ON THE PHARMACOLOGY OF MYANESIN, WITH PARTICULAR REFERENCE TO ITS INTRAMUSCULAR ADMINISTRATION *

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In December 1946, Berger and Bradley (1) introduced a new synthetic relaxing agent, α, β, dihydroxy-γ-(2-methylphenoxy) propane, to which they gave the name of myanesin. From 143 α-substituted ethers of glycerol, which they had submitted to a systematic investigation, this compound was selected because of its ability to produce reversible paralysis and profound muscular relaxation with a considerable degree of safety.

In small doses, myanesin produces reduction of spontaneous movements and relaxation of voluntary muscles, particularly apparent in hypertonic muscles, without reduction in motor power. Larger doses produce a reversible ascending depressant action on the central nervous system, with transient ataxia, flaccid paralysis and loss of the righting reflex (2). In a further analysis of the mode of action of myanesin, Berger (3) found that myanesin possesses only a weak curare-like action, and has local anesthetic properties about equal to those of procaine; both of these actions, however, are insufficient to explain the production of reversible muscle paralysis in the doses used. Because myanesin, in doses which have no overt effect, antagonize the increased spinal irritability caused by strychnine or by tetanus toxin, he inferred that myanesin decreases reflex hyperexcitability and the passage of abnormal excitatory impulses through the spinal reflex arcs.

In nonparalyzing doses myanesin effectively antagonizes strychnine convulsions and less effectively, those of leptazol (metrazol) (3). Epinephrine, amphetamine, atropine, ephedrine, leptazol, nikethamide, physostigmine, picrotoxin, prostigmine, and strychnine fail to shorten appreciably the duration of myanesin paralysis in mice. However, intravenous strychnine given immediately after the myanesin does shorten the duration of paralysis in rabbits. These results support

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the theory that myanesin exerts a selective depressant action on the spinal cord (2). It was suggested (3) that myanesin causes paralysis by a mechanism different from that of narcotics, anesthetics, and curare-like agents, possibly by affecting the same neurons of the spinal cord which react to strychnine, but in the opposite manner.

Somewhat later, Stephen and Chandy (4) reported observations on myanesin which led them to believe that this compound acts somewhere in the brain stem between the cortex and the medulla. Their conclusion was based on the fact that myanesin apparently has no direct cortical action (no effect on motor or sensory powers, nor on electrical activity as registered by the electroencephalogram), and has no effect on spasm or paresthesia of spinal cord lesion origin. It does, however, temporarily relieve intractable pain of thalamic origin, produces eye changes similar to those produced by barbiturates, possibly central in origin, and temporarily abolishes involuntary movements whose origin is in disease of the basal ganglia.

Mallinson (5) was the first to publish results of the clinical trial of myanesin, recording his experiences in 112 cases in which myanesin had been used as a relaxing agent in conjunction with surgical anesthesia. He employed myanesin in doses of 8 to 27 mg. per kilogram, using a 10 per cent solution intravenously, in conjunction with pentothal-nitrous oxide-oxygen, pentothal cyclopropane, pentothal-nitrous oxide-oxygen-ether and nitrous oxide-oxygen-ether anesthesia. He was favorably impressed with the action of myanesin, and believed that it afforded a wider margin of safety than that of curare, since no intercostal paralysis was produced even with doses producing complete abdominal paralysis. Furthermore, abdominal relaxation was obtainable even in conscious patients. He thought that myanesin was more effective with barbiturates than was curare, and that abdominal relaxation was so good when myanesin was used in conjunction with pentothal-nitrous oxide-oxygen anesthesia that it was unnecessary to use the more dangerous cyclopropane to obtain deeper relaxation. Myanesin was effective under the lightest possible anesthesia, and produced no bronchospasm or salivation in patients he observed. He recorded no severe toxic or untoward effects of myanesin.

A few months later, however, Pugh and Enderby (6) reported 3 cases of hemoglobinuria occurring after intravenous administration of myanesin. Spectrographically, oxyhemoglobin was identified. They conclusively demonstrated experimentally in vivo that their preparation of myanesin, when injected intravenously, was hemolytic in any strength greater that 1 per cent in water, when dilutions were prepared from the 10 per cent solution made available for intravenous use. They did not, however, determine whether the hemolytic agent was the myanesin or the vehicle used to increase the water solubility of myanesin. Subsequently, Glazko and Bratton (7) showed by in vitro studies that the myanesin molecule was a hemolytic agent, 10.0 mg.
Intramuscular Myanesin

liberating 24 per cent of the hemoglobin in 5 cc. of human blood in thirty minutes at 38 C.

