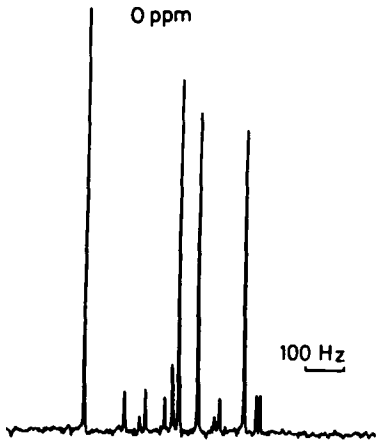

FIG. 1. C.m.r. spectrum of a commercial sample of TETA base in deuterium oxide (details as footnote[a] of Table 1, dioxane signal marked 0 ppm).

impurities of 5% and probably lower are thus capable of detection by this n.m.r. procedure.

The sample of TETA dihydrochloride used in this study was recrystallized several times from ethanol, and melted at 58°–60 °C by capillary and 123°–125 °C by hot-stage (Reichart) procedures. The salt is probably a dihydrate as judged by microanalytical data (Found: C, 28·12; H, 9·09; N, 22·02; Cl, 28·36. Calc. for $C_6H_{20}N_4Cl_2.2H_2O$; C, 28·24; H, 9·4; N, 21·96; Cl, 27·84%) and its infrared spectrum (paraffin mull, probable assignments in parentheses) which showed absorption bands at 3200 (NH), 3420 and 1640 (H_2O) and 2110 cm^{-1} ($^+NH_3$).

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Enhanced rectal absorption of insulin and heparin in rats in the presence of non-surfactant adjuvants

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There are a number of problems associated with current insulin therapy. These include the inconvenience of the injection dosage forms and the antigenicity of parenterally administered foreign polypeptides. Both polypeptide and mucopolysaccharide drug substances are normally either degraded or poorly absorbed after oral administration. The lack of alternative, non-parenteral dosage forms for drugs such as insulin and heparin has limited their use to clinical or semi-clinical situations.

To alleviate these problems considerable effort has been directed to the development of new insulin or heparin dosage forms suitable for oral or rectal absorption. Research involving the use of surfactants as adjuvants for rectal administration has been reported recently (Touitou et al 1978; Shichiri et al 1978; Ichikawa et al 1980; Bakth et al 1980). Some studies have indicated that the use of certain surfactants to enhance rectal delivery of insulin and other drugs results in rectal bleeding or other damage to the rectal mucosa (Nishioka & Kawamura 1978). In an earlier report (Nishihata et al 1980), the use of sodium salicylate to enhance the rectal absorption of theophylline and lidocaine was described. Salicylate appears to enhance rectal absorption by a different mechanism than surfactants and without the lasting changes in the membrane observed with some surfactants (Nishihata et al 1981). This communication reports the use of non-surfactant molecules including sodium salicylate, sodium 5-methoxysalicylate, sodium 3-methoxysalicylate and sodium homovanillate as adjuvants for the rectal absorption of insulin and heparin.

By means of a microenema technique, insulin (Lilly, Regular Iletin, 100 U) was administered to male, Sprague-Dawley rats, 275–300 g. The microenema was prepared with a 0·2 M phosphate buffer, pH 5·0. A volume of 0·3 ml was delivered rectally. Blood samples were taken from a jugular vein at designated time intervals. Plasma concentrations of glucose were then measured using the *o*-toluidine method (Nishihata et al 1978) and insulin concentrations were measured by an enzyme immuno assay (Nakagawa et al 1981) using a kit supplied by the Toyo Jozo Co., Ltd., Japan.

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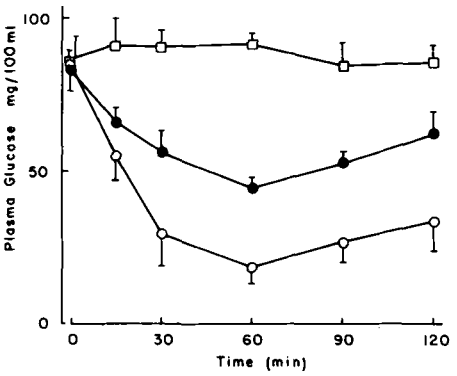

FIG. 1. Plasma glucose concentrations as a function of time after the administration of insulin. Initial concentrations were 1 IU kg^{-1} insulin and no adjuvants (-□-), 1 IU kg^{-1} insulin and 17 mg kg^{-1} 5-methoxysalicylate (-●-), 6 IU kg^{-1} insulin and 17 mg kg^{-1} 5-methoxysalicylate (-○-). The error bars represent standard deviations with n = 4 ($P < 0.001$ for all points, i.e. ○ vs □, ● vs □, ○ vs ● except for ○ vs ● at t = 15 min where $P < 0.025$).

Fig. 1 illustrates the rat's plasma glucose concentrations after a 0·3 ml microenema consisting of 0·3 IU of insulin and 5 mg of sodium 5-methoxysalicylate. Plasma glucose concentrations decreased rapidly after administration of the insulin microenema in the presence of 5-methoxysalicylate. The plasma glucose concentrations seemed to gradually recover 90 min after administration. On the administration of 0·3 ml microenema containing 1·8 IU of insulin and 5 mg of sodium 5-methoxy salicylate, plasma glucose concentrations were correspondingly lower. Again there was gradual recovery from 60 to 120 min. Corresponding increases in insulin concentrations were observed with a maximum occuring at about 20 min.

The effect of salicylate, homovanillate and 3-methoxysalicylate was studied using a microenema containing 1·8 IU of insulin and 5 mg of adjuvant. These compounds also promoted rectal absorption of insulin.

The effect of these adjuvants on the rectal absorption of heparin in 18 h fasted rats has also been studied in some preliminary experiments. Each rat received 1000 units of heparin (Na salt) dissolved in a 0·1 ml aqueous microenema for rectal administration, the microenema of the experimental group contained 20 mg sodium salicylate as an absorption adjuvant. The microenema of the control group contained no absorption adjuvant. There were two rats per group.

The control group displayed no increase in clotting time, with values ranging from 4 to 7 min across the 90-min sampling regimen. The experimental group showed a dramatic increase in clotting time (>120 min) after rectal administration of heparin with adjuvant. In the experimental group, clotting time corresponded to that observed after an i.v. administration of 60 to 120 units of sodium heparin.

In a previous study (Nishihata et al 1981) of the effects of salicylate on the rectal absorption of theophylline, it was observed that whereas sodium lauryl sulphate produced lasting changes on the absorption of theophylline from the rectum, pretreatment of the rectum with sodium salicylate did not. The effect of salicylate was eliminated by washing the rectum for 5 min with buffer after pretreatment with salicylate, while the effects of pretreatment with sodium lauryl sulphate was not eliminated by washing. Preliminary histological examination of rectal tissue treated chronically and acutely with the adjuvants used in this study were not distinguishable from the control group whereas those treated with sodium lauryl sulphate showed damage.

The results indicate that each of the four compounds work effectively as an adjuvant for rectal absorption of insulin and may be of some utility with heparin. A rectal dosage form of insulin which contains 5-methoxy salicylate appears especially promising, and may offer some advantages in human insulin therapy.

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