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Short Communication

Effect of suppository shape on the systemic availability of rectally administered insulin and sodium salicylate

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There is increasing evidence to suggest that the systematic availability of drugs, particularly those that show significant first-pass metabolism, when administered rectally is dependent upon the site of absorption within the rectum (de Leede et al., 1983). The closer to the anus the drug resides the greater the systemic availability. This observation is usually explained in terms of the venous blood drainage within the rectum; the lower rectal area blood drains directly into the general circulation whereas the upper and middle rectal area blood drains directly into the portal system and undergoes first-pass hepatic metabolism. The role of the lymphatic system in drug dissemination and avoidance of first-pass metabolism from the rectum appears to have received little attention. Liversidge et al. (1985) have found that increasing surface area for absorption by increasing suppository size causes a decrease in systemic availability of rectally administered suppositories containing insulin and sodium salicylate. This observation was attributed to suppository formulation differences and physiological differences within the rectum. In this communication we report the effect of suppository shape and consequently site of absorption on the systemic availability of insulin and sodium salicylate.

Glacial acetic acid (analytical grade), crystalline porcine insulin (Eli Lilly and Co.) and Witepsol S55 were used as purchased. Sodium salicylate 99% + (Aldrich) was ground and sieved to obtain particles in the size range 150–175 μm.

Insulin containing suppositories were prepared by dissolving crystalline insulin (1 mg) in 5% acetic acid solution (110 μl). The mixture was then added to molten Witepsol S55 (209 mg) and mixed thoroughly. Sodium salicylate (330 mg) was then added in aliquots and mixed well after each addition. When the additions were completed, the molten mass was cooled with stirring until just above the solidification point; it was then either poured into a 500 mg suppository mold with a diameter of 7 mm and length of 14.4 mm (type A suppository) or sucked into a 500 mg delivery device (Type B suppository). The delivery device consisted of a stainless steel tube (95 × 2.7 mm)

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with a plunger (to eject the suppository). Dye containing suppositories were prepared in a similar manner. However, the Oil Blue Dye (10 mg) was mixed with molten Witepsol S55 (209 mg) prior to mixing with the 5% acetic acid solution (110 μl). No insulin was incorporated into the dye containing suppositories. Just prior to rectal insertion of the delivery device, it was held momentarily in the hand, causing minimal surface melting which enabled the suppository to be released from the mold. Both types of suppository were stored for 24 h prior to administration. In a previous study concerning the effects of formulation on the release of insulin from suppositories (Liversidge et al., 1985) the above suppository formulation when administered to dogs was found to have the most pronounced effect on lowering of blood glucose concentration and was thus chosen for the present study. In vitro release experiments showed no significant differences in release characteristics from Type A and B suppositories using the non-membrane method of Grant et al. (1983) using Sorensens sodium citrate/hydrochloric acid buffer (pH 2.0). The dissolution medium was analyzed for insulin (Liversidge et al., 1985) and sodium salicylate (Nishihata et al., 1982). The in vitro release experiments were also used to check the content uniformity of suppositories. The total amount of insulin and sodium salicylate released from suppositories of either Type A or B was found to vary by less than 5%.

Ten normal healthy adult Beagle dogs, 10.6–14.5 kg, were fasted for 24 h with water ad libitum prior to dosing. Type A suppositories were inserted 4 cm from the outer rectal sphincter. Type B suppositories were inserted with the delivery device (to avoid breaking the suppository) so that the lowest portion of the tube was covered by the outer rectal sphincter. The tube was then withdrawn by sliding it over the plunger. When the tube had been completely removed from the rectum, the plunger was also removed. Thus, upon insertion, the suppository was maintained in the desired position. Blood samples were taken from the front leg cephalic vein at the following times: −15, 0, 15, 30, 45, 60, 90, 120, 180 and 240 min and analyzed for sodium salicylate content by HPLC (Nishihata et al., 1982), and glucose levels were determined by colorimetric analysis using orthotoludine (Sigma 635 Technical Bulletin). To assess rectal spreading in dogs, four Beagles were administered Type A suppositories containing dye and a further four Beagles administered Type B suppositories containing dye in the same manner as described above. The animals were sacrificed after one hour. The rectum and distal colon were removed and examined for dye.

For the rat studies, 5 mg of Oil Blue Dye were mixed with 100 mg of molten Witepsol S55. The mixture was then either poured into a 0.05 ml suppository mold of diameter 4.6 mm × length 3.0 mm (Type A′ suppositories) or sucked into a 0.05 ml delivery device (Type B′ suppositories). The delivery device consisted of a stainless steel tube (1.2 mm × 44.2 mm) with a plunger (to eject the suppositories). Both types of suppository were stored for 24 h prior to administration. Five Sprague–Dawley rats (250 g) were used for each suppository type. They were fasted for 24 h with water ad libitum prior to purging (two purging method of Grant and Liversidge, 1983). After purging, the suppositories were inserted so that the lower portion was covered by the outer rectal sphincter. The suppositories were retained by sealing the rats recta using cyanoacrylate ester glue. After 240 min the rats were sacrificed by humane asphyxiation and dissected to determine the length of ingression of the molten base along the rectum.

