maximum hypotensive response to occur within 2 minutes and at a dose one-tenth that previously employed. Continued infusion only served to maintain the hypotensive effect.

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Pharmaceutical Aspects of a *p*-Aminosalicylate Dialdehyde Starch Compound

By JAMES A. CAMPBELL

A compound resulting from the reaction between sodium *p*-aminosalicylate and dialdehyde starch was investigated. The bland taste and slow rate of dissolution of the compound appeared to offer certain advantages in the administration of NaPAS. The compound was subjected to certain *in vitro* and *in vivo* tests to demonstrate the availability of NaPAS.

THE EFFECT of *p*-aminosalicylic acid upon the tubercule bacillus has been known for a number of years. Bernheim (1) in 1941 observed that benzoic and salicylic acids increased the oxygen consumption of the bacillus. Lehmann (2) discovered that the increased oxygen consumption was accompanied by an inhibition in growth and multiplication, and subsequently found that *p*-aminosalicylic acid was the most effective of a group of related compounds.

A number of salts and other derivatives of the acid have been prepared and investigated (3, 4). Particularly well known are the sodium, potassium, and calcium salts. These salts have the advantage of being more soluble than the acid, and are reputed to be less irritating. Aqueous solutions of the sodium salt are more stable on heating than is a solution of the acid.

Foye and Duvall (5) made a comparative study of the *in vivo* antitubercular activity in mice of cupric and ferrous chelates of PAS. Both compounds were found to be active, but the cupric complex possessed a much higher activity than the ferrous complex.

Due to the large dosage level of PAS (2–4 Gm., with a daily average dose of 12–16 Gm.), the unpleasant taste, the irritant action, and other factors, the administration of PAS is sometimes beset with problems. Intolerance manifested by nausea and vomiting is common with average or large doses (6).

The objective in this effort was to prepare and study a derivative of PAS which might have certain advantages in overcoming the problems associated with the administration of PAS. Dialdehyde starch is known to react with amines and compounds containing the amino group, and the resulting compounds are sometimes noted for their unique properties (7). Dialdehyde starch was thus reacted with sodium PAS and the resulting compound was studied.

EXPERIMENTAL

Formation of the Compound.—A 27.4-Gm. quantity (0.141 mole) of dialdehyde starch (90.4% oxidized; 8.6% moisture) and 24.6 Gm. (0.116 mole) of sodium *p*-aminosalicylate dihydrate was slurried in 100 ml. of dry benzene in a 500-ml. three-necked flask equipped with a stirrer, Barret trap, and condenser. During the refluxing and stirring period of 5 hours, 5.0 ml. of water separated in the Barret trap. After cooling the mixture to room temperature, the pale yellow solid was collected, washed with dry benzene and dried to constant weight in a vacuum oven. Subsequent analysis including infrared spectra showed that a linkage between the compounds had taken place. Total nitrogen and free aldehyde content showed that NaPAS had added to half of the available aldehyde groups. Based upon the action of dialdehyde

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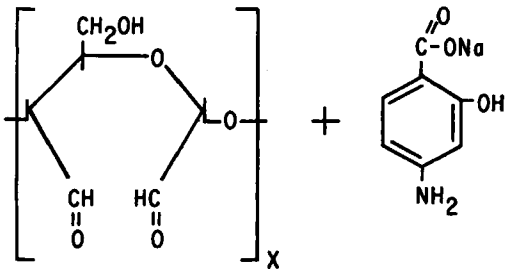
starch with other compounds similar to NaPAS (7), the linkage is believed to have occurred according to the equation shown in Fig. 1.

Description of the Compound.—The compound is a pale yellow to light tan powder, having a bland taste. One gram is soluble in 2.85 Gm. of water.



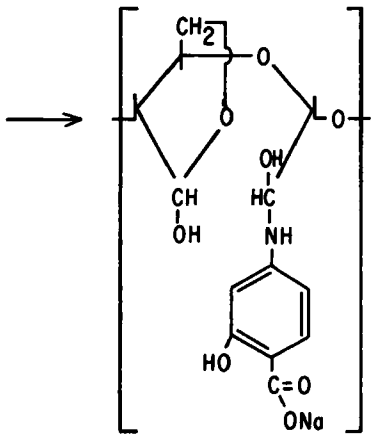


Fig. 1.—Reaction between dialdehyde starch and sodium *p*-aminosalicylate.

Prolonged-Release Experiments.—Accurately weighed, approximately 0.5 Gm., samples of the compound were sealed in small packets made of filter paper (Whatman #41). The packets were heat sealed after application of a heat sensitive adhesive. A packet was then placed in a 1-L. round-bottom flask containing 500 ml. of simulated gastric fluid, T.S. The fluid was stirred constantly with a mechanical stirrer which passed through the neck of the flask by means of a mercury seal. The flask was mounted in a water bath maintained at 37°. At the end of 1 hour and 20 minutes, half of the fluid was removed and replaced by an equal quantity of simulated intestinal fluid, T.S. At the end of 2 hours and 40 minutes, all the fluid was replaced by 500 ml. of fresh intestinal fluid, T.S. Small samples of the fluid were removed by means of a pipet at varying time intervals up to the end

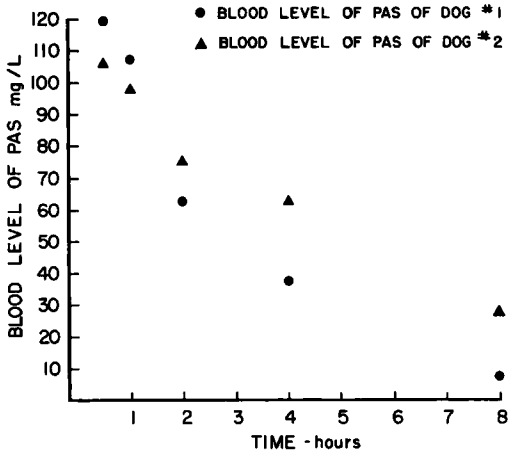


Fig. 3.—Blood levels of free PAS in dogs after oral administration of 100 mg./Kg. of free NaPAS.

