J. Pharm. Pharmac., 1968, **20**, 867–872 Received March 18, 1968

Observations on the efficacy of oral hyoscine *N*-butyl bromide

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Hyoscine *N*-butyl bromide (Buscopan) antagonized the spasmogenic action of acetylcholine on guinea-pig isolated ileum, having a pA_2 of 7·8. The drug also had intestinal antispasmodic activity in the anaesthetized cat after either parenteral or enteral administration. With the enterally administered drug larger doses were required, but the effects were longer lasting. Enterally administered in conscious dogs the drug sometimes produced a small increase in heart rate.

HYOSCINE *N*-butyl bromide is an anticholinergic drug used for relieving spasm of the gastrointestinal. biliary and urinary tracts. Its efficacy after injection has been thoroughly established in animal experiments (Wick, 1951), in clinical investigations (Heinkel, 1951; Laurence, 1966) and in experiments with normal human subjects (Brownlee, Wilson & Birmingham, 1965; Herxheimer & Haefeli, 1966). However, some doubts have been raised as to the efficacy of the orally administered drug in experiments with human subjects (Herxheimer & Haefeli, 1966), although there are numerous clinical reports that the drug is effective orally in the control of various gastrointestinal disorders. There has been little published information from animal experiments on the effects of the drug administered via the gastrointestinal tract, however, Wick (1967) produced evidence that after intraduodenal administration of the drug to rats the LD50 was less than that after subcutaneous injection.

Our observations provide evidence for the absorption of hyoscine *N*-butyl bromide from the gastrointestinal tract in amounts sufficient to exert pharmacological effects.

Experimental

GUINEA-PIG ISOLATED INTESTINE

Segments of guinea-pig ileum were suspended in a 25 ml bath containing Tyrode solution maintained at 34° and bubbled with 5% carbon dioxide in oxygen. Contractions were recorded by means of an isotonic lever writing on a smoked drum. pA_2 values were estimated in a manner similar to that described by Schild (1947).

ANAESTHETIZED CATS

Cats weighing 1·5–3·0 kg were anaesthetized with intraperitoneal injections of chloralose (80 mg/kg) and pentobarbitone sodium (6 mg/kg). The trachea was intubated and the animals were ventilated from a respiration pump. Blood pressure was measured from a femoral artery by means of a Statham pressure transducer (P23AA) and recorded on a Beckman Offner Dynograph. The electrocardiogram was recorded from

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leads corresponding to human limb lead II. The femoral vein was cannulated for intravenous administration of drugs. A midline incision in the abdomen was made and the duodenum cannulated for intraduodenal administration of drugs. Movements of a segment of ileum were measured by anchoring one end of the segment to a fixed rod and attaching the other to a strain gauge transducer recording on a Beckman Offner Dynograph. Resting tension was about 5 g. The skin was closed around the transducer, care being taken not to interfere with the movements of the ileum.

The right vagus nerve was cleared, separated from the vago-sympathetic trunk and tied centrally. The peripheral end was stimulated with 1 msec, 8 to 10 V pulses at a frequency of 20/sec for 30 sec.

Contractions of the nictitating membrane were elicited by stimulation of the left preganglionic cervical sympathetic nerve with 1 msec, 3 V pulses at a frequency of 10/sec for 10 sec at 2 min intervals, and recorded by means of a strain gauge transducer.

CONSCIOUS DOGS

The electrocardiogram was recorded from leads corresponding to human limb lead II. Drugs were administered by mouth or by intravenous injection into one of the leg veins.

DRUGS

The drugs used were: acetylcholine hydrochloride, atropine sulphate, histamine acid phosphate, hyoscine *N*-butyl bromide (Buscopan). All doses of drugs are quoted in terms of these salts.

Results

GUINEA-PIG ISOLATED INTESTINE

The pA_2 values for hyoscine *N*-butyl bromide against acetylcholine and histamine were 7·8 and 4·6 respectively, from which it can be seen that the drug is a relatively specific acetylcholine antagonist. It was less potent than atropine, for which the corresponding pA_2 values were 8·5 and 5·2.

ANAESTHETIZED CATS

Intravenous injections of 0·3 to 3 mg/kg of hyoscine *N*-butyl bromide in 8 cats produced an immediate fall in blood pressure, decrease in gut motility and reduction in the size of contractions of the nictitating membrane elicited by preganglionic sympathetic nerve stimulation. The heart rate did not change significantly during the depressor response. The cardiac responses to vagal nerve stimulation, as measured from the ECG or blood pressure records, were abolished and the depressor responses to injections of acetylcholine were diminished by doses of hyoscine *N*-butyl bromide greater than 1 mg/kg. Intestinal responses to vagal stimulation were diminished and intestinal responses to acetylcholine

