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THE EFFECT OF THE LAXATIVE OXYPHENISATIN ON THE INTESTINAL ABSORPTION OF GLUCOSE IN RAT AND MAN

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The mode of action of laxatives has received little attention in recent years and it is generally accepted that "irritant laxatives" produce peristalsis by stimulating nerve plexuses or by acting directly on the smooth muscle. Recently we showed that some laxatives are capable of inhibiting the intestinal absorption of glucose in anaesthetized rats and suggested that this is of significance in the normal action of these compounds (Hart & McColl, 1967). The present paper describes the investigation of the effects of low concentrations of oxyphenisatin on the intestinal absorption of glucose in rats and man. Oxyphenisatin (3,3-di-(*p*-hydroxyphenyl)oxindole) is a synthetic non-anthraquinone laxative which is the active principle in several proprietary preparations.

METHODS

Rats

Male albino rats weighing 300 g were anaesthetized with sodium pentobarbitone (50 mg/kg subcutaneously) and the lumen of the proximal 60 cm of the small intestine washed with warm 0.9% NaCl solution and emptied. Then 20 ml. of 0.9% NaCl solution containing 0.1% D-glucose and 4.5% ethanol was circulated through the lumen of the intestine for 20 min using the method described by Nissim (1965). At the end of the perfusion the rat was killed, the perfusate collected, its volume measured and the glucose concentration estimated by the glucose-oxidase method (Watson, 1962) using an Auto-Analyser. The difference between the initial and final amounts of glucose present in the perfusate was expressed as a percentage of the initial amount and called percentage absorption. The rate of disappearance of glucose from the lumen was also calculated and expressed in μg/cm/min.

The ethanol was necessary as a solvent for the oxyphenisatin and was present in both test and control experiments.

Man

The method was similar to that described previously (McColl & Nissim, 1965). During an abdominal operation a 30 cm length of upper jejunum was emptied by digital manipulation and isolated with two spring clamps. Fifty millilitres of 0.9% NaCl solution at 37° C was injected into the lumen of the loop of jejunum which was then emptied. This manoeuvre was repeated

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and a third spring clamp placed transversely across the intestine in such a position as to produce two isolated segments of approximately equal mucosal surface area. Into each segment was injected 50 ml. of 0.9% NaCl solution containing 0.1% D-glucose and 0.05% ethanol. One of the segments also contained oxyphenisatin in a concentration of 3×10^{-6}, 3×10^{-5} or 3×10^{-4}M. After an interval of 5 min the solutions were withdrawn, their volumes noted and their glucose content measured. The percentage absorption of glucose from the control and test segments was calculated as described above. The drug effect was expressed as the difference between the percentage absorption of glucose in the control and test segment in the same patient. This difference is the figure presented in Table 2. It was necessary to treat the results in this manner because of the large variation in the absorption of glucose from the control solution in different patients (McColl & Nissim, 1965).

The permission of each patient was obtained after it had been fully explained that the proposed procedure had no therapeutic value. The only patients approached were those undergoing uncomplicated abdominal surgery who were otherwise healthy and placid.

RESULTS

In the rat, significant inhibition of glucose absorption was obtained at each of the three doses of oxyphenisatin examined (Table 1). With the same technique it was found that phloridzin at a concentration of 2×10^{-4}M reduced the percentage absorption of glucose to 40.1 compared with the value of 24.2 obtained with oxyphenisatin 3×10^{-4}M. When the percentage inhibition of absorption was plotted against the logarithm of the dose, a straight line was obtained which, on analysis, had a regression coefficient of 27.3 ± 1.8 (Fig. 1). The two higher doses of oxyphenisatin produced significant inhibition of fluid absorption ($P<0.001$) and the values suggest that oxyphenisatin has a greater effect than phloridzin on fluid absorption.

TABLE 1

EFFECT OF OXYPHENISATIN AND PHLORIDZIN ON THE INTESTINAL ABSORPTION OF GLUCOSE AND FLUID IN THE RAT

* Excluding one animal in which fluid was secreted into lumen at a rate of 2·08 µl./cm/min.

Treatment	No. of experiments	% absorption of glucose (mean ± S.E.)	*P* value between glucose absorption in test and control	Rate of glucose absorption (µg/cm/min)	Rate of fluid absorption (µl./cm/min)
Controls	14	91·6±1·8		15·50	1·81±0·17
Oxyphenisatin 3×10^{-4}M	9	24·2±1·7	$\ll$0·001	4·04	0·28±0·30
3×10^{-5}M	8	46·3±2·4	$\ll$0·001	8·19	0·64±0·17
3×10^{-6}M	4	75·3±3·1	<0·001	12·24	1·53±0·21*
Phloridzin 2×10^{-4}M	6	40·1±2·3	<0·001	6·55	1·25±0·19

In man, significant inhibition of glucose absorption was obtained with concentrations of 3×10^{-4}M and 3×10^{-5}M oxyphenisatin (Table 2). McColl & Nissim (1965) found that with phloridzin in the test segment, the difference in percentage absorption compared with that in the control segment was 4.9% with a concentration of 2×10^{-5}M and 21.5% with a concentration of 2×10^{-4}M. The comparable figures with oxyphenisatin were 12.4% and 31.6% respectively and thus in both rats and man oxyphenisatin is somewhat more active than phloridzin.