Recently, Lyall (8) has published his observations on 250 cases in which myanesin was used in anesthesia. He confirmed many of the original observations of Mallinson. Lyall thought that the combination of light ether and myanesin was ideal for many abdominal operations, and that little postoperative sickness was seen in these cases. For shorter procedures he recommended an intravenous anesthetic plus myanesin. For thoracic surgery, however, curare offered advantages over myanesin because of the effect of curare on intercostal muscles. He warned against the occasional decided fall in blood pressure seen when myanesin was employed. Also, in 44 of 50 patients examined for evidence of intravascular hemolysis within one hour following the injection of myanesin, some degree of hemoglobinemia was found; however, no case of hemoglobinuria occurred. Venous thrombosis occurred in 1 case following the second of two procedures in which myanesin was used. Lyall used a 10 per cent solution of myanesin in water, presumably with urea or a urea derivative added to increase the solubility of myanesin.

Wilson and Gordon (9) were enthusiastic over the use of myanesin for appendectomies in children, in conjunction with light nitrous oxide-oxygen-ether, or with pentothal-nitrous oxide-oxygen with or without cyclopropane. They based their dose upon the following formula:

cubic centimeters of myanesin (10 per cent) = \( \frac{\text{age}}{2} + 1 \) cc.

These basic studies have demonstrated that myanesin or a similar compound may find a useful role in the field of anesthesia. However, its hemolytic action, its vasodepressant properties in paralyzing doses, and its cardiototoxicity in producing severe cardiac depression or heart block in animals in doses causing respiratory paralysis (10) militate against the enthusiasm shown myanesin thus far. In fact, Burke (11) was of the opinion that curare is the safer of the two agents, since in full paralyzing doses of curare the animal can be carried along quite satisfactorily with artificial respiration, whereas under similar doses of myanesin other systemic actions cause dangerous alterations in physiology.

Experimental

We have thought it important to evaluate more fully the pharmacologic properties of myanesin, particularly with reference to finding a safer manner in which it may be used. This paper is concerned with various aspects of myanesin. We have studied the intravenous and intramuscular use of myanesin, and compared depressant action, blood levels and hemolytic action by the two routes. We have further evaluated the effect of myanesin on thiobarbiturate anesthesia, and have studied the role of the liver in the detoxication of myanesin.
Finally, we are reporting a comparison of the actions of benzimidiazole and myanesin when administered independently and in combination.

**Intravenous Administration in Dogs**

*Method.*—Myanesin was administered to 18 dogs intravenously in doses ranging from 10 to 200 mg. per kilogram. The dogs varied in weight between 6.6 and 17.5 kg. Solutions employed were 1.0 to 2.5 per cent aqueous solutions, except that a 10 per cent solution in 40 per cent propylene glycol was given to 3 dogs in doses of 10, 15, and 25 mg. per kilogram, respectively. All dogs were observed for objective manifestations of myanesin activity. Six were also followed for evidence of intravascular hemolysis following the administration of myanesin.

*Results.*—Transient unsteadiness and depression of activity were observed in all dogs receiving a dose of 25 mg. per kilogram or more. The duration of this response varied with the magnitude of the dose given. Ataxia existed for fifteen to twenty minutes after the administration of 50 mg. per kilogram, and for about eighty minutes after a dose of 200 mg. per kilogram.

Paralysis and loss of the righting reflex occurred in all dogs given 50 mg. per kilogram or more. The duration ranged from about two minutes with a dose of 50 mg. per kilogram, to thirty-seven minutes with a dose of 200 mg. per kilogram. With the smaller doses mentioned the action was chiefly a loss of weight-bearing function of the hind legs; with the larger doses general flaccidity resulted, affecting predominantly the hind legs and posterior portions of the body. During the period of actual paralysis the dogs did not react to painful stimuli. Stephans and Chandy (4) have shown that doses up to 40 mg. per kilogram administered intravenously in cats produced no effect on (1) nerve and muscle action potentials, (2) neuromuscular junction transmission, (3) conduction along sciatic nerves, and (4) spinal cord synaptic transmission. However, doses of 50 mg. per kilogram or greater produced marked depression of these functions. Our results with intravenous myanesin in dogs are probably explained by these effects of the drug on the function of the nervous system.