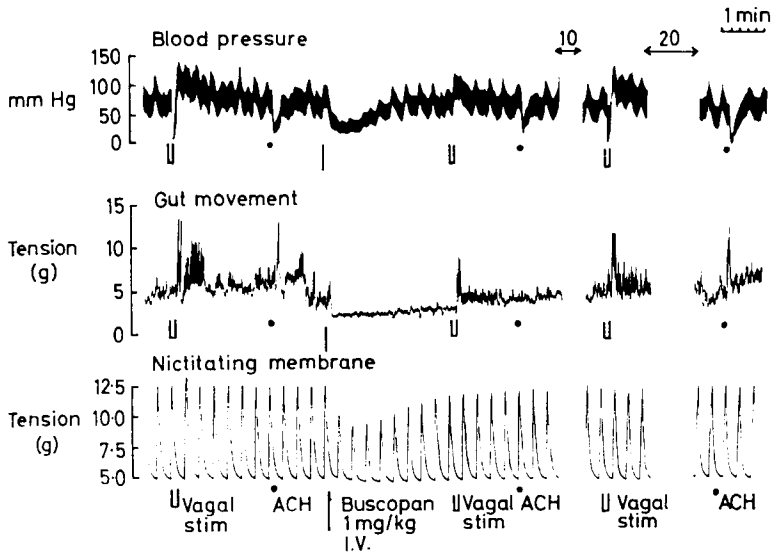

FIG. 1. Effects of intravenous hyoscine *N*-butylbromide in an anaesthetized cat. Records of blood pressure, gut movement and contractions of the nictitating membrane elicited by preganglionic sympathetic nerve stimulation. The drug (1 mg/kg) caused a fall in blood pressure, depression of gut movements and reduction in contractions of the nictitating membrane. The cardiovascular effects of vagal stimulation (∪) were abolished by the drug for a period of 40 min. The intestinal responses to vagal stimulation were reduced and recovered in 40 min. The depressor response to acetylcholine (• ACH) (2 μg) was slightly reduced by the drug and the intestinal response was abolished but recovered within 60 min.

were abolished immediately after the drug. Cardiovascular and intestinal responses to vagal stimulation and acetylcholine, recovered from the effects of the drug given intravenously within 1 hr (Fig. 1). After a 1 mg/kg dose, there was an immediate fall in blood pressure, decrease in gut motility and reduction in contractions of the nictitating membrane with a gradual return to control levels. The depressor response to vagal stimulation was blocked but returned within 40 min. The depressor response to acetylcholine was diminished but returned within 60 min. The intestinal response to vagal stimulation was reduced and that to acetylcholine was abolished for periods of 40 and 60 min respectively.

Intraduodenal administration of 5 to 10 mg/kg of hyoscine *N*-butyl bromide in ten cats was without effect on the blood pressure, heart rate or contractions of the nictitating membrane, but decreased gut motility and affected the cardiovascular and intestinal responses to vagal stimulation and acetylcholine. The depressor response to vagal stimulation was either reduced or abolished and the depressor response to injected acetylcholine was reduced but never abolished. Intestinal responses to vagal stimulation and acetylcholine were both abolished after intraduodenal administration of the drug and these effects lasted for longer than 2 hr. Fig. 2 illustrates the effect of intraduodenal administration of 10 mg/kg of the drug. The decrease in gut motility was evident within 15 min. The

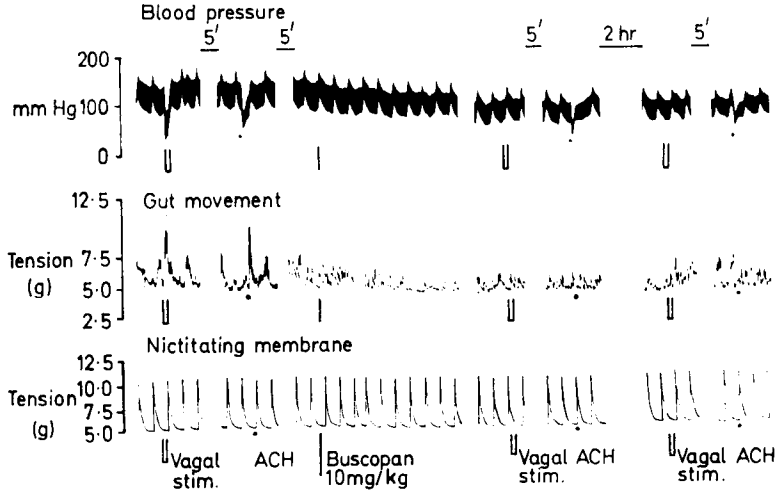

FIG. 2. Effects of intraduodenal hyoscine *N*-butylbromide in an anaesthetized cat. Records as in Fig. 1. The drug (10 mg/kg) decreased gut movements but did not affect blood pressure or contractions of the nictitating membrane. The cardiovascular, and intestinal effects of vagal stimulation (∪) were abolished within 20 min of the administration of the drug and had not returned in 2 hr. The depressor response to acetylcholine (• ACH) (2 μg) was reduced and the intestinal response to acetylcholine was abolished within 30 min of the administration of the drug and these effects lasted for longer than 2 hr.

depressor response to injected acetylcholine was reduced. Intestinal responses to vagal stimulation and acetylcholine were both abolished. These effects lasted for more than 2 hr.

