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REVIEW

New curare-like agents

D. A. KHARKEVICH

Institute of Pharmacology, Academy of Medical Sciences, Department of Pharmacology First Medical Institute, Moscow, USSR

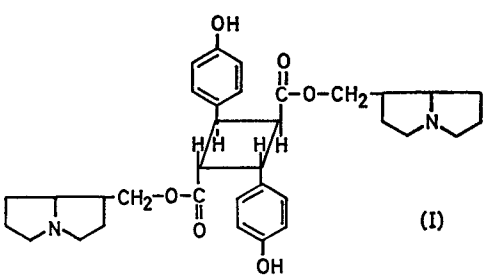
Curare-like agents belong in general to two chemical groups. The larger group includes quaternary ammonium compounds such as tubocurarine, allopherine, diplacinum, paramyonum, succinylcholine and decamethonium. In the other group is a number of myorelaxants which are tertiary amines; these include erythrina and delphinium alkaloids. Unlike quaternary ammonium salts, the latter easily penetrate through tissue membranes, such as those of the gastrointestinal tract and the blood-brain barrier.

For practical purposes, both groups of drugs are worthy of interest. Anaesthetists prefer to inject the blocking drugs intravenously, thus providing rapid development of muscle relaxation. On the other hand, for the treatment of neurological disturbances involving increased tone of striated muscles, relaxants which are well absorbed from the gastrointestinal tract and which depress respiration only to a small degree, are preferable.

Relaxants with different durations of action (from 5–10 min up to several hours) are necessary in practice. This is because some drugs are required for short manipulations (intubation, setting of bones), and others for prolonged relaxation during operations or in the treatment of tetanus. It may also be required that the drug rapidly and completely depresses breathing, for example in operations on the thoracic organs, whereas in some cases it may be beneficial to perform operations during spontaneous respiration, but with sufficient relaxation of specific groups of muscles. The latter is especially important in operations in childhood and old age in which the cessation of spontaneous respiration is undesirable.

Experience testifies to the fact that non-depolarizing (competitive) curare-like agents are the most convenient, because, unlike depolarizing relaxants, they have antagonists (inhibitors of cholinesterase). Therefore, the search for new drugs of non-depolarizing (competitive) action is most important.

Taking into account the need of practical medicine for neuromuscular blocking drugs, a search for new substances with muscle relaxant activity in different series of compounds has been made. In this respect, bis-quaternary ammonium derivatives of diphenylcyclobutanedicarboxylic acids are of interest. The reason for systematic

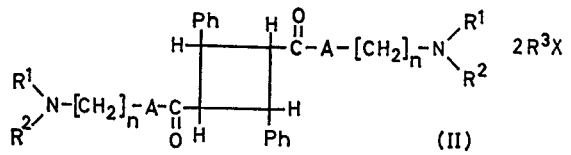


(I)

investigation in this direction was the data about curare-like activity of the alkaloid thesine (I) and its diiodomethylate (Mashkovsky, 1943, 1955).

On the basis of the thesine structure (Arendaruk, 1953) there were synthesized (Arendaruk & Skoldinov, 1960 a, b, c; Arendaruk, Proskurina & Konovalova, 1960) bis-quaternary derivatives of bisalkylaminoesters (II) and bisalkylaminoamides (VI), which showed high curare-like activity during preliminary pharmacological investigations.

The chemical modifications concerned the distance between the quaternary nitrogens, the nature of the radicals on the quaternary nitrogen atoms and the structure of the part of the molecule separating the cationic centres (Arendaruk, Kravchuk & others, 1963; Kharkevich & Kravchuk, 1963, 1964; Kharkevich, 1963, 1965a, 1966c; Arendaruk, Skoldinov & Kharkevich, 1965, 1967a, b; Kharkevich, Arendaruk & Skoldinov, 1968). The main attention was paid to studying the relation between chemical structure and curare-like activity of esters of diphenylcyclobutanedicarboxylic acids (II; A=O).



(II)

where: n = 2 — 5,7; R^3X = HCl, MeI, EtI; NR^1R^2 = —N(Me_2); —N(Me) (Et); —N(Et_2); pyrrolidinyl; piperidino; morpholino; A = O; NH.

As is known, radicals attached to the quaternary nitrogen atoms play an extremely important role in cholinolytic activity of the substances. In the above-mentioned series of compounds, bis-trimethylammonium salts proved to be less effective. Successive replacement of *N*-methyl groups for ethyl is followed by an increase in curare-like activity. Diiodomethylates and diiodoethylates with NR^1R^2=N(Et_2), pyrrolidinyl, piperidino belong to the most effective compounds. Bis-morpholinium salts (NR^1R^2=morpholino) possess comparatively slight curariform activity (Fig. 1).

