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LOCAL ANAESTHETICS

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At the present time, alkaloids and in particular local anaesthetics are most generally used in the form of their salts of mineral acids, as at the time of their discovery.

However, for some years, it has been endeavored to utilize other salts, prepared with acids weaker than mineral acids.

These endeavours are based, among other searches, on those of Overton (Vierteljahresschr. d. Naturf. ges. Zurich 1896, 41 383; 1899 44 88), of Ruhland (Yahrber. Bot. 1914 54 391), of Tröndle (Biochem. Ztschr. 1920 112 259) and chiefly, in the present case, of Oscar Gros (Arch. f. exp. path. u. pharm. 1910, 62, 380; 1910 67 126).

From the studies of these authors, the following deductions can be made: When an aqueous solution of a salt of an alkaloid is caused to act on a living cell, only the alkaloidic base is active; the acid that salifies this base would then have no other function than to permit of dissolving the alkaloid in water. If, therefore, it is admitted, as it was admitted by the authors above referred to, that only the base is active (which, by the way, was also in accordance with the hypothesis, which was then admitted, of a lipoidic layer at the surface of the cell (Meyer-Overton)) one is led to consider, as these authors did, the utilization of the salts of weak acids.

As a matter of fact, for O. Gros, in particular:

The weaker the acid, the more complete will be the hydrolysis of the salt and, consequently, the greater the amount of the base set free.

On the other hand, for other authors, such as Copeland:

The weaker the acid, the lesser this acid, set free by hydrolysis, will be ionized, and the lesser the number of hydrogen ions set free, which are detrimental of a good anaesthesis.

On the basis of these principles, tests were made, after Oscar Gros, of mixtures of cocaine chlorhydrate novocaine chlorhydrate, etc., with salts of weak acids, such as sodium carbonate, sodium bi-carbonate, sodium acetate, and the following salts were prepared and applied: dextro acid tartrate of pseudococaine (or psicaine) dextro formiate of pseudococaine (or delcaine), carbonate of novocaine (or carbaine), borates of various local anaesthetics (or borocaines).

Although the experiments above referred to were performed several years ago, it does not seem that these ideas gave rise to particularly advantageous practical results. So much so that local anaesthetics prepared recently, such as "Butyne" are salts of a strong acid, to wit sulphuric acid. The failure of the various experiments that have been made is due not only to a bad conception at the origin, as it will be hereinafter explained, but also to practical difficulties of utilization. Thus, concerning more particularly the solutions that were proposed by Oscar Gros, the fact that these solutions, due to their alkalinity, which is detrimental of a good preservation of the alkaloid, could not be prepared in advance and sterilized, but had to be prepared immediately before being used, constituted a technical complication which was not negligible.

An analogous remark is applicable also to some salts of weak acids, such as borates, the aqueous solution of which has a pH which is alkaline or too near to neutrality, such a pH being unfavorable to a normal sterilization and to a normal preservation. The lack of success in some clinical cases in the use of these salts of weak acids of local anaesthetics can perhaps be attributed to these phenomenons.

The object of the present invention is to produce salts of alkaloids, and in particular salts of local anaesthetics, permitting to obtain physiological results wholly out of proportion with the results to which the conceptions above stated could lead.

As a matter of fact, while the authors above mentioned believed that only the alkaloidic base acts on the eell, it is proved, by the present invention, that the whole of the salt of alkaloid is active.

The consequence of the present invention is to be conducive to choosing salts that are not necessarily salts of weak acids, as advised by the authors above mentioned, but that are capable, owing to some of their properties, of improving the action of the salt. These essentially favorable properties are the following: tensio-activity, easy adsorbability, properties of dissolving substances that are not hydrosoluble, considerable increase of the hydratation of the proteins with, as a consequence, a favorable modification of the cellular charge, of the swelling of the limiting cellular layers or other phenomenons facilitating the penetration into the cell.