Similar effects on gut motility and cardiovascular and intestinal responses to vagal stimulation and acetylcholine were produced by intraduodenal and intravenous administration of the drug, but the effects of the enterally administered drug were much longer lasting and much higher doses were required by this route.

Evidence of sympathetic ganglionic blockade, that is a decrease in blood pressure and reduction in contractions of the nictitating membrane, was demonstrated only when the drug was given intravenously.

DOGS

Intravenous injections of atropine-like drugs produce tachycardia in conscious dogs by blocking vagal inhibitory tone to the heart. The six dogs used in these experiments had control heart rates of 70 to 120 beats/min, and their heart rates increased to more than 220 beats/min after intravenous injections of atropine methylnitrate.

Hyoscine *N*-butyl bromide was administered orally to these dogs in tablets, solution and mixed with food, and their heart rates were determined from ECG records taken before and at intervals after the drug. In one dog given 8 tablets (6·1 mg/kg), the heart rate was slightly increased

above the control level (to 140 beats/min) between 1½ and 3 hr after dosing. However, in another dog of the same weight given the same number of tablets (6·1 mg/kg) there was no increase in heart rate. Further, in two dogs given 4 tablets each, in one there was a slight but drawn-out increase in heart rate to 120 beats/min (with 2·6 mg/kg), but in the other there was no change (with 2·5 mg/kg). In two dogs given 2 tablets each (doses corresponding to 1·2 and 2·0 mg/kg) there were no changes in heart rate. An intravenous injection of 1·6 mg/kg of the drug produced an immediate increase in heart rate to 220 beats/min, but the effect declined rapidly, the heart rate returning to the control level in 45 min.

Discussion

Our findings indicate clearly that hyoscine *N*-butyl bromide can be absorbed from the gastrointestinal tract of cats and then exert its anticholinergic effects as evidenced by blockade of the effects of vagal stimulation on the heart rate, blood pressure and intestine, and blockade of intestinal responses to injected acetylcholine. The time course of the effects of the drug by the intravenous and enteral routes differed considerably. The effects by the parenteral route were short lasting, presumably because the drug was rapidly eliminated, either from metabolism or excretion. This confirms earlier observations. Thus, Brownlee & others (1965) and Herxheimer & Haefeli (1966) reported that in man the effects of the subcutaneously administered drug disappeared within an hour. However, when intraduodenally administered, the drug had a long duration of action. This was probably a result of its relatively slow absorption, which is to be expected since the drug is a quaternary nitrogen compound. The maximal effect apparently depends on the concentration of the drug in the circulation, and its effect enterally must depend, therefore, on the balance between the rates of absorption and elimination. It follows from these considerations that it is impractical to compare doses given by the two routes in terms of the magnitude of effects at any one time.

A further complication that arises in comparing the effects of different blood concentrations of hyoscine *N*-butyl bromide (arising from administration by the two different routes) is that it has two distinct pharmacological actions: it antagonizes the muscarinic effects of acetylcholine (the so-called anticholinergic action) and it antagonizes the nicotinic actions of acetylcholine and thereby blocks ganglionic transmission (Herman, Shaw & Rosenblum, 1958). The latter effect undoubtedly explains the reduction in contractions of the nictitating membrane and the depressor action of the drug intravenously, but these effects were not observed enterally which suggests that the blood concentration may not rise to a level sufficient for the drug to exert a significant ganglion blocking action.

Our experiments were not designed to investigate whether hyoscine *N*-butyl bromide is more effective on the gastrointestinal tract than on other tissues but they did not disprove that this might be so. In one experiment we observed a relaxation of a segment of intestine (which

had been made hypermotile by injections of neostigmine) with enteral doses of the drug that did not abolish the cardiac responses to vagal stimulation. If it is true that effectors other than the gut (e.g., the heart, salivary glands and ciliary muscle) are relatively insensitive to the drug, then indirect tests for the efficacy of orally administered drug involving responses of these effectors may not be valid, even though it is possible to produce fleeting effects on, say, the heart rate by giving the drug parenterally. The weak and inconstant effect after the drug orally on heart rate of dogs is in accord with the findings on heart rate in man (Herxheimer & Haefeli, 1966). Unfortunately, these authors base their conclusions on the lack of efficacy of the drug orally entirely on effects which are unrelated to the therapeutically desired actions on the gastro-intestinal tract, and which would have amounted to side-effects if they had occurred.

Acknowledgements. We are indebted to Miss A. Glover, Miss A. Przeczek and Mr. M. Rush who made the experiments using dogs and to Miss S. Czechowicz for her skilled assistance with the other experiments. Part of the expenses of this work was defrayed by a grant from the National Health and Medical Research Council. We are indebted to Dr. K. Higgins, the Medical Director of Boehringer Ingelheim (Australia) for helpful discussion and for a supply of Buscopan.

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