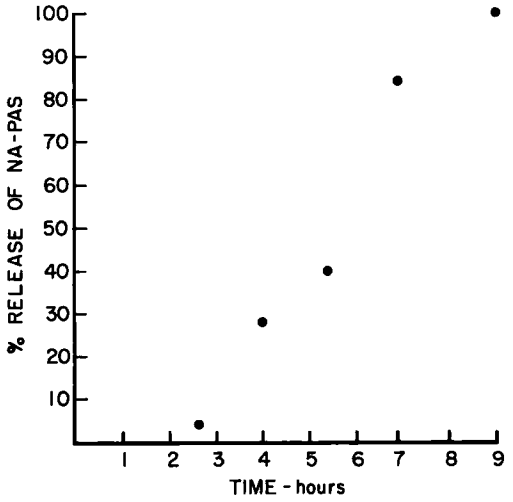


Fig. 2.—Rate of passage of NaPAS from a compound through a filter paper barrier when bathed in simulated gastrointestinal fluids.

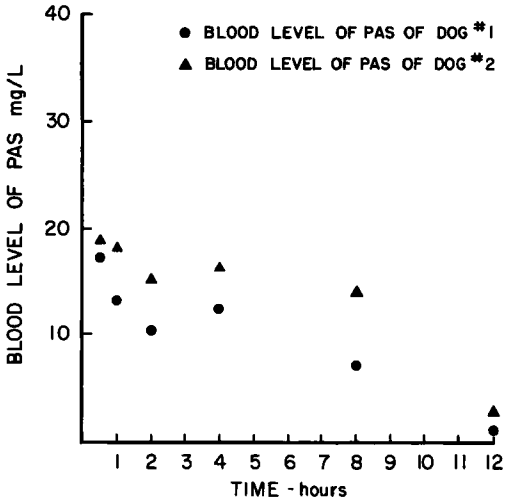


Fig. 4.—Blood levels of free PAS in dogs after oral administration of a quantity of a compound equivalent to 100 mg./Kg. of free NaPAS.

of a 9-hour period from the beginning of the experiment. Each time a sample was removed, an equal volume of fluid was placed back into the flask to maintain a constant volume.

The samples of fluid removed were used to assay for NaPAS content in the following manner. A 5-ml. quantity of the solution to be assayed was placed in a 250-ml. volumetric flask containing 12.5 ml. of concentrated pH 7 buffer (prepared by dissolving 34 Gm. of C.P. anhydrous KH_2PO_4 in 136 ml. of 1 *N* NaOH and diluting to 1000 ml. with distilled water). This was diluted to volume with distilled water and mixed well. A blank was prepared by diluting 5 ml. of concentrated pH 7 buffer to 100 ml. with distilled water. The absorbance of the sample solution was determined at 265 and 299 mμ in a 1.0-cm. quartz cell by means of a Beckman DU spectrophotometer using the blank solution (diluted pH 7 buffer) as the reference liquid.

Calculations

$X = A\text{-}265\ (136.1) = \%$ NaPAS based on absorbance at 265 mμ

$Y = A\text{-}299\ (208.8) = \%$ NaPAS based on absorbance at 299 mμ

$\frac{X + Y}{2} = \%\ C_7H_6NNaO_3$ on anhydrous basis

The rate of passage of NaPAS is shown in Fig. 2. When the free NaPAS was treated under identical conditions, all had passed out of the packet within 1 hour.

PAS Blood Level in Dogs.—Two dogs were administered NaPAS by intubation at a dosage level of 100 mg./Kg. Blood samples were taken at 0, 1/2, 1, 2, 4, and 8 hours. The free PAS content in whole blood was determined by a modified Bratton-Marshall method (8). The concentration of PAS found in the blood is given in Fig. 3. Approximately 10 days later, the compound was administered to the same dogs and with the dosage level being the same in regard to NaPAS content. Blood samples were taken on the same schedule as in the former experiment with additional samples being taken at 12 and 24 hours. The PAS blood levels found are shown in Fig. 4.

SUMMARY AND CONCLUSIONS

Sodium *p*-aminosalicylate was reacted with dialdehyde starch and the resulting compound was characterized. The compound was tested for the rate of passage of NaPAS through a filter paper barrier when bathed in gastrointestinal fluids ranging from all gastric fluid to all intestinal fluid. It was found that very little passed through in the presence of all gastric fluid, but the rate of passage began to increase as part of the fluid was changed to intestinal fluid. The rate of passage appeared to be proportional to the percentage of intestinal fluid. All was found to have passed through at the end of a 9-hour test period.

When the compound was administered to dogs, PAS was detected in the blood during a 12-hour period, but at a lower level than when the uncombined NaPAS was administered.

The bland taste of the compound provides a definite advantage in the problems associated with the administration of NaPAS; however, the lower rate of absorption in the bloodstream of the dog might possibly be considered a disadvantage. The question as to the efficacy of the compound in the *in vivo* control of tuberculosis is yet to be determined.

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