The facts, successively discovered, that have led to the present conception, are briefly stated as follows:

In 1923, 1924 and 1925, Régnier (C. R. 4 Aout 1924, 355; B. Sc. Pr. 31, 1924, 513; Thèse doct. ès sciences Paris 1925, imprim. André Brilliard à St-Dizier) finds the favorable influence, concerning anaesthesis, of the alkalinization of solutions of chlorhydrate of cocaine. He measures the an-

aesthetic gain. He also finds that the cocaine base is more active than the chlorhydrate but he is the first to show that the quantities of base set free by adding known quantities of soda are not sufficient for explaining the anaesthetic gain. He further finds that, by alkalinizing solutions of cocaine-base, in this case also there is obtained an anaesthetic gain which cannot be explained by the theory of O. Gros. He is therefore led to conclude that alkalinization increases the anaesthetic action not only by setting free the base (the only side of the question considered by O. Gros and the other authors above referred to) but also, and to a much greater degree, owing to the action of the alkali on the cell that receives the product, with a better fixation of the whole of the salt.

In 1933, Regnier and his associates (B. Sc. Pharm. 40 1933, 271, 650; 41 1934, 321) consider the question of the destruction of chlorhydrate of cocaine by heat and the ageing; he ascertains the following facts:

(*a*) the anaesthetic undergoes a destruction which is certain but relatively small, with a tendency toward a state of equilibrium;

(*b*) The solutions of chlorhydrate of cocaine that are prepared in such manner that after heating, the concentration in hydrogen ions is about pH=4 keep nearly the whole of their anesthetic power;

(c) When the solution of chlorhydrate of cocaine has been sufficiently acidified (pH≤3) their may occur failures in the anaesthesis, a fact that had already been observed by Regnier previously.

Starting from these observations, Régnier and David have prepared solutions of chlorhydrate of cocaine brought at a pH equal to 4 by means of various salts. They have thus found the fundamental fact that: the solutions mixed with sodium phosphates have, after heating, a very low anaesthetic power, while the solutions prepared with sodium acetate have, after heating a relatively high anaesthetic power. However, in both cases, the pH after heating was the same. I was therefore led to the conclusion that the acid of the salt mixed with the solution of chlorhydrate of cocaine plays an important part. I therefore prepared a whole series of solutions of salts of cocaine containing the same quantity of cocaine base as a 1% solution of chlorhydrate of cocaine and adjusted with the acid corresponding to the salt in such manner that the pH obtained may be equal to 4. These solutions were tested, before and after sterilization, on the cornea of a rabbit, according to the method described by Régnier in 1923 (B. Sc. Pharm. 1923, 30 580, 646) and I obtained wholly unexpected results in view of the admitted theories. These results are expressed by the following table:

	Fresh solution before sterilization	Solution sterilized for 15 minutes at a temperature of 120° C.
Citrate	[1] 0	
Tartrate	0.6	0.2
Sulphate	0.8	0.6
Phosphate	1	0.4
Chlorhydrate	1	0.8
Iodide	1.2	0.5
Sulphocyanate	1.5	0.6

[1] Does not penetrate at all.

Considering the order in which the salts that are studied are disposed, it is found that the activity of these salts before sterilization can be classed according to a series analogous to that found by Hofmeister, for the swelling of a gelatin or else (but however in the reverse order) for the flaking of an albumin.

It therefore results obviously from these experiments:

1. that the strength of the acid is not the only factor as stated by the theory above mentioned (O. Gros) because the salts are not classed in accordance with their degrees of hydrolysis;

2. that some acids (citric acid in particular) have an action which is quite unfavorable to the utilization of the alkaloid, so much so that citrate of cocaine does not permit, under the conditions of the tests, any appreciable anaesthesis, this solution being wholly unabsorbed by cornea;

3. that cellular lipoids are not the only factors in play, as would be the case according to the theory of Meyer and Overton, since the salts are classified according to a series which has been essentially found by Hofmeister on albuminoid substances.

