The effect of polyethylene glycol by gavage on electrolyte and water excretion in the rat

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Summary
1. The effects of polyethylene glycol (PEG) 200 administered by gavage on electrolyte and water excretion were investigated in the rat.
2. PEG 200 led, in intact rats, to dose-related increased drinking and to diuresis.
3. In the first 2 h after PEG 200 administration, water consumption in intact rats exceeded urine output.
4. PEG 200 enhanced the excretion of both sodium and potassium, but the sodium excretion was proportionately greater, resulting in an elevation of the urinary sodium/potassium ratio.
5. Bilateral nephrectomy was not accompanied by increased drinking in PEG 200-treated rats, although raised serum osmolality was seen.
6. Thus, given by gavage, PEG 200 is not an inert vehicle for drug administration.

Key words: angiotensin II, diuresis, drug vehicle, polyethylene glycol, potassium, serum osmolality, sodium, thirst.

Abbreviations: PCV, packed cell volume; PEG, polyethylene glycol.

Introduction
One of the many uses of the polyethylene glycols (PEG) is as a vehicle for the administration of drugs [1]. In previous experiments we utilized a polyethylene glycol (PEG 200) for this purpose in experiments in rats. In the control rat group, that received by gavage only the vehicle PEG 200, evidence of increased sodium and water output was observed.

Subcutaneously injected high molecular weight PEG is known to cause changes in salt and water balance [2–4]. It is, however, not established whether orally administered PEG of lower molecular weight can give rise to similar effects. It has been reported that PEG 4000, given to rats in isosmotic dilution in the drinking water for a week or more, causes hypertrophy of the caecum, together with enhanced absorption of salt and water [5].

The present study was designed to examine the effect of ingested PEG on electrolyte and water excretion in the rat.

Materials and methods
Male Wistar rats weighing 200–250 g were used. In each experiment, except the water-deprivation studies (experiment 4), a 6 h drinking test was carried out [6], beginning 08.00 hours. During the test each animal was housed in a metabolic cage, in which it had been placed for a similar period the previous day. During the test no food was provided, but tap water was available as desired. Urine was collected in an Erlenmeyer flask placed directly under the funnel in the cage floor and cooled in a jacket of iced water. Over the period of each test drinking water consumption and urinary output were measured. At the end of the experiment, the animal was lightly anaesthetized with ether and blood for biochemical determinations was taken by puncture of the abdominal aorta.

In experiment 1, the animals were divided into three groups. The first group (10 rats) received 0.5 ml of tap water by gavage. The second group (10 rats) received 0.2 ml of PEG 200 (polyethylene
glycol 200, Catalogue no. 4801 h, Koch–Light Laboratories Ltd., Colnbrook, Bucks, U.K.) per 100 g body weight. The third group of 10 rats received 0.5 ml of PEG 200 per 100 g body weight. Blood samples from all three groups were taken for measurement of packed cell volume (PCV) and of serum total protein, sodium and potassium concentration. Urine samples were tested for sodium and potassium concentration and osmolality.

In experiment 2, there were two groups of 11 rats. The first group received 1 ml of tap water by gavage, and the second group received 1 ml of PEG 200 per 100 g body weight. The same determinations were made as in experiment 1, with the addition of blood urea.

In experiment 3, two groups of eight rats each were treated as in experiment 2. The water drunk and urine passed were measured in each hourly period for 6 h.

In experiment 4, the animals were lightly anaesthetized with ether, and bilateral nephrectomy was performed via a dorsal incision 16 h before the drinking test. Ten rats were given 1 ml of tap water by gavage and nine were given 1 ml of PEG 200 per 100 g body weight, as in experiment 2. PCV and osmolality determinations were made on the blood samples.

In experiment 5, there were two groups of nine rats which received the same treatment as in experiment 2, but drinking water was not available after dosing. PCV was determined and urinary output was measured.

Results were evaluated statistically, comparing experimental animals with controls by Student's two-tailed t-test.

Results

Table 1 gives the results of experiment 1. Both doses of PEG 200 significantly increased sodium and potassium excretion and urinary osmolality, while the higher dose additionally increased water consumption and urinary output. Natriuresis was more marked than kaliuresis, as indicated by the rise in the urinary sodium/potassium ratio.

The results of experiment 2 are presented in Table 2. With the higher dose of PEG 200, the differences in the individual measurements noted in experiment 1 were even stronger and the increase in serum total protein and PCV also became significant. The blood urea was not different in the treated group as compared with the control animals.

