Comparative spasmolytic potencies of atropine sulphate and *N*-butyl hyoscine bromide following intravenous injection, injection into a mesenteric vein, and intraduodenal instillation

It is generally accepted that drugs can be absorbed from the gastrointestinal tract only if they are unionized and sufficiently lipid-soluble (Travell, 1938, 1940; Schanker & Hogben, 1957; Schanker, Shore & others, 1957; Travell, 1960; Schanker, 1962). If this were true for all drugs, it would be anticipated that atropine sulphate would not be absorbed because it is completely ionized up to a pH of 7·5 and is poorly lipid-soluble (only 0·25% w/v in chloroform). These considerations should also apply to *N*-butyl hyoscine bromide, which, being a quaternary base, is also completely ionized, although it is somewhat more lipid-soluble (approx. 10% w/v in chloroform). However, with atropine sulphate, it is well known that dryness of the mouth occurs after small doses given orally, the oral effective dose being only 3 times higher than the corresponding subcutaneous dose (Unna, Glaser & others, 1950).

These discrepancies between prediction and clinical observation prompted us to investigate the spasmolytic potency of atropine sulphate after intravenous and intraduodenal administration and, to exclude problems of absorption and to evaluate the role played by the liver, also after injection into a mesenteric vein. The spasmolytic activity of *N*-butyl hyoscine bromide was evaluated under identical conditions.

Female mongrel dogs (32) were premedicated with 1 mg/kg morphine sulphate subcutaneously and anaesthetized with chloralose-urethane (80 mg/kg chloralose: 400 mg/kg urethane) intravenously. Pressure in the urinary bladder was measured with a Statham pressure transducer by means of a catheter in the urethra. The nerves in the ligamentae vesicae urinariae were stimulated with a square wave of duration 1ms and of pulse rate 50/s using a Grass stimulator. This stimulation was repeated every 5 min. Contractions of the urinary bladder, blood pressure, and heart rate were recorded on a Grass Polygraph. Atropine sulphate and *N*-butyl hyoscine bromide were given (*a*) intravenously, (*b*) intravenously into a mesenteric vein, and (*c*) intraduodenally.

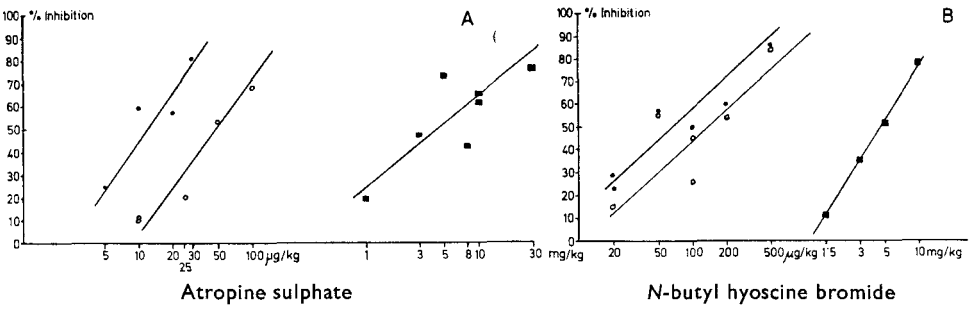

FIG. 1.A. Inhibitory effect of atropine sulphate on electrically stimulated urinary bladder contractions in dogs. Only the effect of the first dose of atropine sulphate given in each experiment is included in this diagram. B. Inhibitory effect of *N*-butyl hyoscine bromide on electrically stimulated urinary bladder contractions in dogs. Only the effect of the first dose of *N*-butyl hyoscine bromide given in each experiment is included in this diagram. —●—●— intravenous injection v. femoralis; —○—○— intravenous injection into a mesenteric vein; —■—■— intraduodenal instillation.

The results are presented in two graphs plotted on a semilogarithmic scale (Fig. 1A and B). Each point of the dose-response curves represents one experiment with a dog, and only the first dose given is included in the diagrams. By interpolation, the doses of atropine sulphate and of *N*-butyl hyoscine bromide which diminished the contractions by 50% were determined, the results are summarized in Table 1.

Table 1. *Inhibitory effect of atropine sulphate and* N-*butyl hyoscine bromide on electrically stimulated urinary bladder contractions in dogs*

Compound	ED 50 intravenously	ED 50 intravenously into a mesenteric vein	ED 50 intraduodenally	Ratio of equi-effective doses
Atropine sulphate ..	0·01 mg/kg	0·05 mg/kg	4·5 mg/kg	1:5:450
N-Butyl hyoscine bromide	0·07 mg/kg	0·14 mg/kg	4·7 mg/kg	1:2:67

With both drugs, a large difference was found between the doses required to produce an equivalent spasmolytic effect after intravenous and intraduodenal administration. One explanation for this quantitative difference could be that in the case of atropine sulphate only 0·25% is absorbed from the gastrointestinal tract and with *N*-butyl hyoscine bromide, only 1·5% of the oral dose is absorbed. Alternatively, both drugs may be well absorbed after intraduodenal administration and the difference in potency could be due to inactivation by the liver, either by storage, metabolism or excretion into the bile.

Comparison of the doses required for an equivalent spasmolytic effect after intravenous administration into the femoral or mesenteric veins has distinguished between these two possibilities. Atropine sulphate retained 20% and *N*-butyl hyoscine bromide retained 50% of its activity after circulation through the liver, indicating that low activity after intraduodenal administration is due to poor enteric absorption of the two drugs. However, this conclusion is surprising in view of the known therapeutic efficacy of oral atropine sulphate and the recently reported efficacy of *N*-butyl hyoscine bromide after oral administration (Schmid, Bleichert & others, 1968).

One could be tempted to conclude that there exists a species difference between man and dog in enteral absorption, the dog absorbing the two drugs much less than the man. On the other hand, the ratio of equi-effective doses after intravenous and oral administration varies according to the test organ chosen for comparison. *N*-Butyl hyoscine bromide is more effective in dogs after intrajejunal instillation when the spontaneous contractions of the duodenum are used as a parameter for efficacy; in these experiments the ratio of the intravenous dose to the dose administered into the jejunum is in the order of 1 to 20 (Bauer, Gross & others, 1968) compared with 1 to 70 reported here. It is concluded that additional pharmacological data are required before precise conclusions can be drawn about the enteral absorption rates of the two drugs.

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