J. Pharm. Pharmacol., 1965, **17**, 434–439 Received January 14, 1965

Observations on the pharmacology of halquinol

C. L. KAUL* and the late J. J. LEWIS

Halquinol non-specifically depresses tone and motility in isolated intestinal smooth muscle and reduces intestinal motility in intact animals. These properties may be involved in its therapeutic effects.

HALQUINOL (chlorhydroxyquinoline) is prepared by controlled chlorination of 8-hydroxyquinoline. It is a mixture of 5-monochlor-8-hydroxyquinoline (34·27%), 5,7-dichlor-8-hydroxyquinoline (64·22%) and 7-monochlor-8-hydroxyquinoline (2·24%). It is effective *in vitro* against a wide range of micro-organisms including bacteria, yeasts and fungi (Heseltine & Freeman, 1959). Studies in rats indicated only slight absorption after oral administration, but later investigation in man and other species showed that substantial portions of oral doses of the drug could be found in the urines (Heseltine & Freeman, 1959; Heseltine & Campbell, 1960; Freeman & Heseltine, 1963). This investigation was undertaken to obtain more information on the actions of halquinol on smooth muscle-containing tissues and organs.

Experimental

Solutions for use with isolated tissue preparations were prepared by dissolving the drug or any one of its constituents in the minimum quantity of 2N sodium hydroxide solution, and adjusting to pH 11 with 2N hydrochloric acid. Lower pH values caused precipitation. Matching control solutions were prepared in an identical fashion. Since the amount of drug solution added to the bath was small compared with the bath volume there was no precipitation and little effect on pH.

The effects of halquinol, 5-monochlor-8-hydroxyquinoline, 5,7-dichlor-8-hydroxyquinoline and 7-monochlor-8-hydroxyquinoline have been assessed using the isolated frog rectus abdominis muscle, the isolated guinea-pig ileum, the rat diaphragm-phrenic nerve and the gastrocnemius muscle-sciatic nerve preparation, blood pressure and nictitating membrane of the cat.

To investigate gastrointestinal actions, the effect of halquinol upon the peristaltic reflex, using the Trendelenburg preparation, was examined. Certain experiments were made only upon intact animals. These were:

(1) Groups of ten male albino mice, 18–25 g, were fasted for 36 hr. The drug was then given by intraperitoneal injection and 1 hr later the animals were allowed to feed from a "charcoal" diet (see below) for ½ or 3 hr. After a further 3 hr, they were killed and the intestines removed and examined to find the distance travelled by the charcoal diet. Since in the controls, the distance travelled by the charcoal varied from animal to animal, the colour of the appendix was taken as the criterion (Janssen &

From the Experimental Pharmacology Division, Institute of Physiology, University of Glasgow, Glasgow, W.2.

* Present address: C.I.B.A. Research Centre, Goregaon East, Bombay 62, India.

Jageneau, 1957). After giving the drug, blackening of the appendix with charcoal was taken to indicate no slowing of the passage of the gut contents.

(2) Groups of 20 mice [as (1) above] and Wistar strain male rats, weighing 200–250 g, were fasted for 36 hr. Ten animals were given 5 g of ordinary diet, and 10 given 5 g of halquinol diet (see below). Each animal was kept in a separate cage during the experiment and allowed free access to water. After each hour, the faecal pellets from each cage were collected and counted. Separate experiments were made in which groups of 5 rats or mice were kept similarly but without food to see if fasting influenced the output of faecal pellets. A similar series of experiments was made in which the drug in suspension in 0·25% tragacanth mucilage was given by stomach tube at either 50 or 100 mg/100 g body weight. In these experiments, the animals were fasted for only 18 hr. The number of faecal pellets was used as a qualitative index of gastrointestinal motility but as the pellets varied in size and weight, in one experiment the weights as well as the numbers were recorded.

Because of the great variations in numbers of faecal pellets from animal to animal, animals were selected which gave fairly similar numbers of pellets over hourly intervals, but, even in selected animals, the numbers were not reproducible from day to day.

