Isotonic, Buffered and Preserved Intranasal Ephedrine Sulfate Solutions

*By G. A. Tozer and Louis Arrigoni**

The use of nose drops and nasal sprays in the alleviation of the symptoms of head colds and other ailments producing congestion of the nasal passages has become exceedingly widespread in recent times. In spite of the popularity of this form of medication, very few of the nasal preparations obtainable at the present time are prepared with sufficient scientific forethought to produce the most effective product possible from the materials at hand. Many of the nose drops and sprays, still in prevalent use, contain an oily base, a condition which in itself is undesirable, since it is common knowledge that in many cases some of the oil reaches the lung tissues and there causes decreased effectiveness of the ciliary beat, interstitial fibrosis, giant cell formation and, in extreme conditions, lipoid pneumonia (1, 2).

IMPROVEMENTS IN THE PREPARATION OF INTRANASAL SOLUTIONS

Some attempt has been made in recent years, both by commercial concerns and private workers, to improve and develop more efficacious and plausible nasal preparations. The first step taken has been the substitution of an aqueous base for the oily type. The next and, in most cases, final improvement considered by both the manufacturers and research workers was directed largely at the elimination of the irritant properties of these preparations. With this object in view, the solution was made isotonic with the blood stream, an adjustment which actually only partially removes the irritating effects produced by the common aqueous nasal preparations, since these are, in part, due to the fact that the reaction of the solution does not approximate that of the nasal secretions close enough to be within the range of comfort.

Recently Robinson and Goldner (3) prepared two isotonic solutions of ephedrine sulfate which they suggested for inclusion in the next edition of the National Formulary. These solutions have several obvious faults: first, the active ingredients are dissolved in physiological solution of sodium chloride in one case and isotonic solution of dextrose and sodium chloride in the other. This method produces solutions which are slightly hypertonic and does not introduce a standard procedure for the manufacture of isotonic solutions containing additional active ingredients without further disturbing the tonicity of the solution. Second, these solutions are not buffered, a condition which, together with the adjustment of the tonicity, entirely eliminates the irritant properties of the common nasal preparations when adjusted to the proper p_H level and which aids materially in the treatment of colds as will be discussed further in the following paragraphs. Another disadvantage of the aforementioned solutions is that they contain but 0.1 per cent ephedrine sulfate which is hardly enough to produce effective constriction of the nasal mucosa. In general practice 1 per cent of ephedrine sulfate is used, and rarely less than 0.5 per cent is employed.

REQUIREMENTS FOR AN IDEAL NASAL PREPARATION

The authors, in an attempt to manufacture a scientific and effective nasal preparation, first set up the specifications to which the ideal preparation should conform and then prepared three solutions containing one-half per cent, one per cent and two per cent ephedrine sulfate, respectively, which embraced the conditions set forth for the ideal solution. A preparation fulfilling these requirements should have the following properties:

1. The solution should contain an effective vasoconstrictor in aqueous solution.

2. The tonicity of the solution should approximate that of the blood stream very closely, thus producing more effective absorption of the active ingredients, as well as partially eliminating its irritant properties.

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3. The preparation should be buffered to the p_H level that is consistent with comfort and effective treatment of inflammation of the nasal mucosa.

4. The solution should be adequately preserved in order to prevent the growth of various microörganisms in the preparation which might in some cases cause the subsequent reinfection of the patient.

PREPARATION

Ephedrine sulfate was chosen as the vasoconstrictor because it is so well adapted for use in nasal preparations. This compound has marked vasoconstrictive properties, is stable in aqueous solution and is readily attainable.

The preservative used to prevent the growth of microörganisms in the solution upon exposure to infection was 0.04 per cent of a combination of 65 parts methyl *p*-hydroxy benzoate and 35 parts of propyl *p*-hydroxy benzoate. This compound produces no irritation and has proved to be effective (4). Butyl *p*-hydroxy benzoate (Butoben, Merck) in 0.01 per cent concentration can also be used as the preservative; however, this compound produces slight irritation in particularly sensitive individuals.

To obtain an isotonic solution, buffered at the proper p_H level, two separate isotonic 0.5 per cent ephedrine sulfate buffer solutions were prepared. One solution consists of an isotonic alkaline buffer solution, buffered with dibasic sodium phosphate and the other consists of an isotonic acid buffer solution, buffered with monobasic potassium phosphate. The phosphate salts were chosen as buffer system because they are one of the natural buffer systems of the blood and also because of their great buffering power.

These two buffered isotonic solutions were then titrated one against the other until the proper p_H was attained as measured with an accurate Beckman p_H meter. The p_H of the final product was adjusted to 6.7; this p_H level was obtained by mixing equal parts of the two buffer solutions.

The ideal isotonic nasal preparation, in so far as the removal of the irritant properties is concerned, is one whose p_H is the same as that of the nasal secretions (approximately 7.2). The above solution was adjusted to a p_H of 6.7 because experimental results proved that a solution which is within the p_H range of 6.0 to 7.6 is also non-irritating. In addition, a solution which is slightly acid in reaction according to work recently performed by Fabricant (5) is much more effective in the treatment of colds and sinus troubles. This can be explained by the fact that the nasal and sinus secretions of patients afflicted with colds tend to become more strongly alkaline than normal, and hence the most effective manner in which to relieve the inflammation and congestion is to acidify the nasal passages.

