Isoval response was determined by giving epinephrine in isotonic saline solutions before, together with, and after injection of the drug.

Results. Fig. 1 a and b show responses obtained at dose levels of 5, 20, 30, 40 and 60 mg/kg Isoval in single cats. The top tracing is respiration measured by means of intrathoracic cannula. As the dose of Isoval was increased, the hypotensive effect became more severe until at higher doses there was no recovery. Concomitant with the drop in blood pressure there was an increase in both rate of respiration and magnitude of intrathoracic pressure variations. Pneumotachographic recordings made on other animals showed that depth of respiration was also increased at higher dose levels.

Giving epinephrine together with and after the drug, had no appreciable effect on ultimate response to the drug. However, when 25 μg/kg of epinephrine was followed by 60 mg/kg of Isoval, a milder response to the drug was seen. In one experiment 25 μg/kg epinephrine was given after blood pressure had dropped to a low level (20 mm Hg) following injection of a mixture of 60 mg/kg of Isoval and 25 μg/kg of epinephrine. No response to this second injection was seen immediately. However, after several minutes, a rapid increase of blood pressure to 100 mm of Hg was seen, followed by a later collapse with ultimate death.

On the assumption that some of the actions of Isoval were mediated centrally, a few experiments were done, in which the injections were given via the carotid artery. However, there seemed to be no change in pattern of blood pressure response from that obtained with intravenous injections.

Another approach, to determine any central effects, involved 3 different types of preparations: Cats with spinal cord sectioned at C-4; cats bilaterally vagotomized; and cats sectioned at C-4 and bilaterally vagotomized.

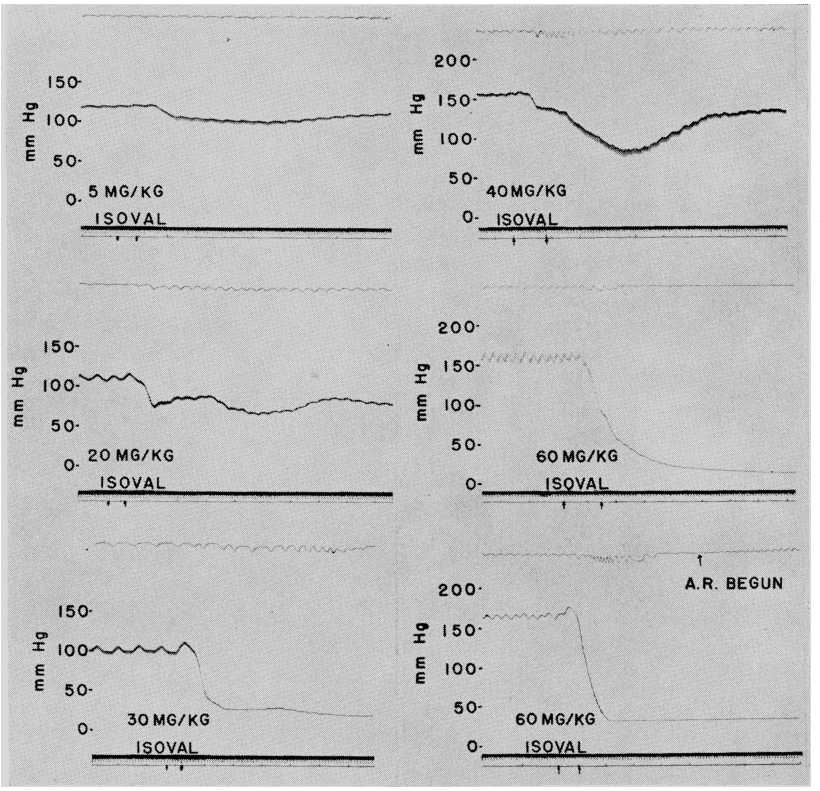

FIG. 1a (left). Blood pressure and intrathoracic respiration recordings at doses of 5, 20, and 30 mg/kg Isoval.

