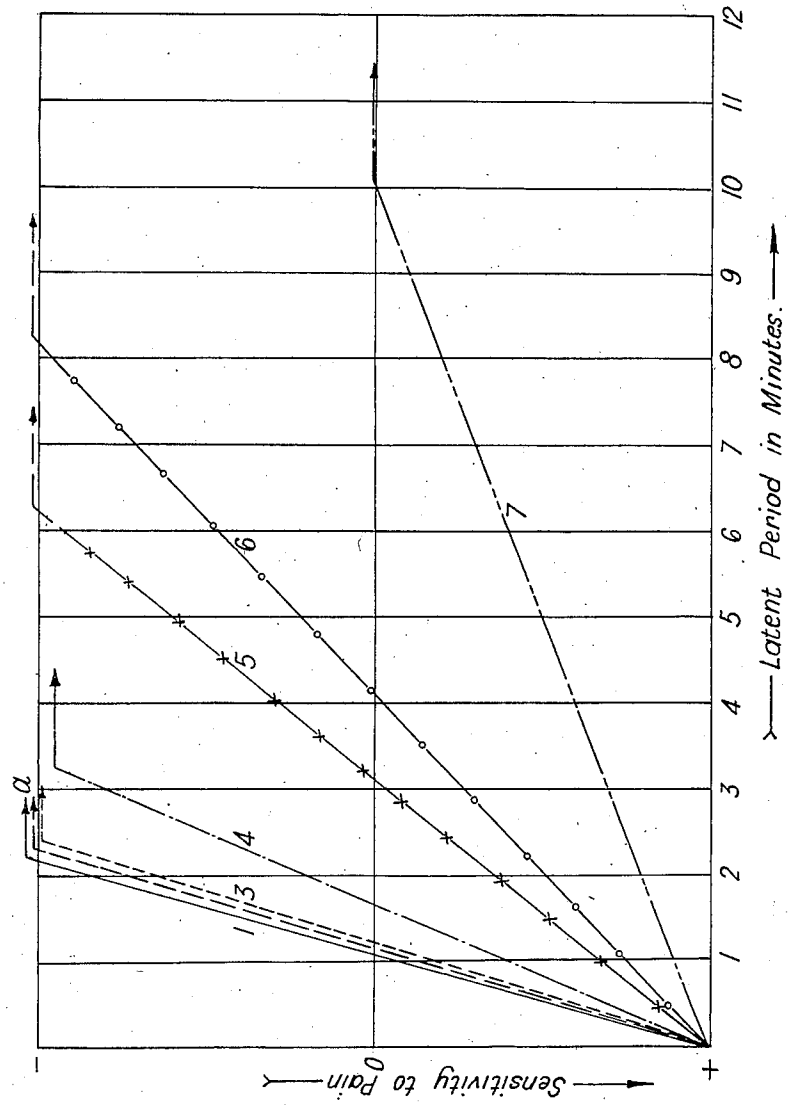
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ANAESTHETIC COMPOSITIONS

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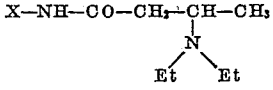
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6 Claims. (Cl. 167—52)

This invention relates to improved anaesthetic compositions of particular use in local anaesthesia.

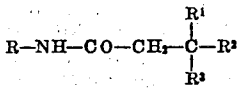
In copending application Serial No. 555,305 filed December 27, 1955 of Emil Hofstetter there are described certain new compounds of the general formula



I

(where X is selected from the group consisting of phenyl and monoalkoxyphenyl groups, said alkoxy substituents having from 1 to 5 carbon atoms), which compounds have pronounced local anaesthetic activity.

In copending application Serial No. 475,282 filed December 14, 1954 of Arthur E. W. Smith et al. there are also described certain new compounds having the general formula



II

(where R is a monochlorophenyl radical or a dichlorophenyl radical which dichlorophenyl radical has at least one chloro-substituent in the meta- or para-position, R^1 is hydrogen or an alkyl group having from one to five carbon atoms, R^2 is an alkyl group having from one to five carbon atoms and R^3 is a dialkylamino group containing from two to four carbon atoms or a piperidyl or monoalkyl piperidyl group), which have local anaesthetic activity.

We have now found that an anaesthetic composition having unexpectedly advantageous properties is obtained by mixing together the compound of the Formula I above in which X represents a phenyl radical, that is β-diethylamino butyric acid-anilide, or its non-toxic water- or alcohol-soluble salts with the compound of Formula II above in which R is an o,p-dichlorophenyl radical, R^1 is hydrogen, R^2 is methyl and R^3 is piperidyl, that is β-piperidylbutyric acid-(o,p-dichloro)-anilide or its non-toxic water- or alcohol-soluble salts.