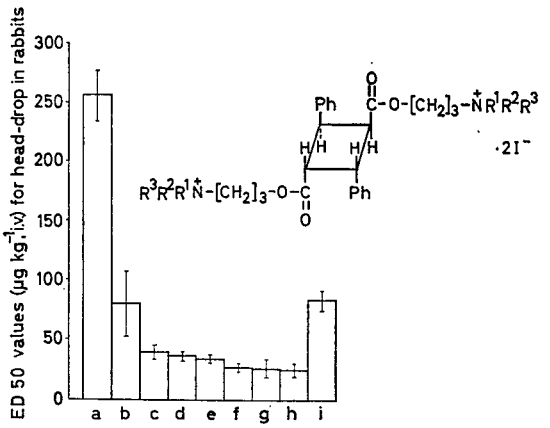


FIG. 1. Significance of the radicals on the quaternary nitrogen atoms (—$N^+R^1R^2R^3$). Vertical lines = confidence limits. a. R^1=R^2=R^3=Me. b. R^1=R^2=Me R^3=Et. c. R^1=Me R^2=R^3=Et. d. R^1=R^2=R^3=Et. e. R^1=Me. R^2,R^3=  . f. R^1=Et. R^2R^3=  . g. R^1=Me. R^1R^2=  . h. R^1=Et. R^1R^2=  . i. R^1=Me. R^1R^2=  O.

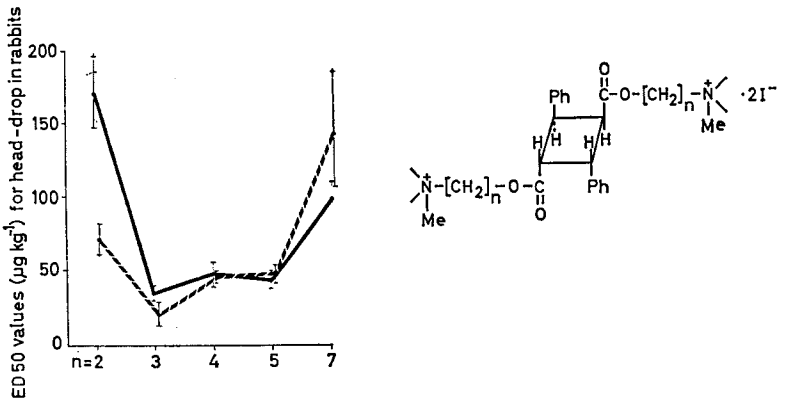
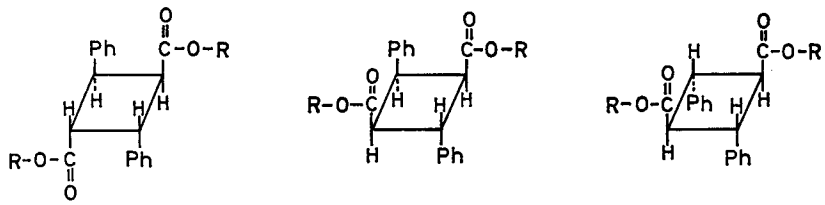


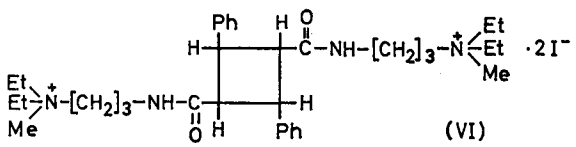
FIG. 2. Significance of distance between quaternary nitrogen atoms. —— Graph for bis-diethylmethyl ammonium derivatives of α-truxillic acid; ---- graph for bis-methyl-piperidyl derivatives. Vertical lines = confidence limits.

Changing the distance between the quaternary nitrogen atoms influenced the activity significantly. The curariform properties were most pronounced when n=3 and slightly less when n=4 or 5. Elongation of the chain to n=7 or shortening to n=2 reduced the activity of the substances considerably (Fig. 2). Thus, the optimum distance between cationic centres is when n=3–5, i.e. when they are separated by 13–17 atoms. In this respect, the tested compounds have an intermediate place between such drugs as tubocurarine and decamethonium on the one hand, and the analogue of decamethonium with 18 methylene groups on the other hand.

An important factor in relation to the degree of curariform properties is the structure of the central part separating the cationic heads of the compounds. To reveal the role of spatial isomerism of the central portion of the molecule, various derivatives of α-, γ- and ε-truxillic acids were tested.



In a comparison of the diiodomethylates of bisalkylamino-esters (diethylamino-butyl or piperidinobutyl derivatives of acids) III-V, the derivatives of the α-truxillic acid were the most active while those of ε- and γ-truxillic acids were 3–5 times less effective (Fig. 3). Thus, the structure of α-truxillic acid was found to be optimal for interaction with cholinoreceptors in a spatial respect. The latter difference was more pronounced for amides of α, ε- and γ-truxillic acids with common structure II (A=NH).