Vomiting was a frequent sign, occurring in 4 of the 7 dogs receiving from 25 to 100 mg. per kilogram, following the injection by one to five minutes. With the large doses, salivation of a rather marked degree was seen in several dogs not vomiting. Diarrhea was also frequently seen with large doses.

Signs of stimulation were noted in dogs receiving doses from 100 to 200 mg. per kilogram. These were chiefly transient nuchal rigidity and neck extension, rigid foreleg extension, and hyperextension of the back. Similar observations were made by Burke and Linegar (10) who also noted nystagmus at the peak of paralysis. While these signs may be manifestations of the action of the central nervous system, Berger (3)
was of the opinion that they possibly represented a direct myotoxic effect of myanesin.

Respiratory depression and brief periods of apnea were caused by doses of 150 mg. per kilogram. Doses of 200 mg. per kilogram caused apnea of a degree requiring artificial respiration for salvage of the animal. In one dog given 150 mg. per kilogram, sudden bradycardia occurred, the rate dropping from 144 to 50 beats per minute. The pulse was shallow and weak. This sudden bradycardia was accompanied by sudden respiratory depression. The likelihood of transient complete heart block exists, but no electrocardiographic records were obtained to substantiate this impression. Burke and Linegar, however, noted severe cardiac depression or block at respiratory paralytic doses, and this possibly exemplified such a phenomenon.

It appears, therefore, that a dose of 15 to 25 mg. per kilogram must be given intravenously in dogs to produce appreciable ataxia, about 50 mg. per kilogram to produce actual paralysis, and about 200 mg. per kilogram to produce fatal respiratory paralysis.

**Intramuscular Administration in Dogs**

**Method.**—A. Myanesin was administered intramuscularly to 10 dogs in doses ranging from 25 to 150 mg. per kilogram. Dogs varied in weight between 9.0 to 19.2 kg. A 10 per cent solution of myanesin was employed, dissolved either in 40 per cent propylene glycol, or in a vehicle consisting of 10 per cent urea in 8 per cent (by volume) propylene glycol in water. This latter solution is supersaturated and must be warmed to about 30 C. in order to give a clear 10 per cent solution of myanesin. In 5 dogs the blood levels were followed, employing the method of analysis previously published (12) with only one modification: 0.1 cc. of 2.5 N sodium hydroxide was added to the 5 cc. plasma sample before chloroform extraction. This alkalization was found to reduce the incidence of emulsification of the plasma and the chloroform, and found not to reduce the recovery of myanesin from plasma. Blood samples from all 10 dogs were examined for hemolysis at various periods of time following the injection, as reported below.

B. Preliminary observations on the use of myanesin intramuscularly in conjunction with barbiturate anesthesia in dog surgery are also reported.

**Results.**—A. No loss of the righting reflex was seen even with the largest dose of myanesin given. Transient ataxia was observed for varying periods of time following the injection of 50 mg. per kilogram or more; for three to four minutes following 50 mg. per kilogram doses, up to almost sixty minutes following a dose of 150 mg. per kilogram. In a few previously excited dogs, relaxing and definite sedative effects were noted, lasting up to an hour with large doses. No signs of stimulation, no emesis or salivation, and no diarrhea were observed. Respiration was not appreciably affected.
The myanesin in 40 per cent propylene glycol produced irritation in most dogs, and they objected to the administration by this route. The injection of myanesin in the urea-propylene glycol vehicle produced little or no irritation, except for 2 dogs who experienced pain near the end of the injection, probably from the distention caused by the large volume of fluid injected. Quantities up to 10 cc. were deposited in any one site. No sloughing or signs of induration or tissue irritation were seen as sequelae in dogs observed for several days following the intramuscular administration of myanesin in 40 per cent propylene glycol. However, rather marked local edema developed in those dogs receiving the urea-propylene glycol vehicle, probably because of the osmotic activity of this vehicle.