The tonicity of the solution was adjusted using the method suggested by Nicola (6) which sets forth a formula for the calculation of the amounts of salts to be added to a given solution to make it isotonic with the blood stream. The general formula employed is as follows:

$$\left(0.027026 \text{ (Isotonic factor of blood stream)} - \frac{\text{Percentage of active ingredient w/v in solution}}{\text{Mol. wt. of active ingredient in solution}} \times \text{Approximate dissociation} \times \text{constant of active ingredient}\right) \times \frac{\text{Mol. wt. of salt to be used to make solution isotonic}}{\text{Dissociation constant of solute to be used to make solution isotonic}} = \text{Number of Gm. of solute to add per 100 ml. of solution to make it isotonic}$$

ISOTONIC ACID BUFFER SOLUTION FOR 0.5 PER CENT EPHEDRINE SULFATE

$\frac{0.5}{428.33} \times 1.0 = 0.001167$ (tonicity factor for ephedrine sulfate)

$\frac{1.0}{136.14} \times 1.5 = 0.01102$ (tonicity factor for $K-H_2PO_4$)

$\frac{0.3}{74.55} \times 1.5 = 0.006$ (tonicity factor for K-Cl)

$0.027026 - (0.001167 + 0.01102 + 0.006) = 0.008839$

$\frac{0.008839 \times 180.09}{1.0} = 1.5918$ (Gm. dextrose to each 100 cc. of solution)

The average p_H of this solution was found to be 4.42.

ISOTONIC ALKALINE BUFFER SOLUTION FOR 0.5 PER CENT EPHEDRINE SULFATE

$\frac{0.5}{428.33} \times 1.0 = 0.001167$ (tonicity factor for ephedrine sulfate)

$\frac{1.0}{142.02} \times 2.0 = 0.01408$ (tonicity factor for Na_2HPO_4)

$\frac{0.3}{58.45} \times 1.86 = 0.009547$ (tonicity factor for NaCl)

$0.027026 - (0.001167 + 0.01408 + 0.009547) = 0.002232$

$\frac{0.002232 \times 180.09}{1.0} = 0.4020$ (Gm. dextrose to each 100 cc. of solution)

The average p_H of this solution was found to be 8.25.

From these calculations and the fact that the two buffer solutions were mixed in equal parts to attain the desired p_H, 6.7, the following formula for preserved, isotonic, buffered ephedrine nose drops was obtained and is suggested for inclusion in the next edition of the National Formulary.

0.5 PER CENT EPHEDRINE SULFATE

Ephedrine sulfate	0.5 Gm.
Potassium phosphate monobasic	0.5 Gm.
Sodium phosphate dibasic	0.5 Gm.
Potassium chloride	0.15 Gm.
Sodium chloride	0.15 Gm.
Dextrose, anhydrous	0.9969 Gm.
Preserved water, a sufficient quantity, to make	100.00 cc.

If a one per cent solution of ephedrine sulfate is desired, the amount of dextrose in the above formula is reduced to 0.7867 Gm., and for a two per cent solution the dextrose is reduced to 0.3663 Gm.

The quantity for each component of the above formula must be weighed accurately on an analytical balance and made up to the indicated volume in a volumetric flask in order to obtain the desired tonicity and p_H values. In addition the chemicals used must be of the highest purity. The chemicals employed by the authors were all Merck's Reagent brand.

SUMMARY

1. Several improvements in the manufacture of nasal solutions have been developed. These include the substitution of water for the oily base and the adjustment of the osmotic pressure to approximate that of the blood.

2. Specifications for an ideal vasoconstrictive nasal preparation are advanced.

3. The method of manufacture, the calculations involved and the formula for such an ideal nasal preparation are submitted.

4. It is recommended that the formulas submitted for one-half, one and two per cent ephedrine sulfate intranasal solutions be included in the next edition of the National Formulary.

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"Read not to contradict and confute; nor to believe and take for granted; nor to find talk and discourse; but to weigh and consider".—Sir Francis Bacon

The Fungistatic Value of Certain Ointments*,†

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Numerous bacteriological investigations have been made for the purpose of determining the fungicidal value of various substances in solution form. As a result of some of these investigations (1) the conclusion has been reached that there is a close relationship between the bactericidal and the fungicidal action of most substances but that there are exceptions to this rule. Copper salts, for example, are good bactericides but poor fungicides (2, 3). Thymol, oil of cinnamon and oil of clove are much more efficient as fungicides than as bactericides (4).

Other investigations have shown that a substance having a high bactericidal value in solution form may have little or no value when used in the form of an ointment or that its value may depend upon the base into which it has been incorporated (5, 6). Phenol, for example, although highly bactericidal in solution form, loses this value completely when incorporated into a base of petrolatum, but retains it when incorporated into a vanishing cream base.

The primary purpose of this investigation was to determine the fungistatic value of some of the official ointments and certain other non-official ointments prepared from substances which have known fungicidal value in solution form. The secondary purpose was to determine whether the base used in the preparation of the ointment had any effect on the fungistatic value.

The official ointments of iodine, ammoniated mercury, yellow mercuric oxide, phenol, sulfur and compound benzoic acid, and non-official ointments made from thymol, oil of cinnamon and chlorthymol were tested for fungistatic value.

EXPERIMENTAL

Method Used.—Since there is no standard in the literature for testing the fungistatic property of

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