RELAXANT ACTION IN MAN OF DIPYRANDIUM CHLORIDE (M&B 9105A)
(A steroid bis-quaternary ammonium salt)

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SUMMARY
In a number of animal species dipyrandium chloride (M&B 9105A) was known to be a curare-like relaxant with an effect-time curve similar to that of suxamethonium (Biggs, Davis and Wien, 1964). The drug was tested in eight conscious human volunteers by stimulating the median nerve at the wrist and recording the contraction of the short muscles of the thumb. The drug was found to be 3.5 to 4.5 times as potent as gallamine but recovery from it was very variable—sometimes it was faster than from gallamine, sometimes it was slower, and never as rapid as from suxamethonium. It is suggested that, in anaesthetized patients, recovery from dipyrandium chloride might be more consistent, and perhaps faster on the average than from gallamine, but clinical observations in six patients who received the drug were inadequate to confirm or contradict this hypothesis.

Our attention was drawn to dipyrandium chloride, a synthetic, non-hormonal, steroid substance which in animal experiments, had muscle-relaxant properties of a curare-like type, but with an effect-time characteristic approaching that of suxamethonium. A preliminary account of the chemical structure (fig. 1) and pharmacological action of the compound has been given by Biggs, Davis and Wien (1964).

The chloride (M&B 9105A), containing 85.8 per cent active cation, is freely soluble, forming a neutral solution which can be sterilized by boiling. It is miscible with aqueous solutions of thiopentone sodium at room temperature. In the animal studies the iodide (M&B 9105), containing 62.8 per cent active cation, was used. Pharmacological study in experimental animals by Biggs, Davis and Wien (1964) revealed that the myoneural block was of the competitive type and was antagonized by anticholinesterases such as neostigmine. The effect-time characteristics of dipyrandium in most of the animals used were of a similar order to those of suxamethonium and it was hoped that they would be so in man. In these animal experiments no evidence was found of androgenic, oestrogenic or progestational activity. No untoward effects were observed in cats and dogs when the drug was used with ether, nitrous oxide, halothane or thiopentone. Like gallamine, it produced some vagolytic effect, shown by moderate tachycardia, but no changes in cardiac output or in electrocardiogram were found.

The promising pharmacological report by Biggs, Davis and Wien (1964) encouraged us to undertake human studies, first in volunteers and then in patients.

METHOD
The drug was studied in conscious human volunteers in our laboratory, using the method of Mapleson and Mushin (1955a) to measure the degree of relaxation produced. In addition, some
observations were made on six anaesthetized patients to whom the drug was given in the operating theatre.

Briefly, the laboratory method consists of stimulating the median nerve at the wrist and recording the near-isometric tension developed by the short muscles of the thumb. Tetanic stimuli were used which happened to differ slightly from those used in 1955. They consisted of square-wave current pulses of 6 msec pulse width at a frequency of 52.5 pulses/sec. Each tetanus lasted 1.2 sec and was repeated 10 times per minute. The current within each pulse was adjusted to give a developed tension in the recording wire of about 800 g and lay between 2.5 and 6 mA, shared equally between the five wicks of the multi-wick electrode (Mapleson, 1955). The only other change from the original technique was to strap the forearm into a plaster cast, made individually for each subject. This helped to obtain a more stable "normal" developed tension.

In addition to the measurement of relaxation, several other parameters were observed. Minute-volume ventilation was measured by means of a facepiece and Wright respirometer. Pulse rate and blood pressure in the finger were measured at frequent intervals by a Sonopulse (M.I.E. Ltd.). Electrocardiograms were taken at the beginning and end of each experiment.

Sixteen subjects volunteered for the experiments. Eight were rejected on the grounds of their inability to achieve adequate voluntary relaxation between the stimuli. Even some of the remaining eight volunteers were far from ideal subjects but it seemed preferable to obtain approximate results in a range of subjects rather than precise results in one or two. Some data on one of the subjects from the earlier work with gallamine (Mapleson and Mushin, 1955b) are included for comparison.