(3) Inhibition of intestinal motility was measured using the method of Bryant, Felton & Krantz (1957). Male Wistar rats weighing 150–250 g were fasted for 36 hr. A suspension of halquinol in 1% sodium carboxymethylcellulose was given by stomach tube (100 mg/100 g weight). 30 min later an aqueous suspension of 10% charcoal in 5% gum acacia mucilage was given. The control animals received an equal volume of 1% sodium carboxymethylcellulose suspension. After 15 min the animals were killed, the intestines removed from the pylorus to the appendix and the most advanced point of travel of the charcoal measured. The distance was calculated as a percentage of the total pylorus-appendix distance (Table 3).

In all instances a statistical analysis was made using Students' "*t*" test. Because of the great variations in the output of faecal pellets per rat, it was decided to take as a measure the increase in the numbers of pellets from the second to the seventh hr after drug-administration.

Charcoal diet. Diet No. 41 was powdered; 10% by weight of powdered animal charcoal and 5% by weight of powdered gum acacia was added and the whole made into a paste with water. The mass was formed into suitably shaped pieces and dried in an oven.

Halquinol diet. This was made similarly but instead of charcoal and acacia, 10% by weight of drug was incorporated. No heat was used during drying.

Results

There was no direct effect on the frog rectus (50 μg to 1 mg; 10 ml bath). No graded inhibition of acetylcholine-induced contractures was observed but 1 mg or more irreversibly depressed the ability to respond to acetylcholine. No effects were seen on neuromuscular transmission in the rat

diaphragm (0·5 to 8·0 mg; 80 ml bath) or the cat gastrocnemius-sciatic preparation (1 to 3 mg/kg).

Variable effects were seen on the guinea-pig ileum. There was no direct effect (10 to 40 μg; 10 ml bath); the responses to acetylcholine and histamine were slightly depressed while antagonism was neither graded nor specific and incompletely reversible even after repeated washings.

All the compounds tested (0·5 to 2·0 mg; 62 ml bath) produced a marked inhibition of peristalsis (Fig. 1). The effects were similar to those

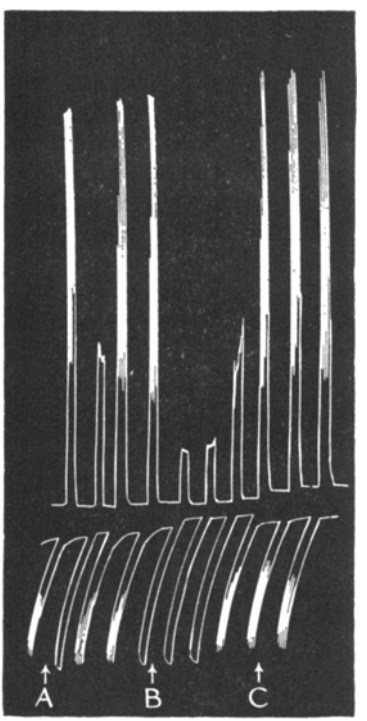

FIG. 1. Effect of halquinol upon contractions of the longitudinal muscle (upper trace) and peristalsis (lower trace) in the guinea-pig ileum. At A, 1 mg hexamethonium. At B, 1 mg halquinol. At C, 1 ml control solution. 5-Monochlor-8-hydroxyquinoline, 5,7-dichlor-8-hydroxyquinoline and 7-monochlor-8-hydroxyquinoline had similar effects to halquinol on this tissue.

of hexamethonium (Fig. 1). No reduction in the height of contraction of the nictitating membrane of the anaesthetised cat was caused by 1 to 5 mg/kg. 1 to 5 mg/kg caused a marked but short-lived fall in blood pressure in the anaesthetised cat which was not prevented by atropine or mepyramine.