According to the invention, therefore, we provide a local anaesthetic composition comprising a sterile injectable solution of a mixture of a member of the group consisting of β-diethylamino butyric acid-anilide and non-toxic water- and alcohol-soluble salts thereof and a member of the group consisting of β-piperidyl butyric acid-(o,p-dichloro)-anilide and non-toxic water- and alcohol-soluble salts thereof.

By the term "non-toxic" as applied to the salts of the two compounds mentioned above is meant such salts as are not substantially more toxic under normal conditions of administration than the compounds themselves. Such non-toxic salts specifically include the citrates, tartrates, acetates, sulphates and particularly the hydrochlorides of these compounds.

The local anaesthetic compositions provided according to the invention have important and unexpected advantages over either of the component compounds comprising the composition. Thus, a local anaesthetic should have ideally inter alia, the following properties.

(1) It should have a short latent period; that is the period between the injection of the anaesthetic and the time when it takes effect should be as short as possible.

(2) The level of anaesthesia induced should be deep and should be maintained for a sufficient period.

(3) There should be no substantial irritation of the tissue on injection, and no substantial ill-effects on the patient.

Now, it was found that although β-diethylamino butyric acid-anilide is a good anaesthetic in many respects it has a long latent period; also anaesthesia is not maintained for as long a period as might in some cases be desirable. The compound β-piperidyl butyric acid-(o,p-dichloro)-anilide also has a long latent period, and whilst it is long acting it gives rise to some tissue irritation in concentrations of greater than about 0.5%.

The anaesthetic compositions of the present invention have the unexpected property of a very short latent period, which is considerably less than that of either β-diethylamino butyric acid-anilide or β-piperidyl butyric-(o,p-dichloro)-anilide. The duration of anaesthesia is also long and a considerable depth of anaesthesia is maintained.

We have found it particularly advantageous to use a composition in the form of a sterile injectable solution containing a mixture of from about 1.5 to 4.0%, preferably 2.0%, of β-diethylamino butyric acid-anilide or its non-toxic water- or alcohol-soluble salts with from about 0.2 to 0.5%, preferably 0.4%, of β-piperidyl butyric acid-(o,p-dichloro)-anilide or its non-toxic water- or alcohol-soluble salts the percentages being expressed as a weight by volume on the metric scale based on the volume of the injectable solutions. A preferred non-toxic salt is the hydrochloride. When used in these proportions the tissue irritant properties of β-piperidyl butyric acid (o,p-dichloro)-anilide are not noticeable on injection of the composition.

The anaesthetic compositions according to the invention are particularly applicable to dental surgery or surgery of a minor nature, although they are also applicable as ganglionic blocking agents in major surgical intervention. In the case of dental surgery they are conveniently made up in the form of dosage units adapted for parenteral administration each unit conveniently comprising 1 to 3 ccs. of the anaesthetic composition of our invention.

According to a feature of the invention we provide a local anaesthetic composition in dosage unit form adapted for parenteral administration in dental surgery each dosage unit comprising from 1 to 3 ccs. of a sterile injectable solution comprising a mixture of about 2.0% of a member of the group consisting of β-diethylamino butyric acid-anilide and non-toxic water- and alcohol-soluble salts thereof and about 0.4% of a member of the group consisting of β-piperidyl butyric acid (o,p-dichloro)-anilide and non-toxic water- and alcohol-soluble salts thereof.

In the case of minor surgery such a dosage unit can conveniently be of the order of 1 to 5 ccs. of the composition having the concentration above-stated.

In the case of major surgical intervention the composition according to the invention finds application as a ganglionic blocking agent which may be parenterally administered as and where necessary, provided that not more than 80 ccs, of a solution of the above-mentioned concentration is used.

The compositions according to the invention may be made up in any convenient liquid medium which is suitable for injection. Where the components of the com-

position are in the form of their water-soluble salts for example as hydrochlorides, then they are preferably made up in the form of an aqueous solution. The injectable compositions according to the invention may advantageously contain a vaso-constrictor such as adrenaline.

In order clearly to demonstrate the unexpectedly short latent period possessed, extensive experiments have been carried out to compare the latent period of the local anaesthetic compositions of our invention with that of β-diethylamino butyric acid-anilide and β-piperidyl butyric acid-(o,p-dichoro)-anilide.

In the experiments carried out the persons being studied were injected with a particular anasthetic in aqueous solution the solutions in all cases containing 15–20 γ of adrenalin-noradrenalin per cc of solution. The latent period for each anaesthetic solution was then determined, this period being the time elapsing between the moment of injection and the onset of full anaesthesia; the experiments were carried out in all cases on the gums of the patients.