Blood levels were followed in 5 dogs given myanesin intramuscularly, in 4 given myanesin in the urea-propylene glycol vehicle and in 1 given myanesin in 40 per cent propylene glycol. Figure 1 shows the levels obtained, comparing them with 3 levels obtained after the

![Graph showing plasma levels following intravenous and intramuscular administration of myanesin. The figures refer to doses of myanesin in milligrams per kilogram. The Roman numerals appended to the figures refer to the solution given: I, 2 to 3 per cent myanesin in water; II, 10 per cent myanesin in 10 per cent urea and 8 per cent propylene glycol; III, 10 per cent myanesin in 40 per cent propylene glycol.](image-url)
intravenous administration of 50 mg. per kilogram, using 2 to 3 per cent supersaturated aqueous solutions (12). It is shown that myanesin is rapidly absorbed from intramuscular depots, since significant blood levels, maximal in five to ten minutes, are obtained with all doses given. The decay curve of myanesin in plasma following intramuscular administration is markedly less rapid than following intravenous injection. Approximately twice the intravenous dose must be given intramuscularly to yield equivalent plasma levels at about five to fifteen minutes after the injections.

Approximate correlation of plasma levels with signs of relaxation would indicate that a level of about 2 mg. per 100 cc. of plasma is the minimal level necessary to produce ataxia and relaxation of muscles when myanesin is administered alone. Levels necessary to be effective in conjunction with anesthetic agents have not yet been determined.

B. Myanesin was used on one occasion in conjunction with pentobarbital sodium anesthesia in a 16.2 kg. dog undergoing surgery for the production of a double loop, denervated-inervated, Thiry-Vella fistula. As the surgeons were closing the peritoneum and the packs were removed, the anesthesia was becoming light and muscular tenseness bulged bowel loops into the field. The injection of 10 cc. of myanesin (10 per cent in 40 per cent propylene glycol) directly into the rectus abdominalis muscle produced immediate and complete abdominal relaxation for the time necessary for closure, about fifteen to twenty minutes. The dose in this case was about 62 mg. per kilogram.

The Hemolytic Effects of Myanesin

The initial enthusiasm engendered by the clinical report of the use of myanesin by Mallinson (5) was tempered somewhat by the observations that intravenous myanesin was a hemolytic agent (6, 8). We have endeavored to determine experimentally in dogs whether the hemolytic action of myanesin could be circumvented by intramuscular administration without sacrificing the valuable relaxing qualities as obtained by the intravenous route.

Method.—Eighteen dogs, ranging in weight from 7.2 to 19.2 kg., were used in this study, 9 receiving intravenous and 9 intramuscular injections. Various solvents and various strength solutions of myanesin in these solvents were tested for hemolytic action. Hemolysis was evaluated by using the following modification of the standard procedure for determining the icterus index. Blood samples were drawn before and after the administration of myanesin, using a heparin-rinsed syringe to prevent coagulation. The blood was then centrifuged for fifteen minutes at 1,500 to 1,800 r.p.m., and 1 cc. of supernatant plasma placed in a test tube containing 9 cc. of normal saline solution. After mixing by inversion, the solutions were read in the photoelectric colorimeter, with a normal saline blank set to zero, using Klett filter No. 42 (400 to 460 milliecrons wave length transmission). A 1 to 10,000 solu-
tion of potassium dichromate (with 2 drops of concentrated sulfuric acid per liter added) was used as a standard of comparison, and given an arbitrary index value of 10.0. The plasma index of the sample being measured was then determined as follows (13):

\[
\frac{\text{Reading of unknown} \times 10}{\text{Reading of standard}} = \text{Index of sample}
\]

While this method of evaluation merely indicates an increase in the color density of the plasma, and is by no means a specific determination of free hemoglobin, it served the purpose of rapidly obtaining a fairly accurate evaluation of the hemolytic properties of any given solution. Animals were examined for a variable period of time after the injections, with periodic blood samples being withdrawn and tested. The normal index by this method was found to be from 3.3 to 8.5.

Results.—It was found that the solutions tested possessed various hemolytic potentialities, depending partially upon the dose given and the route of administration. Arbitrarily, dependent upon the degree and duration of the increase of the index over control values, we have divided the solutions into four groups, those causing:

I. No hemolysis
   1. Intravenous saline solution.
   2. Intravenous myanesin, 1 per cent in saline.
   3. Intramuscular myanesin, 10 per cent in 10 per cent urea and 8 per cent propylene glycol, up to 50 mg. per kilogram.
   4. Intramuscular myanesin, 10 per cent in 40 per cent propylene glycol, up to 25 mg. per kilogram.