All eight subjects received dipyridam chloride intravenously in various doses. For comparison five of them also received doses of gallamine triethiodide and one received suxamethonium chloride. The order of magnitude of dose of dipyridam chloride required was determined in the first experiment by starting with a very small dose, as judged by the reports on animal experiments, and then giving further, gradually increasing, doses until a recordable effect was obtained. Apart from this first experiment, which is excluded from the results given below, there was always an interval of at least three days between successive doses of relaxant in any one subject.

All the dipyridam came from a single production batch, T1066, although two strengths of solution were used. All the gallamine likewise came from a single batch, 693.

RESULTS

Following each injection of drug there was a rapid fall in developed tension to a minimum, followed by a slower rise. The final steady tension was not always the same as that before the drug was injected, but in over half the recordings it was within 5 per cent of the original level and in only one instance did it deviate by more than 25 per cent. It was usually assumed that, in the absence of any drug, the normal developed tension would have changed linearly from the pre-injection level to the final steady level. Actual developed tensions at any moment were then expressed as percentages of the "normal" or as percentage depressions below normal.

Potency.

In figure 2 the maximum depression (the minimum tension) is plotted, as a percentage of normal, on a probability scale, against intravenous dose, on a logarithmic scale, for both dipyridam chloride (9105A) and gallamine triethiodide. There are theoretical reasons (Mapleson and Mushin, 1955b) for expecting these scales to yield straight-line plots for each subject. The experimental data from those subjects who received three or more doses of either did not support this expectation closely. But, for those subjects who received only two doses of either drug, no better estimate can be obtained, of the response of each of them to other doses, than by drawing a straight line through the two points. Similarly, for those subjects who received only a single dose, the best estimate of the responses of each to other doses is obtained by drawing a straight line through the one point, at a slope approximating to the average slope for the other subjects (broken lines in figure 2). On this basis it was possible to estimate the ratios, tabulated in figure 2, of gallamine...
Dose-effect curves in man for intravenous injections of dipyrandium chloride (M&B 9105A) and gallamine triethiodide, obtained by nerve stimulation in conscious volunteers: probability scale for depression, logarithmic scale for dose. The figures refer to the serial numbers of the recordings.

The duration of action of a drug clearly depends on the dose given. If, for the purposes of surgery, it is required that the degree of relaxation shall be at least a specified amount, this may in principle be achieved for as short or as long a time as desired, with any relaxant, merely by administering a dose of the appropriate size. What is more relevant, in a comparison of drugs, is the time it takes for the relaxation to wear off from some specified degree, say that which is acceptable for surgery, to some specified lesser degree, say that at which particular voluntary movements can be made. Therefore attention can be confined to the recovery phase. If observed values of percentage relaxation are plotted on a probability scale against time on a linear scale it is usually found that, during the recovery phase, the points fall close to a straight line (fig. 3). This is to be
expected if the concentration of the compound at the site of action declines exponentially and if the concentration-effect relationship at the site is of the type shown in figure 2. Theory also suggests that the slope of the straight line will not be influenced by the size of any single intravenous dose of the drug given. Therefore the slope of the line provides a convenient single index of rate of recovery. It may be made quantitative by stating the length of time taken for the relaxation to wear off from one specified level to another, or it may be used to give a visual impression, as in figure 4, where a steep slope indicates rapid recovery, and a gentle slope slow recovery.

In preparing figure 4, we have omitted experiments which produced only shallow degrees of relaxation, up to 30 per cent, because experimental and measurement errors are relatively large in those circumstances. In most other cases the observations agreed well with a straight line. Where they did not, a smooth curve has been drawn through the points. Where necessary the straight lines have been extrapolated (broken lines) to the deeper levels of relaxation to give a clear impression of the slope. Where neostigmine was administered to accelerate the return to normal the subsequent recovery is plotted as a dotted line.