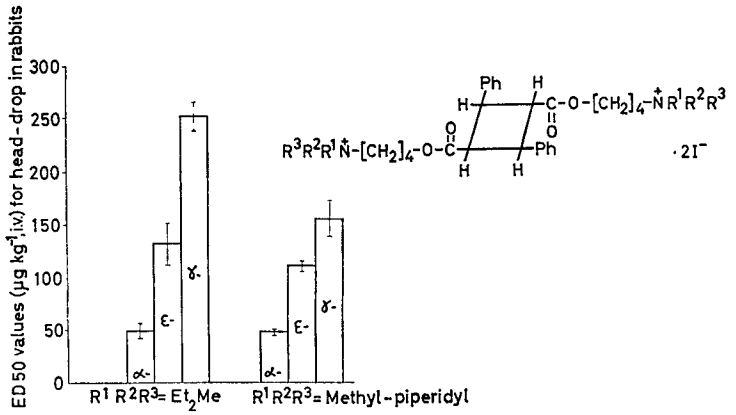


FIG. 3. Significance of spatial isomerism of truxillic acids (α-, γ-, ε-). Vertical lines = confidence limits.

According to the head-drop test in rabbits, the quaternary salt of the amide of α-truxillic acid (VI) was 57 times more effective than the amide of ε-truxillic, and 171 times more effective than the amide of γ-truxillic acids. The amide of α-truxillic acid is 1·75 times more active than the corresponding ester (II; A=O; n=3), whereas the amides of ε- and γ-truxillic acids are 9·5 and 13·8 times less active than the corresponding esters (Fig. 4).

It is worth mentioning that the amide of α-truxillic acid is one of the most active curare-like agents. It evokes head-drop in rabbits at a dose of 21·3 μg kg^{-1} (ED 50) and blocks transmission from the sciatic nerve to the gastrocnemius muscle in cats in a dose of 40–50 μg kg^{-1}. Tubocurarine is much less active than this compound.

These data testify to the fact that evidently the structure of α-truxillic acid promotes a closer approach of the substance to the receptor and, owing to this, favourable conditions for a more complete manifestation of different types of intermolecular connection between the relaxant and the cholinoreceptor occur.

The comparatively less effective compound proved to be the di-*pp'*-hydroxyphenyl derivative of α-truxillic acid, which is a close analogue of the alkaloid thesine. Thus,

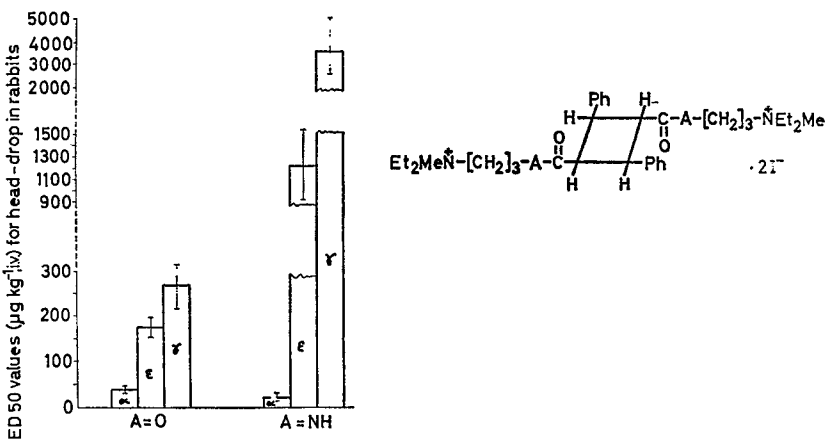
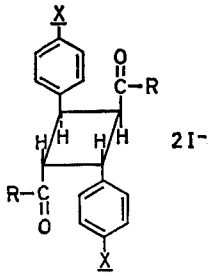
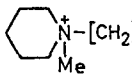
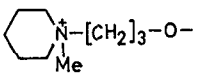


FIG. 4. Significance of the structure of the interonium part of the molecule. Vertical lines = confidence limits.



VII; X=H, R=  VIII; X=OH, R= 

IX; X=H, R=Et_2MeN^+-$[CH_2]_3$-CH(Me)-NH- X; X=H, R= Me_3N^+-$[CH_2]_2$-O-

the bis-quaternary salt VII blocks neuromuscular transmission in cats in a dose of 80–90 μg kg^{-1} and VIII, only in a dose of 150–180 μg kg^{-1}.

Stereoisomerism due to the presence of assymetrical carbon atoms (asterisked) in the aliphatic part of the molecule also considerably influences curariform activity of the above-mentioned compounds. The hypothetical meso-form IX (a higher melting point) is ten times more active than the racemate in its ability to block neuromuscular transmission.