II. Minimal hemolysis
   1. Intravenous myanesin, 1 per cent in distilled water.
   2. Intramuscular myanesin, 10 per cent in 40 per cent propylene glycol, 25 to 100 mg. per kilogram.
   3. Intramuscular myanesin, 10 per cent in urea-propylene glycol, 50 to 150 mg. per kilogram.

III. Moderate hemolysis
   1. Intravenous propylene glycol, 40 per cent in water or in saline, 0.5 cc. per kilogram.
   2. Intravenous myanesin, 10 per cent in 40 per cent propylene glycol, up to 10 mg. per kilogram.

IV. Marked hemolysis
   1. Intravenous myanesin, 2 to 3 per cent in water or saline, 25 mg. per kilogram or more.
   2. Intravenous myanesin, 10 per cent in 40 per cent propylene glycol, 15 mg. per kilogram or more.

From this arbitrary grading one can conclude that intramuscular myanesin produces significantly less hemolysis than the intravenous administration of the same solutions in equivalent doses. Intravenous
myanesin in greater than 1 per cent solution in all vehicles tested produced considerable hemolysis. Myanesin can be administered intravenously only in a 1 per cent solution in saline without destroying some red blood cells. Intramuscularly, myanesin was injected in doses up to 25 mg. per kilogram, if dissolved in 40 per cent propylene glycol, or up to 50 mg. per kilogram or more, if dissolved in a vehicle of 10 per cent urea and 8 per cent propylene glycol, without producing any detectable hemolysis. Even larger doses given intramuscularly produced only minimal degrees of hemolysis, raising the index only 0.5 to 5.7 points. However, 2 to 10 per cent myanesin in various solvents given intravenously produced hemolysis severe enough to raise the index from 8.0 to 19.6 points.

From a practical standpoint, 1 per cent myanesin in saline intravenously, though nonhemolytic, is certainly unwieldy because of the volumes of solution that would be required for satisfactory results. It may be found, however, that 10 per cent myanesin intramuscularly will be efficacious in doses beneath the hemolytic threshold.

**Thiobarbiturates and Myanesin**

Berger and Bradley (1), in evaluating the combined effect of myanesin and barbiturates on mice when administered simultaneously, concluded that myanesin had a potentiating effect on hexobarbitone (evipal) anesthesia. This conclusion was challenged by Walker, Richardson, Loeb and Perog (14), who showed that the simultaneous administration of subparalyzing, or of sublethal, doses of each individual agent (myanesin and pentobarbital) produced combined effects coming within 5 per cent of the expected *additive* effect, using PD–50 and LD–50 criteria in mice.

Nevertheless, clinical studies have attested to the additional relaxation provided by myanesin when used in conjunction with intravenous barbiturates. We have endeavored to evaluate the effects of myanesin on surital (sodium 5-allyl-5-(1-methylbutyl)-2-thiobarbiturate) and on thioethamyl (sodium 5-ethyl-5-isoamyl-2-thiobarbiturate) anesthesia in dogs.

**Method.**—Three groups of 4 dogs each were injected intravenously with the thiobarbiturate, with myanesin, and then with both drugs simultaneously, with at least two days' rest between injections. Solutions were prepared so that the total volume of each injection was 1 cc. per kilogram. The duration of the loss of the ability to stand was determined in each case, and observations of other effects made. The data regarding dosage are given in table 1, together with the results and a statistical analysis of them.

**Results.**—It is apparent from table 1 that myanesin had no effect on the duration of surital anesthesia, in the respective doses given. There was a noticeable effect, however, upon the quality of anesthesia produced. Normally, surital alone produces a rapid, smooth induc-
tion, but it is gradual, requiring thirty to forty-five seconds, and is occasionally accompanied by mild struggling. The addition of myanesin produced an induction which was instantaneous: the transition from the normal conscious state to one of complete flaccidity and unconsciousness occurred in an instant. The effect of myanesin upon thioethamyl anesthesia was then evaluated, since this thiobarbiturate produces marked excitation in dogs during induction and a quality of relaxation unsatisfactory for surgical procedures unless large doses are given (15). From table 1 it may be seen that myanesin added to thioethamyl almost doubled the duration of action of thioethamyl alone.