No inhibitory effect on the passage of the charcoal diet in mice was shown when halquinol was given by intraperitoneal injection. When halquinol diet was given, there was no significant difference from control in the numbers of faecal pellets in rats (Table 1); when groups of selected

TABLE 1. HOURLY OUTPUT OF FAECAL PELLETS IN MICE AND RATS, FED A DIET CONTAINING 10% HALQUINOL. ALL VALUES ARE MEANS ± (S.E.) OF DETERMINATIONS ON 10 ANIMALS

	Time (hr) after feeding						
	Mice						
	1	2	3	4	5	6	7
Control	1·00 ± 0·28	3·00 ± 0·64	6·00 ± 1·02	7·40 ± 0·85	12·10 ± 1·42	13·00 ± 1·43	16·10 ± 2·34
Drug	0·90 ± 0·41	2·80 ± 0·42	4·30 ± 0·50	4·60 ± 0·58 *	4·90 ± 0·75 **	5·20 ± 0·73 **	5·30 ± 0·73 **
	Rats						
Control	2·60 ± 0·88	3·90 ± 0·83	6·20 ± 1·25	7·00 ± 1·29	8·00 ± 1·31	10·10 ± 1·53	11·0 ± 2·22
Drug	1·60 ± 0·65	2·30 ± 0·80	4·20 ± 1·29	5·40 ± 1·07	6·00 ± 0·85	7·10 ± 1·02	7·20 ± 1·07

Significance of difference from control * 0·05 > P > 0·01 ** P > 0·001.

TABLE 2. MEAN DECREASE (± S.E.) IN OUTPUT OF FAECAL PELLETS FROM 2ND TO 7TH HR AFTER HALQUINOL ADMINISTRATION COMPARED TO CONTROLS

Series	Species	Drug treatment	Mean ± s.e.
1	Rats randomly selected	Control Suspension (50 mg/100 g)	7·40 ± 1·37 5·20 ± 1·00
2	Rats randomly selected	Control Suspension (100 mg/100 g)	11·30 ± 1·17 6·88 ± 1·31*
3	Rats randomly selected	Control 10% diet	7·10 ± 2·07 4·90 ± 0·86
4	Mice randomly selected	Control 10% diet	21·77 ± 3·61 4·88 ± 0·88**
5	Rats selected	Control 10% diet	7·80 ± 1·68 2·80 ± 0·53*
6	Mice selected	Control 10% diet	12·55 ± 2·01 1·80 ± 0·81**

Significance of difference from control, * 0·05 > P > 0·01; ** P > 0·001.

rats were used and the average increase in numbers of pellets from the second to the seventh hr taken, there was a significant reduction in the number of pellets in the drug-treated animals (Table 2). In mice, however, a significant decrease in the number of pellets was observed in both selected and non-selected animals (Tables 1 and 2). The control animals consumed all the diet given, but the animals on the halquinol diet all left some. The lower numbers of pellets expelled by the latter may therefore be due to the smaller intake of food. In control experiments, mice and rats fasted for the same period of time expelled a higher number of pellets than the halquinol-treated animals (Figs 2 and 3). The results thus indicate some slowing of the movement of the gut contents by the drug.

When a suspension of the drug was given by mouth to rats, no significant difference was noted between drug and control when the numbers of pellets were compared at hourly intervals. When the increase from the second to the seventh hr was compared, 100 mg/100 g body weight caused a significant decrease (Table 2).

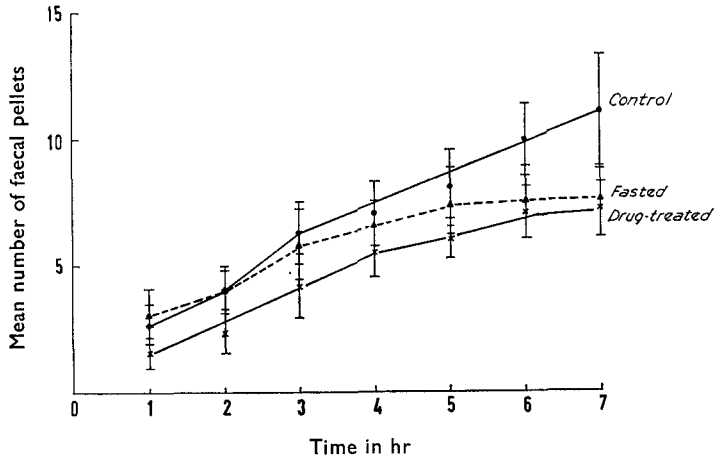

FIG. 2. Effect of 10% halquinol diet on hourly output of faecal pellets in the rat.