The structure of the central part of the molecule of bis-quaternary ammonium truxillic acid derivatives also influences their mechanism of action. It is noticeable that, in the investigated series, bis-trimethylammonium salts possess a non-depolarizing type of action, whereas the analogous salts of aliphatic dicarboxylic acids are depolarizing drugs. Thus, for example, compound X evokes a non-depolarizing block, and compounds XI (when n=2, succinylcholine, and when n=3, glutarylidicholine) evoke a depolarizing action.

$$Me_3\overset{+}{N}-[CH_2]_2-O-\overset{O}{\overset{\|}{C}}-[CH_2]_n-\overset{O}{\overset{\|}{C}}-O-[CH_2]_2-\overset{+}{N}Me_3 \cdot 2I^-$$

(XI)

Thus, curare-like properties of bis-quaternary diphenylcyclobutanedicarboxylic acid derivatives are dependent on the nature of the radicals attached to the quaternary nitrogen atoms, the distance between the cationic centres and also on the structure of the central part of the molecule. All these factors determine the conditions of interaction of relaxants with cholinoreceptors, which underly the activity of the compounds, the duration of neuromuscular block and the mechanism of their action.

A number of promising compounds was investigated more carefully and recommended for clinical trials (Kharkevich & Kravchuk, 1961; Kharkevich, 1965b, 1966 a, b; 1970c). Among them are α-truxillic acid derivatives—anatruxonium (II; A=O, n=3, NR^1R^2=piperidino, R^3X=EtI), cyclobutonium (II; A=O, n=3, N^1R^2=N Et_2, R^3X=Me I) and truxilonium (II; A=O, n=4, NR^1R^2=piperidino, R^3X=Et I), which are highly effective non-depolarizing relaxants. Neostigmine is an effective antagonist (Fig. 5). It must be noted that all three relaxants paralyse some muscles (m. abdominalis, m. phrenicus) in a different order from tubocurarine (Lepakchin, 1967, a,b) (Fig. 6). Ether anaesthesia increases and prolongs the block evoked by anatrux-

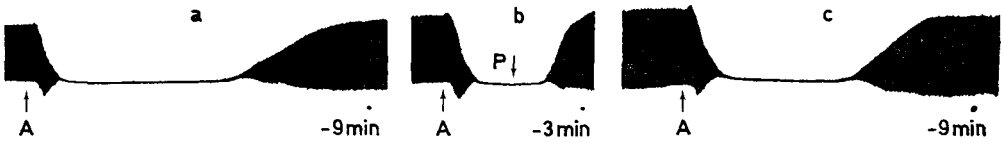


FIG. 5. Effect of proserine (P, 50 μg kg^{-1}) on action of anatruxonium (A, 100 μg kg^{-1}). Contractions of gastrocnemius muscle recorded during stimulation of peripheral end of divided sciatic nerve (supramaximal rectangular stimuli, 1 s^{-1}, 0·5 ms). Intervals between 1–2 and 2–3 = 2 h. Experiment on decerebrate cat. Artificial respiration.

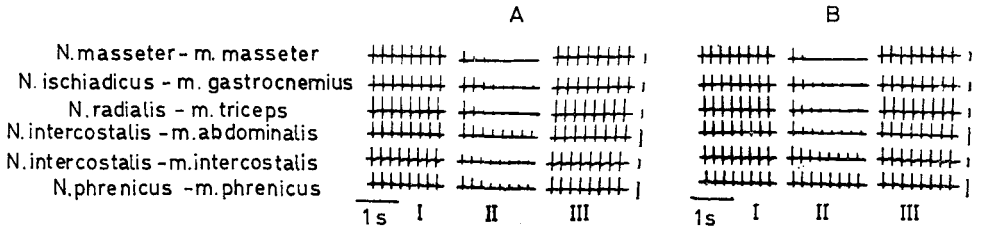


FIG. 6. Simultaneous recording of action potentials of different muscles. A: I—before administration of truxilonium; II—5 min after administration of truxilonium 80 μg kg^{-1}; III—recovery. B: I—before administration of tubocurarine chloride. II—5 min after administration of tubocurarine chloride 150 μg kg^{-1} (injected 1·5 h after truxilonium); III—recovery. Peripheral sections of motor nerves (see the left part of the Fig.) were stimulated (supramaximal rectangular stimuli, 5 s^{-1}, 0·1 ms). Action potentials of the corresponding muscles were recorded by concentric needle electrodes. Vertical lines on the right-voltage scale: 1 mV. Horizontal line-time scale 1 s. Experiment on anaesthetized cat (70 mg kg^{-1} of chloralose and 600 mg kg^{-1} of urethane). All the drugs were injected intravenously.

onium, cyclobutonium and truxilonium (Fig. 7). Sodium thiopentone and hexobarbitone did not show a pronounced influence on the relaxant effects of these curarimimetic drugs. The toxicity of anatruxonium, cyclobutonium and truxilonium is low and the drugs are characterized by large therapeutic indices.