**TABLE 1**

<table>
<thead>
<tr>
<th>Number of Dogs</th>
<th>Drug and Dose, mg./kg.</th>
<th>Duration</th>
<th>1/Value of Duration</th>
<th>1/Value of M-M*</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>Surital 10</td>
<td>—</td>
<td>20.5±1.7</td>
<td>17.3</td>
</tr>
<tr>
<td></td>
<td>Thioethamyl 10</td>
<td>—</td>
<td>27.1±2.1</td>
<td>12.9</td>
</tr>
<tr>
<td></td>
<td>Myanesin 10</td>
<td>—</td>
<td>0.0</td>
<td>—</td>
</tr>
<tr>
<td>4</td>
<td>Surital 5</td>
<td>—</td>
<td>10.8±1.1</td>
<td>9.68</td>
</tr>
<tr>
<td></td>
<td>Thioethamyl 25</td>
<td>—</td>
<td>0.0</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Myanesin 25</td>
<td>—</td>
<td>11.3±1.1</td>
<td>10.13</td>
</tr>
<tr>
<td>4</td>
<td>—</td>
<td>25</td>
<td>17.5±2.02</td>
<td>8.66</td>
</tr>
<tr>
<td></td>
<td>—</td>
<td>25</td>
<td>34.8±4.09</td>
<td>8.90</td>
</tr>
</tbody>
</table>

This effect is statistically significant (P-value less than 0.05, though greater than 0.02) despite the small number of animals used. More important perhaps was the effect of myanesin in converting the anesthesia from a shallow plane to one of deep relaxation, and of partially or entirely counteracting the stimulation seen normally on induction. The increase of duration probably results from a neutralization of the stimulating properties of thioethamyl, permitting the depressant properties to act unopposed. Since surital lacks the stimulating actions of thioethamyl, the addition of myanesin did not have any appreciable effect on the duration of action of surital. The duration of action (loss of righting ability) of surital probably represents only the unopposed effect of its depressant properties, and not the outcome of the competitive action of depressant and stimulating properties working antagonistically, as with thioethamyl.

From these experiments it should follow that a lighter plane of anesthesia would suffice, the quantity of barbiturate required thereby being reduced, if myanesin is used to enhance relaxation and to prevent the stimulating features of intravenous anesthesia.
Detoxication of Myanesin

In previous studies on the urinary excretion of myanesin in dogs it was shown (12) that only 0.1 to 2.0 per cent of the injected dose was excreted as free myanesin, and that from 32 to 42 per cent was excreted in a conjugated form in twenty-four hours.

Since it is known that the liver is the most active of the detoxifying organs of the body, and that its function can be selectively depressed in mice by poisoning with carbon tetrachloride, we decided to evaluate the role of hepatic function in the disposition of myanesin.

Method.—Twenty-four white mice weighing between 19 and 23 Gm. were injected subcutaneously with 500 mg. per kilogram of myanesin, using a 1 per cent aqueous solution. The latent period and the duration of action were determined, measuring to the nearest whole minute. Loss of the righting reflex and regaining it were taken as criteria. Eleven days later these same 24 mice were given 0.02 cc. per gram of a 20 per cent solution of carbon tetrachloride in peanut oil, administered gastrically. Twenty-four hours later, the administration of myanesin was repeated in a manner identical to the first, and similar observations made.

<table>
<thead>
<tr>
<th>TABLE 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>LIVER DETOXICATION OF MYANESIN</td>
</tr>
<tr>
<td>Latent Period</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>Time, Minutes</td>
</tr>
<tr>
<td>Myanesin 500 mg. per kg.</td>
</tr>
<tr>
<td>Before CCl&lt;sub&gt;4&lt;/sub&gt;</td>
</tr>
<tr>
<td>After CCl&lt;sub&gt;4&lt;/sub&gt;</td>
</tr>
</tbody>
</table>

Results.—From table 2 it may be seen that liver damage induced in the manner described shortened the latent period of the action of myanesin by 41.7 per cent, and increased the duration of action 480.3 per cent. Statistically, the differences of the times are unequivocally significant, the P-values of the differences being 0.001 for the latent periods, and less than 0.001 for the durations. This experiment strongly suggests that the detoxication of myanesin is a function of the liver, at least in major part. The impairment of hepatic function probably allows an earlier accumulation of the necessary level of myanesin to produce paralysis, accounting for the decrease in latent period. Impaired destruction probably accounts for the increased duration of action.