It was therefore necessary to make experiments with other acids, and in particular acids having the property of acting on these albuminoid substances (swelling). The particularly interesting results of these new experiments, which were also new, are given in the following table:

	Fresh solution before sterilization	Solution sterilized for 15 minutes at a temperature of 120° C.
Formiate	2.5	1
Acetate	2.9	2.9
Salicylate	4	3
Benzoate	5	4.6

It therefore appears clearly that salts such as salycilates should be utilized, and especially benzoates, which posses, in fresh solutions, such an anaesthetic gain as could hardly have been hoped for, and preserve their anaesthetic power nearly entirely (in particular in the case of benzoate) after sterilization.

These facts therefore lead to pursue other experiments by making use of other acids capable of helping in the same way (and perhaps to a still higher degree) the properties above stated. It is again explained that these properties are: tensio-activity, easy adsorbability, favorable modification of the cellular electrid fields, increase of the swelling of the proteins, and as a rule everything that facilitates the penetration into the cell, according to what has been above explained.

Now that it has been proved that the favorable modification of the cell that receives the product by the acid that salifies the local anaesthetic plays so important a part in the physiological action, it is advisable to add to the anaesthetic gain that results from the utilization of a favorable salt another anaesthetic gain resulting from the use of other ions, which are also favorable.

Among these, use could be made of hydroxyl ions. This has not been done because it is known that in an alkaline liquor does not resist to heating and ageing. But it seemed that it was possible to make use of the favorable influence that potassium and magnesium ions exert, as it is known, on anaesthesis.

For this purpose, I made use not only of the pure saline solutions of the different salts of alkaloids but of solutions prepared for instance by mixing the local anaesthetic with accurately

calculated amounts of salicylates or benzoates of potassium or magnesium.

In this way I found that a solution of chlorhydrate of cocaine of 1% mixed with 2.5% of benzoate of magnesium, which solution had a pH substantially equal to 4, had, before sterilization, an anaesthetic value of more than 12%, that is to say the same anaesthetic value as a solution of chlorhydrate of cocaine of more than 12%; after sterilization for 15 minutes at a temperature of 120° C., its value was still 7 per cent; after having been preserved for two months and a half, six months, and eight months, the anaesthetic value became successively 7.6%, 4.6% and 4%.

The chief conclusion from the preceding explanations is therefore that the local anaesthetic activity of cocaine is very much increased when it is combined with acids which facilitate the reaction on the cell and still more when it is possible to combine together all the favorable conditions.

But it is known that chlorhydrate of cocaine penetrates already by itself with a sufficient facility through the protective layers of the nervous cells (epithelium of the cornea, of the mucous membranes) for which reason it is considered at the present time as the best local anaesthetic, in spite of its well known disadvantages.

It therefore became still more interesting to apply the conceptions to which one is led according to the present invention to the practical utilization of another local anaesthetic base, to wit novocaine, the generally employed salt of which, to wit the chlorhydrate (ordinary novocaine) does not permit, as it is well known, the anaesthesis of the mucuous membranes, of cornea, etc., so that, up to this time, novocaine was considered as devoid of practically any surface activity.

Repeating the experiments above stated, but replacing cocaine by novocaine, I prepared a solution of chlorhydrate of novocaine of 1% mixed with 2.5% of magnesium benzoate, having a pH of 4 and sterilized for 15 minutes at a temperature of 120° C. This solution was tested on the eyes of a rabbit, comparatively either with solutions of chlorhydrate of novocaine of various strengths, prepared extemporaneously in distilled water, or with solutions of chlorhydrate of cocaine of different strengths, prepared in the same manner. The following results were obtained:

The solution of chlorhydrate of novocaine of 1% mixed with magnesium benzoate and sterilized acts more effectively than a solution of chlorhydrate of novocaine of 30% in distilled water. A solution of chlorhydrate of novocaine of 1% mixed with magnesium benzoate and sterilized acts with the same efficacity as a solution of chlorhydrate of cocaine of 3% in distilled water.