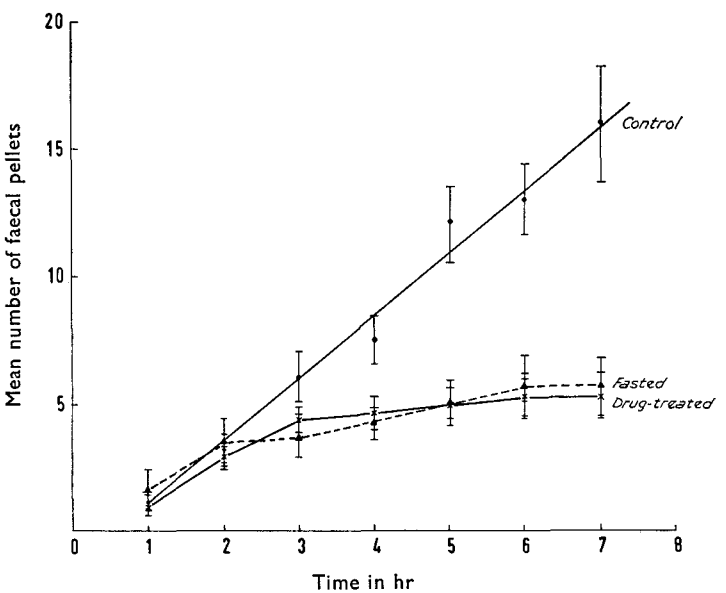

FIG. 3. Effect of 10% halquinol diet on hourly output of faecal pellets in mice.

When the faecal pellets were weighed the total mass expelled from drug-treated animals was not significantly different from the control.

The effect of halquinol on the movement of the charcoal meal in rats is shown in Table 3, from which it can be seen that there was a highly significant inhibition in the drug-treated animals. There was however no correlation between the actual length of intestinal segment and the distance traversed by the charcoal.

TABLE [2]. THE EFFECT, IN RATS, OF ORAL HALQUINOL (100 MG/100 g) ON THE PROGRESS OF A STANDARD CHARCOAL MEAL THROUGH THE INTESTINES
All values are means ± (s.e.)

No. of animals	Length of intestine (a) (cm)	Distance traversed (b)	(a)—(b)	Inhibition %
20 (control)	101·3 ± 1·46	51 ± 2·00	50·3 ± 2·14	49·58 ± 1·88
22 (CHQ)	104·09 ± 1·49	36·68 ± 4·68	67·4 ± 4·96	64·55 ± 4·56*

Significance of difference from control * $P > 0.001$.

Discussion

The results on isolated intestinal muscle indicate a non-specific depression of tone and movement and there is some evidence of ganglion blockade which requires further analysis in view of the failure to reduce the contractions of the nictitating membrane in the cat. The prolonged effects on the guinea-pig ileum which are more pronounced after washing, indicate that the drug is firmly fixed to the tissue. This is of interest because Freeman & Heseltine (1963) have already shown that the gastro-intestinal tract of the guinea-pig is highly susceptible to irritation by high concentrations of halquinol. It appears that the drug has no atropine-like activity, so that its effects upon intestinal motility are probably due to a direct action on the smooth muscle.

Acknowledgements. We thank Mr. W. W. Heseltine, Mr. Ridgeway and Mr. Bisknell for supplies of the drug and 5-monochlor-8-hydroxyquinoline and 5,7-dichlor-8-hydroxyquinoline, for preparing the solutions and for help in other ways; Doctor R. A. Robb of the Department of Mathematics, for much helpful discussion of the results; Mr. R. Callender for drawing the figures and Miss G. Marren and Mr. P. Leitch, for technical assistance.

References

Bryant, H. H., Felton, L. C. & Krantz, J. C. Jr. (1957). *J. Pharmacol.*, **121**, 210–224.
Freeman, F. M. & Heseltine, W. W. (1963). *Nature, Lond.*, **199**, 703–704.
Heseltine, W. W. & Freeman, F. M. (1959). *J. Pharm. Pharmacol.*, **11**, 169–174.
Heseltine, W. W. & Campbell, P. J. (1960). *J. trop. Med. Hyg*, **63**, 163–165.
Janssen, P. A. J. & Jageneau, A. H. (1957). *J. Pharm. Pharmaco.l.*, **9**, 381–400.