Clinical trial of these agents (Michelson, Degtjarjova & others, 1967; Kotomina & Kharkevich, 1968) confirmed that they are among the most active non-depolarizing relaxants. They are 3–5 times more active than tubocurarine. Prolonged relaxation of the abdominal muscles is typical of them (for cyclobutonium and truxilonium in particular). At first, spontaneous respiration is depressed and artificial or assisted respiration is necessary, but 10–20 min later recovery of respiration occurs, and the main part of the operation is performed with spontaneous respiration. Good relaxation of abdominal muscles is preserved in this instance. Total relaxation with depression of respiration and apnoea can be obtained by increasing the dose. However, in this case the effect of the drugs is more prolonged. The use of α-truxillic acid derivatives is most suitable in the operations on the abdominal cavity, which do not

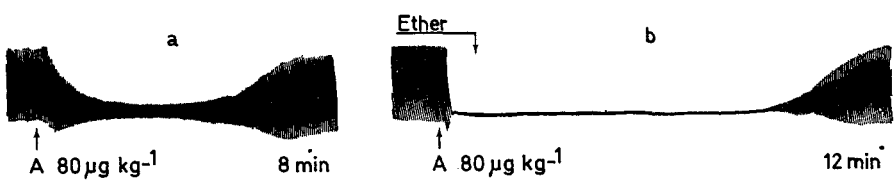


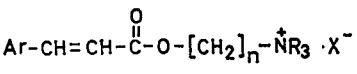
FIG. 7. Effect of diethyl ether on action of anatruxonium (A) a—recording before administration of ether; b—during inhalation of ether (9 min). Period of inhalation denoted by arrow. Contractions of gastrocnemius muscle recorded during stimulation of the peripheral end of the divided sciatic nerve (with supramaximal stimuli, 1 s^{-1}, 0·5 ms). Experiment on decerebrate cat. Artificial respiration.

demand the abolition of respiration and which last 60–90 min and more. Anatruxonium, possessing the less prolonged effect, is also used in operations on the thorax with complete depression of respiration. With ether anaesthesia, the neuromuscular blocking effect of the drugs was more pronounced and prolonged.

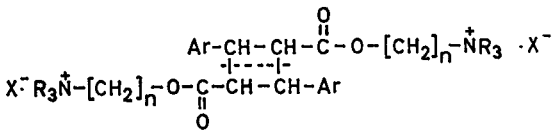
The observations of anaesthetists testify to the fact that neostigmine is an effective antagonist of all three substances.

After successful clinical tests, anatruxonium and cyclobutonium were recommended for use in clinical practice.

Along with the investigation of bis-quaternary ammonium derivatives of diphenylcyclobutanedicarboxylic acids, the search for curare-like agents was also being carried out among mono-quaternary ammonium derivatives of cinnamic acid (Arendaruk, Gracheva & others, 1967; Kharkevich, Arendaruk & others, 1967). These compounds are interesting in two respects. First, derivatives of cinnamic acid (XII) may be considered as being half of the molecules of bis-quaternary ammonium salts of diphenylcyclobutane-dicarboxylic acids (XIII); this is interesting for the analysis of the significance of structural components of the latter compounds in their curariform activity.

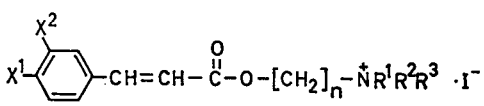


(XII)



(XIII)

Secondly, mono-quaternary ammonium salts deserve attention as substances with short duration of action. According to existing concepts, bis-quaternary compounds with cationic heads interact with cholinoreceptors at two points and mono-quaternary at one point. This may explain the smaller stability of the interaction of the mono-onium compounds with cholinoreceptors, which is the cause of the short duration of their effect. Short duration of effect may also depend on the presence of ester groups and the possibility of their rapid biotransformation. During the investigation of mono-quaternary ammonium derivatives of cinnamic acid (XIV), it was shown that trimethylammonium compounds possess the most pronounced curare-like properties. When $NR^1R^2 = N\,Et_2$, piperidino the activity decreased.



(XIV), $X^1 = X^2 = H$; (XV), $R^1 = R^2 = R^3 = CH_3$, $n = 4$

As to the length of the polymethylene chain, the optimum is when n=4. When the chain was shortened to n=2 or 3, or extended to n=5 or 7 the activity of the substances was reduced. Thus the optimum distance between the carboxylic groups and quaternary nitrogen atoms for bis-quaternary ammonium derivatives of truxillic acids (XIII; n=3–5) and mono-quaternary ammonium derivatives of cinnamic acid (n=4, XIV) is similar.

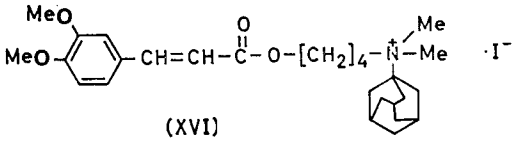
It was found that derivatives of the substituted cinnamic acid (XV) possess the most pronounced curariform properties.

When $X^1=CH_3O$, NO_2 and $X^2=H$ or $X^1=X^2=CH_3O$, the compounds block neuromuscular transmission in cat in very small doses (30–50 μg kg^{-1}) which can be compared with those for the most active relaxants of bis-quaternary ammonium salts.