FIG. 1b (right). Blood pressure and intrathoracic respiration recordings at doses of 40 and 60 mg/kg Isoval.

In spinal vagotomized preparations, 2 animals responded to repeated doses of Isoval with only mild decrease in blood pressure and with subsequent recovery to preinjection levels. The first animal received 3 separate doses: 20, 20, 40 mg/kg; the second animals received 40, 40, 20 mg/kg. The first animal ultimately died.

Two similar preparations each received 40 mg/kg Isoval. There was no recovery from blood pressure reduction, which was as rapid as in intact animals.

In neither vagotomized preparations nor spinal sectioned preparations was there any difference in response to Isoval from that seen in intact animals.

Electrocardiographic recordings made of various animals showed no cardiac abnormalities to which the precipitous blood pressure fall could be attributed.

Discussion. When Isoval is administered intravenously to cats in adequate amounts, the principal effects obtained are: (1) rapid decline in blood pressure from which there is no recovery where the dose is large enough and, (2) a concomitant increase in rate and sometimes depth of respiration.

In high spinal-sectioned, vagotomized cats the blood pressure response was in 2 cases identical with that observed in intact animals. In 2 other cats, however, blood pressure decline appeared less drastic for a given dose than that observed in intact animals. Since there was variability even among intact animals in regard to dose required to produce death, it is difficult to determine if any of the spinal-vagotomized animals gave more or less response to a given dose. Vagotomized animals and spinal-sectioned animals with vagi intact did not differ from intact animals in

their response to the drug. From these observations it can be concluded tentatively that there is little if any centrally-mediated component in the drug response.

Electrocardiographic recordings showed no marked changes throughout the period of injection of the drug, at which time blood pressure was dropping rapidly. This does not rule out the possibility of a direct action of the drug on the heart. Murtha(5) in some experiments using papillary muscle preparations has been able to show some direct effects of Isoval on the myocardium.

Another possible explanation of the action of this drug is that sudden reduction in blood pressure may be due to rapid vasodilation in the vascular bed. Some slight evidence for this is seen in the fact that when epinephrine was given prior to injection of Isoval, a milder response was observed in some cases. This might imply that the vaso-constrictor action of epinephrine counteracts to some extent the vasodilation of Isoval.

It is interesting to note that Wakim *et al.* (6) used dicumarol and obtained results in dogs similar to ours. They attribute the action of acute doses of dicumarol to generalized vasodilation of the capillaries and small vessels, with a resulting vascular collapse. The fact that dicumarol and Isoval are both anticoagulants suggests that the mechanisms of their acute effects may be identical.

The experiments in which 2-pivalyl-1, 3-indandione (Pival) was used indicated a similar response to that obtained with Isoval. Pival seemed to have a somewhat greater hypotensive effect.

Preliminary experiments with 2-acetyl-1, 3-indandione, 2-phenylacetyl-1, 3-indandione, 2-diphenylacetyl-1, 3-indandione, and 2-benzoyl-1, 3-indandione indicated that these compounds exhibit similar effects. They were not investigated completely because of the difficulty of finding a suitable solvent for intravenous administration.

Conclusions. 1. 2-isovaleryl-1, 3-indandione when given intravenously to cats in doses ranging from 5-60 mg/kg produces a decline in blood pressure which increases in severity with increase in dose. 2. Concomitant with the decline in blood pressure there is an increase in respiratory rate and depth. 3. These effects cannot be attributed to direct action on the heart, nor do they appear to be centrally mediated. 4. It is suggested that rapid vaso-dilation, with consequent drop in blood pressure, may produce a fatal vascular collapse.

Authors wish to express their appreciation to the following for their courtesy in supplying the experimental compounds: Motomco, Inc., for 2-isovaleryl-, 2-pivalyl-,2-acetyl-, and 2-phenylacetyl-1,3-indandiones; and Upjohn Co. for 2-diphenylacetyl-1,3-indandione.

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Received September 29, 1955. P.S.E.B.M., 1956, v91.