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EFFECTS OF INTRAVENOUS ADMINISTRATION OF BETA-ETHYL-BETA-METHYL GLUTARIMIDE ON THE HAEMATIC LEVEL OF THIOPENTAL

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Abstract—The intravenous administration of beta-ethyl-beta-methyl glutarimide in rats following the injection of anaesthetic doses of thiopental^{35}S markedly increases the level of blood radioactivity.

These results suggest the possibility that bemegride can compete with thiopental or the active sites.

IT IS well known that administration of beta-ethyl-beta-methyl glutarimide (bemegride) has a pronounced antagonistic action upon the pharmacological effects of thiopental. This property of bemegride has been carefully investigated by several authors,[1, 2, 7–10] and has found useful clinical applications.[3–6]

The speed and reversibility of the pharmacological antagonism of bemegride toward thiopental might suggest that it is due to a competition between the two drugs. If this hypothesis is correct, it would be justified to expect an increase of the blood concentration of thiopental after the injection of bemegride, as a result of substitution of one drug by the other at the active sites.

Previous investigations[1] were not conclusive because they did not give definite evidence of a modification of the blood level of thiopental following the injection of bemegride. In the above mentioned experiments, however, the measurements of the blood radioactivity after injection of ^{35}S labelled thiopental were extended only up to 80 min following the thiopental administration. The authors did not extend further their measurements probably because the antagonistic effect of bemegride toward barbiturates anaesthesia is almost immediate and lasts for no longer than 20 min after the injection.

Taking into account the possibility of some delay in the release of the labelled drug into the blood, we carried out[11] measurements of the radioactivity from ^{35}S labelled thiopental over a much longer period of time. The data obtained showed in this case a profound change in blood level of ^{35}S labelled thiopental, occurring after about 90 min from the injection of bemegride. These results indicated, among other things, that the antagonistic effect of beta-ethyl-beta-methyl glutarimide toward thiopental could be of a competitive type.

In order to find additional evidence on the mechanism of the pharmacological action of beta-ethyl-beta-methyl glutarimide the previous investigations were therefore repeated and extended and the results of these experiments are reported in this note.

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EXPERIMENTAL AND DISCUSSION

Nine Sprague Dawley male adult rats were injected intravenously with 30–45 mg/kg of ^{35}S labelled thiopental corresponding to 30 μc/kg.

The radioactivity measurements were made on blood samples (0·1 ml), collected from the tail vein every 12 min for more than 3 hr. The blood samples were plated on aluminium containers and counted by a Geiger-Muller tube (thin window type 1·5 mg/cm^2) and an E.K.C.O. mod. 530 A scaler in fixed geometric conditions over a period of 1000 sec.

A group of rats was injected first with ^{35}S labelled thiopental and 5 min later with an equal amount of bemegride; a control group of rats was injected only with labelled thiopental ^{35}S.

The blood of the first group, 90 min after the injections, showed a temporary but marked increase of radioactivity which was absent in the blood of the control group (Fig. 1). A similar increase in radioactivity was obtained when, instead of beta-ethyl-

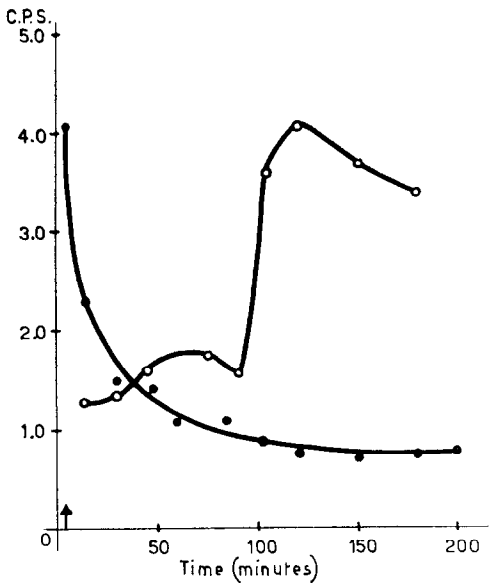

FIG. 1. Blood radioactivity after injection of ^{35}S thiopental as function of time.
●——●: rat intravenously injected with 30 mg/kg of thiopental ^{35}S.
○——○: rat intravenously injected with 30 mg/kg of thiopental ^{35}S and, after 5 min, with 30 mg/kg of bemegride.

beta-methyl glutarimide, non labelled thiopental was administered to the rats (Fig. 2). The only difference was that the rise in the blood radioactivity occurred after a shorter time than in the case of bemegride.