It can therefore be stated that I succeeded in transforming novocaine in such manner that I have changed it into an excellent surface local anaesthetic. This fact, the practical importance of which is obvious, has already been tested in clinical experiments, in which a solution of chlorhydrate of novocaine of 5% mixed with magnesium benozate of 10%, the whole being sterilized and having a pH approximately equal to 4, has permitted of performing the same operatory interventions, in oto-rhino-laryngology for instance, as a non-sterilized solution of chlorhydrate of cocaine of 10% in distilled water. This fact, which corresponds to a local anaesthetic such as novocaine, which up to now had been considered as having no efficacity whatever as a surface ananesthetic, being so modified as to become a surface anaesthetic better than chlorhydrate of cocaine, can truly be considered as very remarkable. In view of the well known low toxicity of novocaine, this fact should render possible a new utilization, much more general of this anaesthetic. This technical result is all the more important as chlorhydrate of cocaine, which is so toxic and so dangerous because of its stupefying properties, is employed at the present time only because of its properties of surface local anaesthetic, which permit of employing it in cases in which it seemed impossible to replace it by other bodies, prior to the present invention.

I wish to insist more particularly on the remarkable property of the new salts or new mixtures according to the present invention of being sterilized or undergoing a substantial ageing while keeping most of their activity.

These advantages are due to two kinds of reasons:

1. To the fact that the pH of the solutions is always made substantially equal to 4, which, as above explained, is essentially favorable to the stability of the active molecule. This pH substantially equal to 4 remains within the necessary limits in order that the cell on which it is desired to act may not undergo any detrimental effect.

It should be further noted that the concentration in hydrogen ions is not the only factor to be taken into account in these phenomenons and it appears that the living cell can much more easily withstand a pH equal to 4 obtained with acids such as those the use of which is advised according to the present invention than a pH equal to 4 resulting from the ionization of mineral acids such as hydrochloric acid.

2. To the fact that the anaesthetic gain before sterilization being very high, it is maintained after sterilization and a substantial ageing, to a degree which remains extremely high.

To sum up, I rely, in the presentation of the present invention, on a combination of new facts, of a theoretical as well as practical nature which, briefly stated, are the following:

I. New theoretical facts

(*a*) The acids that serve to salify the local anaesthetic bases play a quite preponderating part for the anaesthetic action; they participate in this action, at least by facilitating the penetration of the salt into the cell;

(*b*) Everything takes place as if this favorable action was parallel to the influence exerted on the swelling of albuminoid matters (Hofmeister series).

(*c*) It is therefore quite likely that the proteic part of the cell is also brought into play in these phenomenons.

(*d*) If account is taken of the favorable influence probably exerted by the swelling of albuminoid matters, it seems possible to explain in the same manner the favorable influence exerted by the hydroxyl ions on the cell (Regnier) and perhaps alwso that exerted by the potassium ions for instance.

II. New technical facts

(*a*) By making use of the acids above proposed a better penetration of the salt is obtained and therefore a better utilization of the alkaloid. This obviously involves, since it is possible to employ weaker doses, a reduction of the toxicity and a reduction of the cost of the product employed, which is far from negligible. It even happens,

which in some cases is very much important that substances which, up to now, could not be employed for certain applications, due to their inactivity, are rendered perfectly active (utilization of novocain as a surface anaesthetic).

(*b*) With the acids that are proposed according to the present invention it is possible to employ a pH which is relatively acid (pH equal to 4) without injuring the cell, such a pH permitting a much better resistance of the anaesthetic to the causes of destruction involved by heating and a long preservation.

Considering, on the one hand, that the facts revealed by these experiments have an absolutely general value, and, on the other hand, that most of the alkaloidic salts are formed with strong acids, it is believed that the present invention covers in a general manner all the salts of alkaloids prepared with the acids above stated.

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