In an earlier paper (Liversidge et al., 1985), we have shown the anomalous behavior of decreased absorption upon increasing the surface area for absorption. The increased surface area was achieved by increasing the amount of excipient present, i.e. size of suppository. The anomalous behavior was attributed to formulation and physiological factors. These proposed factors have been discussed in the above mentioned paper, but will be briefly listed here as an aide-memoire to the discussion. Formulation factors were: (i) increased drainage time of particles in large suppositories (Schoonen et al., 1980); (ii) increased mean transit time of particles in large suppositories; and (iii) reduction in agglomeration of particles in large suppositories (Crommelin and De Blaey, 1980; Schoonen et al, 1980). The above lead to a reduction in the release of particles from large supposi-

tories. As Type A suppositories (short and thick) melt, they may spread in both lateral and longitudinal directions within the rectal compartment such that the bulk thickness may be similar to Type B suppositories (long and thin). However since there may be a greater degree of lateral spreading with Type A, they would be expected to spread less in a longitudinal direction. Thus, in the present work, factors (i) and (ii), namely transit time and drainage time of particles to the lipid/aqueous interface, would be similar for Type A and B suppositories, since molten bulk thickness would be similar. Agglomeration of particles (factor iii) would obviously be the same for both types of suppositories as they have identical quantities of constituents. Consequently, formulation factors arising from differences in shape would be expected to have a negligible effect on the bioavailability in this case. But physiological factors of differential absorption sites on drug dissemination routes ascending the rectum and corresponding differences in metabolism should show differences in bioavailability.

Figs. 1 and 2 show the plasma levels of sodium salicylate and glucose after rectal administration to dogs of Type A and B suppositories, respectively. Note the reduced levels of sodium salicylate and the reduced effect on glucose levels from Type B suppositories (Fig. 2). Wilcoxon's (1945) rank

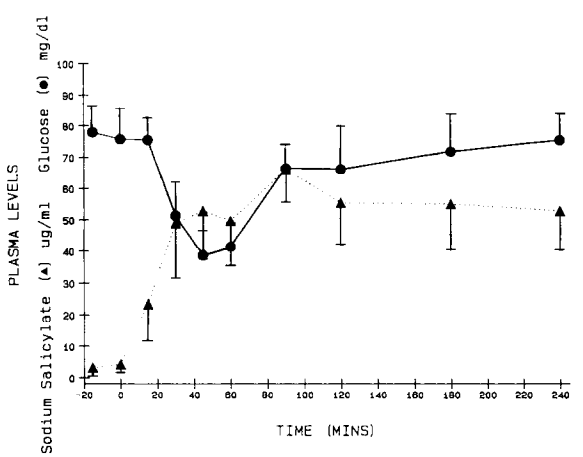

Fig. 1. Plasma levels of glucose and sodium salicylate after rectal administration of Type A suppositories in Beagle dogs (+S.D. for n = 10).

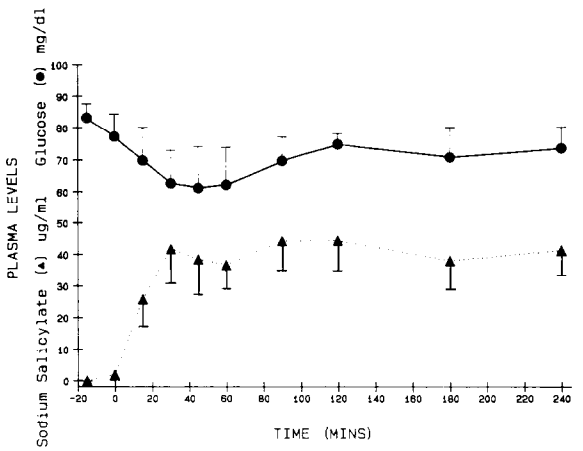

Fig. 2. Plasma levels of glucose and sodium salicylate after rectal administration of Type B suppositories in Beagle dogs (±S.D. for n = 10).

sum test for matched paired mean data points were performed at each time interval. For sodium salicylate, the difference in levels is significant at the 1% probability level, while for glucose the difference in levels is significant at just below the 5% probability level. These effects (Fig. 2) may be attributed to a decreased absorption and/or increased hepatic passage for sodium salicylate and insulin upon ascending the rectum.

It may be argued that Type A and Type B molten suppositories spread to the same extent in a longitudinal direction within the rectum. To test this hypothesis, both dog and rat studies were undertaken using the two types of suppositories.

TABLE 1

THE INGRESSION OF SUPPOSITORIES CONTAINING DYE ALONG THE RECTA OF DOGS AND RATS

	Distance of Ingression (cm)			
	Dogs		Rats	
	Type A	Type B	Type A′	Type B′
	3.6	11.0	3.5	4.5
	4.4	13.3	3.5	4.5
	4.9	13.9	3.5	4.5
	5.7	14.8	3.2	4.6
			3.2	4.8
Mean	4.7	13.3	3.4	4.6
S.D.±	0.9	1.6	0.2	0.1

Table 1 summarizes the results of the dog and rat studies, it can be clearly seen that Type A/A′ (short fat) suppositories are localized in the lower rectal area when compared to Type B/B′ (long thin) suppositories. Thus the decrease in systemic availability of Type B suppositories may be ascribed to the difference in characteristics at the absorptive sites that occur upon ascending the rectal compartment and/or differences in the extent of first-pass metabolism.

The above study suggests that suppository shape is an important parameter in localizing suppository spreading in the lower rectal compartment and obtaining higher plasma levels of sodium salicylate and insulin.

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