The results of these experiments are set out in the accompanying drawing which shows the results in graphical form. Each curve on the graph represents the results obtained for a particular solution, the composition of the various solutions used being as follows:

Solution and Curve No.	Percentage of β-diethylamino butyric acid anilide hydrochloride	Percentage of β-piperidyl butyric acid (o, p-dichloro)-anilide hydrochloride
1	2.0	0.4
2	4.0	0.3
3	2.0	0.3
4	2.0	0.2
5	1.5	0.5
6	2.0	
7		0.5

The results obtained were the averages obtained on treating a number of people, the number of people treated with solution 1 being 1,100; with solution 2, 30; with solution 3, 50; with solution 4, 40; and with solution 6, 300. In the case of solution 5, 15 people were treated of whom 20% complained of tissue irritation, whilst in the case of solution 7 insufficient anaesthesia was produced in the 5 people who were treated.

It will be noted from the above results that the latent period for the compositions of our invention, that is those represented by curves 1–5 is considerably less than that of β-diethylamino butyric acid-anilide alone (curve 6) or of β-piperidyl butyric acid (o,p-dichloro)-anilide (curve 7) even though this is used at so high a concentration that a certain amount of tissue irritation results.

The latent period for "Xylocaine" lies between that of solutions 1–4 whilst that of "Procaine" has a similar latent period to that of solution 6.

Whilst only the use of the hydrochlorides of β-diethylamino butyric acid anilide and β-piperidyl butyric acid (o,p-dichloro)-anilide has been exemplified it will be appreciated by those skilled in the art that other salts can be used, for example, the citrates, tartrates, acetates or

sulphates of these compounds. It will also be appreciated that whilst only water has been exemplified as the injectable medium any other convenient compatible medium may be used. Thus, for example, the medium used may contain alcohol in which case alcohol-soluble salts of the compounds comprising the composition may conveniently be used.

It is thus seen that the new local anaesthetic compositions of our invention possess certain unexpected advantages. In particular they have a short latent period and give a long period of deep anaesthesia.

We claim:

1. A local anaesthetic composition comprising a sterile injectable solution of a mixture of a member of the group consisting of β-diethylamino butyric acid-anilide and non-toxic water- and alcohol-soluble salts thereof and a member of the group consisting of β-piperidyl butyric acid-(o,p-dichloro)-anilide and non-toxic water- and alcohol-soluble salts thereof.

2. A local anaesthetic composition comprising a sterile injectable solution of a mixture of from about 1.5 to 4.0% of a member of the group consisting of β-diethylamino butyric acid-anilide and non-toxic water- and alcohol-soluble salts thereof and of from about 0.2 to 0.5% of a member of the group consisting of β-piperidyl butyric acid-(o,p-dichloro)-anilide and non-toxic water- and alcohol-soluble salts thereof.

3. A local anaesthetic composition comprising a sterile injectable solution of a mixture of about 2.0% of the hydrochloride of β-diethylamino butyric acid anilide and about 0.4% of the hydrochloride of β-piperidyl butyric acid-(o,p-dichloro)-anilide.

4. A local anaesthetic composition in dosage unit form adapted for parenteral administration in dental surgery each dosage unit comprising from 1 to 3 ccs, of a sterile injectable solution comprising a mixture of about 2.0% of a member of the group consisting of β-diethylamino butyric acid-anilide and non-toxic water- and alcohol-soluble salts thereof and about 0.4% of a member of the group consisting of β-piperidyl butyric acid-(o,p-dichloro)-anilide and non-toxic water- and alcohol-soluble salts thereof.

5. A local anaesthetic composition in dosage unit form adapted for parenteral administration in dental surgery each dosage unit comprising from 1 to 3 ccs. of an aqueous solution comprising a mixture of about 2.0% of the hydrochloride of β-diethylamino butyric acid-anilide and about 0.4% of the hydrochloride of β-piperidyl butyric acid-(o,p-dichloro)-anilide.

6. A local anaesthetic composition in dosage unit form adapted for parenteral administration in minor surgery each dosage unit comprising from 1 to 5 ccs, of a sterile injectable solution comprising a mixture of about 2.0% of a member of the group consisting of β-diethylamino butyric acid-anilide and non-toxic water- and alcohol solution salts thereof and about 0.4% of a member of the group consisting of β-piperidyl butyric acid-(o,p-dichloro)-anilide and non-toxic water- and alcohol-soluble salts thereof.

No references cited.