The upper row of lines in figure 4 is for dipyramidium chloride (9105A) and the lower row for gallamine, together with one for suxamethonium in subject I.P.M. When a subject received both gallamine and dipyramidium the lines for gallamine appear vertically below those for dipyramidium in the same subject.

The general impression created by figure 4 is that recovery from dipyramidium is much more variable than from gallamine and in no case is it as rapid as the recovery from suxamethonium chloride in I.P.M. The detailed interpretation of these results is discussed below.

Respiration and circulation.

None of the doses of dipyramidium or gallamine was sufficient to arrest or even to depress the respiration. Indeed there was usually a transient pulmonary hyperventilation, either as the drug began to produce its effect or else during the...
preparations for injection. The 15 mg of suxamethonium chloride given to I.P.M. produced a brief apnoea followed by 2 minutes of marked hyperventilation.

There was no consistent effect on blood pressure, although those changes which occurred were in the upward direction. These increases often appeared in anticipation of the effect of the drug.

The heart rate showed a fairly consistent rise which almost always succeeded the injection rather than preceded it. However, the increased rate usually persisted throughout the measurements; it did not wear off as the relaxation wore off except on the few occasions when this was accelerated by the injection of neostigmine. The increase was usually no more than 10 to 20 beats/min, tending to be rather less for dipyrandium than for gallamine.

No significant differences were observed between the electrocardiograms taken after the experiments and those taken before.

**DISCUSSION**

*Results in conscious volunteers.*

Some anomalies in the dose-effect curves of figure 2 call for comment. Subject E.H. received two doses of gallamine triethiodide, one of 250 μg/kg and one of 350 μg/kg, on widely separated occasions but they both produced the same peak effect. No explanation can be offered for this discrepancy; E.H. was a calm subject, and the two respiration and pulse rate records were closely similar, except for a slightly bigger rise in pulse rate when the larger dose was given.

Subject J.F. showed an apparent very wide potency ratio between dipyrandium chloride and gallamine triethiodide. This may have been spurious for, although there is no special reason for suspecting gross errors in either of the results, the recordings were of low quality. On the other hand, it may have been a genuine difference, but one that arose out of differences of distribution of the drugs due to the marked differences in ventilation, pulse rate and blood pressure. In spite of these considerations it is probably safest to conclude, at this stage, that there is a possibility of some subjects being very sensitive to dipyrandium.

The results for subject D.E. will be considered in relation to the graphs for recovery time.

From figure 4 it may be seen that recovery from dipyrandium was much more rapid than from gallamine in P.S. and somewhat more rapid in J.F. In E.H. there is not much difference between the two drugs although recovery from the large dose of dipyrandium showed a marked spontaneous change of slope at 50 per cent relaxation. The next two subjects received dipyrandium only, A.M. showing a fairly rapid recovery, J.L. a rather slower one. The next subject, A.A. received gallamine only; these data are taken from the earlier work (Mapleson and Mushin, 1955b). The two lines indicate the fastest and slowest of eleven recoveries in this subject.

The range of slopes in these first six subjects is limited, but it is greatly extended by the next three subjects. The first dipyrandium recording in I.P.M. (No. 151) showed only a modest depression followed by a quite rapid recovery. The next (No. 171) appeared to show a very slow recovery; but the recording was of poor quality and was abandoned on the supposition that a fault had developed in the experimental technique and that recovery was really almost complete. But in the next dipyrandium recording (No. 175) exactly the same very slow return of developed tension was observed, until neostigmine was administered, when the tension returned rapidly and completely to normal. In between these two very slow recoveries a quite average recovery from gallamine was obtained in this subject (No. 173) and, earlier, a very rapid recovery from suxamethonium typical of that seen clinically was observed.

Subject J.B. showed a slow recovery from dipyrandium, though not quite as slow as I.P.M. No data were obtained for gallamine in this subject.