Myanesin and Benzimidazole

In 1943, Goodman, Gilman, and Hart (16) reported on the relaxing power of benzimidazole on skeletal muscle. When administered par-
enterally as the hydrochloride to mice, rats, cats and monkeys in doses of 200 to 300 mg. per kilogram, it caused a profound decrease of skeletal muscle tone and of voluntary movement, lasting for hours. Later, Goodman and Hart (17), in a more detailed analysis of the depressant action of benzimidazole on the central nervous system, concluded that it exerted a selective depressant action of the cerebrospinal axis, affecting the lower segments first. The specific antagonist of benzimidazole was found to be coramine; the specific antagonist of myanesin is strychnine (3).

Since many of the features of the action of benzimidazole resemble those of myanesin, we considered the possibility of synergism and potentiation when these two compounds were administered simultaneously.

Method.—A total of 119 white mice, weighing an average of about 25 Gm., were used in this experiment. PD–50 values were determined for benzimidazole and for myanesin, and the LD–50 value also for benzimidazole, using a 2.5 per cent solution for each compound. From 8 to 10 mice were used at each level. Drugs were administered intraperitoneally. Latent periods and durations of action were recorded, using criteria as above. To determine whether these compounds had any mutually potentiating effects, they were then administered together in mice, using a 1.25 per cent solution of myanesin in a 1.25 per cent solution of benzimidazole hydrochloride, again intraperitoneally. Using fractional doses of each drug's individual PD–50 a new value for the combined solution was determined. We did not determine the LD–50 for the combined sublethal fractions of each compound.

Results.—The LD–50 for benzimidazole hydrochloride acid administered intraperitoneally in mice has been given as 675 mg. per kilogram (16). We found the PD–50 and the LD–50 for the intraperitoneal route in mice to be approximately 175 and 500 mg. per kilogram, respectively, giving a therapeutic index of 2.86. All mice given 600 mg. per kilogram died acutely.

The intraperitoneal PD–50 and LD–50 for myanesin in mice have been given as 178 and 610 mg. per kilogram, respectively (1), giving a therapeutic index of 3.42. We redetermined the PD–50 in mice and obtained a value of 175 mg. per kilogram, given intraperitoneally. Thus the PD–50 potency of myanesin and benzimidazole is identical in mice. In comparable doses, however, the latent period of benzimidazole is about two or three times as long as that of myanesin, and the duration of its action equal to (at the PD–50 doses), or longer than, that of myanesin (about eight times as long with PD–90 doses).

In the combined administration of these two compounds it was found that the PD–50 of such mice was not reached by the simultaneous administration of 50 per cent of each drug's individual PD–50, but was exceeded by the administration of 52.5 per cent of each drug's individual PD–50. This, therefore, indicates a purely additive effect of the
Intramuscular Myanesin

Cerebrospinal depressant activity of the two compounds, since a total of less than 105 per cent of combined equivalent fractions of PD-50's is required to produce paralysis in one-half the mice thus treated. This is within 5 per cent of the expected additive effect, a result within the acceptable biologic range of error. We did not attempt to demonstrate additive effects with unequal fractions of individual PD-50's, or to evaluate the influence of combined fractions on the LD-50.

Discussion

The value of myanesin as a relaxing agent in surgical anesthesia seems to have been well established (5, 8). Its ability to hemolyze red blood cells, however, has also been conclusively demonstrated. Although apparently a small degree of hemolysis is well tolerated by many patients as, for example, in the 44 instances reported by Lyall (8), a certain few will show hemoglobinuria (6). Any drug producing hemolysis as a regularly encountered side effect, as does intravenous myanesin, is potentially a dangerous compound. Eventually some patients with an increased susceptibility to hemolysis may receive myanesin, with possible disastrous results. It is, therefore, of prime importance that myanesin, if its use is to be continued, be employed in some manner which does not produce hemolysis.