As was predicted, the tested compounds were found to induce a very short effect. The most active trimethylammonium derivatives of cinnamic acid were shown to be substances of the depolarizing type. After their injection, muscular fasciculation was observed, they evoked spastic paralysis in birds, and neostigmine was synergistic rather than antagonistic.

There is little point in testing substances of type XV clinically because, among depolarizing agents, succinylcholine is satisfactory to anaesthetists. However, the possibility of converting them into non-depolarizing drugs is worthy of attention. One way is to change the structure of the cationic centres.

Taking into consideration the structure of the subsynaptic membrane of the neuromuscular synapse, the main attention was given to lipophilic radicals. It was shown that the replacement of one *N*-methyl group by the high lipophilic adamantyl radical (XVI) in the cinnamic acid derivatives is followed by a change in the mechanism of action. Substance XVI is a non-depolarizing curare-like agent (Kharkevich, Skoldinov & Ibadova, 1973a).

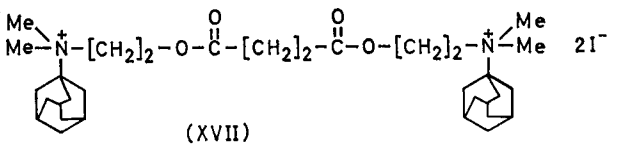


(XVI)

Unfortunately, along with the change in the mechanism of action, the activity of the substance essentially decreased (in comparison with the depolarizing trimethyl ammonium analogue, it decreased about 100 times).

The analogous principle of the transformation of the depolarizing drugs into the non-depolarizing ones was used in respect of the salts of tetramethylammonium, acetyl choline, decamethonium and succinylcholine*. In all these cases the replacement of one methyl by adamantyl on each nitrogen was followed by a change in the mechanism of their action and the substances acquired the properties of non-depolarizing cholinolytics (Kharkevich & others, 1970c, 1971, 1973b).

The adamantyl analogue of succinylcholine, called diadonium (XVII), is of interest (Kharkevich, 1970b).



(XVII)

It evokes head-drop in rabbits in a dose of 130–180 μg kg^{-1} intravenously and blocks neuromuscular transmission in cats in a dose of 250–350 μg kg^{-1} (i.v.). Consequently, diadonium is a curare-like agent with pronounced activity. According to its mechanism of action, the drug belongs to the non-depolarizing (competitive) agents (Fig. 8). Neostigmine is an antagonist of diadonium. With ether anaesthesia the effect of

* The synthesis of drugs, containing adamantyl radicals was carried out by A. P. Skoldinov, A. P. Arendaruk, N. I. Vasetchenkova, N. V. Smirnova and M. I. Shmaryan.

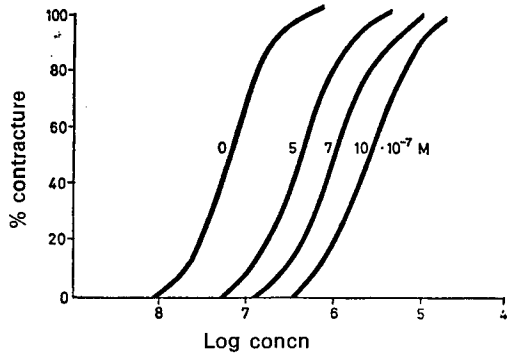
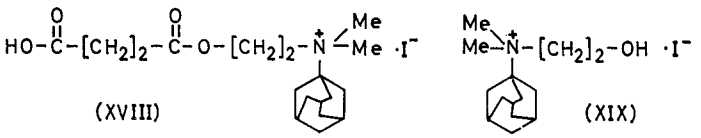


FIG. 8. Cumulative log-concentration-response curves for agonist carbocholine (o). Effect of a competitive antagonist diadonium (5:7:10·10⁻⁷ M). Abscissa:—log-concentrations of carbacholine (M). Ordinate: % contracture. Experiments on isolated frog rectus abdominis.



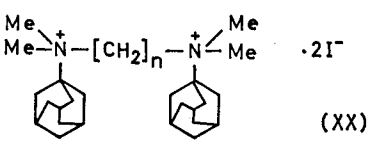
(XVIII) (XIX)

diadonium increases and is prolonged. The toxicity of the drug is low and the therapeutic index is favourable.

In addition, the possible products of the hydrolysis of diadonium (XVIII and XIX) were tested.

The curariform activity of both compounds turned out to be considerably less (20–40 times) than that of diadonium. It is worth mentioning that both mono-quaternary metabolites as well as diadonium evoke a non-depolarizing block.

Similar relations were obtained when the *N*-methyl groups of decamethonium were replaced by adamantyl radicals (XX). Compound XX when n=10 was called decadonium (Kharkevich, 1970a).



(XX)

Decadonium is a rather effective curare-like drug. It blocks transmission from the sciatic nerve to the gastrocnemius muscle of the cat in a dose of 250–300 μg kg^{-1} and induces head-drop in rabbits in a dose of 100–110 μg kg^{-1}.

Homologues of decadonium with n=9 and 11 possess less activity.