On the assumption of a competitive inhibition of the effect of thiopental by bemegride, one would expect that the simultaneous administration of labelled thiopental and bemegride would produce a higher blood radioactivity level than thiopental alone. The experiment reported in Fig. 3 shows that this is indeed what occurs and gives additional support to the hypothesis that the action of bemegride is a competitive one.

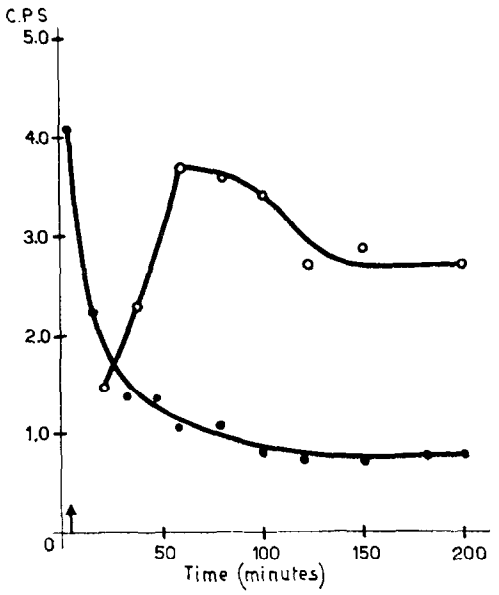

FIG. 2. Blood radioactivity after injection of ^{35}S thiopental as function of time.
●———●: rat intravenously injected with 30 mg/kg of thiopental ^{35}S.
○———○: rat intravenously injected with 30 mg/kg of thiopental ^{35}S and, after 5 min, with an equal amount of the same substance non-labelled.

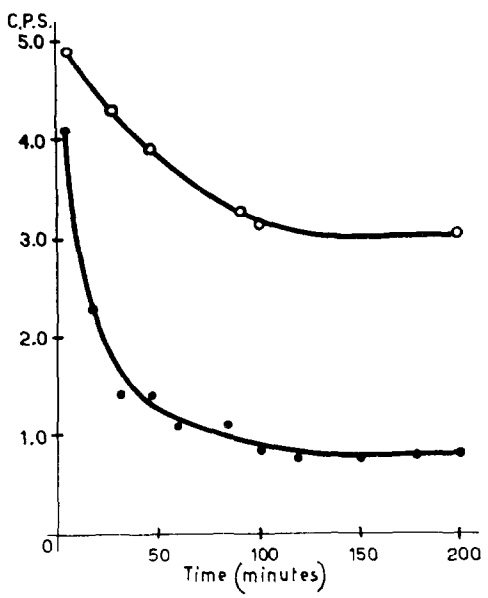

FIG. 3. Blood radioactivity after injection of ^{35}S thiopental as function of time.
●———●: rat intravenously injected with 30 mg/kg of thiopental ^{35}S.
○———○: rat intravenously injected with 30 mg/kg of thiopental and simultaneously with 30 mg/kg of bemegride.

In interpreting these results one might argue that the ^{35}S is not representative of the whole thiopental molecule, but previous works both by Taylor, Richards and Tabern[12–14] and ourselves [11] would suggest that this is unlikely.

It should also be taken into account the fact that bemegride could release the barbiturate from unspecific and pharmacologically unimportant receptors, as such tissue, lipids : however even if this is the case, the presence of a pharmacological effect which preceeds the rise in the ^{35}S blood level, suggests that chemical competition also occurs at the specific receptors.

The hypothesis of direct formation of a complex thiopental-bemegride was excluded by spectrophotometric evidence as already reported.[11] The third other possibility is represented by the bemegride inhibition of the enzyme or enzymes activating the thiopental which is suggested by the simultaneous presence in some organs of both thiopental and bemegride without subsequent rise of ^{35}S blood levels.[11]

It is certain that the choice between the competitive and the inhibitory hypotheses of bemegride requires further work and more direct experimental evidence for the complete elucidation of the mechanism of action of this drug.

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