Subject D.E. showed some bizarre responses. In the first experiment with dipyrandium (No. 152) there was virtually no recovery until neostigmine was administered when recovery was rapid and complete. Nineteen days later recovery from a dose of gallamine was one of the most rapid recorded. Sixteen days later still (recording No. 167) a repeat of the same dose of dipyrandium as in No. 152 gave a much smaller peak relaxation but again with a rather limited recovery.
until neostigmine was given. After another thirty-three days a large dose of dipyridamid gave a more normal recovery pattern (No. 177).

When recordings of this nature are made in conscious subjects, particularly if they are in the least excitable, as were some of the present subjects, there is always a suspicion that an unusual recording can be attributed to artefact. But, in the present work, unusually slow recoveries occurred only with dipyridamid and, in two of the subjects showing this slow recovery, perfectly normal recoveries from gallamine were obtained.

It seems, therefore, that the wide spread of recovery times for dipyridamid, from faster than from gallamine to much slower than from gallamine, is probably a real feature of dipyridamid in the conscious subject.

**Comparison of volunteer results with results in animals.**

Biggs, Davis and Wien (1964) reported that in the rabbit, chicken and cat, recovery from dipyridamid was as rapid as from suxamethonium, but that in the monkey recovery was more like that from gallamine. This is illustrated in figure 5 in which a summary of the present laboratory recovery results in man is compared with similar summaries for the cat and the monkey compiled from data very kindly supplied by R. Wien (personal communication). The figure has been plotted in the same way as figure 4 except that the time scale is more open.

**Fig. 5**

Comparison of speed of recovery from intravenous injections of gallamine, dipyridamid iodide (M&B 9105) or dipyridamid chloride (9105A), and suxamethonium in man, cat and monkey. The per cent depression and per cent of normal tension are on a probability scale as in figure 4. The time scale is still linear, but more open than in figure 4. Broken lines indicate extrapolations. The graphs for man indicate the range of the present results for 9105A (excluding subject D.E. and recording No. 171 in I.P.M.) and for gallamine, and the single result for suxamethonium in I.P.M. The graphs for the cat represent the average rates of recovery for from six to eleven animals, while those for the monkey were all derived from a single animal. The graphs for the cat and the monkey were constructed from data very kindly supplied by Dr. Wien (personal communication) and obtained in anaesthetized animals by single-pulse electrical stimulation of a nerve and recording of the resultant muscular twitch.

It is clear that, in the cat, recovery from dipyridamid was very similar to that from suxamethonium and substantially faster than from gallamine. In man, on the other hand, recovery from dipyridamid is not, on the average, radically different from that from gallamine, but recovery from suxamethonium is very much faster than from either of the other two.
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Typical, complete, effect-time curves (plotted on conventional linear scales) for intravenous injections of dipyrandium chloride (M&B 9105A), gallamine and suxamethonium chloride in human volunteers. Note the similarity in rate of recovery from dipyrandium and gallamine (in the same subject) and the much more rapid recovery from suxamethonium (in another subject).

This is also shown in figure 6 where complete conventional effect-time curves are plotted for suxamethonium in one individual and for gallamine and dipyrandium in another.

The monkey has not commonly been used in animal work in this sphere; yet the general pattern of the recovery of this animal, from the three relaxants considered here, is much nearer to that in man than is that of the cat (fig. 5). In the monkey, recovery from dipyrandium is not very different from that from gallamine, but recovery from suxamethonium is much more rapid—not quite as rapid as in man but more rapid than in the cat.

OBSERVATIONS ON PATIENTS

When the volunteer experiments were well advanced dipyrandium chloride was administered intravenously, as an alternative to some other relaxant, to six patients who had previously given their permission. In two of them it was given to permit tracheal intubation and the effect was then allowed to wear off. In two more, after dipyrandium had been used for intubation, gallamine was used to maintain abdominal relaxation. In another two, dipyrandium was used for intubation and for maintenance. All six patients received atropine and neostigmine (1.25 to 2.5 mg) at the end of the operation.