All three compounds are non-depolarizing relaxants. They do not cause fasciculation of the muscles preceding the block; they prevent the effect of acetylcholine on the rectus abdominis muscle of the frog; after their injections into chickens a flaccid paralysis occurs and, finally, neostigmine is their antagonist.

The drug does not much affect the cardiovascular system, although a slight and transient hypotension may occur. Decadonium, like diadonium, blocks transmission from the vagus nerve to the heart in muscle relaxant doses (Fig. 9). At the same time, the acetylcholine cardiotropic effect (the bradycardia) is abolished, but its hypotensive effect persists. The toxicity of decadonium is low.

It may be supposed that diadonium and decadonium are prospective drugs for anaesthetic practice as non-depolarizing curare-like agents of short action.

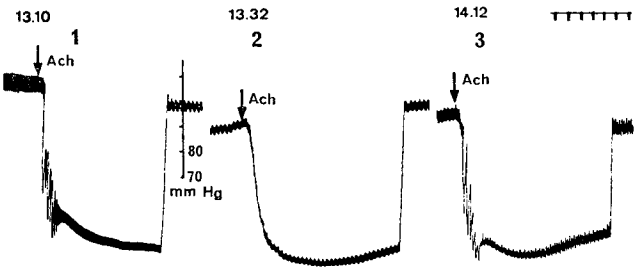
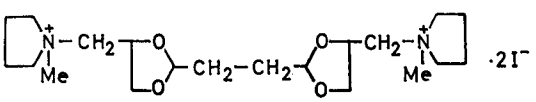


FIG. 9. Effect of decadonium on acetylcholine (Ach 15 μg) action. 1—Arterial pressure and acetylcholine effect before administration of decadonium. 2—2 min after administration of decadonium 100 μg kg^{-1}. 3—42 min after administration of decadonium. Experiment on anaesthetized cat (60 mg kg^{-1} of chloralose and 400 mg kg^{-1} of urethane). All the drugs were injected intravenously. Divisions on time scale: 5 s.

Consequently, the presence of *N*-adamantyl radicals in the mono- and bis-quaternary ammonium salts tested changed their mechanism of action. Trimethylammonium compounds are depolarizing drugs and their adamantyl analogues are non-depolarizing ones. Possibly, the latter is connected with different conditions of fixation of the substances on the subsynaptic membrane. Thus, it may be supposed that adamantyl derivatives penetrate into a lipid layer. On the other hand it can not be excluded that hydrophobic structures are kept out by the hydrated surface of the subsynaptic membrane, which is penetrated only by polar ammonium groups. The latter possibility seems more likely in view of the investigations of Waser (1962, 1967), who has shown, using labelled compounds, that non-depolarizing curarine is concentrated on the end-plates and a less lipophilic depolarizing substance, decamethonium, is distributed more diffusely.

Steric factors, because of the great size of adamantyl radicals should also be taken into consideration.

The distance between quaternary nitrogen atoms of decadonium and diadonium is approximately 14–15Å. Tubocurarine, diplacinum, paramyonum, succinylcholine, and decamethonium possess similar interonium distances. Of the new drugs that may be classified in this group is dioxonium (XXI) (Klusha, 1968; Sokolov, Klusha & others, 1968).

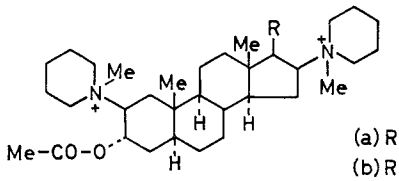


(XXI)

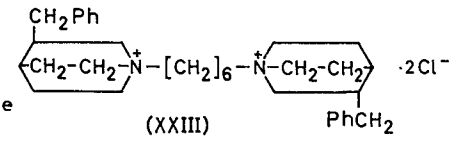
In experiments on animals, dioxonium was shown to be more active than tubocurarine (approximately 22 times). According to its mechanism of action, it belongs to the depolarizing-non-competitive class of drugs. During its clinical tests, dioxonium was confirmed to possess high blocking activity; its antagonist is neostigmine.

At the same time there exist curare-like agents with cationic centres more and less remote from each other. Thus, competitive agents, pancuronium bromide (XXIIa) and dacuronium bromide (XXIIb), have a shorter distance between nitrogen atoms (eight atoms).

Pancuronium bromide is 1·5–10 times more active than tubocurarine chloride, with a similar duration of action (Buckett, Marjoribanks & others, 1968). Dacuronium



(XXII)



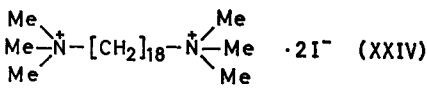
(XXIII)

bromide is distinctive because, along with high curariform activity, it possesses half the duration of activity of tubocurarine chloride (Buckett & Saxena, 1969).

Quaternary nitrogen atoms of a new relaxant, qualidilum (XXIII), are separated by six carbon atoms.