The results of experiment 3 are shown in Fig. 1. Drinking was greatest in the first 2 h after the administration of PEG 200, and then declined. Urine volume lagged behind the consumption of

<table>
<thead>
<tr>
<th>Table 1. Results of experiment 1.</th>
<th>Values are means (SD). Statistical significance: <em>P</em> &lt; 0.05; <strong>P</strong> &lt; 0.01; <em><strong>P</strong></em> &lt; 0.001.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group</td>
<td>Water drunk volume (ml) / 100 g</td>
</tr>
<tr>
<td>Control (n = 10)</td>
<td>(0.29)</td>
</tr>
<tr>
<td>0.2 ml of PEG 200/100 g</td>
<td>(0.35)</td>
</tr>
<tr>
<td>0.5 ml of PEG 200/100 g</td>
<td>(0.31)</td>
</tr>
</tbody>
</table>
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FIG. 1. Hourly measurements of water consumption and urine volume in control (○) and PEG 200-treated (●) rats in experiment 3. Values are means ± SD.

water, rising gradually to a maximum in the third hour after PEG 200, and then subsiding.

The results of experiment 4 (Table 3) show that after bilateral nephrectomy the drinking water consumption in the PEG 200-treated group did not differ from that in the controls. However, the PCV and the serum osmolality were significantly higher in the treated animals.

In experiment 5, in which the drinking water was withdrawn (Table 4), the PEG 200-treated group showed significant increases in both the PCV and urinary output as compared with the controls.

Discussion

The present studies have consistently shown that, in the rat, intragastric PEG 200 is not inert, increasing, in a dose-related manner, water and electrolyte excretion and raising PCV and serum osmolality. Our series of experiments has indicated that there are probably several components involved in these reactions.

Experiment 5 (Table 4) demonstrated a renal effect independent of drinking, since the experimental rats had a marked rise in urine volume (and in PCV) although drinking water was withheld.

However, when intact rats were also permitted to drink (experiment 2, Table 2), PEG 200 led to increased consumption of water. As is shown by experiment 3 (Fig. 1), in the first 2 h after PEG administration, water ingestion was in excess of urine volume. In this connection it is of interest that
the urine output in experiment 2, where the rats had access to water, exceeded that in experiment 5, where it was withheld. However, interpretation of this point must be cautious, as these two experiments were performed on different occasions with different batches of animals and were in that respect possibly not identical.

It seems that PEG 200 by gavage, in addition to its renal effects, causes a loss of fluid from the intravascular compartment, possibly into the gut. The consequent rise in serum osmolality would be expected to stimulate drinking. However, a renal factor is also necessary for this response, because angiotensin II, rats given PEG 200 did not drink more than controls. Angiotensin II is a well-known dipsogen in the rat, and its renal effects, causes a loss of fluid from the intravascular compartment, possibly into the gut. The consequent rise in serum osmolality would be expected to stimulate drinking. However, interpretation of this point must be cautious, as these two experiments were performed on different occasions with different batches of animals and were in that respect possibly not identical.

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Our present findings clearly indicate that the polyethylene glycol PEG 200 administered to rats by gavage can affect water and electrolyte status. These aspects require to be recognized when PEG 200 is used as a vehicle for drugs.

References

### Table 3. Results of experiment 4 (bilateral nephrectomy)

Values are means (sd). Statistical significance: ****P < 0.001.

<table>
<thead>
<tr>
<th>Group</th>
<th>Water drunk (ml/100 g)</th>
<th>Serum osmolality (mosmol/l)</th>
<th>PCV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (n = 10)</td>
<td>4.58 (0.57)</td>
<td>337.93 (5.11)</td>
<td>45.20 (0.47)</td>
</tr>
<tr>
<td>PEG 200-treated (n = 10)</td>
<td>3.59 (0.40)</td>
<td>371.58**** (5.11)</td>
<td>48.67**** (0.53)</td>
</tr>
</tbody>
</table>

### Table 4. Results of experiment 5 (water deprivation)

Values are means (sd). Statistical significance: ****P < 0.0001.

<table>
<thead>
<tr>
<th>Group</th>
<th>Urine volume (ml/100 g)</th>
<th>PCV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (n = 10)</td>
<td>2.69 (0.31)</td>
<td>45.56 (0.60)</td>
</tr>
<tr>
<td>PEG 200-treated (n = 9)</td>
<td>6.76**** (0.18)</td>
<td>50.22**** (0.46)</td>
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