The doses used for tracheal intubation were 15, 20, 15, 15, 22.5 and 25 mg in patients weighing 73, 97, 76, 65, 65, and 74 kg respectively. There was usually some coughing or other muscular reaction on intubation. It seems, therefore, that, in an adult a dose of approximately 0.2–0.4 mg/kg is required for this manoeuvre.

In the two cases, partial gastrectomies, in which relaxation was maintained with dipyrandium chloride, the total doses were 40 mg over 2 hours in a 76-kg man and 75 mg over 2½ hours in a 65-kg man.

In four patients recovery was uneventful. In the two patients in whom the effect was allowed to wear off after intubation this appeared, clinically, to occur quite rapidly. One of these patients, however, a 65-kg woman who received 22.5 mg, reported double vision for 24 hours postoperatively. In the other, a 74-kg woman who received 25 mg, recovery from the anaesthetic was somewhat stormy, but there was no particular reason for connecting this with the relaxant.

These observations on patients are too few and too qualitative to say whether the spread of recovery times in anaesthetized patients is as wide as it was found to be in conscious volunteers; but the prolonged double vision in one patient indicates that slow recoveries may occasionally occur.

RECOMMENDATIONS FOR FURTHER STUDY

Since the occasional slow recoveries found in the present work are absent from the results in animals, it seems possible that these slow recoveries may be in some way associated with the conscious state. If so, recovery from dipyrandium in the anaesthetized patient could be expected to be more consistent than in the conscious volunteer, and possibly a little more rapid, on the average, than from gallamine. Further assessment in anaesthetized patients could elucidate this.
CONCLUSIONS
We conclude that dipyramidium chloride is an effective curare-like relaxant in man. Its potency is about 3.5 to 4.5 times that of gallamine triethiodide but there is a possibility that a few patients may be sensitive to it. Recovery in conscious subjects may be either rather more rapid than from an equipotent dose of gallamine or about the same, or, in some cases, markedly slower. We found no evidence that recovery is ever likely to be as rapid as from suxamethonium, from which recovery is remarkably rapid in man.

Detailed assessment in anaesthetized patients might reveal a more consistent recovery rate and possibly even one which was more rapid on the average, than that from gallamine.

We suggest that for predicting recovery times from new curare-like relaxants in man, the monkey may be a more suitable experimental animal than the cat.

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REFERENCES

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L’ACTION DE RELAXATION DU CHLORHYDRA-TE DE DIPYRAMIDUM CHEZ L’HOMME (M et B 9105 A)
(Un sel d’ammonium bis-quaternaire de stéroïde)

SOMMAIRE
On savait que chez un certain nombre d’espèces animales le chlorhydrate de dipyramidum (M et B 9105 A) agit comme relaxant genre curare avec une courbe d’efficience semblable à celle du suxamétho-nium, (Biggs, Davis et Wien, 1964). La drogue en question a été expérimentée chez huit volontaires humains conscients par stimulation du nerf médian au niveau du poignet et enregistrement de la con-traction du court fléchisseur du pouce. On a constaté que la drogue est 3,5 à 4,5 fois plus puissante que la gallamine, mais la disparition de l’effet est très variable, elle était quelquefois plus rapide que celle de la gallamine et quelquefois plus lente, mais jamais aussi rapide que celle du suxaméthonium. On pense que chez les sujets narcotisés la rémission du chlorhyd-rate de dipyramidum peut être plus régulière et probablement plus rapide en moyenne que celle de la gallamine, toutefois l’observation clinique de six malades qui avaient reçu la drogue en question n’a pas permis de confirmer ou d’infirmer cette hypothèse.

DIE RELAXIERENDE WIRKUNG VON DIP YRAMIDUMCHLORID (M&B 9105A) BEIM MENSCHEN (EIN STEROIDES BI-QUARTER-NÄRES AMMONIUMSALZ)

ZUSAMMENFASSUNG