Qualidilum is an active non-depolarizing relaxant. It causes head-drop in a dose of 55–75 μg kg^{-1} (i.v.). It possesses moderate ganglion-blocking and antihistaminic properties (Mashkovsky & Sadritdinov, 1962). The clinical investigation of the drug was a success.

Anatruxonium, cyclobutonium and truxilonium have 13–15 atoms and carbolonium bromide (Imbretil) has 16 atoms between the quaternary nitrogen atoms and in the analogues of decamethonium, there was a second maximum of activity with the 18-membered polymethylene compound (Paton & Zaimis, 1949, XXIV).



(XXIV)

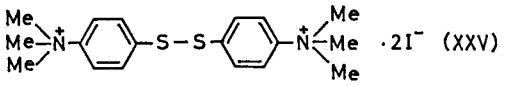
Thus, the distance between the quaternary nitrogen atoms of curare-like agents varies within rather wide limits. This fact is probably connected with different distances between anionic structures of cholinoreceptors. However, it is quite possible that one cationic group may interact with other (not belonging to the specific cholinoreceptors) anionic structures of the subsynaptic membrane ("anchoring site" according to Gill & Ing, 1958).

For most relaxants, the main role in their interaction with cholinoreceptors belongs to the quaternary nitrogen atoms. At the same time, for certain structures, the possibility of the appearance of partial charges $\delta+$, connected with the effects of induction and conjugation, should be taken into consideration (Michelson & Khromov-Borisov, 1964; Aleksandrova & Filatov, 1966; Michelson & Zeimal, 1969, 1970).

The possible calculation for a number of compounds of the total positive charge ($\Sigma\delta+$), determining their physiological activity, is of great interest (Khromov-Borisov, Indenbom & Danilov, 1968). This was convincingly shown in a series of polymethylene-bis-pyridinium salts, by the value of π-electron density on different atoms of pyridinium radicals (in this case a knowledge of the optimum of distance between the cationic centres for the given series of compounds is necessary). The calculated correlation of the activity of the substances practically coincides with the data obtained in the experiments on biological preparations. The importance of such comparisons is obvious for clearing up the nature of cholinoreceptors and also for the directed synthesis of new drugs.

As to the synthesis of new curare-like agents, the idea of Khromov-Borisov and his co-authors (Khromov-Borisov, Gmiro & Magasanik, 1969) about the possibility of creating relaxants which may be inactivated at the necessary moment in the organism by other chemical compounds, deserves attention. As a model, bis-ammonium derivatives of diphenyl-disulphide (XXV) are given.

Neuromuscular block produced by disulphide XXV has been found to be abolished



(XXV)

by sodium sulphite, unithiolum and cysteine. The authors suppose that nucleophilic substitution of the sulphur atom in the disulphide group (-S-S-), with the transformation of the bis-quaternary salt into a mono-quaternary one, form the basis of inactivation. At the same time, not one of the nucleophilic agents tested as inactivators was found to influence the blocking effect of decamethonium, succinylcholine, tubocurarine or the analogues of XXV without the disulphide bridge.

Up to now, some authors have been trying to achieve controlled muscle relaxation by using the curarimimetic agents with short effect (preferably with a competitive mechanism), and also by using physiological antagonists (of neostigmine type). The suggested principle of chemical inactivation of muscle relaxants is an additional way to regulate the duration of neuromuscular block.

The other principle of controlled relaxation is that outlined by Godovicov, Danilov & others (1968). An active neuromuscular blocking agent hydrolysed by pseudocholinesterase (of succinyldicholine type) is suggested as the main drug. The inhibitor of pseudocholinesterase (one such drug—phosphorous organic compound GT-106—is presented in the work) for increasing and prolonging the action of the relaxant is recommended to be administered before the curare-like agent. When there is no longer any necessity for the myoparalytic effect, the reactivator of cholinesterase (pyridoxine) is injected, and within a few minutes neuromuscular transmission recovers. Thus, in this case three agents with different types of action are to be used. Such an approach to controlled muscle relaxation is obviously interesting. However, even if suitable components of the above-mentioned combination of compounds are synthesized, it is not the best variant for anaesthetic practice, as the selection of rational doses for each of the three compounds during the operation will certainly evoke difficulties. Besides, depolarizing substances are suggested as curare-like agents in this case and that is also undesirable. The synthesis of active competitive muscle relaxants of ultrashort action, the effect of which will be determined by duration of intravenous infusion, is evidently most promising for controlled relaxation.

Thus, during the last few years new data about the relations between the chemical structure and the physiological activity of the compounds of different classes of muscle relaxant drugs have been obtained and worth-while drugs have been suggested for clinical use. At the same time, there is a progress in the identification of the nature of cholinoreceptors (Miledi Molinoff & Potter, 1971; O'Brien, Elderfrawi & Elderfrawi, 1972). The solving of this cardinal problem will promote the understanding of many questions, concerning the physiology and pharmacology of neuromuscular transmission and also the more purposeful synthesis of new relaxants.

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