In the foregoing presentation it has been shown that myanesin can be administered intramuscularly in rather large doses with little or no hemolysis. Apparently, reducing the quantity of propylene glycol in the solvent vehicle further reduces the extent of hemolysis of myanesin given intramuscularly, and also decreases the irritating properties of the solution when injected by this route. Propylene glycol itself has hemolytic properties (18). It has also been shown that relaxation and sedation can be obtained by the intramuscular administration of myanesin, although larger doses are required to produce an effect than are necessary by the intravenous route. Further, it has been shown that significant blood levels are obtainable when it is given by the intramuscular route, both in magnitude of the levels reached, and in the duration of the presence of free myanesin in the plasma. It has also been shown in one case that adequate relaxation for abdominal surgery under light pentobarbital sodium anesthesia is obtainable by employing the intramuscular route, with a dose probably producing little hemolysis, if any.

It has previously been noted that the degree of hemolysis can be reduced using a 10 per cent solution of myanesin intravenously, if the solution is injected slowly. However, Lyall (8) noted also that less relaxation is obtained if this precaution is observed. Apparently, the sudden contact of the high concentration of myanesin with vital areas of the central nervous system enables them to react more fully, perhaps by taking up more of the myanesin from the plasma than would be possible with the lower peak that would be reached by slower injection.
rates. Richardson et al. (18) have shown that the tissue of the central nervous system takes up proportionately more myanesin than does other body tissue, some concentrations reaching two to three times the levels found in plasma. Even though myanesin rapidly enters the blood stream from intramuscular depots (fig. 1) it remains to be determined whether its absorption is rapid enough to be as effective as myanesin given intravenously in doses that are safely and practically administered.

Since doses of 8 to 27 mg. per kilogram (5), or priming doses of 0.5 to 1.0 Gm. of myanesin (8), although hemolytic, are effective intravenously, it is entirely probable that doses not impractical to administer intramuscularly may be equally effective yet avoid the dangers attendant upon the intravascular release of hemoglobin. Myanesin has been employed successfully intramuscularly by Hunter and Waterfall (19) in the control of epileptiform convulsions in a patient with subdural empyema.

Conclusions

Myanesin, 10 per cent in 40 per cent propylene glycol, or 10 per cent in 10 per cent urea and 8 per cent propylene glycol, administered intramuscularly, is effective in producing relaxation, mild sedation and a decrease of reflex hyperexcitability in doses giving significant plasma levels and causing little or no hemolysis.

As a solvent vehicle for 10 per cent myanesin, 40 per cent propylene glycol causes slightly more hemolysis and more irritation in intramuscular injection than does 10 per cent urea and 8 per cent propylene glycol, but does not produce local edema as does the urea vehicle.

Plasma levels obtained after intramuscular injection are maximal in five to ten minutes, and the decay curve is less rapid than that following the intravenous injection of doses giving comparable early levels in the plasma.

Intramuscular myanesin was shown to be efficacious in conjunction with barbiturate anesthesia in one case of dog surgery.

Myanesin neutralized the stimulating properties of thioethamyl, thereby increasing the duration and depth of anesthesia with this thio-barbiturate. Myanesin did not appreciably alter the effects of surital, a thiobarbiturate almost devoid of stimulating properties.

Myanesin is detoxified by the liver, at least in part, as shown by carbon tetrachloride poisoning in mice.

Myanesin and benzimidazole have only additive properties, judging from PD-50 data in mice.

REFERENCES


18. Richardson, A. P.: Personal communication.


REGULAR MEETING OF THE NEW ENGLAND SOCIETY OF ANESTHESIOLOGISTS

BOSTON UNIVERSITY MEDICAL SCHOOL

AUDITORIUM, BUILDING A

BOSTON, MASSACHUSETTS

TUESDAY, SEPTEMBER 13, 1949

Scientific Session: 8:00 P.M. (Round Table Discussion)

"Respiratory Problems in Acute Poliomyelitis," by

Dr. William Berenberg, Associate Physician, The Children's Hospital, Boston;

Dr. Carlyle G. Flake, Otolaryngologist, The Children's Hospital, Boston;

Dr. David Grice, Orthopedic Surgeon, The Children's Hospital, Boston;

Dr. Stanley Sarnoff, Associate Professor of Physiology, Harvard School of Public Health.

Moderator: Dr. Robert M. Smith, Anesthesiologist, The Children's Hospital, Boston.