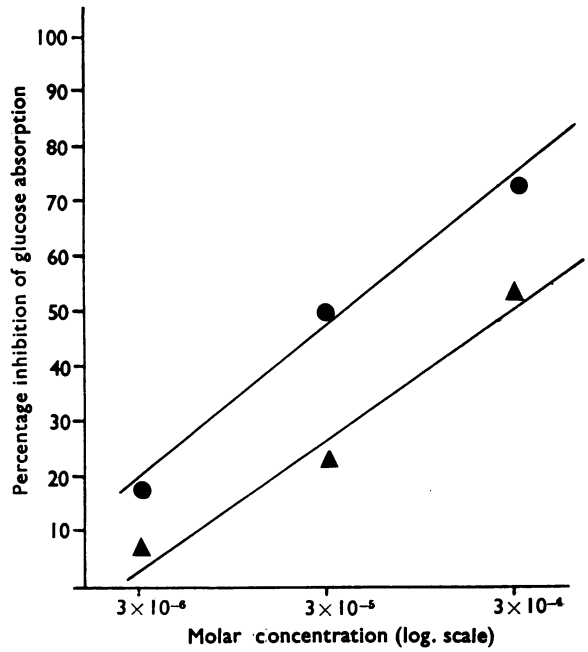

Fig. 1. Dose-response curve of the lumenal molar concentration of oxyphenisatin against the percentage inhibition of glucose absorption in rat (●) and man (▲).

A direct comparison of the results in Table 1 and Table 2 cannot be made but when the percentage inhibition is plotted against the logarithm of the dose (Fig. 1) it is apparent that oxyphenisatin is less active in man than in the rat. The regression coefficient calculated from the human experiments was 23.8 ± 3.8 which is not significantly different from that obtained in the rat ($P > 0.3$).

TABLE 2

EFFECT OF OXYPHENISATIN ON THE INTESTINAL ABSORPTION OF GLUCOSE IN MAN

Concentration of oxyphenisatin	Number of experiments	Difference between % absorption in control and test segments (mean ± S.E.)	*P* value
3×10^{-4}M	4	31·6±4·3	<0·01
3×10^{-5}M	4	12·4±3·0	0·025
3×10^{-6}M	2	3·5±2·7	<0·5

DISCUSSION

The high activity of oxyphenisatin found in the present work shows that this compound is comparable with the classical inhibitor phloridzin, other inhibitors of absorption such as uranyl nitrate (Newey, Sanford & Smyth, 1966), and the protein-binding inhibitors described by Nissim (1964). It is of interest that there is no significant difference between the slopes of the dose-response curves for oxyphenisatin in the rat and man. This suggests that the drug may be acting on a similar stage of the absorption mechanism in

both species. McColl & Nissim (1965) reported that the inhibition of glucose absorption produced by phloridzin and cetrimide in man was, in several details, similar to that occurring in rats.

One question raised by this study is whether the effects of oxyphenisatin on intestinal absorption are of any significance in the laxative action of the drug. The recommended oral dose of oxyphenisatin diacetate is 10 mg which, in the alkaline medium of the duodenum, will give approximately 8 mg of the active oxyphenisatin. The lumenal concentration in the duodenum and jejunum after such a dose has not been measured but a 1:1,000 dilution, giving a concentration of about 10^{-5}M, is not unreasonable. This concentration of oxyphenisatin inhibited glucose absorption by 20% (Fig. 1) and also reduced the absorption of fluid. It may be argued, therefore, that the inhibition of nutrient absorption could lead to an accumulation of fluid within the lumen of the intestine and that part of the laxative action of oxyphenisatin is the result of this bulk effect. Initial studies in the rat suggest that oxyphenisatin reduces the movement of sodium from the lumen of the intestine to the blood; this action may also be expected to lead to the retention of fluid in the lumen.

Although the present investigation has shown that oxyphenisatin is capable of reducing glucose absorption, much more detailed studies in man are necessary before the significance of this inhibition in the laxative action of oxyphenisatin can be determined. Of special interest would be the effects of the drug on nutrient absorption from the lower jejunum and ileum as well as its fate in the body after oral administration.

SUMMARY

1. A concentration of 3×10^{-6}M oxyphenisatin within the lumen of the small intestine of the anaesthetized rat produced significant inhibition of glucose and fluid absorption.

2. In man, significant inhibition of glucose absorption from the jejunum was obtained with a concentration of 3×10^{-5}M oxyphenisatin.

3. The slopes of the dose-response lines for oxyphenisatin were not significantly different in rat and man and in both species oxyphenisatin was more active than phloridzin.

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REFERENCES

HART, S. L. & McCOLL, I. (1967). The effect of purgative drugs on the intestinal absorption of glucose. *J. Pharm. Pharmac.*, **19**, 70–71.

McCOLL, I. & NISSIM, J. A. (1965). Mechanism of intestinal absorption in man. *Nature, Lond.*, **207**, 949–951.

NEWEY, H., SANFORD, P. A. & SMYTH, D. H. (1966). The effect of uranyl nitrate on intestinal transfer of hexoses. *J. Physiol., Lond.*, **186**, 493–502.

NISSIM, J. A. (1964). Mechanism of intestinal absorption: the concept of a spectrum of intracellular plasma. *Nature, Lond.*, **204**, 148–151.

NISSIM, J. A. (1965). The study and assay of substances affecting intestinal absorption in the mouse. *Br. J. Pharmac. Chemother.*, **24**, 205–213.

WATSON, D. (1962). Enzymic determination of glucose and easily hydrolyzable esters in blood. *Analyt. Biochem.*, **3**, 131–144.